Clinical aspects of
Postpartum Hemorrhage

Babette W. Prick

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Content


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Chapter 1
Introduction

Postpartum hemorrhage is characterized by excessive blood loss during delivery and is defined by the World Health Organization as blood loss exceeding 500 mL, while severe postpartum hemorrhage is defined as blood loss exceeding 1000 mL.[1] This thesis describes studies concerning severe primary postpartum hemorrhage, using the term postpartum hemorrhage for blood loss exceeding 1000 mL.

Postpartum hemorrhage has been a major cause of maternal death and morbidity for as long as physicians have studied and written about childbirth. Despite considerable advances in medical care in the last centuries, postpartum hemorrhage is still a frequent cause of death in many parts of the world and continues to plague obstetricians even in developed countries. Nowadays, the incidence is 4-8% in the developed world while it runs up to 19% in developing countries.[2,3] Moreover, an increase in the incidence of postpartum hemorrhage has been reported in developed countries during the last decade.[4-11] Treatment of acute anemic women after postpartum hemorrhage is often based on red blood cell transfusion. The ability to safely transfuse, however, was absent for a long period of time. While attempts to transfuse blood have been described since the 15th century, blood transfusion remained unsuccessful until the 19th century. The first successful human blood transfusion was performed in 1818 by the British obstetrician James Blundell, for the treatment of postpartum hemorrhage. Doctor Blundell used the patient's husband as a donor and extracted four ounces of blood from his arm to transfuse into his wife. During 1825-1830, doctor Blundell performed ten transfusions, of which five were successful. It was not until the beginning of the 20th century that blood transfusion became safer due to the discovery of human blood group systems. Storage of blood was not achieved until 1910-1915 and the first blood banking service was established by a US army officer in France during World War I. Nowadays, over 500.000 red blood cell units are used yearly in the Netherlands of which 4% because of obstetric complications, mainly postpartum hemorrhage.[12,13] These transfusions are associated with infectious disease risks and immune-mediated risks.[14] In patient blood management, hemoglobin (Hb) concentration is the main trigger to transfuse. Besides the Hb concentration, depending on the physician amount of blood loss, physical complaints and social environment are also taken into consideration. Despite the advice of several guidelines,[15-17] transfusion triggers vary widely between physicians. Besides improvement of clinical status and oxygen supply,[14,18] an important purpose of transfusion is to improve a patients health-related quality of life (HRQoL).

The use of HRQoL measures is upcoming in the decision making processes in health

care nowadays. HRQoL is a multidimensional concept that includes domains related to physical, mental, emotional and social functioning. To score HRQoL, several measures have been developed. These measures, provided as questionnaires, can be classified into three categories. Generic questionnaires measure HRQoL in scores that can be compared among differing populations, regardless the presence or absence of specific diseases. Disease-specific questionnaires score the consequences of a specific disease, for example pain and stiffness with arthritis. Domain-specific questionnaires are developed to score a specific domain of HRQoL, for example fatigue.
In the studies described in this thesis three HRQoL measures were used: the generic measures ShortForm-36 and EuroQol-5D and the domain-specific measure Multidimensional Fatigue inventory.

Aim of the thesis

With the increasing incidence of postpartum hemorrhage in developed countries, the variation in incidence, prevention and treatment of postpartum hemorrhage and its sequelae become of great importance. Therefore, the aim of this thesis was to investigate the incidence of postpartum hemorrhage in the Netherlands, adherence to the protocol in the management of the third stage of labor and red blood cell transfusion management in patients with acute anemia after postpartum hemorrhage.

Specific research questions were:

- What is the incidence of postpartum hemorrhage in the Netherlands and does variation across the regions exists?
- Is active management of the third stage of labor, as recommended by the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO), well implemented in the Netherlands?
- Is non-intervention inferior to red blood cell transfusion in acutely anemic women after postpartum hemorrhage with regard to HRQoL, especially physical fatigue?
- Which parameters predict the need for escape red blood cell transfusion in anemic women, after postpartum hemorrhage, initially treated expectantly?
- What are the economic consequences of red blood cell transfusion versus non-intervention in acutely anemic women after postpartum hemorrhage?
- Which baseline characteristics and clinical parameters influence HRQoL in the postpartum period?

Thesis outline

This thesis displays the results of a large cohort study, a clinical observational study and a multicenter randomized controlled trial. Cost-effectiveness analyses were performed and prediction models created, based on data of the randomized controlled trial. Furthermore, data of three randomized

controlled trials were merged to create a large cohort.

In **Chapter 1** an introduction on the subject is provided. **Chapter 2** presents results of a large cohort study, investigating postpartum hemorrhage incidence and variation across regions in the Netherlands. The cohort was created in collaboration with the Dutch Perinatal Registry and consists of deliveries in the Netherlands from 2000 to 2008. Data of maternal mortality due to postpartum hemorrhage were made available by the Dutch Maternal Mortality Committee.

We studied the performance of the active management of the third stage of labor to prevent postpartum hemorrhage after vaginal deliveries. A clinical observational study was conducted in one academic and one teaching hospital in the Netherlands. Results are described in **Chapter 3.**

Chapter 4 presents several studies based on data of the WOMB ('Well-being of Obstetric patients on Minimal Blood transfusions') trial, a multicenter randomized trial that randomized women with acute anemia after postpartum hemorrhage between RBC transfusion and non-intervention. Primary outcome of this trial was physical fatigue, measured with the Multidimensional Fatigue Inventory. The trial was conducted in collaboration with the Dutch Obstetric Consortium; 37 Dutch hospitals participated in this trial.

Chapter 4.1 presents the protocol of the WOMB trial. In **Chapter 4.2** results of a survey, held among Dutch gynecologists, are demonstrated. This survey inventoried prior beliefs on clinical questions regarding postpartum transfusion policy that were to be evaluated by the WOMB trial. Results of the WOMB trial itself are presented in **Chapter 4.3**. In **Chapter 4.4** we describe formulas predicting the need for escape RBC transfusion in anemic women, after postpartum hemorrhage, initially treated expectantly. Also, a cost-effectiveness analysis of RBC transfusion versus non-intervention in acutely anemic women after postpartum hemorrhage was performed: results of this analysis are presented in **Chapter 4.5**.

To explore the relation of several baseline characteristics and clinical parameters with HRQoL in the postpartum period, data of the WOMB trial were combined with data of two other large randomized controlled trials, the Digitat and Hypitat trial (**Chapter 5**). These three multicenter trials were all conducted in collaboration with the Dutch Obstetric Consortium.

A general discussion is presented in **Chapter 6**.

In **Chapter 7** this thesis was summarized.

Chapter 2

Reasons for regional differences in severe postpartum hemorrhage: a nationwide comparative study of 1.6 million deliveries

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Abstract

Objective

The incidence of severe postpartum hemorrhage (PPH) is increasing. Regional differences in its incidences may be attributed to variation in provision of care. We aimed to assess the reasons for regional variation in severe PPH in the Netherlands.

Design

All deliveries (2000 through 2008) from the Netherlands Perinatal Registry and the Dutch Maternal Mortality Committee were used to study severe PPH incidences (defined as blood loss ≥ 1000 mL) across both regions and neighborhoods of cities. First, incidences were presented crude and after exclusion of multiple pregnancies. Logistic multilevel regression analyses, with hospital or community midwife practice as second level, were performed to explore further reasons for regional variation.

Results

A total of 1 599 867 deliveries was studied. The national incidence of severe PPH was 4.5%. Up to 3-fold differences in crude incidences were observed between regions and differences between neighborhoods were even larger. Using multilevel analyses, regional variation was not explained by maternal characteristics (age, parity, ethnic background, socioeconomic status), pregnancy characteristics (singleton, gestational age, birth weight, pre-eclampsia, perinatal death), medical interventions (induction of labor, mode of delivery, perineal laceration, placental removal) and health care setting.

Conclusion

The variation in severe PPH could not be explained by maternal characteristics, pregnancy characteristics, medical interventions or health care setting. Regional variation is either unavoidable or subsequent to regional variation of a yet unregistered variable.

Background

Severe postpartum hemorrhage (PPH), a major obstetric complication and an important cause of maternal morbidity and mortality worldwide,[3,19-21] reported to occur in 2-6% of pregnancies,[2,21] has increased over the last decade.[4-11] The World Health Organization defines severe PPH as blood loss of ≥ 1000 mL,[1] not taking in consideration the mode of delivery i.e. vaginal versus cesarean section (CS). Carolli et al. described variation in severe PPH incidence worldwide varying from 0.3 to 3.8% within the continent Africa, 0.7 to 2.7% in Asia and 1.7 to 5.5% in Europe.[2] With an increasing severe PPH incidence in several developed countries, assessment of PPH at the national and regional level is important. Intercountry variation, particularly between developed and developing countries, may mainly result from differences in medical interventions and health care. At the national level, regional differences are also observed, e.g. 3-fold differences among regions in California.[22] Understanding of variation need to go beyond investigation of incidences as exploring reasons for differences can be helpful in guiding practice improvements. There may be a tendency to attribute the variation at the national level to differences in health care: adjustments for the characteristics of mothers and pregnancies are necessary to understand the variation better.

In this paper, we studied severe PPH incidences in the 12 provinces and four largest cities in the Netherlands, as well as in the neighborhoods of the two largest cities. Variation may be due to the combined effect of maternal and pregnancy characteristics, medical interventions and variation in PPH policy in hospital and community midwife practices. We performed logistic multilevel regression analyses to study if these variables could explain the variation in our dataset. We also present the severe PPH-related mortality per region as PPH-related mortality accounts for almost 8% of all direct maternal deaths in the period 1993-2005.[23]

Methods

We studied all deliveries in the period 2000-2008, registered in the Netherlands Perinatal Registry (PRN). The PRN is a linked national registry in which information on 96% of all pregnancies and pregnancy outcomes are registered by care providers.[24] Predefined information is directly extracted from the mothers' record and sent to the PRN. The PRN distinguishes between data from community midwife practices (LVR1, primary care) providing care to low-risk pregnancies and data from hospitals providing care to women with an increased perinatal risk by obstetricians (LVR2, secondary/ tertiary care). Data on active third stage management and professional performance are not available. Neonatal admissions and complications for each newborn are registered by pediatricians (LNR).[24] The Netherlands comprises 12 provinces. The eight tertiary care hospitals are located within six provinces (Noord-Holland, Zuid-Holland, Utrecht, Gelderland, Limburg and Groningen) while teaching hospitals are present in all provinces. In each of the four largest cities (Amsterdam, Rotterdam, Utrecht and The Hague) a tertiary care hospital is located, except in the city of The Hague. In the Netherlands low-risk women are cared for by independent community midwife practices or general practitioners. Part of these low-risk women deliver at home, which results in a

Dutch home delivery incidence of 24% *(Table 1)*.[25] High-risk women are cared for by gynecologists and deliver in hospital.

The incidence of severe PPH was analyzed per province, the four largest cities were separately analyzed: it is known from previous studies that perinatal outcomes in these cities are inferior to those in the other regions (provinces) of the Netherlands.[26-28] Additionally, the incidence of severe PPH across neighborhoods was analyzed for the two largest cities: Amsterdam and Rotterdam. Differences between neighborhoods were investigated to compare the magnitude of these differences to differences between provinces. In the previous study we mentioned earlier, differences in perinatal morbidity and mortality were also demonstrated between neighborhoods.[26] Incidences were calculated for every province, city and neighborhood using the four-digit zip codes of the women's address as geographical classifier. Therefore, a woman from a rural area delivering in a tertiary hospital was analyzed as woman from that rural region. Maternal mortality numbers were independently obtained from the Maternal Mortality Committee of the Dutch Society of Obstetrics and Gynecology. The committee's methods have been previously described.[23]

Statistical analysis

Primary outcome was the crude incidence of severe PPH across Dutch provinces and the four largest cities. Secondary outcomes were the severe PPH incidence across neighborhoods in the two largest cities, and PPH-related maternal mortality across regions. Deliveries with a gestational age below 24+0 weeks were excluded. Crude severe PPH incidences were tabulated, as well as crude incidences after exclusion of multiple pregnancies. Data were stratified for mode of delivery as there are known differences in PPH incidence between different modes of delivery.[29] The distribution of the severe PPH incidences was projected on a map of the Netherlands. For this figure, quartiles of standardized incidences were chosen as cut offs. We performed logistic multilevel regression analyses to explore the origin of the observed geographical variation using hospitals and community midwife practices as the second level in the analyses. For this purpose, each hospital and community midwife practice was anonymized and identified by a code.

We performed 6 model specifications following the same pattern. All models were fit on the exact same data. First, we estimated a model including regions only to assess the outcome (severe PPH) across regions. Then, we repeated the analysis after addition of covariates, which were added block-wise. Every subsequent model thus consisted of the first model and one specific block of covariates. The second model included maternal characteristics (age, parity, ethnic background, socioeconomic status) as covariates, the third model pregnancy characteristics (singleton, gestational age, birth weight, pre-eclampsia, perinatal death), the fourth model medical interventions (induction of labor, mode of delivery, perineal laceration, placental removal) and the fifth model health care setting (place of delivery). Finally, the last model was performed after inclusion of all blocks (maternal characteristics, pregnancy characteristics, medical interventions and health care setting).

The following definitions were used. Severe PPH was defined as peripartum blood loss ≥ 1000 mL in the 24 hours following delivery. We categorized maternal age in ≤ 35 and > 35 years and parity into nulliparous women (i.e., women who had never given birth) or multiparous women (i.e., women who

had given birth at least once). Ethnicity was categorized in Western or non-Western. Socioeconomic status was derived from the recorded zip code of the women.[30] Gestational age at delivery was categorized into ≥ 37 weeks and < 37 weeks. Pre-eclampsia was defined as a diastolic blood pressure of minimal 90 mmHg in the presence of proteinuria after 20 weeks of gestation.[31] Birth weight percentiles were derived from sex and parity specific growth curves[32] and considered to be undefined for multiple pregnancies and neonates with congenital anomalies or perinatal death. We distinguished between spontaneous onset of labor and induction of labor. Mode of delivery was categorized into spontaneous vaginal, assisted vaginal delivery, elective CS or emergency CS. Perineal laceration was split into 'none or first degree' or 'at least second degree' and a distinction between spontaneous placental delivery and manual placenta delivery was made. The Dutch health care setting was described in more detail above. In case of a discrepancy between LVR1 and LVR2 source data, LVR2 data prevailed, with the exception for the variable ethnic background.

A funnel plot was created using Excel. Tests for differences between groups were performed using SPSS; multilevel analyses were performed using proc glimmix in SAS version 9.3 software.

Results

A total of 1 599 867 pregnancies was studied. General characteristics of all deliveries are tabulated in ***Table 1***. Severe PPH was reported in 69 719 (4.5%) of all deliveries; severe PPH incidence increased from 3.8 to 5.8% during the study period ($p < 0.001$). PPH was unknown in 44 859 deliveries.

Mode of delivery affected the incidence as follows: spontaneous delivery 4.3%, assisted vaginal delivery 6.4%, elective CS 4.3% and emergency CS respectively 3.2%.

Severe PPH incidence per region

In ***Appendix 1*** crude incidence in regions are tabulated.

Crude incidences

The average national crude severe PPH incidence was 4.5%. ***Figure 1*** demonstrates the wide variation in crude incidence per region related to the regional population size. When stratifying by mode of delivery, severe PPH incidence was up to 3 times higher in the region with the highest incidence compared to that with the lowest. After spontaneous delivery, the incidence ranged from 3.3% to 5.1%. After assisted vaginal delivery this range was 4.8% to 7.9% while the ranges after elective and emergency CS were the widest: respectively 2.7% to 6.8% and 1.5% to 4.9%. Crude incidences of severe PPH in the four largest cities exceeded regional results. Altogether, without stratification for mode of delivery, the crude severe PPH incidence in the four cities was 4.9% compared to 4.4% in the provinces ($p < 0.001$).

Singleton pregnancies

After exclusion of multiple pregnancies, average crude severe PPH incidence was 4.2% after spontaneous delivery, 6.2% after assisted vaginal delivery, and 3.5% and 3.0% after respectively elective and emergency CS (***Appendix 1***). The severe PPH incidence decreased in most regions after exclusion of multiple pregnancies. Ranges in incidence per mode of delivery as well as regional ranks in severe PPH incidence remained similar.

Table 1 *Maternal characteristics, pregnancy characteristics, medical interventions, health care setting and severe PPH incidences.*

	All		Spontaneous		Assisted vaginal delivery		Elective CS		Emergency CS	
	%	inci-dence	%	inci-dence	%	inci-dence	%	inci-dence	%	inci-dence
Maternal characteristics										
Age, n (%)										
≤ 35 years	85.6	4.4	86.0	4.3	88.4	6.2	78.9	3.9	83.6	3.0
> 35 years	14.4	5.1	14.0	4.8	11.6	7.7	21.1	5.5	16.4	4.3
Parity										
0	46.2	5.0	39.1	5.1	82.1	6.6	42.0	3.8	67.7	2.8
≥ 1	53.8	4.0	60.9	3.9	17.9	5.5	58.0	4.6	32.3	3.9
Ethnicity										
Western	84.5	4.6	83.9	4.4	88.2	6.6	86.7	4.1	83.5	3.2
non-Western	15.5	4.1	16.1	4.0	11.8	4.8	13.3	5.3	16.5	3.3
Socioeconomic status										
highest (> p80)	17.2	4.9	17.0	4.7	18.2	7.2	18.0	4.7	17.0	3.3
moderate (p20-80)	57.8	4.5	57.8	4.3	58.4	6.4	58.9	4.1	57.0	3.2
lowest (< p20)	25.0	4.2	25.3	4.2	23.5	5.7	23.1	4.2	26.0	3.0
Pregnancy characteristics										
Singleton pregnancy										
yes	98.0	4.3	98.6	4.2	98.2	6.2	94.1	3.5	96.1	3.0
no	2.0	12.1	1.4	11.1	1.8	17.4	5.9	16.0	3.9	7.5
Gestational age										
≥ 37 weeks	93.3	4.4	94.3	4.2	95.2	6.3	81.9	3.7	91.0	3.1
< 37 weeks	6.7	6.0	5.7	5.9	4.8	8.3	18.1	6.6	9.1	3.9
Pre-eclampsia										
yes	2.2	7.4	1.3	8.9	2.7	12.1	8.1	4.6	4.8	4.1
no	97.8	4.2	98.7	4.1	97.3	6.1	91.9	3.9	95.2	2.8
Birth weight neonate										
< 10th percentile	9.7	3.4	9.5	3.5	8.5	4.4	12.0	3.0	11.5	1.7
10-90 percentile	79.7	4.3	81.0	4.2	79.0	5.9	75.6	4.3	72.3	3.0
> 90st percentile	10.5	7.0	9.5	6.8	12.5	10.7	12.4	5.4	16.2	5.0
Perinatal death										
yes	0.8	7.5	0.8	7.3	0.4	10.3	1.0	8.8	0.7	5.5
no	99.2	4.5	99.2	4.3	99.6	6.4	99.0	4.2	99.3	3.2
Medical interventions										
Induction of labor										
yes	14.8	6.2	14.0	6.3	18.7	8.5	NA		29.5	3.6
no	85.2	4.2	86.0	4.0	81.3	5.9	NA		70.5	3.0
Delivery										
spontaneous	74.7	4.3	NA		NA		NA		NA	
assisted vaginal delivery	10.7	6.4	NA		NA		NA		NA	
elective CS	6.5	4.3	NA		NA		NA		NA	
emergency CS	8.1	3.2	NA		NA		NA		NA	

	All		Spontaneous		Assisted vaginal delivery		Elective CS		Emergency CS	
	%	inci-dence	%	inci-dence	%	inci-dence	%	inci-dence	%	inci-dence
Perineal laceration										
intact/ ≤1st degree rupture	71.4	3.8	74.0	3.7	14.8	5.1	NA		99.2	
≥ 2nd degree rupture/ episiotomy	28.6	6.3	26.0	6.2	85.2	6.6	NA		0.8	
Manual placenta removal										
yes	1.9	58.3	2.0	59.6	3.8	53.2	NA		NA	
no	98.1	3.5	98.0	3.2	96.2	4.6	NA		NA	
Health care setting										
Delivery										
home (community midwife)	24.2	2.3	32.4	2.2	NA		NA		NA	
hospital (community midwife)	10.9	4.2	14.6	4.2	NA		NA		NA	
tertiary care hospital	5.8	7.4	4.8	7.3	7.3	8.1	11.5	7.9	8.7	6.5
teaching hospital	30.4	5.6	25.1	6.0	46.9	6.6	44.4	4.0	45.4	3.1
non-teaching hospital	28.8	4.7	23.2	5.0	45.9	5.9	44.1	3.6	45.9	2.7

Total deliveries: 1 599 867, PPH unknown: 44 859, Mode of delivery unknown: 2350
NA = not applicable, CS = cesarean

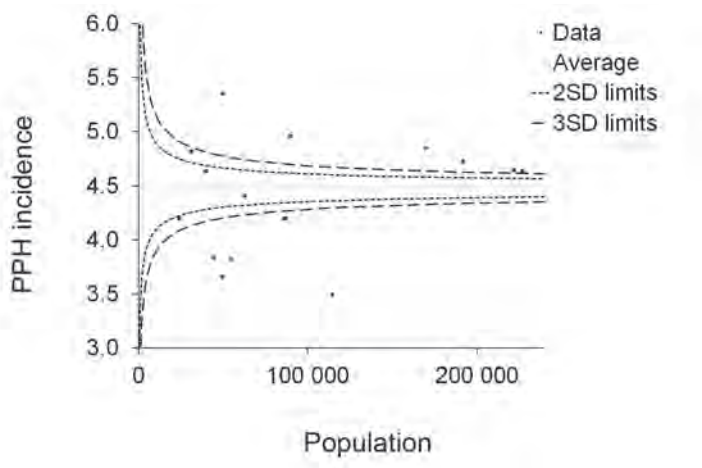


Figure 1 *Funnel plot: variation in regional PPH incidence related to regional population size.*

Logistic multilevel regression analyses

Table 2 presents OR's of severe PPH per region taking into account the level hospital or community midwife practice. Crude, unadjusted regional OR's (the first model) ranged from 0.80 to 1.10 while the OR's of severe PPH in the four largest cities were similar to those in the provinces.

Adjustment for maternal characteristics led to higher severe PPH OR's compared to the unadjusted model although differences were relatively small except for the cities Amsterdam and Rotterdam. Compared to the unadjusted model, adjustment for pregnancy characteristics revealed overall lower severe PPH OR's while adjustment for medical interventions led to an ambiguous effect on the severe PPH OR's. Health care setting adjustment also produced an ambiguous effect with mainly higher severe PPH OR's compared to the unadjusted model. Of the four blocks of variables that were added to the unadjusted model, pregnancy characteristics and health care setting influenced the severe PPH OR's the most.

Compared to the unadjusted model, adjustment for all variables simultaneously had the largest effect on the severe PPH OR's although this too was an ambiguous effect.

The regional variation in severe PPH OR was largest after adjustment for all variables. After stratification for mode of delivery, adjustment for all variables demonstrated ambiguous effects for each mode of delivery too (data not shown).

Severe PPH incidence in Amsterdam

Crude incidences in neighborhoods in Amsterdam are demonstrated in *Appendix 2*.

Crude incidences

The average crude incidence was 5.0%. There was a wide variation in incidence between neighborhoods with differences up to 7.3%, depending on the mode of delivery. After spontaneous delivery, the incidence ranged from 3.6% to 6.4%. After assisted vaginal delivery this range was 3.8% to 10.4% while the ranges after elective and emergency CS were the widest: 1.6% to 8.9% and 0.8% to 5.3%.

Singleton pregnancies

Average crude incidence after exclusion of multiple pregnancies was 4.9% after spontaneous delivery, 7.4% after assisted vaginal delivery and 3.7% and 2.4% after respectively elective and emergency CS.

Severe PPH incidence in Rotterdam

Crude incidences in neighborhoods in Rotterdam are demonstrated in *Appendix 3*.

Crude incidences

The average crude incidence was 4.4%. Differences between neighborhoods were large and reached differences up to 8.0%. After spontaneous delivery, the incidence ranged from 3.8% to 6.2%. After assisted vaginal delivery, the incidence ranged from 4.1% to 12.1% while ranges were widest after elective and emergency CS: 1.8% to 6.6% and 0% to 4.9%, respectively.

Singleton pregnancies

Average crude incidence after exclusion of multiple pregnancies was 4.3% after spontaneous delivery, 5.3% after assisted vaginal delivery and 3.4 and 3.2% after respectively elective and emergency CS.

Table 2 *Results of logistic multilevel regression analyses of PPH per region.*

	Unadjusted	Adjusted for					
		Maternal characteristics	Pregnancy characteristics	Medical interventions	Health care setting	All	% Change in OR: unadjusted vs adjusted for all
Region							
Amsterdam[a]	1.02 (0.92-1.13)	1.12 (1.01-1.24)	1.08 (0.96-1.20)	1.02 (0.92-1.13)	1.00 (0.91-1.10)	1.05 (0.94-1.17)	3
Rotterdam[a]	0.94 (0.85-1.04)	1.05 (0.94-1.17)	0.97 (0.86-1.08)	0.91 (0.82-1.02)	0.86 (0.78-0.94)	0.90 (0.80-1.01)	-5
The Hague[a]	1.00 (0.89-1.12)	1.04 (0.93-1.16)	0.99 (0.88-1.12)	0.91 (0.81-1.03)	0.91 (0.82-1.02)	0.84 (0.74-0.94)	-20
Utrecht[a]	0.89 (0.82-0.97)	0.92 (0.85-1.00)	0.94 (0.86-1.02)	1.00 (0.91-1.10)	0.89 (0.82-0.96)	1.02 (0.92-1.13)	12
Groningen	0.80(0.69-0.92)	0.83 (0.72-0.96)	0.77 (0.66-0.90)	0.73 (0.63-0.84)	0.75 (0.66-0.86)	0.71 (0.61-0.82)	-13
Friesland	0.88 (0.76-1.03)	0.91 (0.79-1.06)	0.78 (0.66-0.91)	0.73 (0.63-0.85)	0.86 (0.75-0.98)	0.70 (0.60-0.82)	-26
Drente	0.83 (0.72-0.95)	0.85 (0.74-0.97)	0.78 (0.67-0.90)	0.73 (0.63-0.83)	0.80 (0.70-0.90)	0.71 (0.62-0.82)	-16
Overijssel	0.91 (0.82-1.01)	0.92 (0.93-1.03)	0.84 (0.74-0.94)	0.81 (0.73-0.91)	0.92 (0.83-1.01)	0.83 (0.74-0.93)	-10
Gelderland	1.01 (0.93-1.08)	1.02 (0.94-1.09)	0.95 (0.88-1.03)	0.92 (0.85-1.00)	1.02 (0.95-1.09)	0.92 (0.85-1.01)	-9
Utrecht	Ref	Ref	Ref	Ref	Ref	Ref	
Noord Holland	1.10 (1.01-1.21)	1.12 (1.02-1.22)	1.06 (0.97-1.17)	1.02 (0.93-1.12)	1.08 (1.00-1.18)	0.98 (0.89-1.08)	-13
Zuid Holland	1.05 (0.96-1.15)	1.07 (0.98-1.16)	1.03 (0.94-1.14)	0.96 (0.88-1.05)	0.99 (0.91-1.07)	0.89 (0.81-0.98)	-18
Zeeland	1.05 (0.87-1.26)	1.07 (0.89-1.28)	0.96 (0.79-1.16)	0.98 (0.81-1.18)	0.94 (0.80-1.12)	0.88 (0.73-1.07)	-19
Noord Brabant	1.03 (0.94-1.13)	1.04 (0.95-1.14)	1.02 (0.92-1.12)	0.95 (0.86-1.04)	1.02 (0.94-1.11)	0.97 (0.88-1.06)	-7
Limburg	1.04 (0.92-1.17)	1.05 (0.93-1.18)	1.00 (0.88-1.14)	0.90 (0.80-1.02)	0.97 (0.87-1.08)	0.86 (0.76-0.98)	-20
Flevoland	1.07 (0.94-1.23)	1.10 (0.96-1.26)	0.93 (0.80-1.08)	0.93 (0.81-1.07)	1.05 (0.93-1.20)	0.87 (0.74-1.01)	-24

[a] City
Level used was the unique code for each hospital and community midwife practice
Maternal characteristics: Age, Parity, Ethnic background, Socioeconomic status
Pregnancy characteristics: Singleton, Gestational age, Birth weight, Pre-eclampsia, Perinatal Death
Medical interventions: Induction of labor, Mode of delivery, Perineal laceration, Placental removal
Health care setting: Place of delivery

Table 3 *Crude maternal mortality per region.*

	Deliveries[a]	PPH cases[a]	Mortality, total[b]	Mortality, due to PPH[b] (% of total)
Region				
Amsterdam[c]	90 738	4656	9	0
Rotterdam[c]	63 571	2891	17	1
Den Haag[c]	53 509	2812	9	0
Utrecht[c]	37 098	1583	4	0
Groningen	50 823	1912	5	0
Friesland	56 079	2201	7	1
Drente	44 942	1795	6	1
Overijssel	118 003	4227	15	2
Gelderland	197 320	9575	15	1
Utrecht	93 408	3828	19	3
Noord-Holland	173 166	8613	16	0
Zuid-Holland	226 040	10 843	20	2
Zeeland	27 505	1047	6	1
Noord-Brabant	230 043	11 081	20	1
Limburg	88 794	3833	10	0
Flevoland	40 107	1941	5	0
Unknown region	8721	430	4	1
Total	1 599 867	73 268	187	14 (7.5%)

[a] Data derived from PRN
[b] Data derived from Maternal Mortality Committee
[c] City

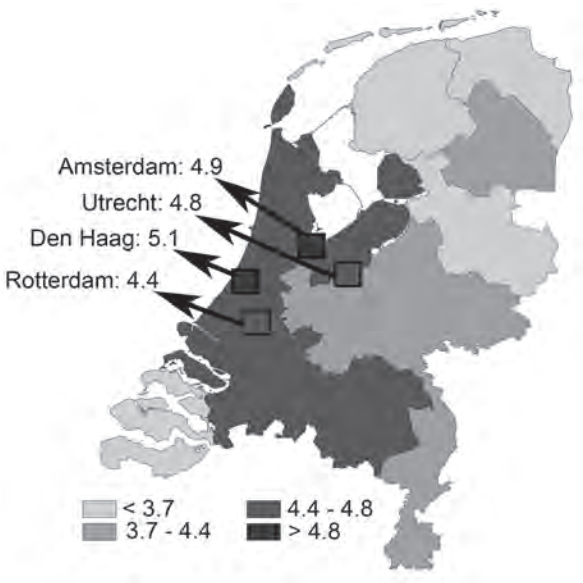


Figure 2 *Crude incidence of PPH following spontaneous delivery per region.*

PPH-related mortality

Almost eight percent of total maternal mortality was related to PPH (see ***Table 3***). PPH-related mortality varied from 0.16% to 0.59% across regions. It showed a pattern dissimilar from the crude severe PPH incidence pattern across regions.

Discussion

The national incidence of severe PPH in the period 2000-2008 was almost 5%. Our results, stratified by mode of delivery, showed a wide variation in severe PPH incidence across regions (provinces, cities) and neighborhoods in the Netherlands: crude incidences ranged from below 2% to well over 8%. ***Figure 1*** demonstrates that variation tends to be larger when the population size is smaller. After elective and emergency CS, the variation in severe PPH incidence was most extreme. As expected, exclusion of multiple pregnancies decreased crude incidences.[21,33,34] A significant higher severe PPH incidence was observed in the four cities compared to the 12 provinces. Across neighborhoods in the two largest cities, variation in severe PPH incidence was even larger than across regions.

Following logistic multilevel regression analyses, to adjust for maternal characteristics, pregnancy characteristics, medical interventions and health care setting, the variation in OR's per region even increased (***Table 2***). Therefore, the epidemiological data cannot elucidate the sources of the remnant variation: results imply they are unavoidable or subsequent to regional variation of a yet unregistered variable.

Regional differences in PPH incidence were previously described. Carolli et al.[2] described similar variation in severe PPH incidence worldwide and Fong et al.[22] found similar variation in PPH incidence in California. Causes of these variations were not investigated in these studies. In addition, Lu et al. found large differences across hospitals in California and also found higher obstetrical trauma, chorioamnionitis, and protracted labor (used as proxy of the quality of health care) in hospitals with a high PPH incidence.[35] To date, various risk factors for PPH in different populations have been described in literature. Risk factors for PPH can be divided in maternal characteristics, pregnancy characteristics, medical interventions and health care setting. In literature, higher PPH incidences are reported with increased maternal age and decreasing socioeconomic status while literature is contradictive regarding ethnicity and parity.[21,33,34,36-38] Other risk factors for PPH that have been described in literature are induction of labor, augmentation of labor, perineal laceration, manual placental removal and an increasing fetal weight.[21,33,34] Additionally, variation in Dutch obstetric care has previously been described.[39] Although these risk factors varied to a large extent across regions (data not shown), PPH variation remained after adjustment for these factors.

In this study, we presented the geographical distribution while taking into account hospital or community midwife practice because on average 24% of women in the Netherlands deliver at home.[25] Regarding place of birth, Davis et al. described no relation to occurrence of PPH in a recent study.[40] The incidence of severe PPH varied for mode of delivery, and conditional on mode of delivery, variation was not uniform. Although reported

in previous studies too,[2,5,9,41] the relatively low severe PPH incidence after (emergency) CS was remarkable. Overall, mean blood loss during delivery is higher in case of CS.[42] However, in case of severe PPH an aggressive policy to halt the bleeding is more quickly available at the surgery ward and might contribute to lower incidence of severe PPH after CS. Also, we cannot neglect the possibility of registration errors. If present however, the magnitude of these errors is not expected to vary across regions and will therefore not have influenced the variation across regions to a great extent.

Almost 8% of maternal mortality in this study was PPH-related while the PPH-related mortality incidence across regions varied between 0.16 and 0.59%. In California, PPH-related mortality across regions has been described to vary between 0.08 and 0.21%.[22] Variation was thus larger in our study, yet our dataset was about 3 times smaller and mortality numbers on average were lower. Haeri et al. described that 13% of maternal mortality in developed countries is caused by PPH.[43] The distribution of mortality was not like the severe PPH pattern, unlike findings of Fong et al.[22] However, mortality numbers in this study were very small.

The following limitations of this study are to consider. Despite the large dataset, numbers of deliveries in some neighborhoods were relatively small. Also, a small number of care providers does not participate in the PRN (5% of community midwife practices, 1% of gynecologists), however it is unlikely non-participation is related to the occurrence of postpartum hemorrhage. Another limitation concerns data on PPH determinants. Body mass index (BMI) data were unavailable which may be relevant as BMI is proposed to be a risk factor for PPH[44-46] and public health reports show regional BMI variation.[47] However, at the aggregate level epidemiological patterns apparently do not relate. Also, data on active third stage management and professional performance were unavailable.

Although literature has shown that estimation of the amount of blood loss is often inaccurate,[42,48,49] blood loss is not routinely weighed in the Netherlands in all deliveries. After vaginal deliveries blood loss is mostly estimated in case of normal blood loss and usually weighed in case of persisting blood loss. In case of CS, abdominal blood loss is collected through suction in a measuring pot and estimated postoperatively based on the amount of fluid in the pot and the vaginal blood loss. To our knowledge, no validation studies on blood loss estimation have been performed in the Netherlands. Blood loss is recorded in the PRN dataset as binary variable with a cut off of 1000 mL (irrespective of the mode of delivery). This cut off was derived from the definition of severe PPH by the World Health Organization[1] and is the most widely used in literature. While blood loss of 1000-2000 mL is usually not a major threat to the maternal condition in developed countries, we believe this cut off is accurate. Results with this cut off are more trustworthy due to the (relatively) large number of cases than with a higher cut off. However, in our dataset the method for blood loss measurement is not registered and might vary. Consequently, reported differences in severe PPH incidence might have their origin also in regional differences in methods of measurements. Despite the inaccuracy of the blood estimation procedure in general,[50] we assume the cut off of 1000 mL to be sufficiently accurate for our purposes, as the great

majority of such cases will involve weighed blood loss. Bias through differences in these estimations is expected to be small as, if present, misclassification is expected to be similar across regions. The major weakness in the dataset is the lack of registration of preventive and therapeutic measures.

The major strength of this study is the very large dataset containing 96% of all deliveries in the Netherlands in the period 2000-2008. These numbers strengthen external validity of the study. Since data were extracted electronically from the medical records, data are trustworthy. Data were prechecked through built-in checks and through post-hoc algorithms of the PRN; note however that the dataset was anonymized excluding the potential for individual retrospective checks.

In conclusion, a large variation in severe PPH incidence exists nationwide in the Netherlands. This variation could not be explained by maternal characteristics, pregnancy characteristics, medical interventions or health care setting. Regional variation may be unavoidable or subsequent to regional variation of a yet unregistered variable.

Appendix 1 *Crude incidences of PPH per region.*

	Total	Spontaneous delivery		Assisted vaginal delivery		Elective CS		Emergency CS	
	All	All	Singleton pregnancies	All	Singleton pregnancies	All	Singleton pregnancies	All	Singleton pregnancies
Region									
Amsterdam[a]	5.0	4.9	4.9	7.6	7.4	4.9	3.8	2.6	2.4
Rotterdam[a]	4.4	4.4	4.3	5.5	5.3	4.3	3.4	3.3	3.2
The Hague[a]	5.4	5.1	5.0	7.6	7.3	6.4	5.5	4.2	4.0
Utrecht[a]	4.8	4.8	4.6	5.9	5.7	4.8	4.1	3.1	2.6
Groningen	3.7	3.4	3.3	4.8	4.5	3.7	3.3	3.0	2.9
Friesland	3.8	3.6	3.4	6.0	5.8	2.9	2.4	3.1	3.1
Drente	3.8	3.8	3.7	6.3	6.1	2.9	2.4	1.5	1.4
Overijssel	3.5	3.3	3.2	5.4	5.2	3.1	2.4	2.6	2.5
Gelderland	4.7	4.3	4.2	6.7	6.4	6.0	5.2	4.9	4.6
Utrecht	4.2	4.1	4.0	5.7	5.4	4.3	3.7	2.6	2.1
Noord Holland	4.9	4.8	4.7	7.9	7.7	3.4	2.7	2.1	2.0
Zuid Holland	4.6	4.5	4.4	6.3	6.1	4.5	3.6	3.8	3.6
Zeeland	4.2	3.5	3.4	6.8	6.6	6.8	6.2	4.5	4.5
Noord Brabant	4.6	4.5	4.4	6.3	6.1	4.4	3.8	3.6	3.3
Limburg	4.2	4.3	4.2	5.9	5.7	2.7	2.2	2.0	1.8
Flevoland	4.6	4.7	4.6	5.2	5.1	4.5	3.7	2.4	2.2
Total	4.5	4.3	4.2	6.4	6.2	4.3	3.5	3.2	3.0

[a] City
CS = cesarean section

Appendix 2 *Crude incidences of PPH in Amsterdam.*

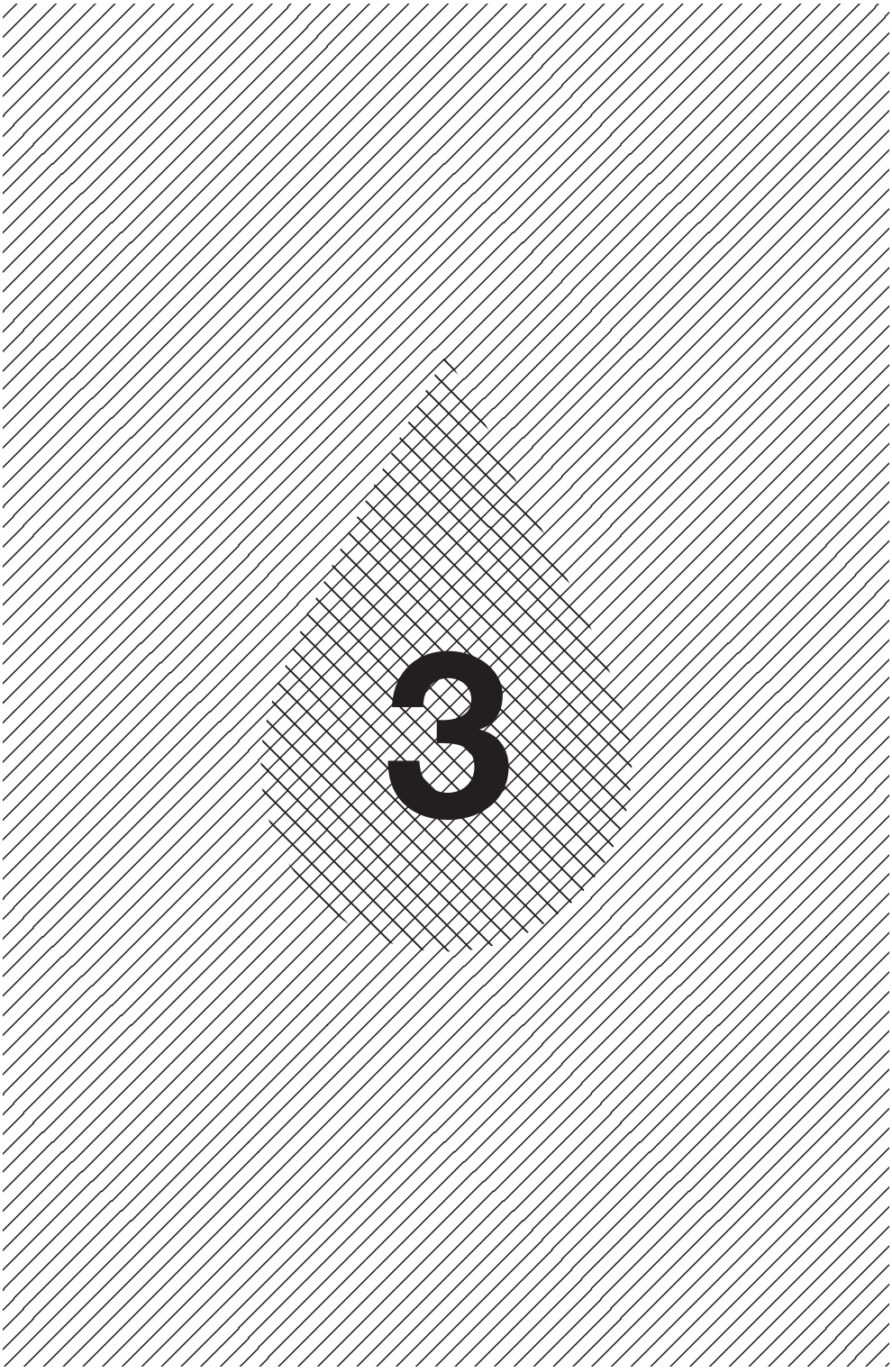
	Total	Spontaneous		Assisted vaginal		Elective CS		Emergency CS	
	All	All	Singleton pregnancies	All	Singleton pregnancies	All	Singleton pregnancies	All	Singleton pregnancies
Neighborhood									
Centrum	5.4	5.6	5.6	7.5	7.6	4.4	4.0	2.4	2.4
de Baarsjes	4.7	4.6	4.5	10.4	10.0	3.2	0.6	1.0	1.0
Bos en Lommer	5.0	5.2	5.1	8.3	8.0	2.9	1.3	0.9	0.9
Geuzenveld-Slotermeer	4.1	4.4	4.3	5.9	5.6	1.6	1.1	1.5	1.5
Noord	4.4	3.6	3.5	6.7	6.5	8.9	7.6	5.3	5.1
Osdorp	5.2	5.3	5.2	9.9	9.8	2.4	1.1	1.4	1.2
Oud-West	5.6	5.9	6.2	7.3	7.0	3.5	3.9	2.7	3.1
Oud-Zuid	5.5	5.8	5.6	7.9	7.5	4.1	2.1	1.6	1.5
Oost-Watergraafsmeer	4.8	4.5	4.4	8.0	7.8	5.1	3.2	3.5	3.4
Slotervaart	5.1	5.3	5.3	9.3	9.0	2.6	0.4	0.8	0.8
Westerpark	6.0	6.4	5.9	8.5	7.6	3.4	1.4	1.4	1.1
Westpoort	4.4	4.6	4.4	5.6	5.2	3.3	3.5	2.0	2.1
Zeeburg	4.8	4.9	4.7	6.7	6.6	4.6	4.1	2.6	2.4
Zuideramstel	5.2	5.1	5.1	9.4	9.4	3.6	1.6	2.2	1.7
Zuid Oost	4.7	4.6	4.5	3.8	3.7	8.1	7.9	3.8	3.7
Total	5.0	4.9	4.9	7.6	7.4	4.9	3.7	2.5	2.4

CS = cesarean section

Appendix 3 *Crude incidences of PPH in Rotterdam.*

	Total	Spontaneous		Assisted vaginal		Elective CS		Emergency CS	
	All	All	Singleton pregnancies	All	Singleton pregnancies	All	Singleton pregnancies	All	Singleton pregnancies
Neighborhood									
Stadscentrum	4.5	4.2	4.2	6.0	6.1	5.7	4.5	3.8	3.9
Charlois	4.2	4.0	3.8	5.3	5.0	3.8	2.8	4.5	4.4
Delfshaven	4.1	4.0	3.9	4.1	4.2	4.4	3.7	4.9	5.0
Feijenoord	3.7	3.8	3.8	4.2	4.2	3.3	3.0	2.1	2.0
Hilligersberg Schiebroek	5.8	6.2	6.2	7.1	7.1	3.8	3.6	1.4	1.4
Hoogvliet	5.0	5.0	4.9	5.8	4.9	4.6	3.9	3.6	3.3
Hoek van Holland	5.0	4.4	4.5	12.1	9.5	3.1	3.3	3.9	4.0
Ijsselmonde	4.2	4.5	4.3	4.5	4.6	4.0	2.8	1.2	1.0
Kralingen Crooswijk	4.4	4.4	4.3	5.8	5.6	4.4	3.4	2.9	2.7
Noord	4.4	4.4	4.3	6.5	6.0	1.8	1.9	2.3	2.4
Overschie	5.1	5.6	5.5	5.2	4.7	3.3	3.5	0.8	0.9
Prins Alexander	4.8	4.3	4.3	6.1	6.0	6.6	4.7	4.9	4.7
Pernis	5.0	5.1	4.8	8.2	8.5	4.6	0	0	0
Total	4.4	4.4	4.3	5.5	5.3	4.3	3.4	3.3	3.2

CS = cesarean section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Chapter 3

The current state of active third stage management to prevent postpartum hemorrhage: a cross-sectional study

B.W. Prick, A.A. Vos, W.C.J. Hop, H.A. Bremer, E.A.P. Steegers, J.J. Duvekot

Abstract

Objective
To investigate the implementation of the International Confederation of Midwives/ International Federation of Gynecology and Obstetrics (ICM/ FIGO) guideline on active third stage management in vaginal deliveries in daily clinical practice.

Design
Observational, cross-sectional study.

Setting
One tertiary and one teaching hospital in the Netherlands.

Population
Women undergoing vaginal deliveries.

Methods
A case record form was completed after every vaginal delivery. Primary outcome was adequate guideline adherence, defined as initial administration of 10 IU oxytocin, performance of controlled cord traction and uterine massage. Adequate guideline adherence was a priori estimated to be 10%. With a sample size of 600, i.e. 300 women per hospital, the standard error of the resulting percentage would be less than 2% for each hospital.

Results
Six hundred and twenty six women were included. Guideline adherence was adequately performed in 48% of vaginal deliveries. Oxytocin was administered after birth in 98% of deliveries and in 80% the correct dose was used. Controlled cord traction was performed in 63% and uterine massage in 93%; however, the latter was performed as advised (at least eight times) in only 8%. The amount of blood loss was not associated with the use of either 5 or 10 IU oxytocin ($p = 0.818$). Controlled cord traction and uterine massage were more frequently performed when blood loss exceeded 500 mL ($p < 0.001$).

Conclusion
Active third stage management according to the ICM/ FIGO guideline is adequately performed in only 48% of all vaginal deliveries.

Results of this study call for training programs to increase adherence to the ICM/ FIGO guideline.

Introduction

Severe postpartum hemorrhage (PPH), defined as more than 1000 mL blood loss after childbirth, is the global leading cause of maternal death with an estimated mortality rate of 140 000 women a year.[3,20] Moreover, an unexplained increase in the frequency of PPH was recently described in developed countries.[2,4-6,9,10] Active third stage management involves interventions that prevent PPH. The primary goal of these interventions is to assist delivery of the placenta, encouraging the uterus to contract. In 2004, the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) made a joint statement and developed a guideline to assist clinicians and midwives in the prevention of PPH. The recommended management in the guideline consists of three interventions: administration of uterotonic medication, controlled cord traction for placental delivery and uterine massage after delivery of the placenta.[51] The guideline is also embedded in the recommendations of the World Health Organization for the prevention of PPH.[1] However, the benefit of the combined use of uterotonic medication, controlled cord traction and uterine massage remains controversial for many clinicians and midwifes.[52] Assessment of the adherence to the guideline is essential to optimize prevention of PPH and maternal health, especially since a great disparity in performance of these interventions among hospitals and clinicians was suspected. This study, the Très Active study, was conducted to investigate the implementation of the ICM/ FIGO guideline for active third stage management in daily clinical practice. We hypothesized that active third stage management is often inadequately performed.

Material and methods

This prospective, observational study, the Très Active study, was conducted at one tertiary hospital (Erasmus MC – University Medical Center Rotterdam, Rotterdam) and one teaching hospital (Reinier de Graaf Gasthuis, Delft) in the Netherlands between September 2010 and December 2010. In both hospitals, active third stage management consisting of administration of 10 IU oxytocin immediately after childbirth (intravenous or intramuscular), controlled cord traction and uterine massage was the standard policy before initiation of the study. The primary outcome of the Très Active study was adherence to the ICM/ FIGO guideline. 'Adequate guideline adherence' was defined as the performance of the three interventions described in the guideline: the administration of 10 IU oxytocin after childbirth, controlled cord traction and palpation for a contracted uterus and/ or uterine massage for at least once. 'Inadequate guideline adherence' was used if one or more interventions were not performed. According to the ICM/ FIGO guideline, uterine palpation should be performed every 15 minutes for the first two hours after childbirth (eight times in total), followed by uterine massage if appropriate. If palpation and/ or uterine massage (further defined as uterine massage) was performed at least eight times, this was defined as 'complete guideline adherence'. Secondary outcomes were postpartum blood loss, additional use of uterotonic medication, severe PPH (≥ 1000 mL blood loss), duration of the third stage of labor, and manual removal of the placenta. Women aged 18 years and older who delivered vaginally were eligible. Women who underwent termination of pregnancy because of congenital fetal anomalies as well as cases of stillbirth were excluded.

All physicians and midwives were asked to complete a case record form after every vaginal delivery. They were informed about the definitions used in the ICM/ FIGO guideline and these definitions were printed on the reverse side of each case record form.[51] No instructions regarding active third stage management were given at the start of the study. Compliance was monitored for study purposes only, there were no disciplinary actions for non-compliance. Data regarding the performance of active third stage management and the method for measuring blood loss (estimated or weighed) were collected from the case record form. In addition, we obtained a copy of the data for the Dutch Perinatal Registry. Institutional approval was obtained from the Ethical Review Boards of the participating hospitals and the need for informed consent was waived because of the observational character of this study. Sample size was based on the estimation of the percentage of adequately performed active third stage management as recommended by the ICM/ FIGO. A priori, the composite measure of adequately performed active third stage management was estimated to be 10%. With a sample size of 600, 300 women per hospital, the standard error of the resulting percentage would be less than 2% for each hospital.

Statistical analysis

Descriptive statistics were used to describe the study population. Differences between groups were assessed using a chi-squared test for categorical data, and an unpaired t-test (normally distributed) or Mann-Whitney U-test (not normally distributed) for numerical data. Multiple linear regression was used to evaluate the relationship of initial oxytocin dose postpartum to the amount of blood loss, while adjusting for considered risk factors obtained from the literature. These risk factors include maternal age, multiple pregnancy, multiparity, gestational age, induced labor with oxytocin or prostaglandins, labor augmentation with oxytocin, instrumental delivery (vacuum or forceps), duration of active first stage of labor (dilation of 3-10 cm), duration of second stage of labor, episiotomy, second, third or fourth degree perineal tear and birthweight.[53-55] For this analysis, blood loss was log-transformed to obtain an approximate normal distribution. Significance was defined as $p < 0.05$. When data were missing, women were excluded from those specific analyses. Statistical analysis was performed using SPSS 17.0 for WINDOWS software (SPSS Inc., Chicago, IL, USA).

Results

Between September 2010 and December 2010, 697 women delivered vaginally in both hospitals. Twenty-one deliveries were excluded at the tertiary hospital and three at the teaching hospital. In 47 vaginal deliveries no case record form was completed (7% of all vaginal deliveries during the study period). A total of 626 vaginal deliveries were analyzed (***Figure 1***). In the tertiary hospital, 157 women delivered with a midwife, 126 with a resident and 29 with an obstetrician, and in the teaching hospital these numbers were respectively 113, 188 and 11. In the teaching hospital, two women delivered with a nurse. ***Table 1*** shows the general characteristics of the women who delivered in both hospitals. Gestational age, birth weight, duration of second stage and intention to breastfeed significantly differed between both hospitals. It is noteworthy that extreme preterm

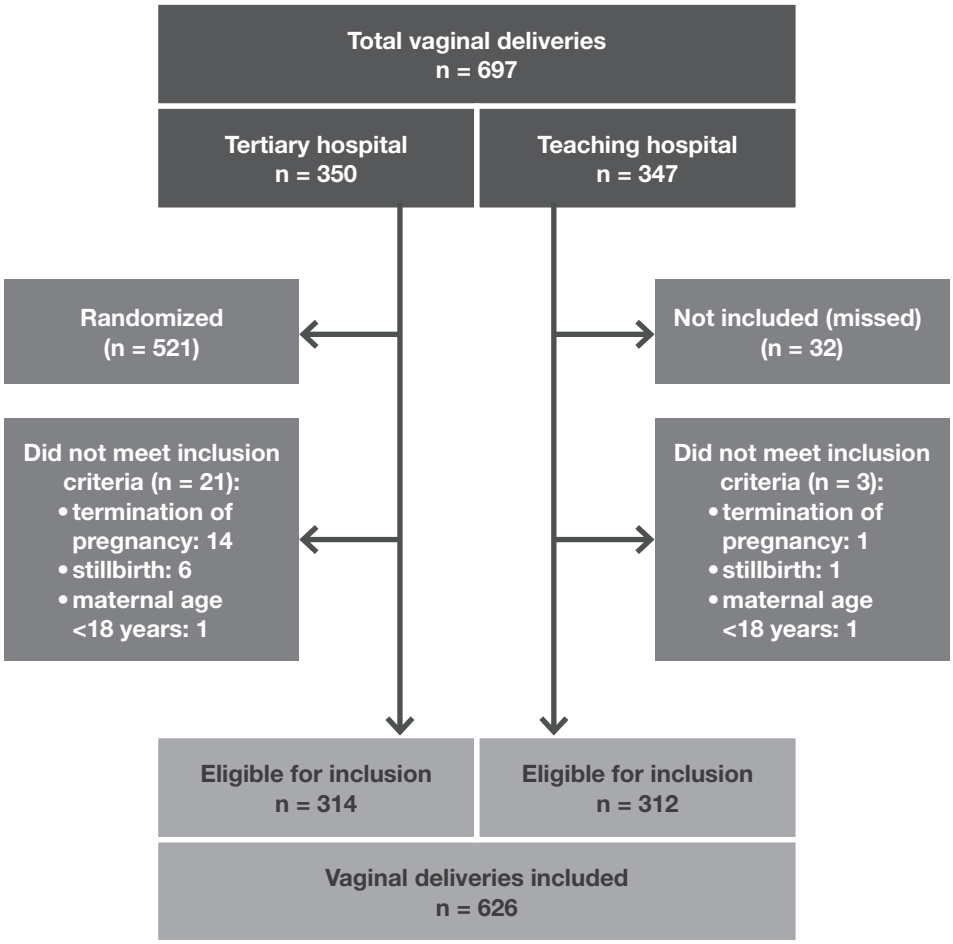


Figure 1 *Flow chart of the women included in the Très Active study.*

deliveries (before 32 weeks of gestation) occur preferably at tertiary hospitals in the Netherlands. Median blood loss was lower at the tertiary hospital (300 mL versus 400 mL, $p < 0.001$) but the incidences of PPH and manual removal of the placenta were similar in both hospitals. However, in 36% of deliveries at the teaching hospital, blood loss was weighed, compared with 12% at the tertiary hospital. Adequate guideline adherence was achieved in 48% (95% CI 44-52%) of all deliveries and complete guideline adherence (including uterine massage at least eight times) in only 5% (95% CI 3-7%). Oxytocin was administered immediately after childbirth in 98% of all deliveries, with a correct dose of ≥ 10 IU administered in 80%. Controlled cord traction was performed in 63%. Uterine massage was performed (at least once) in 93% though in only 8% this was performed at least eight times.

Table 1 *General characteristics of women and their deliveries observed in this study.*

	Tertiary hospital (n = 314)	Teaching hospital (n = 312)	*p*
Characteristics			
Maternal age (y)	30 ± 6	31 ± 5	0.105[a]
Nulliparous	147 (47)	168 (54)	0.093
Twin gestation	11 (4)	3 (1)	0.060
Gestational age	38+4	40+0	< 0.001
extreme preterm (< 32 wk)	22 (7)	0	
preterm (≥ 32 and < 37 wk)	18 (6)	17 (5)	
term (≥ 37 wk)	274 (87)	295 (95)	
Duration active first stage (h)	4.5 (1-14)	4.0 (1-16)	0.744
Induction of labor	115 (37)	100 (32)	0.262
Oxytocin augmentation	125 (40)	145 (47)	0.109
Duration second stage (min)	15 (0-206)	20 (1-161)	< 0.001
nulliparous	27 (0-206)	39 (1-161)	
multiparous	8 (0-110)	10 (1-85)	
Instrumental delivery	60 (19)	74 (24)	0.205
Episiotomy	126 (40)	140 (45)	0.263
2nd – 4th degree lacerations	125 (40)	129 (41)	0.081
Blood loss (mL)	300 (50-3000)	400 (30-4500)	< 0.001
Measured blood loss	36 (12)	112 (36)	< 0.001
PPH[b]	21 (7)	23 (7)	0.858
Manual removal of the placenta	16 (5)	14 (5)	0.866
Blood transfusion	8 (3)	5 (2)	0.577
Birth weight (g)	3290 (425-4700)	3433 (1900-5200)	< 0.001
Breastfeeding	266 (85)	227 (73)	< 0.001
Secondary PPH[c]	0	0	

Data are mean ± standard deviation, median (range), or n (%).
[a] Student-t test.
[b] Defined as more than 1000 mL blood loss postpartum within the first 24 hours postpartum.
[c] Defined as PPH occurring between 24 hours and 6 weeks postpartum.

Overall, no difference in guideline adherence was found between the hospitals, although the performance of the single interventions did differ significantly. At the tertiary hospital, more controlled cord traction was performed, whereas at the teaching hospital oxytocin use (≥ 10 IU) and uterine massage were more frequently performed (***Table 2***). Total blood loss was comparable between deliveries with adequate and inadequate guideline adherence ($p = 0.078$). A tendency towards increased blood loss was found in deliveries with adequate guideline adherence. We therefore stratified for the amount of blood loss by creating three categories (≤ 500 mL, 501-1000 mL and > 1000 mL). We observed that controlled cord traction and uterine massage were more frequently performed in cases with greater blood loss, although this difference was not significant (performance of both interventions increased from 58% when blood loss was less than 500 mL to 71% when there was > 1000 mL blood loss, $p = 0.305$). As expected, additional uterotonic medication was more frequently administrated with increasing blood loss (in 4%, 30% and 65% with blood loss of respectively ≤ 500 mL,

Table 2 *Adherence to ICM/ FIGO guideline in the participating hospitals.*

ICM / FIGO guideline	Total	Tertiary hospital (n = 314)	Teaching hospital (n = 312)	*p*
Interventions				
1. Oxytocin use (≥ 10 IU)	498 (80)	235 (75)	263 (84)	0.005
5 IU oxytocin	117 (19)	78 (25)	39 (13)	< 0.001
no oxytocin	11 (2)	1 (0.3)	10 (3)	0 .015
2. Controlled cord traction (≥ once)	393 (63)	227 (72)	166 (53)	< 0.001
Frequency of controlled cord traction	1 (0-11)	1 (0-11)	1 (0-10)	< 0.001
3. Uterine massage (≥ once)	576 (93)	280 (90)	296 (96)	0.004
Uterine massage (≥ 8 times)[a]	47 (8)	19 (6)	28 (10)	0 .194
Frequency of uterus massage	3 (0-30)	2 (0-30)	3 (0-30)	< 0.001
Adequate guideline adherence[b]	297 (48)	154 (49)	143 (46)	0.541
Complete guideline adherence[c]	28 (5)	10 (3)	18 (6)	0.153

Data are n (%) or median (range) unless otherwise specified.
[a] Defined as performance of uterine massage at least 8 times during the first 2 hours.
[b] Defined as the performance of all three interventions of active third stage management according the guideline (≥ 10 IU oxytocin, controlled cord traction and uterine massage at least once).
[c] Defined as the performance of all three interventions of active third stage management according the guideline, including uterine massage at least 8 times.

Table 3 *Oxytocin dose (5 and 10 IU) in relation to total blood loss, duration of third stage, PPH, manual removal of the placenta and additional use of uterotonic medication.*

	5 IU oxytocin (n = 117)	10 IU oxytocin (n = 486)	*p*
Blood loss (mL)	300 (100-3000)	300 (30-2540)	0.103 0.818[a]
Duration third stage (min)	7 (1-120)	6 (0-129)	0.721
PPH	7 (6)	32 (7)	0.812
Manual removal of the placenta	4 (3)	21 (4)	0.856
Additional use of uterotonic medication	12 (10)	47 (10)	0.964

Data are median (range) or n (%) unless otherwise specified.
[a] Ratio (5 versus 10 IU oxytocin) of geometric mean blood loss equals 0.99 (95% CI: 0.87–1.11; $p = 0.818$), adjusted for multiple gestation, oxytocin augmentation, labor induction, multiparity, instrumental delivery, age, maternal age, gestational age, birth weight, 2nd-4th degree lacerations, duration first and second stage in multiple linear regression analysis.

501-1000 mL and > 1000 mL, $p < 0.001$), while the administration (and dose) of the initial oxytocin administration was not related to the amount of blood loss. As the initial administration of oxytocin is the only intervention that cannot be influenced by the amount of blood loss during delivery, we were able to study differences between the most frequently administered doses (5 and 10 IU). Total blood loss had a tendency to be lower in women who received 10 IU oxytocin than in women who received 5 IU (1% after adjustment for risk factors), although this finding was not significant ($p = 0.817$). Duration of the third stage of labor, PPH, manual removal of the placenta, and administration

of additional uterotonic medication did not significantly differ between the doses (*Table 3*). In 94% of all deliveries, the placenta was expelled within 30 minutes after childbirth. For a third stage lasting longer than 30 minutes, median blood loss increased significantly (300 mL [range 30-2540] versus 650 mL [range 100–4500], $p < 0.001$). When the third stage lasted longer than 30 minutes, 42% of the placentas were still expelled spontaneously.

Discussion

This study provides an insight into the implementation of the ICM/ FIGO guideline regarding active third stage management in vaginal deliveries. We observed suboptimal adherence to the guideline in two Dutch hospitals. All three interventions of the guideline were performed in less than 50% of vaginal deliveries. Moreover, there was complete guideline adherence in only 5%, including the correct frequency for uterine massage (at least eight times after childbirth) (*Table 2*). Poor adherence was especially found for the interventions controlled cord traction and uterine massage. Uterine massage (including palpation to reassure uterine contraction) was performed at least eight times in only 8% of deliveries. Presumably the poor adherence to the guideline has its origin in a lack of belief in the recommended interventions, especially controlled cord traction and uterine massage.

Regarding total blood loss, no significant difference was observed between adequate and inadequate guideline adherence. We observed a tendency towards increased blood loss when adequate or complete guideline adherence was achieved. This finding, also described by Davis et al.,[56] can be explained by the fact that treatment of PPH contains similar interventions: in case of abundant blood loss directly after childbirth, controlled cord traction and uterine massage may be performed more adequately. An interesting finding in our study was the lack of a significant relationship between initial oxytocin dose and the amount of postpartum blood loss. Also, no difference between 5 and 10 IU oxytocin was found regarding manual removal of the placenta and administration of additional uterotonic medication.

A strength is that our study accurately reflects all vaginal deliveries in the defined study period, since 93% of all vaginal deliveries were included and missing data were very minimal. During the study period, we did not detect a learning curve among the birth attendants due to guideline awareness: no significant increase in guideline adherence, oxytocin administration, performance of controlled cord traction or uterine massage was measured in time (data not shown). Another major strength of this study is that we emphasized the performance of each intervention in relation to their influence on the third stage of labor.

The following limitations are acknowledged. There were significant differences in the general characteristics of the two hospitals (*Table 1*). The main reason for these differences was presumably the selection of high risk pregnancies and extreme preterm deliveries in tertiary hospitals in the Netherlands. The observational design of the study limits the ability to analyze the influence of each intervention on blood loss. Although the literature shows that estimation of blood loss is often inaccurate,[42,48,49] blood loss is routinely not weighed in the Netherlands, except in cases with major blood loss. Although we trust that the results are largely generalizable to

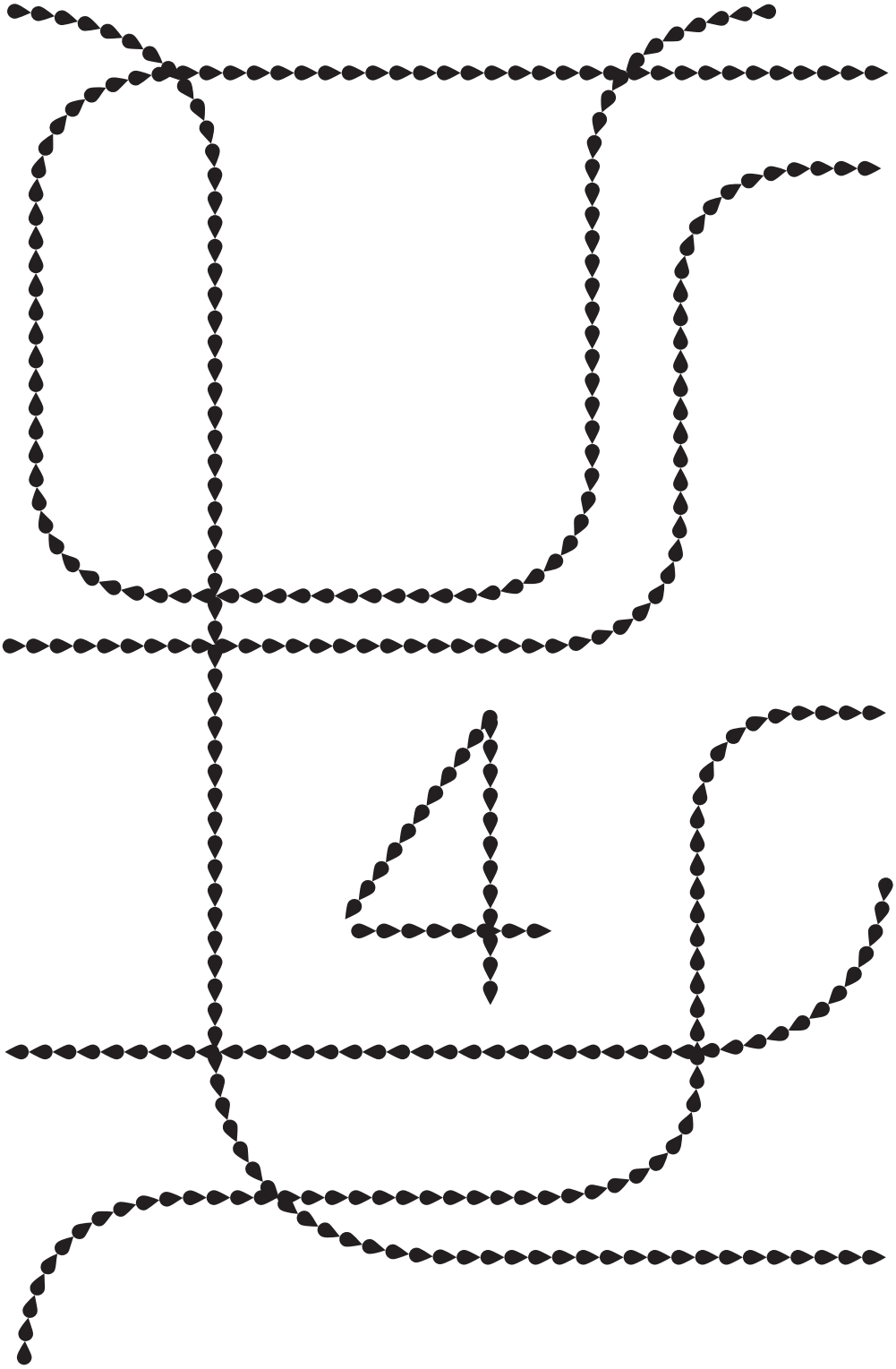
the Netherlands, we should be aware that this study was performed in two hospitals only. The influence of controlled cord traction and uterine massage on the amount of blood loss cannot be investigated based on our data, since the amount of blood loss may influence the performance of these interventions. Our finding that outcomes did not differ significantly between different initial oxytocin doses (5 or 10 IU) should be interpreted with care, since our study was not designed to study the optimal oxytocin dose. To investigate the effect of 5 and 10 IU on total blood loss, as well as on manual removal of the placenta, administration of additional uterotonic medication, and duration of the third stage of labor, a randomized controlled trial should be performed. Further studies are needed to investigate the efficacy of the interventions: if clearly proven effective, these measures can be implemented more easily. Finally, we cannot discount the possibility of a responder bias, since we asked all birth attendants to report their own actions.

The ICM/ FIGO based its guideline on several randomized trials, Cochrane systematic reviews and WHO trials, among which were four large randomized trials investigating active third stage management versus expectant management (summarized by Litch).[51,57-59] The effectiveness of oxytocin administration on postpartum blood loss is confirmed in several trials, also without the performance of other active third stage management interventions, and its administration immediately after childbirth is widely recommended nowadays.[60] However, to our knowledge, the optimal dose for oxytocin in vaginal deliveries was never investigated. Whereas the effectiveness of uterotonic medication seems evident, this is less the case for the other interventions.[61]

Recently two randomized controlled trials demonstrated little effect of controlled cord traction on the occurrence of PPH.[62,63]

Hofmeyr published a Cochrane review regarding uterine massage for the prevention of PPH, supporting the ICM/ FIGO guideline. However, due to limitations and a small number of trials, trials with sufficient numbers to estimate the effects of sustained uterine massage more precisely are needed.[64] Our findings regarding guideline adherence are partly consistent with other studies. A comparable study performed in Nigeria showed 42% adherence to the ICM/ FIGO guideline and no significant difference in postpartum blood loss, additional oxytocin use or placental retention between adequately and inadequately performed active third stage management.[65] Unfortunately, the studied populations are not completely comparable, since the Nigerian study only included women during daytime, excluded instrumental deliveries and performed the study in another health care setting. A nested case-control study in Australia reports lower performance rates of oxytocin administration (91% compared with 98% in our study), but higher rates of controlled cord traction (84% compared with 63%).[66] Performance of uterine massage was not reported and no comparison of total blood loss was made.

Active third stage management according to the ICM/ FIGO guideline is inadequately performed in vaginal deliveries in daily clinical practice in the Netherlands. Prevention of PPH becomes even more important considering the increasing incidence that has been observed in several developed countries.[6]The results of this implementation study indicate the necessity of a training program to enhance adherence to the ICM/ FIGO guideline.



Chapter 4

Investigating red blood cell transfusion in anemic women after postpartum hemorrhage

Chapter 4.1

Protocol of the 'Well-being of Obstetric patients on Minimal Blood transfusions' (WOMB) trial

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Abstract

Background

Primary postpartum hemorrhage is an obstetrical emergency often causing acute anemia that may require immediate red blood cell (RBC) transfusion. This anemia results in symptoms such as fatigue, which may have a major impact on the health-related quality of life (HRQoL). RBC transfusion is generally thought to alleviate these undesirable effects although it may cause transfusion reactions. Moreover, the postpartum hemoglobin concentration seems to influence fatigue only for a short period of time. At present, there are no strict transfusion criteria for this specific indication, resulting in a wide variation in postpartum policy of RBC transfusion in the Netherlands.

Methods

The WOMB trial is a multicenter randomized non-inferiority trial. Women with acute anemia due to postpartum hemorrhage, 12-24 hours after delivery and not initially treated with RBC transfusion, are eligible for randomization. Patients with severe physical complaints are excluded. Patients are randomized for either RBC transfusion or expectant management. HRQoL will be assessed at inclusion, at three days and one, three and six weeks postpartum with three validated measures (Multidimensional Fatigue Inventory, ShortForm-36, EuroQol-5D). Primary outcome of the study is physical fatigue three days postpartum. Secondary outcome measures are general and mental fatigue scores and generic health related quality of life scores, the number of RBC transfusions, length of hospital stay, complications and health care costs.

The primary analysis will be by intention-to-treat. The various longitudinal scores will be evaluated using Repeated Measurements ANOVA. A costs benefit analysis will also be performed. The power calculation is based on the exclusion of a difference in means of 1.3 points or greater in favor of RBC transfusion arm regarding the physical fatigue subscale. With missing data not exceeding 20%, 250 patients per arm have to be randomized (one-sided alpha = 0.025, power = 80%).

Discussion

This study will provide evidence for a guideline regarding RBC transfusion in the postpartum patient suffering from acute anemia. Equivalence in fatigue score, remaining HRQoL scores and physical complications between both groups is assumed, in which case an expectant management would be preferred to minimize transfusion reactions and costs.

Trial registration

ClinicalTrials.gov NCT00335023.
Nederlands Trial Register NTR335

Trial website

http://www.studies-obsgyn.nl/womb/

Background

One of the most frequent complications of delivery is primary postpartum hemorrhage (PPH), defined as blood loss greater than or equal to 500 mL within 24 hours after birth and severe PPH as blood loss greater than or equal to 1000 mL within 24 hours.[1] Between four and five percent of all vaginal deliveries are complicated by severe PPH.[34] Blood loss during cesarean section is usually 50-100% more than during vaginal delivery.[67] An important clinical effect of obstetric hemorrhage is the development of acute anemia, with fatigue as an important symptom. This fatigue is not an isolated physical symptom but rather involves lethargy, decreased mental alertness, physical weakness and poor concentration.[68] It is especially important as it affects women who just have delivered, who have to care for and feed a newborn baby and who are usually full of emotions.

RBC transfusion is one of the few treatments that adequately restore tissue oxygenation when oxygen demand exceeds supply. Apart from the life-saving restoration of the initial hemodynamic instability, RBC transfusion is also used to alleviate the side-effects of acute anemia, including the fatigue mentioned above. This treatment is applied frequently. Previously, a significant correlation between hemoglobin (Hb) concentration postpartum and fatigue scores was found in postpartum patients using the HRQoL measure Multidimensional Fatigue Inventory (MFI), but this correlation was already lost one week after delivery.[69] Thus, postpartum Hb concentration seems to influence fatigue for only a short period of time. Other arguments against RBC transfusion are that RBC transfusion is costly and may cause formation of RBC alloantibodies and other direct and indirect transfusion complications.[70]

Although the respiratory function of blood has been studied intensively, the trigger for RBC transfusion remains controversial, and doctors still rely primarily on clinical experience. At present, criteria for transfusion are not based on alternative criteria, such as HRQoL scores. Worldwide there is no consensus on the optimal transfusion trigger.[15,70-72] A questionnaire study in 2003 on the subject of RBC transfusion practice postpartum in the Netherlands demonstrated large differences between hospitals.[73] Based on Hb concentrations, the transfusion triggers varied between 3.0 and 5.5 mmol/L (4.8 and 8.9 g/dL). Clinical symptoms were used as more or less subjective additional criteria.

The official Dutch guideline for RBC transfusion is the “4-5-6 flexinorm” for patients with acute or chronic anemia.[15] This rule states that ASA I patients should have RBC transfusion when their Hb is below 4 mmol/L (6.4 g/dL), ASA II when their Hb is below 5 mmol/L (8.1 g/dL) and ASA III and IV patients when their Hb is below 6 mmol/L (9.7 g/dL). However, during pregnancy the circulating blood volume increases by 100 mL/kg to a total blood volume of six to seven liters. The several blood components contribute differently to this increase: plasma increases with 40% whereas red blood cell volume increases with 15-20%. Consequently Hb concentration decreases with a maximum of approximately 10%. This natural process of hemodilution improves the placental circulation. As a result of these changes, it is doubtful whether the Hb triggers for RBC transfusion, as described

above, can be used for patients with postpartum hemorrhage.

In the Netherlands all women with PPH will be treated by a gynecologist in a clinical setting. Although almost one third of Dutch women deliver at home with supervision by a midwife, women that experience excessive blood loss during or immediately after delivery will be transferred to a hospital for further treatment by a gynecologist. Most Dutch women that deliver in hospital, leave the hospital a couple of hours after delivery since there is an adequately organized domiciliary postnatal care service. The necessity of RBC transfusion may prolong their stay in hospital.

In the Netherlands, blood products are produced by one blood banking organization. The present study is performed in cooperation with Sanquin, the Dutch blood bank organization, which initiated and funded the costs of the first part of this study.

Acute anemia postpartum, with fatigue as important symptom, is a clinical problem with wide practice variation in treatment regarding RBC transfusion. There are several arguments against RBC transfusion and the postpartum Hb concentration seems to influence fatigue for only a short period of time. We therefore aim to show non-inferiority of expectant management versus a transfusion policy regarding physical fatigue, three days after delivery, in postpartum women with an acute anemia following PPH. The development of a guideline based on clinical parameters, laboratory determinations and HRQoL measures may lead to a more adequate use of RBC transfusions in the postpartum period and possibly reduces costs due to lower frequency of transfusions and hospitalization duration.

Methods/ design

Aims

The aim of this study is to solve the dilemma for the obstetrician regarding the optimal treatment of women with acute anemia postpartum. For that reason we aim to determine whether women with acute anemia postpartum benefit from RBC transfusion.

Our hypothesis is that there is no important difference with regard to physical fatigue, as well as other HRQoL scores and physical complications between RBC transfusion and expectant management as treatment for women with acute postpartum anemia in the absence of (severe) physical complaints.

If this hypothesis is true, an expectant management is to be preferred to minimize transfusion related reactions and costs.

Study design

The study is a multicenter randomized non-inferiority trial in women with an acute postpartum anemia. It is an open label study. This trial is embedded in the Dutch Obstetric Consortium, a collaboration of hospitals in the Netherlands.[74] Approximately 40 hospitals, including university hospitals, teaching hospitals and non-teaching hospitals will participate in this trial.

Participants/ eligibility criteria

Women, older than 18 years of age, who deliver in hospital or are transferred after home delivery because of PPH, are eligible. Patients will be included with an Hb between

3.0 and 5.0 mmol/L (4.8 and 8.1 g/dL), determined 12 to 24 hours after vaginal delivery or cesarean section, and a decrease in Hb of at least 1.2 mmol/L (1.9 g/dL) and/ or a total peripartum blood loss of at least 1000 mL. The initial Hb concentration will be determined when the patient is admitted during the first stage of labor at the labor ward. In other instances, when an initial Hb is absent, inclusion is purely based on the total amount of blood loss. Exclusion criteria include severe (anemic) physical complaints, previous RBC transfusion directly after delivery, severe pre-eclampsia, severely active infectious disease, congenital hemolytic disease, severe compromised immunological status, malignancy, severe comorbidity (ASA II/III), peripartum death or critical condition of the newborn. Severe (anemic) physical complaints were defined as fatigue, headache, dizziness, confusion, dyspnea, syncope, orthostatic complaints, tachycardia (> 100 bpm), angina pectoris and/ or transient ischemic attacks (TIA). Finally, good working knowledge of the Dutch language is required.

Procedures, recruitment, randomization and collection of baseline data

Eligible patients receive participant information. After written consent, participants are randomized by means of a web-based application.[75] Randomization will be blocked in a 1:1 ratio for RBC transfusion or expectant management. Stratification will be applied for mode of delivery and participating hospital.

All data will be collected, coded and processed with adequate precautions to ensure patient confidentiality.

Intervention and control

RBC transfusion will be compared with expectant management. In patients allocated to RBC transfusion, at least one unit of packed cells will be given. The desired Hb concentration after transfusion is 5.5 mmol/L (8.9 g/dL). The units of blood will be matched, pre-treated and tested according to the Dutch guidelines for RBC transfusion. Before and 15-90 minutes after transfusion maternal body temperature, blood pressure and heart rate will be checked and a blood sample is taken to determine Hb, hematocrit, platelet and white blood count.

In the group allocated to expectant management, i.e. no RBC transfusion, it is allowed to give a patient 'escape' RBC transfusion if this is clinically indicated. The indications to give 'escape' RBC transfusion are secondary PPH, resulting in hemodynamic instability or an Hb concentration < 3.0 mmol/L (4.8 g/dL), serious physical complaints or other serious general complications. Possible serious physical complaints are: dyspnea, syncope, orthostatic complaints, tachycardia (> 100 bpm), myocardial ischemia or transient ischemic attacks (TIA).

Additional use of medication to treat anemia, like oral and parenteral iron medication and other types of medication, is allowed in both groups and may be prescribed according to local protocol. Type and duration of the use of this medication will be recorded.

Outcome

Primary outcome is physical fatigue on day three postpartum, scored with a dimension of the HRQoL measure MFI. We aim to show non-inferiority of the expectant management arm and therefore this primary assessment day was chosen: if there would be any

difference between randomized groups, this difference is expected to be the largest three days postpartum.[69] In total three measures of HRQoL will be scored. Secondary outcomes will be the remaining HRQoL measures and the number of RBC transfusions. In addition an anemia related symptoms list will be filled in before randomization and at six weeks postpartum.

Medical process parameters to be evaluated include the increase of Hb concentration after RBC transfusion and acute transfusion complications. Moreover, we will compare the length of hospital stay and serious physical complications during the first six weeks postpartum (infections, thromboembolic events, hemodynamic events, cardiac events, neurologic events, secondary PPH, obstetric interventions, 'escape' RBC transfusion). A costs benefit analysis will also be performed (see 'Economic Evaluation').

HRQoL questionnaires

HRQoL will be scored with three measures: the generic measures ShortForm-36 (SF-36) and EuroQol-5D and the fatigue specific measure MFI.

The SF-36 is a multi-purpose, shortform health survey with only 36 questions. It consists of 36 items, organized into eight scales: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. The number of response choices per item ranges from two to six. The SF-36 yields an eight-dimensional profile, each scale ranging from 0 to 100 (100 = optimal). The SF-36 furthermore provides a physical summary score and a mental summary score. The SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.[76,77]

The EuroQol-5D is a standardized measure of health status and provides a simple, generic measure of health for clinical and economic appraisal. It consists of five items (Mobility, Self-Care, Usual Activities, Pain/ Discomfort, and Anxiety/ Depression), each following the general form: 1 = no problems, 2 = some problems, 3 = extreme problems. The sixth item is a global evaluation of own health on a visual analogue scale (EuroQol-5D VAS) with a range from 0 (worst imaginable health state) to 100 (best imaginable health state). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.[78]

The MFI is a 20-item self-report instrument designed to measure fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Each dimension is covered by a five-item scale. The number of response choices per item is four. Each scale ranges from 4 to 20 (4 = optimal). The MFI was developed as a tool to assess fatigue in a comprehensive way, with a special interest in fatigue as experienced by patients and provides information on the nature of the experience, and its intensity.[79]

The international standard HRQoL measures MFI, EuroQol-5D, and SF-36 have been evaluated in a pilot study; feasibility, reliability, and validity of these measures in a clinical obstetric setting were established.[69]

Follow-up

The follow-up period consists of six weeks. At fixed moments during this period (at inclusion, three days, one, three and six weeks) HRQoL questionnaires will be completed. The EuroQol-5D and MFI will be completed at all these fixed moments while the SF-36 will be used at one, three and six weeks postpartum.

Details of the delivery, RBC transfusion (when prescribed) and follow-up are recorded in the case record form. During the study period all transfusion complications will be recorded. An anemia related symptoms list is filled in before randomization and at six weeks postpartum. Hb concentrations will be determined at inclusion and six weeks postpartum. Six weeks postpartum patients visit the outpatient clinic.

In case of severe adverse events (SAE) during follow-up, a SAE form will be downloaded from the website and completed. SAE forms will be judged and based on this conclusion the study will be discontinued if participation in the study is considered irresponsible.

Patients that withhold informed consent for randomization will be asked to complete the questionnaires and identical case record forms will be used.

Statistics

Sample size:

The HRQoL assessments were tested in postpartum women in a pilot study.[69] For the comparison between RBC transfusion and an expectant management a sample size of 400 patients is planned (200 patients in the RBC transfusion group and 200 patients in the expectant management group). Power calculations showed that with these numbers a difference of 1.3 points or greater in favor of the RBC arm regarding the physical fatigue subscale on day three, the primary outcome, can be excluded with a power of 80% at one-sided alpha of 0.025 assuming that there is no difference on this day.[69] In view of the scale of physical fatigue (ranging from 4 to 20) we think that such a difference is not clinically relevant. Since missing data are not expected to exceed 20%, a total of 500 patients will be included.

Data analysis:

Data will be analyzed according to the intention to treat principle. The primary outcome, the MFI physical fatigue score at three days postpartum, will be compared between groups using Repeated Measurement ANOVA. This analysis allows for occasional missing values and will be performed using an unstructured covariance matrix, while taking account of baseline value (at inclusion) and mode of delivery as covariates. If the two-sided 95% confidence interval for the adjusted difference of means at day three excludes a difference of 1.3 points or greater in favor of the RBC arm, non-inferiority of the expectant policy is considered to be demonstrated.[80] A per-protocol analysis, including only patients without severe protocol violations, will also be performed.

The mean profiles along time of other MFI subscales, SF-36 and EuroQol-5D will be compared similarly to the primary outcome measure. The other secondary outcome measures will be assessed by calculating rates in groups, risk differences and 95% confidence interval.

Economic evaluation

The aim of the economic evaluation is to compare the costs and health effects of RBC transfusion versus expectant management in women with acute anemia after PPH. As the clinical study is designed as an equivalence study, the primary economic evaluation is a cost-minimization analysis. If RBC transfusion is shown to improve the quality of life, the economic analysis will be a cost-effectiveness analysis (time horizon: six weeks postpartum). The analysis will be performed from a hospital perspective. We will calculate direct costs (days in hospital, number of RBC transfusions and costs of complications). Real medical costs will be calculated by multiplying the volumes of health care use with the corresponding cost prices. Unit costs of health care consumption will be estimated according to national guidelines. Data on the volume of care will be available from hospital information systems in the participating hospitals.

Univariate analyses will be used for the analysis of economic outcome data. We will use non-parametric methods to test for differences between treatment groups.

Ethical considerations

This study has been approved by the ethics committee of the Erasmus Medical Center Rotterdam (Ref. No. MEC-2003-247) and by the management of all participating hospitals.

Discussion

Yearly, almost 200.000 women deliver in the Netherlands.[81] The number of women that receive one or more RBC transfusion postpartum is estimated less than 1% after vaginal delivery and between 1% and 7% following cesarean section.[67] The present study may lead to transfusion guidelines that are not only based on Hb concentrations and/or clinical symptoms but also on HRQoL measures. This may lead to a more judicious use of RBC transfusions.

To our knowledge, this is the first study worldwide investigating the effect of RBC transfusion on postpartum HRQoL in women with acute anemia due to PPH. A pilot study investigating the relation between postpartum Hb concentrations and HRQoL measures during the first six weeks postpartum, which is discussed below, was published by our group in 2007.[82]

Several national health organizations have tried to define transfusion triggers.[83-87] General consensus of these guidelines is that RBC transfusion above 6 mmol/L (9.7 g/dL) is not very useful, RBC transfusion below 4 mmol/L (6.4 g/dL) is probably useful, but in case of an Hb concentration between 4 and 6 mmol/L individual characteristics have to be taken in consideration for the decision to prescribe RBC transfusion. In the Netherlands, the Dutch “4-5-6 flexinorm” is empirically based and is intended for use in the treatment of acute and chronic cases of anemia.[15] However, considering the physiologic hemodynamic changes during pregnancy and the postpartum period in obstetric patients, the guideline might not be applicable for this specific patient group.

The hypothesis of the present study is that HRQoL is not or only to a small extent influenced by treatment with RBC transfusion in this group of patients. The results of our previous pilot study showed no correlation

between postpartum Hb concentrations and HRQoL after the first week postpartum. The health effects of this study will be the direct reduction of RBC transfusions, which will result in a decrease of RBC transfusion-related complications (formation of RBC alloantibodies, transfusion complications and infectious complications) and days in hospital. Another possible finding of this study may be the definition of the desired Hb concentration after RBC transfusion.

Chapter 4.2
Prior beliefs

In this chapter results of an inventorial survey are presented. The aim of this survey was to assess the professional beliefs regarding red blood cell (RBC) transfusion policy and health-related quality of life (HRQoL) after postpartum hemorrhage (PPH). More specifically, questions in this survey inventoried transfusion triggers in daily clinical practice, the expected effect of transfusion on HRQoL and occurrence of physical complications as well as the expected economic consequences of RBC transfusion versus non-intervention policy.

The survey was performed before the results of a randomized controlled trial (the WOMB trial; 'Well-being of Obstetric patients on Minimal Blood transfusions' trial),[88] in which RBC transfusion is compared to non-intervention in acute anemic women after PPH, were elaborated and presented.

A questionnaire was sent to all gynecologists primarily responsible for the training of gynecological residents in the Dutch teaching hospitals (one gynecologist per teaching hospital).

A total of 46 gynecologists were invited; the response was 72% (33/46).
Results are presented below.

In almost 50% of the hospitals a local protocol concerning the treatment of postpartum anemia was available. Hemoglobin (Hb) concentration was used in 91% as transfusion trigger, but also the amount of blood loss and physical complaints were frequently reported. In ***Table 1*** the reported transfusion triggers are presented.

Table 1 *Transfusion triggers for RBC transfusion in Dutch teaching hospitals of 33 (out of 46) respondents.*

Trigger	n	%
Hb concentration	30	91
Amount of blood loss	19	58
Physical complaints	30	91
HRQoL	6	18
(Social) environment	6	18
Other		
ASA classification	1	3
combination of all	1	3

We investigated below which Hb concentration RBC transfusion was considered and below which Hb concentration RBC transfusion was actually prescribed.
The Hb concentration below which RBC transfusion was considered was reported as 4.8 mmol/L (mean, SD 0.4; in g/dL mean 7.7 and SD 0.6), while the Hb concentration below which RBC transfusion actually was prescribed was 4.1 mmol/L (mean, SD 0.3; in g/dL mean 6.6 and SD 0.5).

In 2004 a similar survey was performed by our research group using the same methods. This survey demonstrated similar results: RBC transfusion was then considered in case of a Hb concentration below 5.0 mmol/L (mean, SD 0.6; in g/dL mean 8.1 and SD 0.9) while RBC transfusion was actually prescribed in case of an Hb concentration below 4.2 mmol/L (mean, SD 0.5; in g/dL mean 6.8 and SD 0.8).[73]

The survey also investigated whether RBC transfusion was expected to improve HRQoL at day three postpartum, and if so, when the respondents would consider the improvement to be clinically relevant.

Of the respondents, 94% expected an improvement in HRQoL following RBC transfusion at day three postpartum. If RBC transfusion would reduce physical fatigue, most respondents (70%) considered this to be clinically relevant if the reduction lasted at least 14 days. The results of this question are demonstrated in ***Figure 1***.

The following questions concerned physical complications due to postpartum anemia and evaluated whether the respondents expected that a non-intervention policy would result in a higher incidence of physical complications (infections, thromboembolic events, cardiovascular ischemia, and so on)?

Twenty-seven percent of the respondents expected that a non-intervention policy would result in a higher rate of physical complications postpartum while 18% was uncertain (***Figure 2***).

Regarding medical costs (including complications and readmissions), 71% (22/31) of the respondents reported that costs were expected to be higher in case of RBC transfusion, compared to non-intervention policy. One respondent reported to be uncertain while 30% (8/31) believed it would be more costly.

With regard to implementation of the WOMB trial results, 91% of the respondents declared to be willing to adjust their current RBC transfusion policy if trial results would support adjustment.

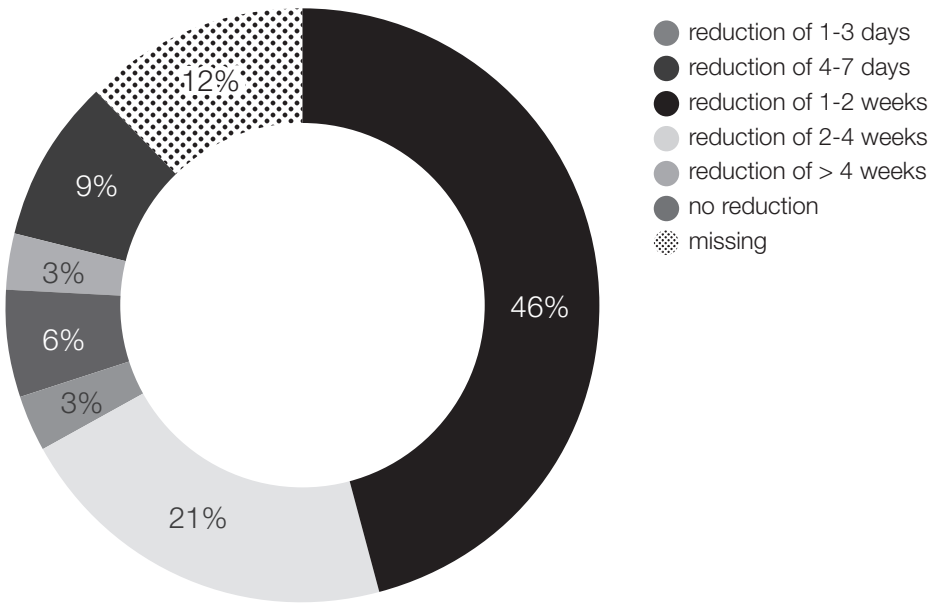

Figure 1 *Response to the question 'Would you expect RBC transfusion to reduce physical fatigue at day three postpartum? If so, when would you consider the reduction to be clinically relevant?'*

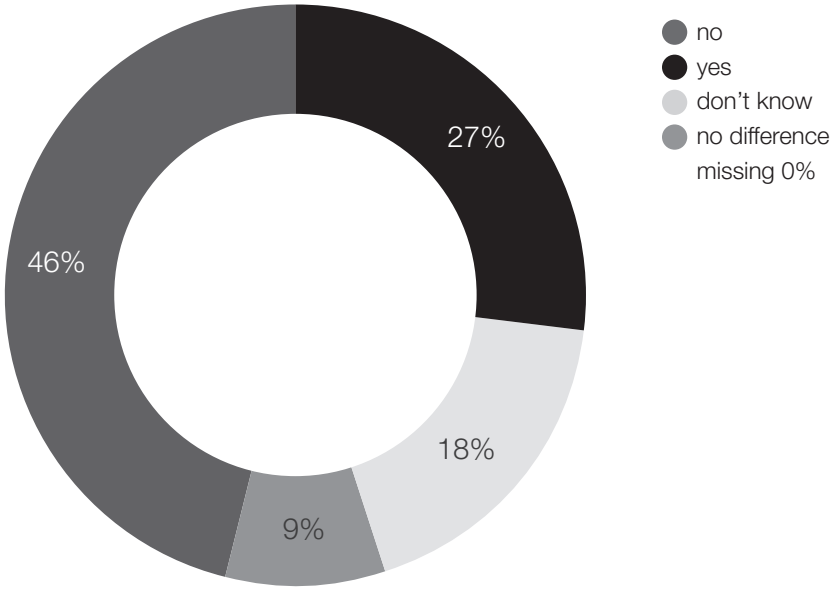

Figure 2 *Response to the question 'Do you expect that a non-intervention policy leads to a higher physical complication rate?'*

Chapter 4.3

Transfusion policy after severe postpartum hemorrhage: a randomized non-inferiority trial

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Abstract

Objective
To assess the effect of red blood cell (RBC) transfusion on quality of life in acutely anemic women after postpartum hemorrhage.

Design
Randomized non-inferiority trial.

Setting
37 Dutch university and general hospitals.

Population
Women with acute anemia (hemoglobin 4.8-7.9 g/dL [3.0-4.9 mmol/L] 12-24 hours postpartum) without severe anemic symptoms or severe comorbidities.

Methods
Women were allocated to RBC transfusion or non-intervention.

Main outcome measures
Primary outcome was physical fatigue 3 days postpartum (Multidimensional Fatigue Inventory, scale 4-20; 20 represents maximal fatigue). Non-inferiority was demonstrated if the physical fatigue difference between study arms was maximal 1.3. Secondary outcomes were health-related quality of life and physical complications. Health-related quality of life questionnaires were completed at five time points until 6 weeks postpartum.

Results
521 women were randomized to non-intervention (n = 262) or RBC transfusion (n = 259). Mean physical fatigue score at day 3 postpartum, adjusted for baseline and mode of delivery, was 0.8 lower in the RBC transfusion arm (95% confidence interval: 0.1-1.5, p = 0.02) and 1 week postpartum 1.06 lower (95% confidence interval: 0.3-1.8, p = 0.01). A median of two RBC units was transfused in the RBC transfusion arm. In the non-intervention arm, 33 women received RBC transfusion, mainly because of anemic symptoms. Physical complications were comparable.

Conclusions
Statistically, non-inferiority could not be demonstrated as the confidence interval crossed the non-inferiority boundary. Nevertheless, with only a small difference in physical fatigue and no differences in secondary outcomes, implementation of restrictive management seems clinically justified.

Introduction

Postpartum hemorrhage (PPH) is an important cause of maternal mortality. It causes acute anemia with physical sequelae varying from fatigue to severe hemodynamic disturbance. A recent systematic review showed a worldwide incidence of severe PPH (blood loss of at least 1000 mL during delivery)[1] of 1.9% in the period 1997 till 2006.[2] The most important treatment of severe PPH is red blood cell (RBC) transfusion. RBC transfusion should be aimed to reduce morbidity. In the past few years increasing concerns have arisen about the supply and safety of this treatment, encouraging a conservative management.[18] Despite the introduction of several new guidelines,[14,15] transfusion criteria still vary widely between clinicians. The decision whether to prescribe RBC transfusion is mainly based on postpartum hemoglobin (Hb) concentrations, as guidelines recommend RBC transfusion when Hb concentration is < 6 g/dL and no transfusion in women with an Hb concentration > 10 g/dL.[15-17] A survey among Dutch gynecologists revealed that RBC transfusion for anemic postpartum women was considered in case of an Hb concentration below 5.0 mmol/l (8.1 g/dL).[73] To provide insight in potential risks of anemia and benefits of transfusion in patients with severe PPH we conducted the Well-being of Obstetric patients on Minimal Blood transfusions (WOMB) study, a multicenter randomized non-inferiority trial assessing the effect of RBC transfusion on HRQoL in women with acute anemia due to severe PPH. A non-inferiority design was chosen as the non-intervention treatment in this study has greater availability, reduced costs, less invasiveness and leads to fewer adverse effects. Physical fatigue was chosen as primary outcome since it was considered the earliest arising complaint in acute anemia. Based on results of a pilot study the largest difference was expected at day three.[82]

Methods

The study was approved by the University of Rotterdam's Institutional Review Board (MEC-2003-247), and had local approval from the boards of all participating hospitals. The study was registered at ClinicalTrials.gov NCT00335023 and at the Dutch Trial Register (NTR335).

The methods have already been reported in detail.[89]

Patients

We enrolled women in 37 Dutch hospitals from May 2004 to February 2011. Eligible women sustained PPH (blood loss of ≥ 1000 mL and/ or a decrease in Hb concentration of ≥ 1.9 g/dL [1.2 mmol/L]) and had an Hb concentration between 4.8 and 7.9 g/dL (3.0-4.9 mmol/L) 12 to 24 hours after delivery. The lower Hb threshold was formulated on request of the Institutional Review Board as in the original protocol no lower threshold was defined. Participants either delivered in hospital or were admitted after a home birth. Exclusion criteria were severe symptoms of anemia (defined as dyspnoea, syncope, tachycardia (> 100 bpm), angina pectoris, and/ or transient ischemic attacks), RBC transfusion administered during or within 12 hours after delivery, severe pre-eclampsia, severe infectious disease, congenital hemolytic disease, compromised immunological status, malignancy, severe comorbidity (ASA II/III), and death or critical condition of the neonate. Finally, a good

knowledge of the Dutch language was required. Participants were seen by research midwives and nurses who provided counseling, obtained informed consent, monitored the study protocol, and collected data.

Randomization

After informed consent, women were randomly allocated in a 1:1 ratio to receive RBC transfusion or non-intervention, using a web-based application for block randomization with a variable block size of two to eight. Randomization was stratified for mode of delivery and participating hospital. Due to the intervention's nature, the study was not blinded. From 2005 onwards, women who declined informed consent were asked to complete questionnaires; follow-up was identical.

Women allocated to RBC transfusion received at least one unit of red blood cells; we aimed to reach an Hb concentration of at least 8.9 g/dL (5.5 mmol/L). Hb and hematocrit concentrations were recorded before and after RBC transfusion. In women allocated to non-intervention, RBC transfusion was allowed if severe symptoms of anemia developed or at their physicians' discretion. Additional use of iron and/ or folic acid supplementation according to local protocol was allowed.

Follow-up and Outcome measures

The follow-up period was limited to six weeks postpartum. HRQoL questionnaires were to be completed at five points in time: at inclusion, three days, one week, three weeks, and six weeks postpartum. Physical complications during follow-up were recorded. Hb concentration was determined at inclusion and six weeks postpartum.

The primary outcome was physical fatigue at day 3, measured with the Multidimensional Fatigue Inventory (MFI).[79] This time point was chosen as the difference between arms was expected to be largest at day 3 since data of the pilot study showed that Hb 12-24 hours postpartum was related to HRQoL at the same time point but not to HRQoL one week after delivery.[69] Secondary outcomes were remaining HRQoL scores, number of RBC units transfused, transfusion reactions, length of hospital stay, and physical complications during follow-up (infections, thromboembolic events, secondary PPH and other physical complications).

Ethnicity was assessed according to the definition of Statistics Netherlands.[90] In twin pregnancies, we used the data of the first child in the analyses. With more than one mode of delivery method, one mode was recorded using the following order: cesarean section, operative vaginal delivery, spontaneous vaginal delivery. With more than one method of analgesia, this was recorded using the following order: general anesthesia, locoregional anesthesia, opiates.

Health-related quality of life

We used internationally validated HRQoL measures: the MFI and the Medical Outcome Study 36-Item Short-Form Health Survey version one (SF-36). The MFI is a domain-specific measure for physical and mental fatigue. The MFI consists of 20 items grouped into five dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.[79] The MFI scores range from 4 to 20; higher scores indicate a higher degree of fatigue. The HRQoL questionnaire MFI scores fatigue on several domains and has a high feasibility, reliability and validity in chronically anemic

patients.[91] The SF-36 is a generic HRQoL measure with eight dimensions: physical functioning, role limitations due to physical health problems (role-physical), bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health (role-emotional), and mental health.[77] The SF-36 scores range from 0 to 100; higher scores indicate better functioning or well-being. The SF-36 is a generic questionnaire widely used for measuring patient-reported outcomes.[92] Population-based norm scores are available for the Dutch adaptation of SF-36.[93] Both HRQoL questionnaires were previously validated in postpartum women in a pilot study.[82] The MFI was to be completed at all five time points, while the SF-36 was to be completed at one week, three weeks, and six weeks.

Sample size

For the subscale physical fatigue (MFI), a minimum clinical important difference had not been established prior to our study. Therefore data from a pilot study, assessing HRQoL in postpartum women,[82] were used. We calculated that, with a sample size of 400 women (200 per arm), a difference of 1.3 points or greater (in favor of the RBC transfusion arm regarding physical fatigue at day 3) could be excluded (power: 80%, one-sided alpha: 0.025). This difference was considered small and clinically irrelevant and therefore used as non-inferiority boundary. Because we observed that 20% of HRQoL data were missing, in 2008 we decided to include 500 women.

Statistics

Analyses were conducted on an intention-to-treat basis. Continuous variables were summarized as means with standard deviations (SD), or medians with interquartile ranges (IQR). HRQoL scores were presented as differences in adjusted means with 95% confidence intervals (CI).

Non-inferiority is intended to show that the effect of one treatment is not worse than that of an active control by more than a pre-specified boundary. When the difference between study arms does not exceed this boundary, non-inferiority is demonstrated. A difference can be statistically significant but too small to be clinically relevant: only when the difference exceeds the non-inferiority boundary, clinical relevance is demonstrated. The significance of the difference between study arms is therefore of minor importance.

Besides evaluation of physical fatigue in both study arms, we tested non-inferiority of the primary outcome measure by assessing if the upper 95% CI lay within the non-inferiority boundary. Adjusted means of primary outcome and remaining MFI scores were calculated using repeated measurement ANOVA with an unstructured covariance matrix, including baseline value (at inclusion) and mode of delivery as covariates. The same statistical method was used for the SF-36 scores, with only mode of delivery as a covariate, since the SF-36 was not completed at inclusion. Additionally, the influence of mode of delivery was analyzed using repeated measurement ANOVA, with an unstructured covariance matrix including baseline value as covariate.

MFI scores were analyzed if data were available at inclusion and at least one additional time point. SF-36 scores were analyzed if at least one questionnaire (1 week, three weeks, or six weeks) was completed. Internal consistency within questionnaires was assessed for each MFI and SF-36

subscale by calculating Cronbach's alpha; this showed high reliability, with $\alpha > 0.70$ for all HRQoL subscales except the SF-36 dimension bodily pain ($\alpha > 0.5$).

Pre-specified exploratory subgroup analyses of the primary outcome were performed for Hb concentration at inclusion with categories 4.8-6.5, 6.6-7.3, and 7.4-7.9 g/dL (3.0-4.0, 4.1-4.5, and 4.6-4.9 mmol/L) and for physical fatigue score at inclusion using quartiles. The significance of differences in primary outcome between subgroups (effect modification) was calculated. A post-hoc per-protocol analysis was performed after excluding women allocated to non-intervention who received RBC transfusion, and women allocated to RBC transfusion who did not receive RBC units. ANOVA estimates of HRQoL means were calculated to create graphics. Superiority analyses were used to analyze secondary outcomes. For secondary analyses, we used the chi-square test for comparing proportions and the Mann-Whitney test for comparing continuous variables. Two-sided *p*-values are given and 0.05 was considered the limit of significance. Data was analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

During the study, 1011 women were approached; 521 gave informed consent for randomization: 259 were allocated to RBC transfusion and 262 to non-intervention. After randomization, two participants were excluded because they did not meet the inclusion criteria (***Figure 1***). Table 1 shows the baseline characteristics of both randomized and non-randomized women. Among randomized women, no significant differences were found between study arms. Two neonatal deaths in preterm neonates occurred during follow-up due to sepsis and necrotising enterocolitis.

Baseline characteristics of responders versus non-responders (at least one completed questionnaire versus no questionnaires) showed significant differences for ethnicity, age, and blood loss (responders versus non-responders; Western ethnicity in 81% versus 54%, mean age 31 versus 28 years, median blood loss 1500 mL versus 1150 mL).

Hb concentration at inclusion was comparable between study arms (***Table 1***). Women randomized to RBC transfusion received a median of two RBC units. In these women, median Hb concentration after transfusion was 9.0 g/dL and median Hb concentration at discharge was significantly higher than in women allocated to non-intervention (***Table 2***). Among women allocated to RBC transfusion, seven received no RBC transfusion: four withdrew consent, one appeared to have no health insurance, one had fever, and one had irregular erythrocyte alloantibodies. Of women allocated to non-intervention, 33/261 (13%) received RBC transfusion during follow-up. Indications were anemic symptoms (n = 28), blood loss following retained placenta (n = 3), discomfort with parenteral iron supplementation (n = 1) and readmission for endometritis (n = 1). Compared to women who did not receive a transfusion on second instance, these women had lower Hb concentrations and higher physical fatigue scores at inclusion (median Hb 7.4 versus 6.9 g/dL, $p = 0.02$ and median physical fatigue score 19 versus 17, $p = 0.08$). In those women who suffered

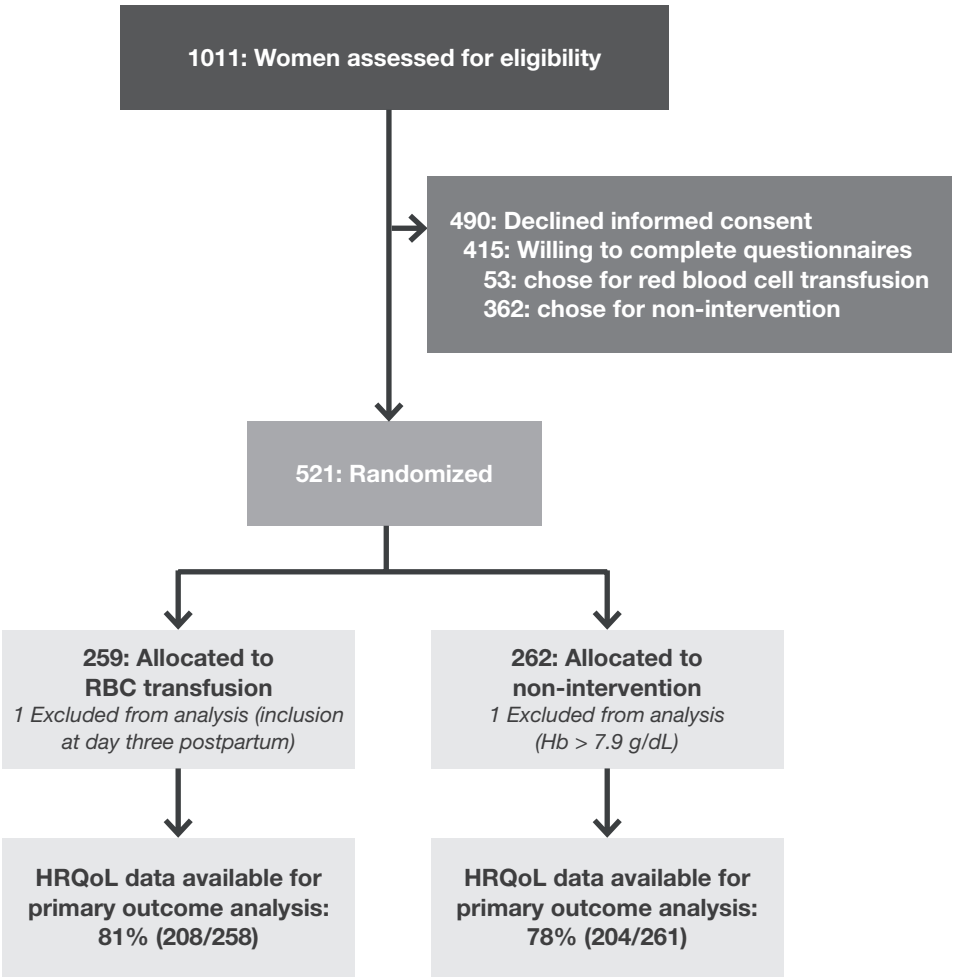

Figure 1 *Randomization flow chart.*

from symptoms of anemia, RBC transfusion was given at a median of two days (IQR 1-3), and five were readmitted. Three transfusion reactions (3/291) were recorded, all in the RBC transfusion arm: one developed a rash (WHO Category 1, mild transfusion reaction) and two a rise in temperature (WHO Category 2, moderate-severe transfusion reaction).[94] Hb concentrations at six weeks were comparable between study arms, as demonstrated in Table 2.

Primary outcome (physical fatigue at day three) was analyzed in 208 women in the RBC transfusion arm and in 204 women in the non-intervention arm. Women randomized to non-intervention had a 0.78 higher mean physical fatigue score at day three

Table 1 *Baseline maternal characteristics of randomized and non-randomized women.*

	Randomized women		Non-randomized women	
	Transfusion (n = 258)	Non-intervention (n = 261)	Transfusion (n = 53)	Non-intervention (n = 362)
Characteristics				
Age (y)	30.7 ± 5.0	30.9 ± 5.3	31.8 ± 4.8	31.2 ± 5.2
Preconception body mass index[a]	23.3 (21.1-26.6)	22.9 (20.8-26.5)	22.3 (20.9-25.1)	23.4 (21.1-26.0)
Western ethnic origin[b]	186 (78%)	177 (76%)	38 (91%)	255 (84%)
Highest education[c]				
none/ primary school	4 (3%)	5 (3%)	0	4 (2%)
lower/ senior secondary vocational education	88 (56%)	77 (51%)	6 (24%)	91 (46%)
higher professional education and university	64 (41%)	70 (46%)	19 (76%)	102 (52%)
Nulliparous	152 (59%)	143 (55%)	31 (59%)	207 (57%)
Delivery by community midwife[d]	41 (16%)	29 (11%)	8 (15%)	58 (16%)
Mode of delivery				
vaginal	213 (83%)	206 (79%)	45 (85%)	292 (81%)
of which operative[e]	62 (30%)	48 (24%)	6 (15%)	55 (20%)
elective CS	8 (3%)	15 (6%)	2 (4%)	23 (6%)
emergency CS	37 (14%)	40 (15%)	6 (11%)	47 (13%)
Twin pregnancies	13 (5%)	16 (6%)	5 (9%)	18 (5%)
Gestational age (weeks+days)	40+1 (38+5-41+1)	40+0 (38+3-41+0)	40+2 (38+6-41+1)	40+0 (38+4-41+0)
Birth weight neonate[f]				
< 10th percentile	8 (3%)	20 (8%)	3 (6%)	16 (5%)
10 ≤ percentile ≤ 90	188 (75%)	189 (74%)	34 (69%)	258 (74%)
> 90st percentile	54 (22%)	47 (18%)	12 (25%)	75 (22%)
Estimated blood loss during delivery (mL)	1485 (1000, 1950)	1500 (1000, 1975)	1500 (925, 2000)	1500 (1000, 2000)
Hb concentration at inclusion (g/dL)	7.3 (6.8-7.7)	7.4 (6.8-7.7)	6.9 (6.4-7.4)	7.4 (6.9-7.7)

Data are n (%), mean ± SD, or median (Interquartile Range). CS = cesarean section. [a]Randomized: n = 232 and n = 234 respectively. Non-randomized: n = 49 and n = 322 respectively. [b]Randomized: n = 239 and n = 232 respectively. Non-randomized: n = 42 and n = 304 respectively. [c]Randomized: n = 156 and n = 152 respectively. Non-randomized: n = 25 and n = 197 respectively. [d]Randomized: n = 253 and n = 255 respectively. Non-randomized: n = 52 and n = 352 respectively. [e]Randomized: n = 205 and n = 197 respectively. Non-randomized: n = 39 and n = 279 respectively. [f]Randomized: n = 250 and n = 256 respectively. Non-randomized: n = 49 and n = 349.

than women randomized to RBC transfusion (95% CI: 0.1-1.5, p = 0.024) (***Figure 2***, ***Table 3***). The non-inferiority boundary is just exceeded by the 95% CI. At one week, the difference in physical fatigue scores between study arms was 1.06 (95% CI: 0.3-1.8, p = 0.007) (***Table 3***). In ***Figure 3***, mean differences in physical fatigue scores between study arms and confidence intervals are presented with the non-inferiority boundary. Primary outcome was not significantly affected by mode of delivery (interaction p = 0.40).

The remaining HRQoL scores are presented in ***Table S1***. All MFI subscales, with the exception

Table 2 *Blood loss, hemoglobin concentration and RBC transfusion.*

	Transfusion (n = 258)	Non-intervention (n = 261)	*p*
Variable			
RBC units per woman	2 (2-2)	0 (0-0)	< 0.001
Total RBC units[a]	517	88	< 0.001
Hb concentration after transfusion, g/dL[b]	9.0 (8.5-9.6)	8.9 (8.2-9.7)	0.56
Hb concentration at discharge (g/dL)[c]	9.0 (8.5-9.5)	7.4 (6.8-7.7)	< 0.001
Crossover	7 (3%)	33 (13%)	< 0.001
refused RBC transfusion	5		
fever	1		
erythrocyte alloantibodies	1		
anemic symptoms		28	
retained products of conception		3	
parenteral iron intolerance		1	
infection (endometritis)		1	
Hb concentration at six weeks (g/dL)[d]	12.1 (11.3-12.6)	11.9 (10.9-12.6)	0.18

Data are n (%) or median (Interquartile Range).
[a]Including units transfused during follow-up. [b]Non-intervention: n = 220. RBC transfusion: n = 25 (transfusion on second instance). [c]Non-intervention: n = 231. RBC transfusion: n = 238. [d]Non-intervention: n = 165. RBC transfusion n = 178. Blood samples for determining Hb at six weeks postpartum were collected at 45 (41-53) and 43 (40-48) days postpartum in the RBC transfusion and non-intervention arm respectively.

of mental fatigue at three days, showed slightly higher mean scores in the RBC non-intervention arm: the largest difference was 1.1 (physical fatigue at one week). Regarding the SF-36, differences in subscale scores between arms ran up to 5.5 points (physical functioning at one week) with a tendency to lower health scores in the non-intervention arm. The difference was significant only in the subscale physical functioning at one and three week (scores respectively 5.5 and 4.3 points lower in the non-intervention arm). Again though, significance of the difference is of secondary interest to its magnitude, which seems relatively small on the scale of SF-36.

HRQoL results were similar after excluding questionnaires not completed within prescribed time frames after follow-up (0-2, 2-5, 6-10 days, 2-4, and 5-7 weeks postpartum) (138/1803 questionnaires excluded).

Length of hospital stay after delivery was equal in both study arms (median days: 2, $p = 0.37$) and physical complications were comparable (***Table 4***). Use of iron supplementation was more frequent in women allocated to non-intervention. The percentage of women who breastfed initially, as well as those who continued until six weeks postpartum, was not different between study arms (***Table 4***).

Results were consistent in a per-protocol analysis (mean physical fatigue score at day three was 0.80 higher in the non-intervention arm, $p = 0.03$, 95% CI: 0.1-1.5).

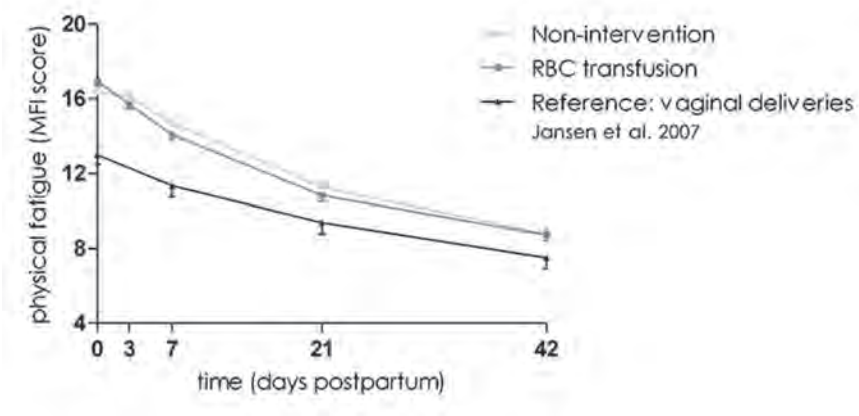

Figure 2 *Physical fatigue score in randomized women. n = 447.*

ANOVA estimates of means, error bars represent standard errors. Reference curve obtained from the pilot study that included 141 consecutive women delivering in hospital. 71 women delivered vaginally. In these women, median blood loss was 300 mL[82]

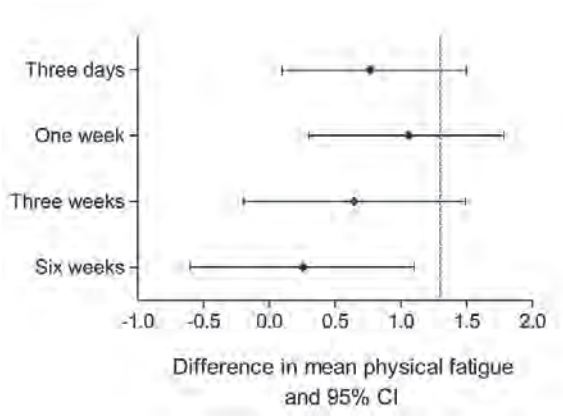

Figure 3 *Mean differences and confidence intervals for physical fatigue in view of the non-inferiority boundary.*

Table 3 *Difference in mean physical fatigue in randomized women, n = 382.*

		Mean adjusted for baseline and mode of delivery					
	Non-inferiority boundary	Transfusion	Non-intervention	Difference	*p*	95% Confidence Interval	
						Lower limit	Upper limit
Time point							
Three days	1.30	15.68	16.45	0.78	0.024	0.1	1.5
One week	1.30	14.02	15.08	1.06	0.007	0.3	1.8
Three weeks	1.30	10.88	11.54	0.66	0.14	-0.2	1.5
Six weeks	1.30	8.69	8.95	0.26	0.56	-0.6	1.1

Table 4 *Follow-up in randomized women.*

	Transfusion		Non-intervention		*p*
	n		n		
Variable					
Iron supplementation	231		246		< 0.001
oral		93 (40%)		187 (76%)	
continued until six weeks[a]	66	37 (56%)	130	84 (65%)	0.31
intravenous		0		30 (12%)	
none		138 (60%)		29 (12%)	
Breastfeeding at randomization	252	194 (77%)	250	193 (77%)	1.00
continued until six weeks	154	99 (64%)	143	101 (71%)	0.30
Complications					
transfusion reactions	227	3 (1%)	30	0	0.54
thromboembolic event	227	2 (0.9%)	226	2 (0.9%)	1.00
urinary tract infection	228	10 (4.4%)	225	14 (6.2%)	0.52
infected surgery wound	41	0	46	1 (2.2%)	1.00
infected episiotomy/ rupture	145	6 (4.1%)	137	6 (4.4%)	1.00
endometritis	228	5 (2.2%)	225	3 (1.3%)	0.74
Infectious complications, total	209	22 (10.5%)	211	24 (11.4%)	0.90

n are number of women in which variable is known. Data are n (%) unless otherwise specified.
[a]Oral supplementation users.

The difference at day three in mean physical fatigue scores per category Hb at inclusion (Hb 4.8-6.5, 6.6-7.3, and 7.4-7.9 g/dL) was 1.19 (± SE 1.07), 0.91 (± SE 0.60), and 0.73 (± SE 0.44) respectively. These differences did not significantly differ from each other (p = 0.91). Per category physical fatigue score at inclusion (< 14, 14-17, 18-19, 20) these differences were 1.58 (± SE 1.02), 1.22 (± SE 0.68), 0.61 (± SE 0.71), and 0.10 (± SE 0.49) respectively and did not significantly differ from each other (p = 0.42).
Ten randomized women were retrospectively identified with an exclusion criterion: HIV (three), severe pre-eclampsia (four), and thalassemia (three). Primary outcome analysis after excluding these women gave similar results (data not shown).

Non-randomized women

Of the 490 women who declined informed consent; 415 (85%) were willing to complete questionnaires: 53 chose RBC transfusion and 362 non-intervention. Characteristics of non-randomized participants are described in ***Table 1***. Compared to randomized women, non-randomized women were less often of Western ethnicity: 363/471 (77%) versus 293/346 (85%), p = 0.01; and had less often had an operative vaginal delivery (110/402 [27%] versus 61/318 [19%], p = 0.01).

Among non-randomized women, Hb concentration was significantly lower in women who chose RBC transfusion (median Hb 7.4 versus 6.9 g/dL, p < 0.001). The women who chose RBC transfusion all received RBC units. Of women who chose non-intervention, 41/362 (11%) received RBC transfusion, 34 (9%) because of anemic symptoms. These rates are comparable to the rates in randomized women.

Discussion

Main findings

In this study, the difference in physical fatigue at day three postpartum between both study arms was small. While the difference was only 0.78, the 95% CI of this difference (0.1-1.5) just exceeded the non-inferiority boundary of 1.3. Although non-inferiority cannot be demonstrated, clinically relevance of this difference seems negligible. No differences were found between study arms for secondary outcomes.

Regarding non-inferiority, its boundary is ideally based on the minimum clinical important difference, however, minimum clinical important differences for the MFI subscales had not been established in 2004. The pre-specified level of 1.3 was the feasible detectable difference in physical fatigue calculated using data obtained in a pilot study:[82] this was not considered a valid estimate of the score's clinical relevance. Retrospectively, our pre-specified level seems too strict considering the following arguments. First, the minimum clinical important difference for physical fatigue has recently been determined to be larger, namely 2.04, in radiotherapy patients.[95] Second, the difference in physical fatigue score in this study is very small, given the large difference between scores after uncomplicated deliveries (derived from the pilot study) and scores after PPH (this study). These scores, demonstrated in ***Figure 2***, indicate that PPH greatly increases physical fatigue irrespective of the treatment policy. Third, in social sciences, Cohen's effect size (d) is used to determine a relevant difference (relevant when $d \geq 0.50$).[96] In our data, d's were < 0.20 for all MFI subscales (calculated at all time points), indicating no relevant differences. The disadvantage of Cohen's effect size, and reason not to include this in study design, is that the measure is distribution-based, whereas we think determining clinical relevance should be content-based. In addition, we analyzed all randomized and non-randomized patients together and found that the difference in physical fatigue between study arms was equal (0.8) to the difference in randomized patients alone, while its 95% CI was smaller (0.23-1.27) and thus does not exceed the non-inferiority boundary.

Interpretation

Most trials investigating transfusion policy were conducted in intensive care, cardiovascular, and orthopedic patients[97-105] while recently a trial in patients with gastrointestinal bleeding has been published.[106] Six trials used as restrictive trigger an Hb threshold of ≤ 8 g/dL[98-102,106] and two used hematocrit thresholds of 24% and 30%.[103,104] To our knowledge, only Hébert conducted a randomized controlled trial with Hb thresholds below 8 g/dL (Hb < 7g/dL versus < 9 g/dL).[97] This study in intensive care patients showed that a restrictive threshold was at least as effective regarding mortality, multi-organ failure, and length of hospital stay in patients without cardiac disease. A recent update on Cochrane evidence regarding Hb thresholds, including 19 randomized trials and more than 6000 patients, demonstrated a relative risk for 30-day all-cause mortality of 0.85 (95% CI: 0.70-1.03) in patients allocated to a lower Hb threshold (threshold varying from 7-10 g/dL) compared to a more liberal transfusion policy. Also, a lower threshold was not associated with any significant differences in major complications.[107] In our study, physical complications between study arms were also comparable, as was duration of hospital stay.

Previously, few studies investigated postpartum HRQoL. The MFI was only used in our pilot study, to validate HRQoL measures in Dutch postpartum women.[82] This study found significant differences in MFI scores after different modes of delivery though the present study has not confirmed this finding. After vaginal delivery, women in the pilot study had significantly more favorable scores than in the present study, while the scores after cesarean section in the pilot study were comparable to scores in the present study. Differences in physical fatigue between modes of delivery might be concealed by the large effect of PPH on physical fatigue.

Minimum clinical important differences of SF-36 subscales have not yet been determined in a postpartum population. Minimum clinical important differences determined in orthopedic, COPD, asthma and cardiac disease are at least 10 points so the differences found in SF-36 subscales in this study (maximal difference 5.5) seem not clinically relevant.[108-110]

Strengths and limitations

Main strengths of this study are the comparison of randomized arms and the large study population. Questionnaires to score HRQoL outcomes were internationally validated. Primary outcome was available in 412/519 (80%) of randomized participants, a usual response rate in HRQoL studies. A large percentage of eligible women declined informed consent, mainly because they did not want an intervention. Baseline characteristics of randomized versus non-randomized participants showed only differences in ethnicity and frequency of operative delivery.

The majority of participants in our study delivered vaginally. Women presumably receive RBC transfusions more reluctantly in operating theatres than after vaginal deliveries. As a result of the small numbers, comparisons between emergency and elective cesarean sections could not be made. Although iron supplementation is assumed to have no effect after RBC transfusion, still a remarkable percentage of women in the RBC transfusion arm used iron supplementation. Wide variations in type, dosage, and duration of iron supplementation made it impossible to make comparisons. Though the assumption is that anemia compromises breastfeeding,[111] our study showed that more women in the non-intervention arm were still breastfeeding six weeks postpartum while the intention to breastfeed had been similar in the study arms. These results should be interpreted with caution, since reasons for discontinuation of breast feeding were not reported.

A minority of clinicians is unaware of or reluctant to accept lower transfusion thresholds.[112] Implementing a restrictive approach to RBC transfusion would lead to a striking decrease in demand for RBC units and adverse events. In our study, the use of RBC units in the non-intervention arm was 88/517 (17%) of that in the RBC transfusion arm (*Table 2*). A high percentage of women in the non-intervention arm (28/261, 11%) secondarily received RBC units for anemic symptoms. Among non-randomized women this percentage was similar, even though they were expected to be more motivated for non-intervention.

The randomized women allocated to non-intervention that received RBC transfusion on second instance had significantly lower Hb concentrations at inclusion. Also, a trend towards a larger difference in physical fatigue

between study arms was seen in the women in the lowest category Hb concentrations and in highest category of physical fatigue scores at inclusion. Therefore, Hb concentration should be considered when counseling postpartum anemic women: RBC transfusion seems to have the largest effect in women with the lowest Hb and highest physical fatigue scores.

The difference in mean physical fatigue score between study arms was only small (0.78). The clinical relevance of this difference seems negligible even though non-inferiority of non-intervention policy could statistically not be demonstrated. The recently established minimum clinical difference of physical fatigue,[95] suggests that non-intervention policy is safe with regard to physical complications and only accompanied by slightly higher physical fatigue scores; we feel that our results justify implementation of non-intervention in daily clinical practice. Future studies are needed to establish the optimal iron supplementation in these women and justify implementation of non-intervention policy.

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Table S1 *HRQoL in randomized women during follow-up.*

	Mean score			Difference in mean score (95% CI) between study arms				
	Baseline				3 days	1 week	3 weeks	6 weeks
	n	Transfusion	Non-intervention	n				
MFI								
General fatigue	401	16.8	16.9	378	0.7* (0.1-1.3)	0.7 (-0.1-1.4)	0.2 (-0.6-1.0)	0.2 (-0.7-1.2)
Physical fatigue	401	16.4	16.9	382	0.8* (0.1-1.5)	1.1† (0.3-1.8)	0.7 (-0.2-1.5)	0.3 (-0.6-1.1)
Reduced activity	401	16.4	16.4	382	0.7* (0.1-1.4)	1.0† (0.3-1.8)	0.6 (-0.3-1.4)	-0.1 (-0.9-0.8)
Reduced motivation	401	13.0	13.1	382	0.6 (-0.2-1.3)	1.0† (0.3-1.8)	0.4 (-0.3-1.1)	-0.2 (-0.9-0.5)
Mental fatigue	401	11.9	12.2	381	-0.2 (-0.9-0.5)	0.5 (-0.3-1.3)	0.3 (-0.5-1.1)	0.6 (-0.3-1.5)
SF-36								
Physical functioning	NA	NA	NA	380	NA	-5.5* (-10.3--0.7)	-4.3* (-8.4--0.2)	-0.1 (-3.5-3.2)
Role-physical	NA	NA	NA	381	NA	-4.7 (-10.7-1.3)	-5.4 (-14.2-3.4)	-4.1 (-12.0-3.8)
Bodily pain	NA	NA	NA	382	NA	2.2 (-1.7-6.1)	-0.7 (-5.4-5.2)	0.4 (-5.7-6.5)
General health	NA	NA	NA	382	NA	-1.4 (-5.1-2.3)	-1.0 (-4.1-2.1)	-0.7 (-4.4-3.0)
Vitality	NA	NA	NA	382	NA	-1.7 (-5.6-2.1)	-2.3 (-5.9-1.3)	1.0 (-2.9-4.9)
Social functioning	NA	NA	NA	382	NA	-4.8 (-10.0-0.4)	-2.3 (-6.8-2.2)	-0.6 (-4.4-3.4)
Role-emotional	NA	NA	NA	382	NA	-4.0 (-12.8-4.8)	2.1 (-6.0-10.2)	-3.2 (-10.2-3.8)
Mental health	NA	NA	NA	382	NA	-1.1 (-4.5-2.4)	-0.5 (-3.7-2.7)	-0.4 (-3.3-2.6)

Baseline columns represent raw data. Difference in non-intervention arm minus RBC transfusion arm: differences in mean MFI score were adjusted for baseline value and mode of delivery, differences in mean SF-36 score were adjusted for mode of delivery.
NA = not applicable.
*$p < 0.05$. †$p < 0.01$.

Chapter 4.4

Prediction of escape red blood cell transfusion in expectantly managed women with acute anemia after postpartum hemorrhage

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Abstract

Objective
To determine clinical predictors of escape red blood cell (RBC) transfusion in postpartum anemic women, initially managed expectantly, and the additional predictive value of health-related quality of life (HRQoL) measures.

Design
Secondary analysis of women after postpartum hemorrhage, either randomly allocated to, or opting for expectant management.

Setting
Thirty-seven hospitals, the Netherlands.

Population
261 randomized and 362 non-randomized women.

Methods
We developed prediction models to assess the need for RBC transfusion: one using clinical variables (model 1), and one extended with scores on the HRQoL-measures Multidimensional Fatigue Inventory (MFI) and EuroQol-5D (model 2). Model performance was assessed by discrimination and calibration. Models were internally validated with bootstrapping techniques to correct for overfitting.

Main outcome measures
Escape RBC transfusion.

Results
Seventy-five women (12%) received escape RBC transfusion. Independent predictors of escape RBC transfusion (model 1) were primiparity, multiple pregnancy, total blood loss during delivery and hemoglobin concentration postpartum. Maternal age, body mass index, ethnicity, education, medical indication of pregnancy, mode of delivery, preterm delivery, placental removal, perineal laceration, Apgar score and breastfeeding intention had no predictive value. Addition of HRQoL-scores (model 2), significantly improved the model's discriminative ability: c-statistics of model 1 and 2 were 0.65 (95% CI: 0.58-0.72) and 0.72 (95% CI: 0.65-0.79), respectively. The calibration of both models was good.

Conclusions
In postpartum anemic women, several clinical variables predict the need for escape RBC transfusion. Adding HRQoL-scores improves model performance. After external validation, the extended model may be an important tool for counseling and decision making in clinical practice.

Introduction

Severe postpartum hemorrhage (PPH), defined as peripartum blood loss of at least 1000 mL,[1] is a common obstetric complication with a worldwide incidence of 1.9%.[2] An increase in incidence has been described in several developed countries.[4-6,8-10,113] During the acute phase of postpartum hemorrhage, transfusion of blood components may be inevitable. After the acute phase, however, anemia can be treated by either red blood cell (RBC) transfusion or expectantly, using iron and/ or folic acid supplementation.

Recently, we performed a randomized trial comparing RBC transfusion with expectant management in acute anemic women, without severe anemic complaints, following PPH. This multicenter trial, the Well-being of Obstetric patients in Minimal Blood transfusions (WOMB) trial, hypothesized non-inferiority in physical fatigue, measured by validated health-related quality of life (HRQoL) questionnaires, of expectant management compared to RBC transfusion.[89] Although non-inferiority could not been proven, results of this trial demonstrate that RBC transfusion leads only to a small, probably clinical irrelevant improvement in physical fatigue. No differences were found in physical complications. Based on this trial, expectant management seems justified in an obstetric population and thus current standard care is to avoid RBC transfusion. However, 13% of randomized women in the expectant management arm of the WOMB trial received an escape RBC transfusion, mainly for anemic complaints.[88] Averting escape RBC transfusion would prevent unnecessary burden for the patient, as this changeable policy leads to commotion and possible readmission, and avoid higher costs. For these reasons, we believe that identification of those women with a very high probability of escape RBC transfusion would be useful and will prevent suboptimal health care in those women. It could also lead to a uniform policy and less uncertainty for both patient and physician when formulas would identify and diminish the probability of escape RBC transfusion. To avert escape RBC transfusion in postpartum anemic women, initially treated with expectant management, predictors need to be identified.

Data of the WOMB trial comprise clinical variables and scores on the HRQoL measures Multidimensional Fatigue Inventory (MFI) and EuroQol-5D. We hypothesized that, besides clinical variables, HRQoL-scores measured 12-24 hours postpartum have incremental value in the prediction of RBC transfusion. Therefore, two study aims were formulated: to investigate which combination of variables, available in daily clinical practice, predicts escape RBC transfusion (model 1) best and, whether HRQoL-scores have additional predictive value over these variables (model 2).

Methods

For this study, we used data from the WOMB trial, a multicenter randomized trial conducted in the Netherlands. In short, after informed consent, women with an acute anemia (Hb 4.8-7.9 g/dL [3.0-4.9 mmol/L]) after postpartum hemorrhage (blood loss of ≥ 1000 mL and/ or a decrease in Hb concentration of ≥ 1.9 g/dL [1.2 mmol/L]) were randomized between RBC transfusion and expectant management. Main outcomes were HRQoL-scores and physical complica-

tions up to six weeks postpartum. HRQoL-scores were measured at inclusion (12-24 hours after delivery) by two validated questionnaires: the MFI and the EuroQol-5D.[78,79] Women who declined randomization, were asked if they were willing to complete questionnaires. They were treated by RBC transfusion or expectant management based on their preference and at discretion of their physician. Non-randomized women were registered and had identical follow-up as randomized women. The design and results of the trial are presented elsewhere.[88,89] We used data of all randomized and non-randomized women in the expectant management arms. Thus, women who were initially treated with RBC transfusion were excluded. For this particular study, a study protocol was written and is available upon request.

Outcome

The outcome of the study was the need for escape RBC transfusion, which was defined as RBC transfusion prescribed secondarily within women randomized to expectant management and non-randomized women who chose expectant management. As follow-up in the trial lasted up to six weeks postpartum, all escape RBC transfusions up to six weeks postpartum were analyzed.

Candidate predictors

Based on clinical reasoning we selected candidate predictors that are available 12-24 hours after delivery and are readily available in daily clinical practice. Candidate predictors for model 1 were the following: maternal age, preconceptional body mass index (BMI), non-Western ethnicity, low maternal education, primiparity, multiple pregnancy, high-risk pregnancy, mode of delivery, preterm delivery, placenta removal, perineal laceration, Apgar score below 7 at 5 minutes, total blood loss, Hb concentration (12-24 hours after delivery) and intention to breastfeed.

Preconceptional BMI, determined at first pregnancy visit, was defined as the maternal weight in kilograms divided by the maternal height in meters squared. Non-Western ethnicity was assessed according to the definition of Statistics Netherlands in which the category 'Western' consists of persons from Europe (excluding Turkey), North America, Oceania, Japan and Indonesia (including the former Dutch East Indies).[90] None or preparatory vocational education was considered as low maternal education. Mode of delivery was registered as vaginal delivery (used as reference), elective cesarean section or emergency cesarean section. Preterm delivery was defined as gestational age less than 37 weeks at delivery. The following categories were analyzed: gestational age less than 34 weeks at delivery, gestational age of 34 to 37 weeks and no preterm delivery (gestational age of 37 weeks and/ or more; used as reference). Placenta removal was categorized in complete (no manual placental removal) or incomplete (manual placental removal directly postpartum). High-risk pregnancies are characterized by pre-existing maternal disease, complicated obstetric history, pregnancy and delivery.[24] Perineal laceration was defined episiotomy or at least second degree perineal rupture.

Additionally, the interaction of Hb concentration (12-24 hours after delivery) with total blood loss was investigated. On top of the identified candidate predictors of model 1, the following candidate predictors were considered for model 2: all subscales of the MFI, as well as the EurQol-5D index score and VAS score. See below

for a more extensive description of the HRQoL measures. As both randomized and non-randomized women were analyzed, the association of the randomization status with the outcome (escape RBC transfusion) was also investigated in both models.

HRQoL measures

The MFI and EuroQol-5D are validated HRQoL measures. The MFI is a 20-item self-report instrument designed to measure fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Each dimension is covered by four questions on a five-item scale. MFI scores range from 4 to 20 (20 represents maximal fatigue).[79] The MFI was developed as a tool to assess fatigue in a comprehensive way and provides information on the nature of the experience, and its intensity.

The EuroQol-5D is a standardized measure of health status and provides a simple, generic measure of health for clinical and economic appraisal. The questionnaire consists of a short questionnaire and a visual analogue scale (index score and VAS score, respectively). The index score is based on five questions on the items Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression, with a three-item scale (no problems, some problems, extreme problems). The VAS score represents the patient's value of their own health state (score 0-100, the higher the better). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.[78] The international standard HRQoL measures MFI and EuroQol-5D have been evaluated in a pilot study; feasibility, reliability, and validity of these measures in a clinical obstetric setting were established.[82]

Data analysis

Baseline characteristics were presented as raw data. These data were analyzed using descriptive statistics and presented as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables as appropriate, and as numbers and percentages of the whole population for categorical and dichotomous variables.

Various candidate predictors had missing values. Because these are often selectively missing, it is well documented that a complete case analysis likely yields biased results.[114-116] Hence, we used multiple imputation (10 times) to handle missing values (see also Appendix). The imputation model included all potential predictors and the outcome.

Univariable and multivariable logistic regression analyses were performed with escape RBC transfusion (yes/ no) as outcome measure to determine the association between the candidate predictors and the outcome. Maternal age, preconceptional BMI, Hb concentration (12-24 hours after delivery), total blood loss, MFI subscale scores and EuroQol-5D scores were analysed as continuous variables. For these, we assessed its association with the outcome (escape RBC transfusion) using cubic spline analyses.[117] Variables were transformed (e.g. using a log-transformation) or categorized when they showed non-linear association with escape RBC transfusion.

Although not generally recommended,[118] we performed a pre-selection based on the *p*

(< 0.10) in univariable analyses in order to retain a reasonable number of events per variable in the multivariable model.[119] The combination of predictors that best predicted escape RBC transfusion was obtained with a backward selection procedure using Akaike's Information Criterion.[120] As imputed data sets differ from each other, predictor selection was performed in each imputation set separately. For inclusion in the final prediction model, we used the majority method, i.e. predictors were included in the final model if selected in at least five out of ten imputed data sets.[121] The final model was applied to each imputation separately, and the regression coefficients and standard errors of these final predictors were combined from the ten data sets using Rubin's rules to come to the final prediction model.[122]

With each model development there is a chance of overfitting, meaning that the model is too strongly fit to the data on which it was developed and consequently may perform poorly when externally validated. To assess the degree of overfitting or optimism in this study, we internally validated the model using bootstrapping techniques. One hundred bootstrap samples were drawn from the original data set with replacement, allowing for multiple sampling of the same individual. Within each sample the entire modeling process, described above, was repeated. This yielded a shrinkage factor, with which the regression coefficients of the predictors were multiplied (uniformly shrunken) to correct the model for optimism and overfitting.[117] We developed two models. Model 1 was based on variables available in daily clinical practice (i.e. without HRQoL-scores). For model 2, the HRQoL-scores, with *p*-value < 0.10 in univariable analyses, were added to the first model. Again, the same procedure as described previously was used, including the backward stepwise selection, repetition in the imputed dataset separately, and correction for optisim using bootstrapping techniques.

Model performance was assessed using discrimination and calibration. Discrimination refers to the ability of the models to distinguish between those with and without escape RBC transfusion, and was assessed with the c-statistic. The c-statistic is similar to the area under the Receiver Operating Characteristic curve.[123] The c-statistic ranges from 0.5 (no discrimination) to a theoretical maximum of 1 (perfect discrimination) and models are typically considered reasonable when the c-statistic is higher than 0.7. Calibration refers to the agreement of predicted and observed predictions: e.g. is in a group of women with an average 70% predicted chance of the outcome the average observed proportion also 70%? In case of perfect calibration there is perfect agreement between predicted probabilities and observed proportions (45 degree line).[117,124,125] To investigate whether the HRQoL-scores had added value over the identified candidate predictors in model 1 for the prediction of escape RBC transfusion, we compared the c-statistics of model 1 and 2.[126] Additionally, we investigated whether the second model was able to better reclassify individuals using the continuous Net Reclassification Improvement (NRI(> 0)).[127-129] The NRI(> 0) was used instead of a general NRI, because there are currently no clearly defined prediction categories to identify individuals being at low, intermediate, or high risk for escape RBC transfusion.[130] This reclassification measure was investigated only when calibration of the models was good, since these measures tend to be less reli-

able when models calibrate poorly.[131] Furthermore, the following accuracy measures were assessed: sensitivity (or true positive rate), specificity, positive predictive value, negative predictive value, and false positive rate. Since no clear relevant cut off value exists, these measures were presented for different cut off values based on the deciles of the predicted probabilities.

Data were analyzed using *R* version 3.0.1 (The R Foundation for Statistical Computing, 2013).

Results

Between May 2004 and February 2011, 624 women entered the study in the expectant management arms; 262 randomized and 362 non-randomized (***Figure 1***). One randomized woman did not fulfil inclusion criteria and was excluded, resulting in 623 women analyzed. Baseline characteristics of all women are presented in ***Table 1***. No significant differences were found between randomized and non-randomized women expect for ethnicity (non-Western ethnicity in 24 versus 16% respectively, $p = 0.037$). Among randomized women, 33 (13%) received escape RBC transfusion while 42 non-randomized women (11%) received escape RBC transfusion. Indications reported were retained products of conception, secondary PPH or infections in 5% while in 14% the cause was unknown. About 80% of women who received escape RBC transfusion reported anaemic complaints as primary cause, while 29% of these women also had another indication. Escape RBC transfusion was given at a median of 2 days (interquartile range of 1-3 days) while 95% percent was prescribed within 14 days after delivery. Among women with escape RBC transfusion the median physical fatigue score was 2 points higher (worse) than in women without escape RBC transfusion (***Table 1***). Results for other MFI subscales were similar. Likewise, women with escape RBC transfusion scored worse on the EuroQol-5D.

The cubic spine analyses demonstrated a linear correlation association between the outcome (i.e., escape RBC transfusion) and Hb concentration (12-24 hours after delivery), all MFI subscale scores and the EuroQol-5D VAS. No linear association with the outcome was found for the following variables, therefore, these were categorized: maternal age (< 36, ≥ 36 years), preconceptional BMI (≤ 25, > 25), total blood loss (≤ 1500 mL, > 1500 mL) and the EuroQol-5D index score (< 0.88, ≥ 0.88).[132]

Univariable and multivariable analyses

Predictors related to the outcome in univariable analysis were primiparity, multiple pregnancy, complicated obstetric history, total blood loss > 1500 mL, Hb concentration (12-24 hours after delivery) and MFI subscales general fatigue, physical fatigue, reduced motivation and mental fatigue and EuroQol-5D VAS score (***Table 1***). As no interaction was found for Hb concentration (12-24 hours after delivery) and total blood loss, this interaction term was not considered a candidate predictor for the multivariable models.

The multivariable analysis identified four clinical variables that independently predict escape RBC transfusion (model 1): primiparity, multiple pregnancy, total blood loss

Table 1 *Characteristics of the study population and the univariable association between potential predictors and the need for escape RBC transfusion.*

	Total	Escape RBC transfusion		Univariable association	
	n = 623	Yes n = 75	No n = 548	OR (95% CI)	*p*
Clinical variables					
Participation, non-randomized	362 (58%)	42 (56%)	320 (58%)	0.91 (0.56-1.47)	0.69
Age (years), ≥ 36 years[a]	107 (17%)	10 (13%)	97 (18%)	0.728 (0.39-1.34)	0.31
Preconceptional body mass index > 25[b]	145 (26%)	17 (23%)	128 (26%)	0.992 (0.59-1.68)	0.98
Ethnic origin: non-Western[c]	104 (19%)	12 (18%)	92 (20%)	1.18 (0.62-2.26)	0.60
Highest education[d]					
none – preparatory vocational education	82 (24%)	5 (14%)	77 (25%)	0.765 (0.32-1.85)	0.38
Primiparity[e]	350 (56%)	50 (67%)	300 (55%)	1.653 (0.99-2.75)	0.05
Multiplet pregnancies[e]	34 (6%)	9 (12%)	25 (5%)	2.85 (1.28-6.37)	0.01
Medical indication[f]					
pre-existent disease	47 (8%)	4 (6%)	43 (8%)	0.691 (0.24-1.98)	0.48
obstetric history	112 (19%)	8 (12%)	104 (20%)	0.52 (0.24-1.11)	0.08
pregnancy	220 (37%)	30 (44%)	190 (37%)	1.39 (0.83-2.32)	0.19
delivery	301 (51%)	35 (51%)	266 (51%)	0.93 (0.56-1.54)	0.76
Mode of delivery[e]					
Elective CS	38 (6%)	5 (7%)	33 (6%)	1.266 (0.42-3.81)	0.67
Emergency CS	87 (14%)	14 (19%)	73 (13%)	0.836 (0.31-2.23)	0.72
Preterm delivery (weeks)[e]					
34-37 weeks	43 (7%)	3 (4%)	40 (7%)	0.52 (0.16-1.74)	0.29
< 34 weeks	29 (5%)	3 (4%)	26 (5%)	0.81 (0.24-2.73)	0.73
Placenta: incomplete[g]	162 (28%)	17 (25%)	145 (28%)	1.050 (0.62-1.77)	0.85
Perineal laceration: > 1st degree[h]	384 (62%)	44 (59%)	340 (62%)	0.86 (0.53-1.41)	0.56
Apgar 5 minutes < 7[i]	11 (2%)	2 (3%)	9 (2%)	1.641 (0.35-7.74)	0.53
Total blood loss > 1500 mL[e]	244 (39%)	39 (52%)	205 (38%)	1.792 (1.10-2.91)	0.02
Hb concentration 12-24h after delivery (g/dL)[e]	7.4 (6.8-7.7)	6.4 (6.6-7.6)	7.4 (6.9-7.7)	0.38 (0.25-0.59)	< 0.001
No intention to breastfeed[j]	138 (22%)	15 (21%)	123 (23%)	0.87 (0.48-1.57)	0.64
HRQoL-score					
Multidimensional Fatigue Inventory					
general fatigue	17 (14-19)	19 (17-20)	17 (14-19)	1.14 (1.01-1.29)	0.003
physical fatigue	17 (14-20)	19 (17-20)	17 (14-19)	1.16 (1.04-1.28)	0.001
reduced activity	16 (14-19)	18 (14-19)	16 (14-19)	1.06 (0.97-1.16)	0.14
reduced motivation	12 (9-16)	15 (11-18)	12 (9-16)	1.07 (0.98-1.18)	0.02
mental fatigue	11 (8-15)	12 (10-17)	11 (8-15)	1.05 (0.98-1.11)	0.02
EuroQol-5D					
index score < 0.88[k]	0.43 (0.24-0.78)	0.31 (0.10-0.78)	0.43 (0.30-0.78)	0.86 (0.38-1.93)	0.67
VAS score	60 (45-65)	50 (40-60)	60 (46-69)	0.98 (0.96-1.00)	0.005

Odds ratios for dichotomous and categorical variables are presented in relation to the reference category. Hb concentration and HRQoL scores are presented as median (IQR). CS = cesarean section. [a]Total n = 618 (99%). [b]Total n = 556 (89%). [c]Total n = 536 (86%). [d]Total n = 349 (56%). [e]Total n = 623 (100%). [f]Total n = 588 (94%). [g]Total n = 587 (94%). [h]Total n = 622 (100%). [i]Total n = 613 (98%). [j]Total n = 600 (96%). [k]0.88 is the Dutch reference score.[132]

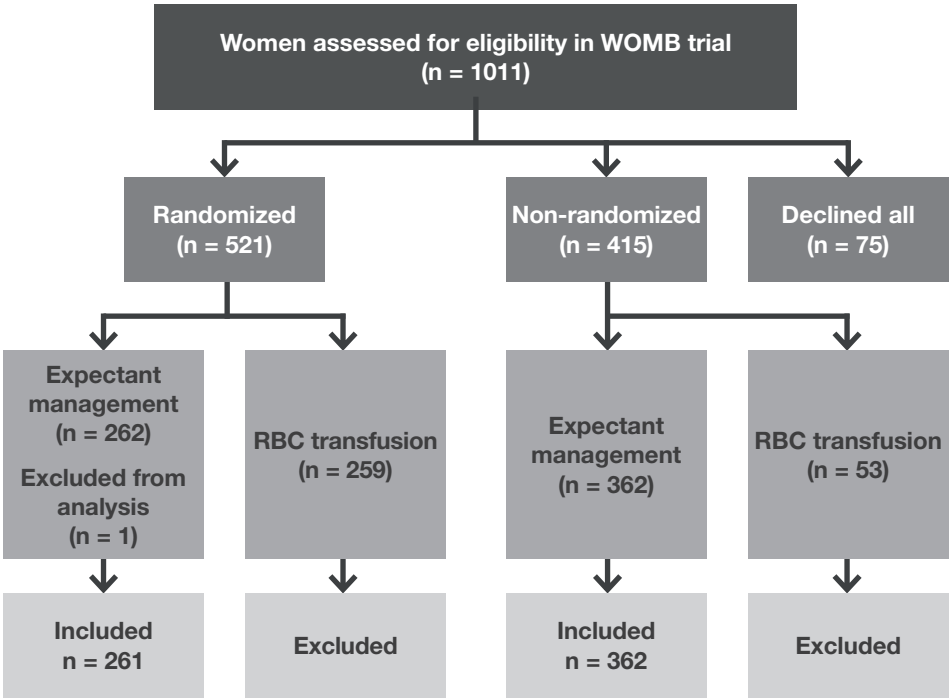

Figure 1 *Flowchart of the WOMB trial and women included in this study.*

> 1500 mL and Hb concentration (12-24 hours postpartum) (*Table 2*). Addition of HRQoL-scores as predictors to model 1 yielded that, in addition to predictors revealed in model 1, the MFI subscales physical fatigue, reduced activity and reduced motivation, and the EuroQol-5D VAS score were independent predictors of escape RBC transfusion (model 2) (*Table 2*).

For model 1, internal validation showed good calibration (*Figure 2*) and a moderate discriminative ability with a c-statistic of 0.65 (95% CI: 0.58-0.72). The predicted probabilities ranged from 4.5% to 59.1%.

Model 2 showed good calibration (*Figure 3*) and an improved discriminative performance as compared to model 1 with a c-statistic of 0.72 (95% CI: 0.65-0.79), $p = 0.008$. The predicted probabilities ranged from 0.9% to 55.7%.

Apart from the statistically significant higher c-statistic, also the NRI(> 0) showed a significant difference in classification between the two model (0.39 (95% CI: 0.15-0.63; $p < 0.0015$)). These results suggest that including HRQoL-scores in the model led to a significant improvement of model performance. The sensitivity and specificity of both models for different for different cut off values of the predicted risk are presented in *Table 3*.

Table 2 *Multivariable associations for model 1 (clinical variables) and model 2 (both clinical variables and HRQoL-scores).*

	Model 1		Model 2	
	Beta[a]	OR (95% CI)	Beta[b]	OR (95% CI)
Intercept	2.15		1.38	
Clinical variable				
Primiparity	0.48	1.61 (0.95-2.72)	0.43	1.54 (0.90-2.64)
Multiplet pregnancy	0.92	2.51 (1.07-5.91)	0.71	2.03 (0.83-4.95)
Total blood loss > 1500 mL	0.44	1.55 (0.93-2.58)	0.46	1.58 (0.93-2.67)
Hb concentration 12-24h postpartum (g/dL)	-0.66	0.52 (0.35-0.77)	-0.63	0.53 (0.35-0.80)
HRQoL-score				
MFI subscale physical fatigue			0.12	1.13 (0.99-1.29)
MFI subscale reduced activity			-0.08	0.92 (0.81-1.04)
MFI subscale reduced motivation			0.03	1.03 (0.93-1.14)
EuroQol-5D VAS score			-0.01	0.99 (0.97-1.01)

[a]Shrunken with an average shrinkage factor of 0.88
[b]Shrunken with an average shrinkage factor of 0.82

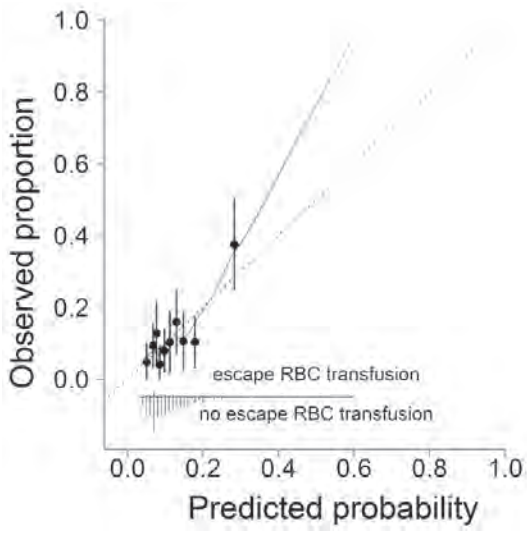

Figure 2 *Calibration plot of Model 1 with the observed risk of escape RBC transfusion by predicted probabilities.*

The dots indicate deciles of women grouped by similar predicted risk of escape RBC transfusion. The vertical bars through the dots indicate the 95% confidence interval of the observed risks for the grouped women.

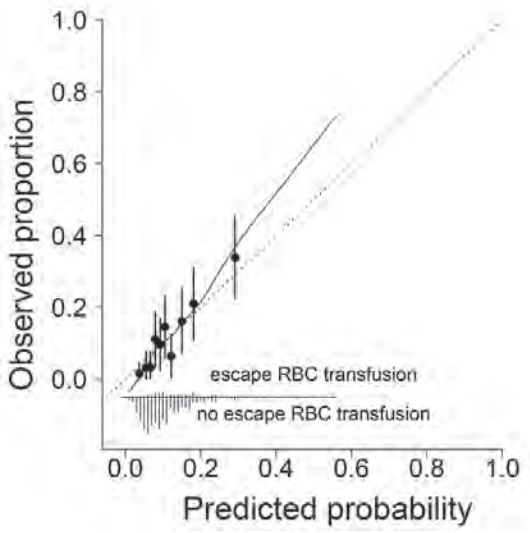

Figure 3 *Calibration plot of Model 2 with the observed risk of escape RBC transfusion by predicted probabilities.*

The dots indicate deciles of women grouped by similar predicted risk of escape RBC transfusion. The vertical bars through the dots indicate the 95% confidence interval of the observed risks for the grouped women.

Table 3 *Accuracy measures (%) for different cut off values of the predicted risk.*

Cut off value	Sens	Spec	PPV	NPV	TPR	FPR
Model 1						
> 10%	72.0	50.1	16.5	92.9	72.0	49.9
> 20%	30.7	92.0	34.3	90.6	30.7	8.0
> 30%	12.0	98.9	60.0	89.1	12.0	1.1
> 40%	8.0	99.5	66.7	88.8	8.0	0.5
> 50%	2.7	100.0	100.0	88.2	2.7	0.0
> 60%	NA	NA	NA	NA	NA	NA
> 70%	NA	NA	NA	NA	NA	NA
> 80%	NA	NA	NA	NA	NA	NA
> 90%	NA	NA	NA	NA	NA	NA
Model 2						
> 10%	77.1	54.6	18.8	94.6	77.1	45.4
> 20%	30.4	90.7	30.9	90.5	30.4	9.3
> 30%	16.8	98.4	59.2	89.6	16.8	1.6
> 40%	7.1	99.3	58.9	88.6	7.1	0.7
> 50%	3.7	99.8	71.8	88.3	3.7	0.2
> 60%	0.3	100.0	100.0	88.0	0.3	0.0
> 70%	NA	NA	NA	NA	NA	NA
> 80%	NA	NA	NA	NA	NA	NA
> 90%	NA	NA	NA	NA	NA	NA

Sens = sensitivity. Spec = specificity. PPV = positive predictive value. NPV = negative predictive value. TPR = true positive rate (or sensitivity). FPR = false positive rate. NA = not applicable.

Implications for daily clinical practice
In expectantly managed women with acute anaemia after postpartum haemorrhage, the clinical variables primiparity, multiple pregnancy, total blood loss and Hb concentration (12-24 hours postpartum) influenced the probability of the need of an escape RBC transfusion. The probability was enhanced in case of primiparity, multiple pregnancy and total blood loss > 1500 mL while a higher Hb concentration reduced this probability.

Addition of the following HRQoL measures improved the prediction of RBC transfusion in expectantly managed women: MFI subscale physical fatigue, MFI subscale reduced activity, MFI subscale reduced motivation and the EuroQol-5D VAS score. In case of higher physical fatigue and less motivation the probability of escape RBC transfusion was enhanced while the probability was diminished in case of a poorer score on reduced activity and a better EuroQol-5D VAS score (e.g. better well-being).

The predicted chance for escape transfusion using model 1 can be calculated for an anemic woman after postpartum hemorrhage using the following formula: Predicted chance = 1 / (1 + exp (-(2.15-0.48*primiparity + 0.92*multiple pregnancy + 0.44*total blood loss > 1500 mL - 0.66*Hb concentration))).

This predicted chance for escape transfusion using model 2 can be calculated using the following formula: Predicted chance = 1 / (1 + exp (-(1.38-0.43*primiparity + 0.71*multiple pregnancy + 0.46*total blood loss > 1500 mL - 0.63*Hb concentration + 0.12*MFI subscale physical fatigue – 0.08* MFI subscale reduced activity + 0.03*MFI subscale reduced motivation - 0.01*EurQol-5D VAS score))).

In both formulas, the woman's value of each continuous variable (Hb concentration, all MFI subscales and the EuroQol-5D VAS score) can be used. For the categorical variables (primiparity [reference: multiparity], multiple pregnancy [reference: singleton pregnancy] and total blood loss [reference: ≤ 1500 mL]), the value '0' should be used in case the patient belongs to the reference category and '1' in case she belongs to the non-reference category.

Discussion

Main findings
In this study, we developed two models to predict the need for escape RBC transfusion in anemic women (without severe anemic complaints) after postpartum hemorrhage, treated with expectant management. In model 1, the clinical variables parity, multiple pregnancy, total blood loss and Hb concentration (12-24 hours after delivery) were associated with escape RBC transfusion. The predictive value of HRQoL-scores was evaluated in model 2 by adding these scores to model 1.

Model 2 had significantly better discriminative ability according to the c-statistic (0.72 for model 2 and 0.65 for model 1) and NRI(> 0), indicating that HRQoL-scores have additional value over clinical variables in the prediction of escape RBC transfusion.

Our study aimed to predict the need for escape RBC transfusion in postpartum anemic women treated with expectant man-

agement. Predictive variables of (massive) RBC transfusion were previously identified in trauma patients[133-138] and in patients undergoing orthopedic surgery,[139-142] cardiac surgery,[143-146] liver transplantation,[147-150] or liver surgery.[151,152] In these studies, identified predictors for (massive) transfusion included age, gender, weight, heart rate, blood pressure, preoperative Hb or Ht concentration, platelet concentration, creatinine concentration, base deficit, surgical time and thrombo-elastography. Only one study has been performed on prediction of RBC transfusion in the obstetric field. This study inventoried RBC transfusion requirements in women with placenta accreta undergoing cesarean section and reported no relation between RBC transfusion requirements and laboratory values.[153] No previous study investigated predictors of the need for escape RBC transfusion in anemic postpartum patients, managed expectantly.

Limitations/ strengths

We present predictors for escape RBC transfusion identified in anemic postpartum women. Results are based on data obtained in a randomized trial. As all patients allocated to RBC transfusion in the trial were excluded, allocation status was not taken into account. We have demonstrated that participation status (e.g. whether women were included in the trial as randomized or non-randomized women) was no predictor for escape RBC transfusion. An advantage of these data is the prospectively collection in 37 hospitals, strengthening external validation and generalization of results.

Since we focussed on the prediction of escape RBC transfusion using clinical information available at 12-24 hours after delivery we did not account for all known causes of escape RBC transfusions. For example, secondary postpartum hemorrhage, infections and retained products of conception are known to be associated with escape RBC transfusion, but are not available within 12-24 hours after delivery. Therefore, at the time point 12-24 hours after delivery, it is impossible to predict all escape RBC transfusions: in this study 14 (19%) of the women who received escape RBC transfusion were reported to have suffered from secondary postpartum hemorrhage, (treatment for) retained products of conception or infections (e.g. endometritis, urinary tract infection or fever without known cause). Anemic complaints were reported as only cause in 50 (67%), while the reason for escape RBC transfusion was unknown in 11 (14%).

The identified predictors were internally validated by bootstrapping techniques. External validation is needed to investigate the performance of the models in other populations before the models can be integrated in daily clinical practice, especially since postpartum hemorrhage incidences vary across countries and even across regions.[2,22,113] All variables of model 1 are readily available in daily clinical practice in contrary to the HRQoL-scores identified in model 2. As the predictive value of model 2 was significantly better than that of model 1, we believe that once the model is externally validated, use of HRQoL measures in postpartum anemic women should be implemented to improve postpartum health care and complement clinical decision making. We are aware that RBC transfusion rates and protocols may differ from center to center and from provider to provider, e.g. by age, experience and years out of training. An obvious way to include these differences would be to account for centers in a multilevel regression model.

Therefore, center effects were investigated using a logistic multilevel model of model 2 whereby we fitted a random intercept per center. This analysis showed that the random intercepts of the different centers were not significantly different from zero for all centers, suggesting there is no need to account for differences between centers.

Interpretation

Model 1 demonstrated that escape RBC transfusion is more likely in primiparous women, after multiple pregnancy, in case of total blood loss above 1500 mL and less likely in case of a higher Hb concentration. These findings were expected: both primiparous as women giving birth to multiples may experience more difficulties coping with the new situation after giving birth, possibly altering the need for escape RBC transfusion. Also, a higher need for escape RBC transfusion could be expected based on higher total blood loss and lower Hb concentration (12-24 hours after delivery).

Model 2 showed that escape RBC transfusion is more likely in women with higher physical fatigue and less motivation while it was less likely in case of a poorer score on reduced activity and better EuroQol-5D VAS score (e.g. better well-being). Of these findings, results on the subscales physical fatigue and reduced motivation were expected, in contrary to findings regarding the MFI subscale reduced activity and the EuroQol-5D VAS score. In case of higher reduced activity score (worse HRQoL), the chance at escape RBC transfusion decreases while the contrary was to be expected. A possible explanation for this finding is that less active women might experience fewer anemic complaints. The EuroQol-5D VAS had a beta of -0.01 and an OR of 0.99, implying low to no clinical relevance.

The estimated probability of escape RBC transfusion ranged from 0.9 to 55.7% for model 2. Given that the incidence of escape RBC transfusion in the entire study population was 12%, this range of probabilities indicates that the model may be of high value in daily clinical practice. Both prediction models provide the ability to make informed choice for all postpartum anemic women following postpartum hemorrhage, whereas this was previously not possible. Identification of women with either a very low or very high risk of escape RBC transfusion may greatly improve counseling of these patients and clinical decision making. In daily clinical practice, considering risk at adverse events and costs, an unnecessarily prescribed RBC transfusion is worse than an escape RBC transfusion. While the chance of escape RBC transfusion is 12% in case of expectant policy, the clinician wants to be rather specific than sensitive in the decision to prescribe RBC transfusion directly postpartum.

Conclusion

Independently clinical predictors of escape RBC transfusion in women following postpartum hemorrhage, initially treated by expectant management, are primiparity, multiple pregnancy, blood loss > 1500 mL and lower Hb concentration (12-24 hours after delivery). Use of the MFI subscales physical fatigue, reduced activity and reduced motivation and the EuroQol-5D VAS score significantly improve prediction of escape RBC transfusion in these women.

After external validation and proof of generalizability, our formulas predicting escape RBC transfusion may be of great value in obstetric daily clinical practice and use of HRQoL measures should be implemented.

Chapter 4.5

Cost-effectiveness of red blood cell transfusion versus non-intervention in women with acute anemia after postpartum hemorrhage

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Abstract

Background

Red blood cell (RBC) transfusion is frequently used to treat women with acute anemia after postpartum hemorrhage. We aimed to assess the economic consequences of RBC transfusion compared to non-intervention in these women.

Methods

A trial-based cost-effectiveness analysis was performed alongside the 'Well-Being of Obstetric patients on Minimal Blood transfusions' (WOMB) trial. Women with acute anemia (hemoglobin 4.8 to 7.9 g/dL [3.0 to 4.9 mmol/L]) after postpartum hemorrhage, without severe anemic symptoms, were randomly allocated to RBC transfusion or non-intervention. Primary outcome of the trial was physical fatigue (Multidimensional Fatigue Inventory, scale 4 to 20; 20 represents maximal fatigue). Total costs per arm were calculated using a hospital perspective with a six weeks time horizon.

Results

Per woman, mean costs in the RBC transfusion arm (n = 258) were €1957 compared to €1708 in the non-intervention arm (n = 261) (p = 0.024). The 13% difference in costs between study arms predominantly originated from costs of RBC units, as costs of RBC units were six times higher in the RBC transfusion arm. RBC transfusion led to a small improvement in physical fatigue of 0.58 points per day, thus, the costs to improve the physical fatigue score with one point would be €431.

Conclusion

In women with acute anemia after PPH, RBC transfusion is on average €249 more expensive per woman than non-intervention, with only a small gain in health-related quality of life after RBC transfusion. Taking both clinical and economic consequences into account, implementation of a non-intervention policy seems justified.

Introduction

The use of blood components imposes a substantial economic burden and can generate (severe) adverse events.[94] Severe postpartum hemorrhage (PPH), defined as blood loss of at least 1000 mL during delivery,[1] complicates 1.9% of all deliveries worldwide[2] and represents the most important cause of acute anemia postpartum. PPH is commonly treated by red blood cell (RBC) transfusion.[67] Following the acute phase of PPH, however, the effectiveness of RBC transfusion policy remains controversial and a wide variation in daily clinical practice exists. We recently performed a randomized controlled trial on the effectiveness of RBC transfusion in women with acute anemia after PPH: the 'Well-being of Obstetric patients on Minimal Blood transfusions' (WOMB) trial.

In that trial, we found that RBC transfusion led to a small improvement in physical fatigue scores while physical complications were comparable between both study arms.[88] Since the benefit of RBC transfusion on physical fatigue was only small, insight in the costs contributes to the decision for transfusion or no transfusion. At present, evidence on costs and cost-effectiveness of management of women with acute anemia after PPH is limited. In this paper, we report on the results of the economic evaluation that we conducted alongside the WOMB trial. This cost-effectiveness analysis compares direct costs of RBC transfusion with non-intervention in women with acute anemia after PPH.

Materials and methods

Population

This cost-effectiveness analysis was linked to the WOMB trial. Full details of the WOMB trial were reported previously.[89] The trial was approved by the University of Rotterdam's Institutional Review Board (MEC-2003-247), and had local approval from the boards of all participating hospitals. The trial has been registered at ClinicalTrials.gov as NCT00335023.

In short, the study was a multicenter non-inferiority randomized trial conducted from 2004 to 2011 in 37 hospitals in the Netherlands (*Appendix S1*). Women with acute anemia, defined as a hemoglobin (Hb) concentration between 4.8 and 7.9 g/dL (3.0 to 4.9 mmol/L), after PPH were allocated to either RBC transfusion or non-intervention. In women allocated to RBC transfusion, the target was to transfuse up to an Hb concentration of at least 8.9 g/dL (5.5 mmol/L). In the non-intervention arm, the use of iron and/ or folic acid supplementation according to local protocol was allowed and a RBC transfusion was prescribed only if clinically indicated. Women who declined randomization, but gave authorization for use of their medical records, were treated according to one of the two protocols at the discretion of the attending obstetrician. Data of these non-randomized women were registered to compare them with data of randomized women.

We used internationally validated health-related quality of life (HRQoL) measures, among which the Multidimensional Fatigue Inventory (MFI) and the EuroQol-5D. The MFI is a domain-specific measure for physical and mental fatigue with five dimensions:

general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. MFI scores range from 4 to 20 (20 represents maximal fatigue). The EuroQol-5D is a generic questionnaire consisting of a short questionnaire (index score) and a visual analogue scale (VAS), that represents the patient's value of their own health state (score 0-100, 100 represents best health state). All measures were completed at inclusion (12-24 hours after delivery) and 3 days, 1 week, 3 weeks and 6 weeks postpartum.

The primary outcome of this trial was physical fatigue three days postpartum, measured by the MFI. Secondary outcomes were remaining HRQoL scores, transfusion reactions, and physical complications until six weeks postpartum. The pre-specified non-inferiority boundary of physical fatigue was 1.3 and had been determined based on results of a pilot study.[154] Five hundred women had to be randomized to exclude such a difference.

Economic evaluation

A cost-effectiveness analysis was performed alongside the trial, using a hospital perspective and a time horizon from 12-24 hours postpartum to six weeks postpartum. For analyses, all unit costs were calculated in 2011 Euros, as 2011 was the last year in which the trial was conducted. Costs were than updated to 2013 using the consumer pricing index.

Resource use and unit costs

Health care utilization was documented in the Case Record Form. The following items were collected: length of hospital stay in days, readmission in days, daycare, visits outpatients clinic, phone consultation, units of RBC transfused, consultation of other medical specialists, iron and folic acid supplementation (daily dose and duration) and physical complications until six weeks postpartum.

Costs associated with health care utilization were calculated by multiplying volumes of resource use by unit costs of that item. A gross costing method was used to estimate costs.

Unit costs were estimated using the Dutch Costing manual,[155] standardized prices[156] and tariffs and data from the financial department of the Erasmus MC. Prices derived from the Dutch Costing manual[155] were used for costs of admission, readmission, daycare, outpatient clinic visits and phone consultations, estimated costs for laboratory use[156] were added to costs for (re)admission and outpatient clinic visits, as costs for specialist care[155] and medical surgeries[156] were added to daycare costs.[155] Standardized prices[156] were used for costs of consultations of other medical specialists and medical surgeries. RBC transfusion costs were calculated by using the bottom-up method as described in the Dutch costing manual:[155] costs for nursing hours and laboratory were added to transfusion costs. The number of nursing hours was estimated based on a protocol for nurses made available by the obstetric department of the Erasmus MC. The number of laboratory tests after RBC transfusions depended on the number of packed cells. The hourly cost of nurses was derived from Dutch costing manual.[155] Costs for iron supplementation were based on medicine prices derived from the Dutch website for costs of medication, Medicijnkosten.nl.[157] In case of a missing daily dose and/ or duration of iron supplementation, we imputed the mean of the specific study arm.

In case iron supplementation was administered at the hospital, nursing hours were added (as with RBC transfusion). Use for folic acid supplementation was estimated to be 0.5 mg daily.[158] Costs were based on those from Medicijnkosten.nl.[157]

Considering complications: costs for thromboembolic events or pulmonary embolisms were derived from Dutch standardized prices.[156] Costs for infections (wound infections, urinary tract infections, endometritis, fever without known cause, pneumonia and mastitis) were based on estimated use of antibiotics: prices for medication were based on those from Medicijnkosten.nl.[157] Please note that costs for (re)admission, outpatient visits, consultations of medical specialists and phone consultations were not included in the costs per complication and thus were calculated separately. Estimates for direct costs of postpartum depression were made available by the financial department of the Erasmus MC. Costs for retained products of conception were based on estimated medication use and costs[157] while operative removal costs were based on Dutch standardized prices.[156] Costs of the remaining complications (urinary tract infection, endometritis, fever without known cause, pneumonia and mastitis with admission) were calculated bottom-up by adding costs for medication[157] and estimated laboratory[156] to costs for (re)admission days.

In case of missing data regarding admission days (n = 7), we imputed the mean number of days of that specific study arm. With respect to a missing daily dose and/ or duration of iron supplementation, we imputed the mean of the specific study arm. Details regarding use of folic acid supplementation were inaccurately registered and therefore daily dose and duration according to protocol were used to estimate costs.

Statistical analysis

Normality of data was determined using the Shapiro-Wilk's test and visual assessment. Categorical data are presented as numbers with percentages, and numerical data are presented as means ± SDs (normally distributed) or medians with IQRs (not normally distributed). Unit and total costs are presented in means as well as in medians: as data are not normally distributed, medians represent the best average. However, in cost-effectiveness analyses means are used for more extended calculations as these results are more trustworthy than calculations performed with medians. As we intended to present the most accurate average but also used means for further calculations, we chose to present both. Mean costs per woman for each study arm and mean differences in costs between study arms were estimated. The 95% confidence intervals around the costs were determined by bootstrapping. HRQoL figures were created using raw data for baseline HRQoL values and estimated means, after adjustment for baseline and mode of delivery (Repeated Measurements ANOVA), for all other time points. Cost-effectiveness was expressed as differences in HRQoL scores (physical fatigue, EuroQol-5D index score and EuroQol-5D VAS score) between study arms, per day: we calculated the difference in area under the curve of each HRQoL score between study arms and divided this difference by amount of days, using the time horizon of 42 days. For calculation of the area under the curve we used raw data for baseline HRQoL values and estimated means, after adjustment for baseline and mode of delivery (Repeated Measurements ANOVA), for all other time

points. Robustness of the findings to unit cost estimates were evaluated in sensitivity analyses. We created tornado diagrams to investigate and illustrate sensitivity of results, varying those costs with the highest impact on total costs per woman by 50%. Statistical, economic and sensitivity analyses were performed using SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2007.

Results

For the cost analysis, data of all 521 randomized women were available; 259 had been allocated to RBC transfusion and 262 to non-intervention. In both arms one woman was excluded because she did not meet inclusion criteria. Baseline characteristics of all women included in analyses are demonstrated in *Table 1*. Baseline characteristics of women that declined informed consent though participated as non-randomized women, were previously presented. Compared to randomized women, these women were less often of Western ethnicity.[88]

A summary of the trial results is provided in *Table 2*. The most notable differences in outcome between study arms were obviously present in the use of RBC units. As expected, a significant higher percentage of women in the non-intervention arm crossed over: 13% of women in the non-intervention arm received RBC units during follow-up. Also, the rate of readmission was higher among women allocated to non-intervention. Physical complications were comparable between study arms. *Figure 1* shows HRQoL scores. The difference in physical fatigue score between study arms, adjusted for baseline and mode of delivery, was significant at day 3 and 1 week postpartum; while a significant difference in estimated EuroQol-5D index score was found at day 3 postpartum. No significant differences were found for the EuroQol-5D VAS score.

Costs

Units of resource use and unit costs are presented in *Table 3*; the mean and median costs per resource volume per woman are presented in *Table 4*. Mean costs of women allocated to non-intervention were €1708 (95% CI: €1546 - €1889) compared to €1957 (95% CI: €1835 - €2094) in women allocated to RBC transfusion ($p = 0.024$). Largest differences between study arms were found for costs of RBC transfusion while costs of readmission also differed.

HRQoL and cost-effectiveness

Investigating the difference in HRQoL scores per day between RBC transfusion and non-intervention (see Statistical Analysis), we found that physical fatigue score (scale 4-20, 20 represents maximal fatigue) was 0.58 points/day lower in the transfusion arm than in the non-intervention arm. The EuroQol-5D index score (scale 0-100, represents best health state) was 3.6 points/day higher in the RBC transfusion arm. The EuroQol-5D VAS score (scale 0-100, 100 represents best health state) was 1.3 points/day higher in the transfusion arms. The total price to improve HRQoL per day to this extent was €250. Thus, improvement of physical fatigue with one point costs €431.

Table 1 *Basic characteristics.*

	Non-intervention (n = 261)	Transfusion (n = 258)
Variable		
Age (years), mean ± SD	30.9 ± 5.3	30.7 ± 5.0
Preconceptional body mass index[a]	22.9 (20.8 to 26.5)	23.3 (21.1 to 26.6)
Western ethnic origin[b]	177 (76%)	186 (78%)
Highest education[c]		
none/ primary school	5 (3%)	4 (3%)
lower/ senior secondary vocational education	77 (51%)	88 (56%)
higher professional education and university	70 (46%)	64 (41%)
Primiparous	143 (55%)	152 (59%)
Mode of delivery		
vaginal	206 (79%)	213 (83%)
elective CS	15 (6%)	8 (3%)
emergency CS	40 (15%)	37 (14%)
Twin pregnancies	16 (6%)	13 (5%)
Gestational age (weeks+days)	40+0 (38+3 to 41+0)	40+1 (38+5 to 41+1)
Birth weight neonate[d]		
< 10th percentile	20 (8%)	8 (3%)
10 ≤ percentile ≤ 90	189 (74%)	188 (75%)
> 90st percentile	47 (18%)	54 (22%)
Estimated blood loss during delivery (mL)	1500 (1000, 1975)	1485 (1000, 1950)
Hb concentration at inclusion (g/dL)	7.4 (6.8 to 7.7)	7.3 (6.8 to 7.7)

Median (IQR) presented unless otherwise specified. CS = cesarean section. [a]n = 234 and n = 232 respectively. [b]n = 232 and n = 239 respectively. [c]n = 152 and n = 156 respectively. [d]n = 256 and n = 250 respectively.

Sensitivity analysis

In *Figure 2* the sensitivity analysis is illustrated. Altering admission costs had the largest influence on total costs: if the admission costs are decreased or increased with 50%, total costs would range from €666 to €1372. By halving or doubling RBC transfusion costs, total costs ranged from respectively €931 to €1107. Altering prices of costs by 25% would lead to similar ranking of deviation in total costs. By decreasing or increasing admission costs with 25%, total costs would range from €842 to €1196 while altering transfusion costs with 25% would lead to total costs ranging from €975 to €1064.

Additional analyses

The majority of women had Hb concentrations 12-24 hours after delivery in relatively higher ranges. A subgroup analysis was performed to investigate the total costs per woman for each Hb concentration (12-24 hours after delivery) quartile. Median costs for the quartiles Hb concentration < 6.8 g/dL, 6.8-7.2 g/dL, 7.3-7.7 g/dL and > 7.7 g/dL were for the non-intervention arm €1417, €1114, €1193 and €1617, respectively, and for the RBC transfusion arm respectively €1790, €1651, €1651 and €1769.

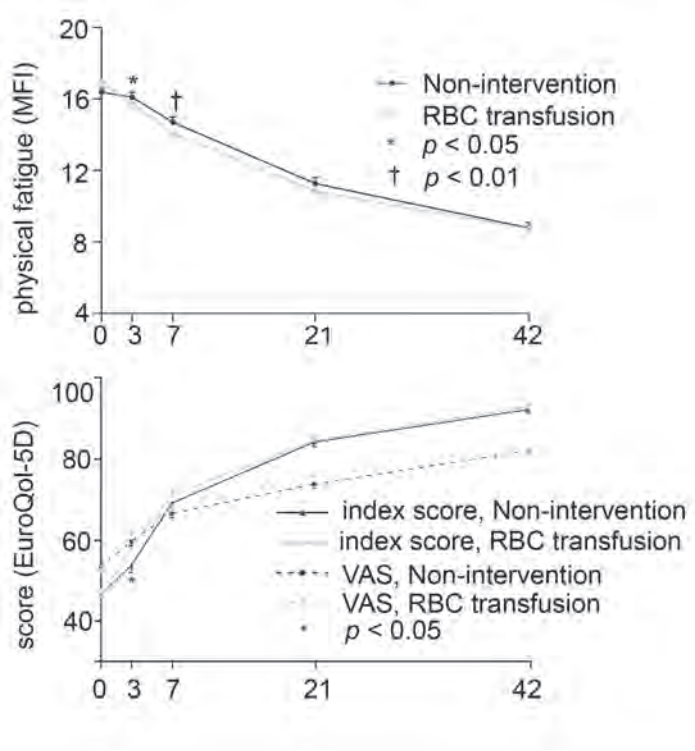

Figure 1 *The HRQoL scores physical fatigue (A) and EuroQol-5D (EuroQol-5D index score and VAS) (B) during follow-up.*

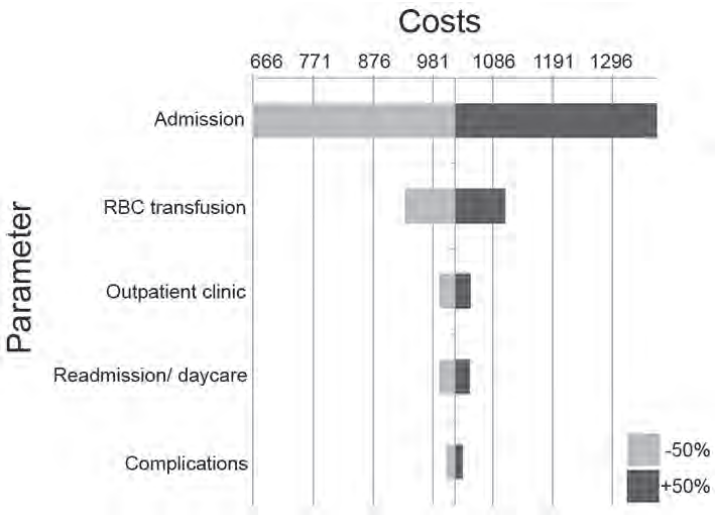

Figure 2 *Tornado diagram.*

Table 2 *Results trial.*

	Non-intervention (n = 261)	Transfusion (n = 258)
Variable		
Red blood cell units per woman		
median (IQR)	0 (0-0)	2 (2-2)†
mean (SD)	0.34 (1.0)	2.0 (0.7)
Crossover, n (%)[a]	33 (13%)	7 (3%)†
Length of hospital stay		
median (IQR)	2 (1-4)	2 (1-3)
mean (SD)	2.6 (1.8)	2.4 (1.5)
Readmission or daycare, n (%)	18 (7%)	6 (2%)*
median (IQR)	0 (0-0)	0 (0-0)*
mean (SD)	0.3 (1.2)	0.1 (0.8)
Outpatient clinic visits, n (%)	192 (74%)	200 (78%)
median (IQR)	1 (1-1)	1 (1-1)
mean (SD)	0.9 (0.8)	0.9 (0.7)
Visits to medical specialist (other than gynecologist), n (%)	4 (2%)	6 (2%)
median (IQR)	0 (0-0)	0 (0-0)
mean (SD)	0.03 (0.2)	0.03 (0.2)
Phone consultations, n (%)	12 (5%)	8 (3%)
median (IQR)	0 (0-0)	0 (0-0)
mean (SD)	0.06 (0.1)	0.04 (0.2)
Maternal complications		
thromboembolic event	0	2 (2%)
pulmonary embolism	2 (0.8%)	0
urinary tract infection	14 (5%)	11 (4%)
treated by hospital	11 (4%)	6 (2%)
endometritis	3 (1%)	5 (2%)
fever without known cause	4 (2%)	3 (1%)
pneumonia	1 (0.3%)	0
mastitis (with admission)	1 (0.3%)	0
postpartum depression	0	1 (0.4%)
retained products of conception		
medication	1 (0.3%)	2 (0.8%)
operative	10 (4%)	2 (0.8%)

[a]Initially or during follow-up.
*$p < 0.05$, †$p < 0.01$.

Table 3 *Cost-analysis: resource use and unit costs.*

	Unit	Costs, 2013 €
Admission		
Admission	day	502.64
Readmission	day	524.37
Daycare	day	300.38
RBC transfusion	1 unit	290.48
	2 units	537.15
	3 units	783.80
	4 units	1070.18
	5 units	1316.85
	10 units	2621.66
Consultation medical specialist (other than gynecologist)	consultation	97.53
Outpatient clinic		
Outpatient visit	visit	107.79
Phone consultation	consultation	15.24
Consultation other specialist	consultation	97.53
Medication follow-up		
Iron supplementation administered at hospital		
ferrioxidesaccharate	first dose, 200 mg	92.37
	each following dose	59.37
ferric carboxymaltose	first dose, 100 mg	73.61
	each following dose	40.60
	first dose, 500 mg	199.12
	each following dose	166.12
Iron supplementation by formulation		
ferrous fumarate	tablet 200 mg	0.02
ferrous sulfate	tablet 105 mg	0.08
ferrous gluconate	tablet 80 mg	0.22
Folic acid supplementation	tablet 0.5 mg	0.03
Medication and specialist care for physical complications		
thromboembolic event		3476.81
pulmonary embolism		4415.18
Medication for physical complications		
urinary tract infection		8.46
endometritis		44.70
fever without known cause		46.80
pneumonia		36.03
mastitis		10.28
Postpartum depression		1556.69
Retained products of conception		
removal by medication		11.70
operative removal		478.17

Table 4 *Comparison of costs between Non-intervention and RBC transfusion.*

	Non-intervention		Transfusion	
	Mean costs per woman (€)	Median costs per woman (€)	Mean costs per woman (€)	Median costs per woman (€)
Admission	1324.56	1005.27	1217.16	1005.27
Readmission and daycare	135.20	0	52.85	0
Outpatient clinic	94.16	107.79	95.68	107.79
Phone consultation	0.87	0	0.54	0
RBC transfusion	89.44	0	546.11	537.15
Consultation other medical specialist	0.75	0	1.89	0
Iron supplementation	6.39	0.24	0.08	0
Folic acid supplementation	1.16	1.29	-	-
Complications total	55.42	0	43.24	0
Total (95% CI of the mean)	1707.95 (1545.99-1889.19)	1212.15	1957.60 (1835.10-2093.81)	1650.41

95% Confidence Intervals calculated using bootstrap.

Analyses repeated after exclusion of women who had not completed the physical fatigue score at day 3 (primary outcome in the WOMB trial) demonstrated similar costs per women (median costs for the non-intervention and RBC transfusion arms €1217 and €1652, respectively) and similar differences between study arms.

Discussion

This study assessed the economic consequences of a RBC transfusion versus non-intervention strategy in women with acute anemia after PPH, taking into account direct medical costs. We showed that mean costs were €250 higher in women randomized to RBC transfusion than in women randomized to non-intervention. All outcome measures were comparable between study arms, except for RBC units transfused and readmission rate. The readmission rate in the non-intervention arm was threefold higher though this was outweighed by the six-fold lower use of RBC units (88 versus 517 units). In search for an explanation of the difference in readmission rates (data not shown), we found that basic characteristics were not significantly different between study arms, though RBC units and crossovers were ($p < 0.001$). Additional testing showed that these two variables were also significantly related to readmission and therefore seem explanatory ($p = 0.005$ and $p < 0.001$, respectively). Retained products of conception may also play a role as 46% of all patients randomized to non-intervention with retained products of conception crossed over ($p = 0.002$). Overall, the difference in costs between study arms predominantly originated in costs of RBC units. Our sensitivity analyses demonstrated that total costs were influenced mostly by costs of admission.

Mean costs generated by non-intervention were €250 lower than costs generated by RBC transfusion. The occurrence of retained products of conception was remarkably higher in the non-intervention arm (dimin-

ishing the difference in costs between study arms). These differences in retained products of conception between study arms were however not significant (p = 0.1). As the incidence of retained placenta products is assumed to be unrelated to treatment allocation, we believe this is a chance coincidence. The optimal transfusion policy was previously studied in trials among intensive care and orthopedic patients.[97,102] A liberal transfusion policy was not beneficial compared to a restrictive policy regarding clinical parameters. Moreover, a recent meta-analysis demonstrated a reduced risk of infection among hospitalized patients with a restrictive RBC transfusion strategy compared with a liberal transfusion strategy.[159] HRQoL was not investigated in these studies. Little is known about the treatment costs and quality of life of women after postpartum hemorrhage.

Considering HRQoL results, the WOMB trial demonstrated that physical fatigue was significantly lower in women randomized to RBC transfusion up to one week postpartum (maximal difference 1.06 at one week postpartum).[88] However, significance does not indicate that this difference is clinically relevant. Regarding the MFI subscales, the minimal clinical important difference has only been determined in radiotherapy women, where it was set at 2.04 for the subscale physical fatigue.[95] Regarding the EuroQol-5D, the minimal clinical important difference was estimated at average 7.4,[160] indicating that no clinical relevant differences were detected between study arms during this study. However, for none of the HRQoL measures a minimal clinical important difference has been determined in obstetric patients.

To optimize health care in postpartum anemic women, benefits of RBC transfusion (HRQoL) should be considered opposed to disadvantages like costs and risks of transfusion reactions[14,71,161] RBC transfusion led to an improvement of 0.58 points in physical fatigue per day; average costs to improve physical fatigue score with one point daily are therefore €431 per woman. In this study, three (mild) transfusion reactions were observed, all in the RBC transfusion arm.[88]

Limitations in this study are the following. Women included in the WOMB trial present a skewed Hb concentration after delivery with most women in the higher Hb ranges. We assume this results from exclusion of women with previous (recent) transfusion and/ or symptoms of severe acute anemia and therefore believe our study population is a good representation of women eligible for non-intervention in daily clinical practice. The lower Hb threshold in this study was formulated on request of the Institutional Review Board; in the original protocol no lower threshold was defined. Results of the subgroup analyses regarding Hb concentration 12-24 hours after delivery demonstrated no obvious trends towards lower or higher costs in case of differing Hb concentration. Data were primarily registered to determine differences in HRQoL between study arms and therefore some variables were not collected in as much detail as preferable for cost-effectiveness analyses. It is possible that women were admitted for a longer period of time not for their own health but because of admission of the neonate. Unfortunately, reasons for admission were not registered in this trial. However, since length of hospital stay was not significantly different between study arms, the influence of this limitation seems minimal. Also, the

assumption was made that women who had not been admitted to hospital after delivery, had not suffered from complications that inflected direct medical costs. Some complications, known to be treated by the general practitioner, were not taken into account in this study. Costs of complications will therefore be underestimated if considered from a societal point of view. The time horizon used in this cost-effectiveness analysis has been limited to six weeks postpartum and costs were evaluated from a medical perspective. This was explicitly done because detailed information was available on both medical costs and effects from the WOMB trial.

The prospective design, the large number of women and diversity of participating hospitals, the well-organized structure of randomization and data collection within the Dutch Obstetric Consortium are strengths of this trial: although not tested, these are likely to extend both the internal and external validity of our results in Dutch non-symptomatic anemic women.

RBC transfusion in women with acute non-symptomatic anemia (Hb concentration 4.8 to 7.9 g/dL) after PPH only leads to a small improvement of physical fatigue. The results as described in this economic evaluation study indicate that this strategy is also associated with higher costs per woman. In conclusion, in otherwise healthy women with acute non-symptomatic anemia RBC transfusion is found to be a more costly strategy with only marginal gain in HRQoL compared to non-intervention.

Appendix S1 *Participating hospitals in the WOMB trial*

Participating hospital	City
Academic Medical Center	Amsterdam
Albert Schweitzer Hospital	Dordrecht
Amphia Hospital	Breda
Atrium Hospital	Heerlen
Bronovo Hospital	Den Haag
Canisius Wilhelmina Hospital	Nijmegen
Deventer Hospital	Deventer
Diakonessen Hospital	Utrecht
Elkerliek Hospital	Helmond
Erasmus Medical Center	Rotterdam
Flevo Hospital	Almere
Gelderse Vallei Hospital	Ede
Gelre Hospital	Apeldoorn
Gemini Hospital	Den Helder
Groene Hart Hospital	Gouda
Haga Hospital	Den Haag
Ikazia Hospital	Rotterdam
Jeroen Bosch Hospital	s-Hertogenbosch
Kennemer Gasthuis	Haarlem
Lange Land Hospital	Zoetermeer
Leiden University Medical Center	Leiden
Maasstad Hospital	Rotterdam
Maasziekenhuis Pantein	Boxmeer
Martini Hospital	Groningen
Máxima Medical Center	Veldhoven
Meander Medical Center	Amersfoort
Medical Center Leeuwarden	Leeuwarden
Mesos Medical Center	Nieuwegein, Ouderijn
Onze Lieve Vrouw Gasthuis	Amsterdam
Radboud University Medical Center	Nijmegen
Reinier de Graaf Gasthuis	Delft
Scheper / Leveste Hospital	Emmen
Spaarne Hospital	Hoofddorp
St. Elisabeth Hospital	Tilburg
St. Fanciscus Gasthuis	Rotterdam
St. Lucas Andreas	Amsterdam
University Hospital Maastricht	Maastricht
University Medical Center Utrecht	Utrecht


5

Chapter 5

Determinants of health-related quality of life in the postpartum period after obstetric complications

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Abstract

Objective

To determine the influence of socio-demographic, clinical parameters and obstetric complications on postpartum health-related quality of life (HRQoL).

Methods

We used data of three randomized controlled trials to investigate HRQoL determinants in women after an obstetric complication. The DIGITAT and HYPITAT trials compared induction of labor and expectant management in women with intra-uterine growth restriction (IUGR) and hypertensive disorders. The WOMB trial randomized anemic women after postpartum hemorrhage to red blood cell transfusion or expectant management. The HRQoL-measure ShortForm-36 was completed at six weeks postpartum. Multivariable analyses were used to identify which parameters affected the ShortForm-36 physical component score (PCS) and mental component score (MCS).

Results

HRQoL analyses included 1391 women (60%) of the 2310 trial participants. HYPITAT and DIGITAT participants had significantly lower MCS scores than WOMB participants. In multivariable analysis, PCS after elective and emergency cesarean section was 5-6 points lower than after vaginal delivery. Gestational hypertension, neonatal admission and delivery in an tertiary hospital had a small negative effect on PCS. No effect was found for randomization status, maternal age, BMI, country of birth, education, parity, induction of labor, analgesics, birth weight, perineal laceration, delivery of placenta, postpartum hemorrhage, congenital anomaly, urinary tract infection, thromboembolic event or endometritis. MCS was influenced only mildly by these parameters.

Conclusions

IUGR and hypertensive disorders lead to lower HRQoL scores postpartum than PPH. In a heterogeneous obstetric population, only mode of delivery by cesarean section has a profound, negative impact, on physical HRQoL (PCS). No profound impacts on MCS were detected.

Introduction

Health-related quality of life (HRQoL) postpartum is potentially influenced by socio-demographic parameters as well as by clinical parameters and obstetric complications. Socio-demographic parameters described to influence HRQoL postpartum negatively are black ethnicity,[162] low education,[163] low income[164] and large number of children at home.[164] A supportive social network influences postpartum HRQoL positively.[68,62,165] Common obstetric complications are intra-uterine growth restriction (IUGR), hypertensive disorders of pregnancy and postpartum hemorrhage (PPH).[3,34,166] Pregnancies with these complications are at increased risk for neonatal and/ or maternal morbidity and mortality.[1,167-169] Poor physical and mental health have been described in mothers with obstetric complications like preterm birth.[170-172] HRQoL is also compromised in women with postpartum complications like postpartum depression,[68,173,174] pregnancy-related deep vein thrombosis[163] and urinary and/ or fecal incontinence.[175-179] Recently, three multicenter trials were conducted that investigated maternal and/ or neonatal outcomes and measured HRQoL in the postpartum period. The DIGITAT and HYPITAT trial primarily investigated the effect of induction of labor on neonatal and maternal outcome in pregnancies complicated by respectively IUGR and hypertensive disorders.[180,181] The WOMB trial primarily studied the effect of red blood cell (RBC) transfusion on physical fatigue in women after PPH.[88] The availability of such large number of postpartum HRQoL data provided a unique opportunity to assess which parameters influence postpartum HRQoL after obstetric complications by combining data of the three trials.

We hypothesized that several socio-demographic and clinical parameters, as well as obstetric complications, affect postpartum HRQoL. Insight in these parameters will contribute to postpartum care and will provide the opportunity to develop individual strategies after obstetric complications.

Methods

We used data of three randomized controlled trials: the DIGITAT, HYPITAT and WOMB trial. Details of these studies and their ethic approval have been previously published.[89,182,183] The trials were conducted within the Dutch Obstetric Consortium (http:/www.studies-obsgyn.nl/). In the DIGITAT, HYPITAT and WOMB trial 52, 38 and 37 Dutch hospitals participated, respectively. In each trial, women who refused randomization were asked to participate as non-randomized women. Results of the trials have been described elsewhere.[88,180,181] The 'Disproportionate Intrauterine Growth Intervention Trial At Term' (DIGITAT) included women with a singleton pregnancy, a fetus in cephalic presentation, between 36+0 and 41+0 weeks gestational age, with suspected IUGR (defined as fetal abdominal circumference below the 10th percentile, estimated fetal weight below the 10th percentile and/ or a decreased relative growth).[180] Women were allocated to induction of labor or expectant management. Primary outcome was composite neonatal adverse outcome.

The 'Hypertension and Pre-eclampsia Intervention Trial At Term' (HYPITAT) had a similar design and included women with a singleton pregnancy, a fetus in cephalic presentation, between 36+0 and 41+0 weeks of

gestation, complicated by gestational hypertension (defined as diastolic blood pressure ≥ 95 mmHg, measured on two occasions, at least 6 hours apart) or mild pre-eclampsia (defined as diastolic blood pressure ≥ 90 mmHg measured on two occasions, at least 6 hours apart, combined with ≥ 2+ protein on dipstick, > 300 mg total protein within 24 h urine collection or protein/creatinine ratio > 30 mg/mml).[181] Again, women were allocated to induction of labor or expectant management. Primary outcome was a composite measure of poor maternal outcome.

The 'Well-being of Obstetric patients on Minimal Blood transfusions' (WOMB) studied women after PPH (defined as peripartum blood loss ≥ 1000 mL and/ or decrease in Hb concentration ≥ 1.9 g/dL), with an Hb concentration between 4.8 and 7.9 g/dL (3.0-4.9 mmol/L) 12 to 24 hours after delivery. Women were allocated to RBC transfusion or expectant management. Primary outcome was physical fatigue at day 3 postpartum, measured by the HRQoL measure Multidimensional Fatigue Inventory.

Six hundred fifty-eight DIGITAT women (60%), 818 HYPITAT women (71%) and all WOMB women participated in the HRQoL study. Questionnaires were completed at several time points; the only common time point in the trials was six weeks postpartum. Each trial used the SF-36 version 1 (SF-36), a generic HRQoL measure with eight scales (physical functioning, role limitations due to physical health problems [role-physical], bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health [role-emotional], and mental health) ranging from 0 to 100; higher scores indicate better well-being. The SF-36 has been validated in a random nationwide sample of the adult Dutch population.[93] For this study, age and gender matched reference scores were provided by this research group (unpublished data based on 367 women aged from 16 to 40 years, Aaronson et al.). The pilot study of the WOMB trial[69] provides postpartum reference scores based on 141 women that subsequently delivered in three Dutch hospitals.

The SF-36 allows for computation of the summary scores Physical Component Score (PCS) and Mental Component Score (MCS). These are norm-based with a mean of 50 and a standard deviation of 10, based on US population reference scores.[184] No Dutch population reference scores are available for the summary scores.

The SF-36 is competent in the assessment of HRQoL differences in the postpartum period.[69,88]

Statistical analysis

We studied the PCS and the MCS at six weeks postpartum in women who suffered obstetric complications. Normality of data was determined by using visual assessment and the Shapiro-Wilk's test. Categorical data are presented as numbers with percentages, and numerical data are presented as means ± SD of the mean (normally distributed) or medians with IQRs (not normally distributed). To create a homogeneous cohort, women from the WOMB trial that delivered before 36+0 weeks of gestation and multiple gestations were excluded. We used multiple imputations to handle missing values of all socio-demographic and clinical parameters:[122] ten imputed data sets were created using a fully conditional specified model. Imputations were based on the relations between the covariates in the study, which

were used to calculate the most likely value for a missing response. Data were analyzed separately in each imputed data set to obtain the effect estimates. Pooled estimates were generated from these ten imputed data sets and used to report estimates and their corresponding 95% confidence intervals.

SF-36 subscale scores were compared to Dutch population reference scores and to postpartum reference scores. As no Dutch population reference scores are available for the SF-36 summary scores PCS and MCS, these were compared to US population reference scores.[184]

We used univariable linear regression analysis to investigate parameters that were assumed to be related to HRQoL postpartum. The following socio-demographic and clinical parameters were analyzed: randomization status, age, BMI, country of birth (Dutch versus non-Dutch), highest education, parity, hypertensive disorders, gestational age at birth, induction of labor, analgesics, mode of delivery, perineal laceration, manual placenta removal, birth weight, PPH, admission of the neonate, congenital anomaly of the neonate, urinary tract infection, thromboembolic event, endometritis and hospital setting. To investigate the relationship of these parameters with HRQoL, we performed multivariable linear regression analysis, including those parameters with a significant relation to primary outcome measures in the univariable analyses ($p < 0.10$). Data were managed using SPSS version 20.0.

Results

A total of 3191 women were included in the three trials. Figure 1 shows the flowcharts of this study. A total of 2310 participated: 1399 (61%) were randomized while 911 women (39%) refused randomization but participated as non-randomized women. HRQoL data at six weeks postpartum were available in 1391 women as the response at this time point was 60% (61%, 65% and 55% in the DIGITAT, HYPITAT and WOMB trial, respectively). We will refer to responding women as responders while women with no HRQoL data at six weeks postpartum will be referred to as non-responders.

Socio-demographic and clinical parameters

The mean age of women was 30 years and 64% was primiparous. About 85% of women delivered vaginally, 46% had a hypertensive disorder while 41% suffered from PPH. Among our study population, one maternal death occurred. This patient was allocated to induction of labor in the DIGITAT trial and died at home 10 days after a vaginal delivery of a healthy neonate. A cause for her death could not be found. Furthermore, one perinatal death occurred in the DIGITAT trial, among the non-randomized women.

Table 1 shows socio-demographic and clinical parameters and the differences between responders and non-responders. Compared to non-responders, responders were significantly older, more frequently born in the Netherlands and had a higher education. Also, many differences were found in clinical parameters like parity, perineal laceration, rate of hypertensive disorders and rate of PPH.

Table 1 *Socio-demographic and clinical parameters.*

	Total n = 2310	Responders n = 1391	Non-responders n = 919	Responders vs Non-responders *p*-value
Socio-demographic				
Maternal age in years, mean (SD)	29.9 (5.2)	30.5 (4.9)	28.9 (5.5)	< 0.001
missing	7 (0.3%)	2 (0.1%)	5 (0.5%)	
BMI				0.05
< 18.5	98 (4%)	59 (4%)	39 (4%)	
18.5-25	1168 (51%)	698 (50%)	470 (51%)	
> 25	763 (33%)	483 (35%)	280 (31%)	
missing	281 (12%)	151 (11%)	130 (14%)	
Country of birth				< 0.001
Dutch	1838 (80%)	1199 (86%)	639 (70%)	
non-Dutch	287 (12%)	111 (8%)	176 (19%)	
missing	185 (8%)	81 (6%)	104 (11%)	
Highest education				< 0.001
none/ primary education	178 (8%)	91 (7%)	87 (10%)	
secondary education	848 (37%)	506 (36%)	342 (37%)	
higher professional education/ university	520 (23%)	376 (27%)	144 (16%)	
missing	764 (33%)	418 (30%)	346 (38%)	
Pregnancy				
Parity				0.004
primiparous	1476 (64%)	922 (66%)	554 (60%)	
multiparous	834 (36%)	469 (34%)	365 (40%)	
missing	0	0	0	
Hypertensive disorder				< 0.001
none	1298 (56%)	747 (54%)	551 (60%)	
gestational hypertension	619 (27%)	412 (30%)	207 (23%)	
pre-eclampsia	373 (16%)	225 (16%)	148 (16%)	
missing	20 (1%)	7 (0.5%)	13 (1%)	
Delivery				
Gestational age, mean (SD)	39+4 (10)	39+4 (10)	39+4 (10)	0.16
missing	0	0	0	
Induction of labor	1300 (56%)	822 (59%)	478 (52%)	< 0.001
none	964 (42%)	554 (40%)	410 (45%)	
missing	46 (2%)	15 (1%)	31 (3%)	
Mode of delivery				0.003
vaginal, spontaneous	1590 (69%)	966 (69%)	624 (68%)	
vaginal, operative	346 (15%)	227 (16%)	119 (13%)	
elective CS	57 (3%)	26 (2%)	31 (3%)	
emergency CS	317 (14%)	172 (12%)	145 (16%)	
missing	0	0	0	
Fetal position				0.03
cephalic	2250 (97%)	1364 (98%)	886 (96%)	
other position	20 (1%)	11 (1%)	9 (1%)	
missing	40 (2%)	16 (1%)	24 (3%)	

	Total n = 2310	Responders n = 1391	Non-responders n = 919	*p*-value Responders vs Non-responders
Analgesics				0.01
none	1298 (56%)	818 (59%)	480 (52%)	
opiates	288 (13%)	165 (12%)	123 (13%)	
epidural/ spinal	593 (26%)	343 (25%)	250 (27%)	
general anesthesia	13 (0.6%)	5 (0.4%)	8 (1%)	
missing	118 (5%)	60 (4%)	58 (6%)	
Birth weight				0.002
< 10th percentile	596 (26%)	362 (26%)	234 (26%)	
10-90 percentile	1418 (61%)	856 (62%)	562 (61%)	
> 90st percentile	266 (12%)	165 (12%)	101 (11%)	
missing	30 (1%)	8 (0.6%)	22 (2%)	
Perineal laceration				0.001
none or first degree[a]	1069 (46%)	605 (44%)	464 (51%)	
second degree or higher	1228 (53%)	781 (56%)	447 (49%)	
missing	13 (0.6%)	5 (0.4%)	8 (1%)	
Hospital setting				0.05
tertiary	644 (28%)	367 (26%)	227 (30%)	
teaching	1563 (68%)	954 (69%)	609 (66%)	
non-teaching	103 (5%)	70 (5%)	33 (4%)	
missing	0	0	0	
Postpartum				
Delivery placenta				0.13
spontaneous[a]	1990 (86%)	192 (14%)	124 (14%)	
MPV or curettage	316 (14%)	1195 (86%)	795 (87%)	
missing	4 (0.2%)	4 (0.3%)	0	
PPH	940 (41%)	523 (38%)	417 (45%)	0.001
none	1339 (58%)	849 (61%)	490 (53%)	
missing	31 (1%)	19 (1%)	12 (1%)	
none	386 (17%)	224 (16%)	162 (18%)	0.001
RBC transfusion	1379 (60%)	873 (63%)	506 (55%)	
missing	545 (24%)	294 (21%)	251 (27%)	
Neonatal admission	1240 (54%)	764 (55%)	476 (52%)	0.32
none	1066 (46%)	625 (45%)	441 (48%)	
missing	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Congenital anomaly (severe)	22 (1%)	12 (1%)	10 (1%)	0.74
none	2288 (99%)	1379 (99%)	909 (99%)	
missing	0	0	0	
Maternal complications				
Urinary tract infection	47 (2%)	27 (2%)	20 (2%)	< 0.001
none	2058 (89%)	1280 (92%)	778 (85%)	
missing	205 (9%)	84 (6%)	121 (13%)	
Thromboembolic event	6 (0.3%)	4 (0.3%)	2 (0.2%)	< 0.001
none	2100 (91%)	1301 (94%)	799 (87%)	
missing	204 (9%)	86 (6%)	118 (13%)	
Endometritis	21 (1%)	11 (1%)	10 (1%)	< 0.001
none	2086 (90%)	1296 (93%)	790 (86%)	
missing	203 (9%)	84 (6%)	119 (13%)	

[a]including cesarean sections. n (%) unless otherwise specified.
BMI = body mass index. CS = cesarean section. PPH = postpartum hemorrhage. MPV = manual placenta removal. RBC = red blood cell.

Table 2 *SF-36 summary and subscale scores: This study, Dutch population reference scores and Postpartum reference scores.*

	This study, Total		This study, DIGITAT		This study, HYPITAT		This study, WOMB		Dutch population reference [93]	Postpartum reference [69]
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	mean (SD)	mean (SD)
Summary scores										
PCS	1364	46 (9)	393	45 (10)	526	44 (9)	445	48 (9)	NA	
MCS	1364	53 (9)	393	51 (10)	526	52 (9)	445	54 (8)	NA	
Subscales										
Physical functioning	1383	86 (17)	403	86 (18)	528	85 (16)	452	86 (17)	92 (13)	85 (19)
Role-physical	1379	60 (42)	401	57 (42)	528	50 (42)	450	73 (38)	86 (29)	74 (37)
Bodily Pain	1385	61 (28)	401	77 (19)	528	54 (25)	456	73 (28)	79 (19)	78 (28)
General Health	1379	78 (18)	398	76 (19)	527	78 (17)	454	79 (18)	77 (17)	78 (18)
Vitality	1382	60 (18)	401	57 (18)	527	57 (17)	454	66 (18)	68 (16)	68 18)
Social Functioning	1386	78 (23)	402	75 (25)	528	75 (23)	456	84 (20)	86 (19)	86 (19)
Role-emotional	1379	84 (33)	399	82 (34)	528	83 (33)	452	85 (32)	82 (33)	83 (34)
Mental health	1382	82 (15)	401	79 (16)	527	80 (15)	454	86 (15)	76 (15)	86 (14)

SF-36; 36-item Short Form. PCS; Physical Component Score. MCS; Mental Component Score. NA; not available.
No Dutch references for the summary scores were available. However, US population reference scores for the PCS and MCS, with a mean of 50 and a standard deviation of 10, are previously published[184]
For SF-36 subscales, Dutch population reference scores, matched for both gender and age, were made available by Aaronson et al. (unpublished data, see Methods)[93]
Also, postpartum reference scores are presented; these scores were derived from the pilot study of the WOMB trial[69]

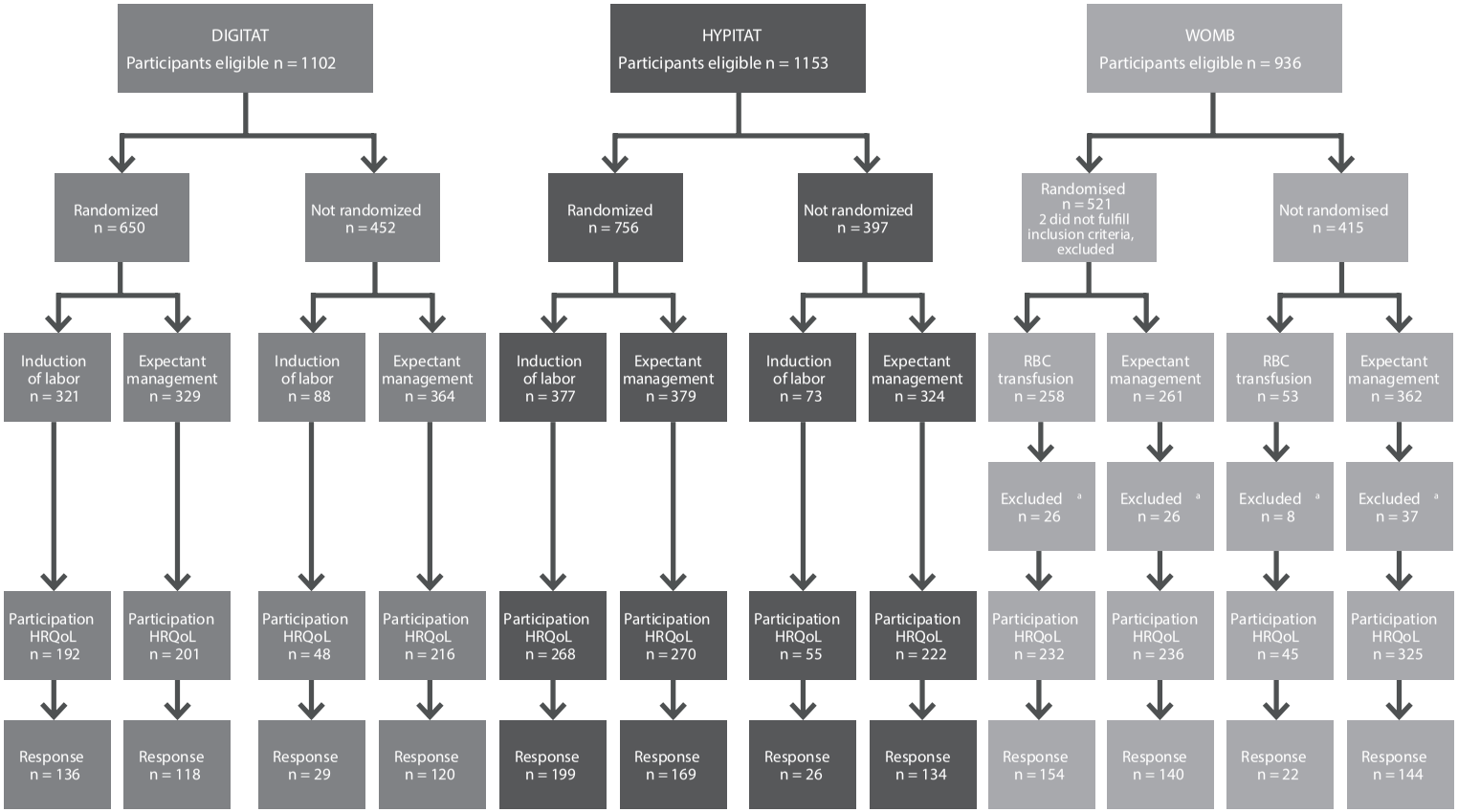


Figure 1 *Flowchart of women participating in this study.*

[a]women that delivered before 36+0 weeks of gestation and multiple gestations

Table 3 *Multivariable associations between socio-demographic parameters, clinical parameters and obstetric complications, and the Physical and Mental Component Score.*

	Physical Component Score			Mental Component Score		
	Estimate	SE	*p*	Estimate	SE	*p*
Intercept	48.142	0.975	< 0.001	53.694	0.866	< 0.001
Parameter						
BMI						
< 18.5	-0.682	1.337	0.61			
18.5-25	ref	1.057				
> 25	-0.889	0.588	0.13			
Country of birth						
Dutch				ref		
not Dutch				-1.943	0.855	0.02
Highest education						
none/ primary education	0.318	1.069	0.77	-1.761	1.230	0.16
secondary education	ref			ref		
higher professional education/ university	0.874	0.634	0.17	-0.034	0.592	0.95
Parity						
primiparous	ref					
multiparous	1.087	0.583	0.06			
Hypertensive disorder						
none	ref			ref		
gestational hypertension	-1.519	0.711	0.03	0.246	0.707	0.73
pre-eclampsia	-1.335	0.773	0.08	-0.144	0.782	0.85
Induction of labor						
no	ref			ref		
yes	-0.161	0.517	0.76	-1.405	0.520	0.01
Mode of delivery						
vaginal, spontaneous	ref					
vaginal, operative	-0.615	0.705	0.38			
CS, elective	-5.566	1.868	0.003			
CS, emergency	-6.331	0.891	< 0.001			
Analgesics						
none	ref					
opiates	-0.226	0.777	0.77			
epidural/ spinal	-0.066	0.626	0.92			
general anesthetics	-1.263	1.904	0.51			
Birth weight						
< 10th percentile	-0.173	0.668	0.80	-0.192	0.675	0.78
10th-90st percentile	ref			ref		
> 90st percentile	-0.053	0.795	0.95	-1.172	0.788	0.14
Perineal laceration						
none or first degree[a]	ref			ref		
second degree or higher	-0.345	0.608	0.58	0.669	0.513	0.19
Hospital setting						
non-teaching	0.277	1.118	0.80	0.952	1.142	0.40
teaching	ref			ref		
tertiary	-1.174	0.565	0.04	-0.762	0.575	0.19
Delivery placenta						
spontaneous[a]	ref			ref		
MPV or curettage	-0.473	0.809	0.56	-0.580	0.814	0.48

	Physical Component Score			Mental Component Score		
	Estimate	SE	*p*	Estimate	SE	*p*
PPH						
no	ref			ref		
yes	1.231	0.769	0.11	1.845	0.761	0.02
Neonatal admission						
no	ref			ref		
yes	-1.320	0.631	0.04	-0.892	0.643	0.17
Congenital anomaly (severe)						
no				ref		
yes				-4.233	2.647	0.11

[a]including cesarean sections.
BMI = body mass index. CS = cesarean section. MPV = manual placenta removal. PPH = postpartum hemorrhage.

Health-related quality of life

Table 2 demonstrates the SF-36 scores (total and per trial) and available reference scores. *Figure 2* presents the PCS and MCS per trial. Maximal differences between trials for these summary scores were 4.6 and 3.2 points, respectively (both $p < 0.001$). Women in the WOMB trial had higher PCS and MCS scores than women in the HYPITAT and DIGITAT trial; though only the differences in MCS score were significant (p for the difference in MCS score 0.01 and < 0.001, respectively). With regard to the SF-36 summary scores, the average PCS in our study population was 4 points lower than the US population reference score[184,185] while the average MCS in our study was 3 points higher (both $p < 0.001$).

Dutch population reference scores for the SF-36 subscales were made available for women aged from 16 to 40 years (unpublished data, see Methods). Average general health perception and role-emotional scores in our study were comparable to these reference scores ($p = 0.04$ and $p = 0.053$, respectively) while the mental health score in our study was six points higher ($p < 0.001$). The remaining subscales in our study population had lower average scores than their Dutch reference (all $p < 0.001$). Largest differences between subscale scores in our study and Dutch population reference scores were found for the subscales role-physical and bodily pain (26 and 18 points, respectively).

Comparing scores in our study to postpartum reference scores demonstrated that all SF-36 subscale scores in our study had a lower average (all $p < 0.001$), except for the subscales physical functioning and role-emotional that were similar, and general health perception that was equal. Again, largest differences were found for the subscales role-physical and bodily pain (14 and 17 points, respectively).

Univariable regression analyses

Results of the univariable analyses are tabulated in *Appendix 1*. High BMI, gestational hypertension, pre-eclampsia, elective and emergency cesarean section, induction of labor, epidural or spinal anesthetics, birth weight below 10th percentile, neonatal admission and delivery in an tertiary hospital affected the PCS at six weeks postpartum negatively (all $p < 0.10$). High education, multiparity, perineal laceration, manual placenta removal and PPH were positively associated with PCS (all $p < 0.10$).

Parameters influencing the MCS negatively (all $p < 0.10$) were foreign country of birth, low education, pre-eclampsia, induction of labor, birth weight below the 10th percentile, neonatal admission, neonatal congenital anomaly, and delivery in a tertiary hospital, while the MCS was higher (all $p < 0.10$) in women who had had perineal laceration, MPV or curettage and PPH.

Multivariable regression analyses

We used multivariable regression analyses to assess the influence of socio-demographic and clinical parameters on PCS and MCS. Gestational hypertension, elective cesarean section, emergency cesarean section, neonatal admission and delivery at a tertiary hospital were negatively related to PCS (*Table 3*): the PCS score was on average 1.5 points lower in women with gestational hypertension, 1.3 points lower in case of neonatal admission, 1.2 points lower after delivery at a tertiary hospital and respectively 5.6 and 6.3 points lower after elective or emergency cesarean section. As demonstrated in *Table 3*, the MCS was found to be influenced negatively by a foreign country of birth (1.9 points lower) and induction of labor (1.4 points lower) while the score of women who had had a PPH was 1.8 points higher than the score of women who had not suffered from PPH. scores than PPH.

Discussion

Determinants of postpartum HRQoL after obstetric complications were investigated. We found that women with pregnancies complicated by IUGR and hypertensive disorders overall had lower mental HRQoL. Gestational hypertension, delivery by cesarean section, neonatal admission and delivery in a tertiary hospital were found to be negatively related to PCS in this study. The impact of a cesarean section was the largest. MCS was, only mildly, influenced by foreign country of birth, induction of labor (both negatively) and PPH (positively).

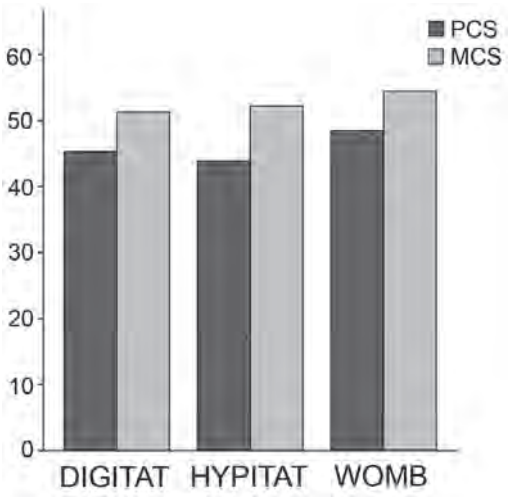


Figure 2 *The SF-36 summary scores PCS and MCS, demonstrated per trial.*

For the interpretation of results, it is important to realize that a significant difference in HRQoL score does not necessarily indicate that this difference is meaningful. The magnitude of the difference determines whether the difference is of clinical importance. Estimates of the minimal clinical important change in the scores PCS and MCS vary from 5 to 10.[110] This implies that the differences in average scores between trials, as found in this study, were relatively small. Also, all effects on PCS and MCS seem small, except for the negative influence of mode of delivery by cesarean section on PCS: after elective and emergency cesarean section women scored on average 6 points lower than after spontaneous vaginal delivery. Consequently, only mode of delivery seems to have a profound impact on HRQoL postpartum.

All parameters, found to be related to either PCS or MCS, can be reasonably explained, though the finding that women after PPH were found to have a relatively high MCS was unexpected. All women in our study suffered from an obstetric complication and PPH apparently had a relatively positive effect in comparison to the other complications (IUGR and hypertensive disorders).

Compared to US-based population,[184] our study population demonstrated overall lower PCS though higher MCS scores. Furthermore, our population had on average lower scores on all subscales, except for general health, role-emotional and mental health, compared to Dutch reference scores (unpublished data, provided by Aaronson et al.).[93] Presumably physical HRQoL is suboptimal after delivery and even worsened by obstetric complications; while mental HRQoL is most likely positively influenced by new motherhood.

Our population had significantly lower scores on all subscales than the postpartum reference scores demonstrated in ***Table 2***,[69] except for physical functioning and role-emotional (similar) and general health (equal). The obstetric complications that our study population suffered from, presumably account for these differences.

Factors associated with HRQoL as described in previous literature like ethnicity, education, and preterm birth were not confirmed in this study. However, HRQoL scores might already have normalized to a large extent at six weeks postpartum: findings in this study and the pilot study indicate that measuring SF-36 scores at one or two additional time points (earlier than six weeks postpartum) might have been very informative.[69] Previous literature regarding the influence of mode of delivery on HRQoL is contradictive. Of previous studies that used the SF-36, two studies demonstrated similar results, one study found better HRQoL after a cesarean section than after vaginal delivery and one study described no influence of mode of delivery on physical HRQoL.[68,69,186,187] These studies however, were based on much smaller populations. Two studies that used different HRQoL measures did not find lower HRQoL after a cesarean section.[164,188] Although numbers in these studies were relatively large (n > 1000), results cannot be compared due to the different measurement methods.

The selection of women with an obstetric complication in this study should be taken into consideration. Another limitation of the current study is the use of combined data collected in three randomized controlled trials, although no effect of randomization on postpartum HRQoL was detected.

Furthermore, Bijlenga et al. found no treatment effect on HRQoL in women randomized to induction of labor or expectant management in the DIGITAT and HYPITAT trial[189,190] while in WOMB trial differences in HRQoL between study groups were small at six weeks postpartum.[88] The effect of both randomization and treatment strategy on our results seems therefore minimal.

Many differences between responders and non-responders were found. These were partly predictable, as socio-demographic differences like age, ethnicity and education are parameters known to influence response rates.[191] Due to the large numbers many differences were significant even when the magnitude of the difference was small.

The major strengths of this study are the nationally collected data and the large numbers.

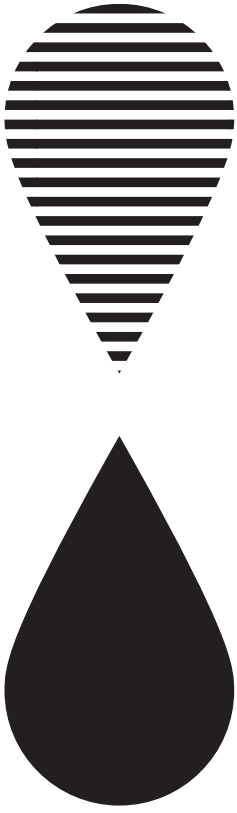
In a heterogeneous obstetric population, delivery by elective and emergency cesarean section are the only factors that have a profound, negative impact on physical HRQoL. No profound impacts on mental HRQoL were detected. Of the studied obstetric complications, PPH seems to influence postpartum HRQoL less than IUGR and hypertensive disorders. These results emphasize the need for careful consideration while determining mode of delivery and bring in reliable information to support discussions about (determinants of) HRQoL after obstetric complications.

Appendix 1 *Univariable associations between socio-demographic parameters, clinical parameters and obstetric complications, and the Physical and Mental Component Score.*

	Physical Component Score			Mental Component Score		
	Estimate	SE	*p*	Estimate	SE	*p*
Parameter						
Randomization status						
not randomized	ref			ref		
randomized	0.041	0.528	0.94	0.158	0.523	0.76
Maternal age	0.014	0.051	0.78	0.008	0.051	0.88
BMI						
< 18.5	-0.416	1.352	0.76	-0.570	1.363	0.68
18.5-25	ref			ref		
> 25	-2.165	0.550	< 0.001	0.133	0.549	0.81
Country of birth						
Dutch	ref			ref		
not Dutch	-1.059	0.859	0.22	-1.675	0.844	0.05
Highest education						
none/ primary education	1.070	1.089	0.33	-2.401	1.164	0.04
secondary education	ref			ref		
higher professional education/ university	1.838	0.632	0.004	0.566	0.565	0.32
Parity						
primiparous	ref			ref		
multiparous	1.981	0.529	< 0.001	-0.802	0.526	0.13

	Physical Component Score			Mental Component Score		
	Estimate	SE	*p*	Estimate	SE	*p*
Hypertensive disorder						
none	ref			ref		
gestational hypertension	-2.847	0.564	< 0.001	-0.626	0.565	0.27
pre-eclampsia	-3.031	0.702	< 0.001	-1.379	0.703	0.05
Mode of delivery						
vaginal, spontaneous	ref			ref		
vaginal, operative	-0.803	0.669	0.23	0.306	0.684	0.66
CS, elective	-4.289	1.784	0.02	0.136	1.823	0.94
CS, emergency	-6.868	0.746	< 0.001	-1.194	0.762	0.12
Induction of labor						
no	ref			ref		
yes	-1.333	0.520	0.01	-2.009	0.505	< 0.001
Analgesics						
none	ref			ref		
opiates	-0.773	0.796	0.33	-0.102	0.791	0.90
EDA/ spinal	-1.930	0.595	0.001	-0.522	0.596	0.38
general anesthetics	-2.565	1.951	0.19	-0.929	2.519	0.72
Perineal laceration						
none or first degree[a]	ref			ref		
second degree or higher	1.792	0.504	< 0.001	1.229	0.500	0.01
Delivery placenta						
spontaneous[a]	ref			ref		
MPV or curettage	2.861	0.726	< 0.001	1.371	0.723	0.06
Birth weight						
< 10th percentile	-1.061	0.584	0.07	-1.502	0.578	0.01
10th-90st percentile	ref			ref		
> 90st percentile	0.312	0.790	0.69	-0.550	0.784	0.48
Postpartum hemorrhage						
no	ref			ref		
yes	2.780	0.514	< 0.001	2.486	0.511	< 0.001
Neonatal admission						
no	ref			ref		
yes	-3.395	0.496	< 0.001	-2.159	0.496	< 0.001
Congenital anomaly (severe)						
no	ref			ref		
yes	3.445	2.682	0.20	-4.528	2.657	0.09
Urinary tract infection						
no	ref			ref		
yes	0.165	1.742	0.93	2.279	1.823	0.21
Thromboembolic event						
no	ref			ref		
yes	-0.093	2.813	0.97	-0.417	2.367	0.86
Endometritis						
no	ref			ref		
yes	2.410	2.708	0.38	1.862	2.803	0.51
Hospital setting						
non-teaching	0.194	1.152	0.89	0.488	1.143	0.67
teaching	ref			ref		
tertiary	-1.513	0.574	0.01	-1.199	0.570	0.04

[a]including cesarean sections.



6

Chapter 6
Discussion

Worldwide, postpartum hemorrhage is still the most prevalent cause of maternal death. One of the Millennium Development Goals, set by the United Nations in 2000, is to reduce maternal mortality by three-quarters by 2015:[1,192] although hypertensive disorders of pregnancy are the leading cause of maternal death in developed countries, postpartum hemorrhage remains among one of the most frequent causes.[23] Incidence, prevention and treatment of postpartum hemorrhage are therefore of great importance, especially with an increasing incidence reported in several developed countries.[4-11] This trend has been related to factors as the advanced maternal age at childbirth and the increase in the cesarean section rate in theory, but till now factors causing the rise in the incidence of postpartum hemorrhage have not been identified.[193]

Apart from the observed increase, a wide variation in the postpartum hemorrhage incidence is described across continents and between urban and rural populations.[2] Fong et al. also described a wide variation in postpartum hemorrhage incidence across Californian regions.[22] In this thesis, we demonstrated comparable results: large regional differences in the incidence of postpartum hemorrhage (range 1.8 to 8.1%) were found in the Netherlands.

A major issue in studies on postpartum hemorrhage is the subjectivity of its diagnosis, which depends on the accoucheur's estimate of blood loss.[42] Although a more accurate estimation of blood loss in the last decade might have contributed to the increase in postpartum hemorrhage, regional differences are less likely to be explained by this feature. We studied the incidence and variance of postpartum hemorrhage from 2000 to 2008 in the Netherlands using data of the Dutch Perinatal Registry. Strengths of this study are the completeness of data and the large sample size of almost 2 million Dutch deliveries. A limitation of the Dutch Perinatal Registry data is that these comprise only basic elements of labor and delivery: data on active management of the third stage, the exact amount of blood loss and causes of postpartum hemorrhage are lacking. Also, the effect of registration errors is unknown.[194] The wide variation in postpartum hemorrhage incidence across regions in the Netherlands could not been explained. Therefore, future research should focus on detection of parameters which explain this variance. Identification of these parameters would allow for improvement of health care and could also put the increase in postpartum hemorrhage incidence to a stop.

Apart from awareness of postpartum hemorrhage, focus on prevention is essential. In this thesis, adherence to the guideline of active third stage of labor by the International Confederation of Midwives (ICM) and the International Federation of Gynecology

and Obstetrics (FIGO)[51] was investigated. Interventions described in the guideline are intended to prevent postpartum hemorrhage, but adherence was found to be low. In less than 50% of the studied deliveries, all three recommended interventions (administration of oxytocin, controlled cord traction and uterine massage) were performed. Previous studies found similar results: a comparable study performed in Nigeria showed 42% adherence,[65] while a nested case-control study in Australia reported lower performance rates of oxytocin administration, but higher rates of controlled cord traction.[66] Although our study was performed in two hospitals only, it accurately reflected all vaginal deliveries in the defined study period and missing data were minimal. We assume that adherence to the guideline was low due to low awareness and contradicting literature on the effectiveness of controlled cord traction and uterine massage.[63,195-198] Besides a training program to enhance awareness, more research is needed to investigate the effectiveness of the intervention controlled cord traction and uterine massage.

Postpartum hemorrhage may lead to acute anemia. Hallmark of the treatment of the acute anemic patient is red blood cell transfusion. In the Netherlands, 4% of all red blood cell transfusions are prescribed in obstetrics.[13] A Dutch retrospective audit reported that a significant proportion of the postpartum red blood cell transfusions are possibly inappropriate, partly due to over-transfusion.[199] Conclusions of this audit, however, were based on hemoglobin concentrations alone which is, to our opinion, not accurate enough.[200] The effectiveness of red blood cell transfusion is controversial. Previous trials investigating red blood cell transfusion policy in the intensive care unit and among orthopedic and surgical patients demonstrated that a restrictive policy was not inferior to red blood cell transfusion regarding complications, mortality and length of hospital stay.[97,99,102] In this thesis, we found similar results in an obstetric population (the WOMB trial). Red blood cell transfusion, compared to non-intervention, in women with acute anemia after postpartum hemorrhage led only to a small improvement in physical fatigue. The clinical relevance of the difference in physical fatigue seems small while no differences in complication rates or length of hospital stay were found between study arms.[95,201] Therefore, a restrictive red blood cell transfusion policy seems justified in women with acute anemia due to postpartum hemorrhage. The clinical relevance of these findings is high as results of previously trials cannot be extrapolated to obstetrics due to the hemodynamic changes during pregnancy and especially in the first days of the postpartum period.[202,203] Although the randomized design of the WOMB study strengthens results, the chosen primary outcome was, retrospectively, not optimal. The most important disadvantage was that no minimal clinical relevant difference of the HRQoL score physical fatigue (primary outcome) had been determined yet. Although a pilot study[69] demonstrated that differences could be observed, interpretation of the magnitude of differences remained unclear. Additionally, as primary outcome was obtained by questionnaires, 20% of the data were missing; although this is a common percentage in HRQoL studies, it is not ideal for primary outcome analysis. Moreover, to add strength to interpretation of the trial results, addition of a more objective physical measure like a physical performance test or Karnofsky performance score should have been considered.[204]

In the WOMB trial, over 10% of women treated without red blood cell transfusion needed an escape red blood cell transfusion, mostly for anemic complaints. We therefore developed prediction models to identify women prone for escape red blood cell transfusion. Although external validation yet needs to be investigated, these models are the first instruments to calculate a woman's individual probability of escape transfusion. Implementation of these formulas, that use both clinical features and HRQoL scores, could improve postpartum care and lead to informed consent in this population.
For the development of our prediction models, WOMB data on randomized and non-randomized women were analyzed together. Although the participation factor (e.g. randomized or non-randomized) was no predictor for escape red blood cell transfusion, this may be considered to be a limitation.

While health care costs resume their rise, especially in times of financial crisis, one should evaluate treatment costs and use this knowledge in daily clinical practice. Previous literature reported that red blood cell transfusion is beneficial and cost-effective in case of severe symptomatic anemia,[161] though little was known about costs-effectiveness of red blood cell transfusion in anemic women without severe complaints in the obstetric field. These are young and healthy women in whom a red blood cell transfusion was often not necessary in the acute phase of postpartum; they represent a specific population as vital functions are not easily threatened by postpartum hemorrhage.

We performed a cost-effectiveness analysis alongside the WOMB trial and demonstrated the following. In acutely anemic women after postpartum hemorrhage, direct medical costs were significantly higher in women receiving red blood cell transfusion than in women managed with non-intervention (respectively €1957 versus €1707). Moreover, full nationwide implementation of a non-intervention policy would reduce health care costs in these women with €619.478 per year, while costs of performing the WOMB trial were just once €225.000. Although a cost-effectiveness analysis alongside a randomized clinical trial provide timely information with high internal validity,[205] some variables were not collected in as much detail as would have been preferred for the costs effectiveness analyses.

Use of HRQoL measures is gaining more importance in medical decision making processes. Although HRQoL is frequently used in neurologic and oncologic populations, its use is relatively unknown in obstetrics. It is impossible to separate disease from an individual's personal and social context.[206] We therefore believe that the use of HRQoL measures in clinical trials should be expanded as improvement of our patient's well-being is the primary goal for each physician. To improve interpretation of HRQoL results, it needs to be investigated in various populations.

In this thesis we investigated postpartum health-related quality of life in women who suffered from an obstetric complication and demonstrated that this is influenced by various clinical variables. Physical health at six weeks postpartum is influenced by gestational hypertension, elective cesarean section, emergency cesarean section, neonatal admission and delivery at a tertiary hospital. Birth country, onset of labor and postpartum hemorrhage were related to scores of mental health, measured by the SF-36.

Compared to an US-based population,[184] our study demonstrated lower physical HRQoL while mental HRQoL was higher. Compared to a Dutch population reference (unpublished data based on 367 women aged from 16 to 40 years, Aaronson et al.[93]), only mental health scored higher than in the reference population. Presumably, physical HRQoL is reduced after delivery while mental HRQoL is positively influenced in a new mother. Compared to a relatively healthy postpartum reference population,[69] subscales in the current study scored generally lower. The obstetric complications (intra-uterine growth restriction, pregnancy-induced hypertension, pre-eclampsia or postpartum hemorrhage), that our study population suffered from, presumably account for the lower scores.

Selection bias by the use of combined data of three trials (on intra-uterine growth restriction, pregnancy-induced hypertension, pre-eclampsia or postpartum hemorrhage) is a limitation in our study. For the interpretation of results, it is important to realize that HRQoL scores are reflected against HRQoL in mothers with an obstetric complication, not against healthy controls. Also, HRQoL scores were only available at six weeks postpartum; we cannot rule out other parameters influencing HRQoL scores earlier postpartum. The strength of this study however is the large number that was created by merging data of these three trials. Since all trials were conducted through the Dutch Obstetric Consortium, data were collected in a similar manner, and information bias was minimal.

Conclusions

This thesis has increased our knowledge and insights regarding postpartum hemorrhage and health-related quality of life in the postpartum period. Postpartum hemorrhage was, is and will remain a topic that requires alertness. With the increasing incidence of postpartum hemorrhage in developed countries,[4-11] it becomes more and more important to focus on prevention. Better implementation and evaluation of the FIGO/ ICM guideline on active third stage management of labor should be achieved. Furthermore, the large variation in postpartum hemorrhage indicates that there is an opportunity to lower the risk at postpartum hemorrhage by identifying and altering the unidentified causes.

Red blood cell transfusion, often used in the treatment of anemic women postpartum after postpartum hemorrhage, carries a serious risk at adverse events like transmission of infectious disease and is a financial burden for our society. More than ever in times of financial crisis, red blood cell transfusion should only be provided when undeniable beneficial compared to non-intervention. Although non-inferiority of non-intervention (in acutely anemic women after postpartum hemorrhage) could not be proven, the difference in physical fatigue was small and seems clinically irrelevant. Implementation of a non-intervention policy would therefore prevent transfusion adverse events and diminish the financial burden, without disadvantages for these women.

HRQoL should play a role in the decision to transfuse: the aim of each physician is to optimize well-being of women postpartum and HRQoL can contribute by indicating probability of the need for escape transfusion. The

formulas on the probability of the need for escape red blood cell transfusion, in which HRQoL were used, may be of great value while counseling these women.

HRQoL in the postpartum period is influenced by several socio-demographic and clinical parameters though only mode of delivery influences postpartum HRQoL to a large extent. Awareness of the influence of socio-demographic and clinical parameters on HRQoL will improve both counseling of women and health care.

Once formulas will have been externally validated, an individual probability of the need for escape red blood cell transfusion should be used for counseling.

4. Increase awareness of socio-demographic and clinical parameters that influence HRQoL in the postpartum period. When counseling women for cesarean section or vaginal delivery the effect of mode of delivery on physical HRQoL, up to six weeks postpartum, should be taken into account.

Recommendations for clinical practice

Based on results presented in this thesis, we recommend the following actions:

1. Increase awareness of postpartum hemorrhage, especially in regions with a relatively high incidence, and improve accuracy of estimated blood loss by routinely weighing.

2. Provide training on active third stage management for midwives, residents and obstetricians to improve adherence to the FIGO/ ICM guideline.

3. Implement a non-intervention policy in acutely anemic women after postpartum hemorrhage without severe anemic complaints.

   Counsel these women regarding the effects on physical fatigue, the risks of red blood cell transfusion and the chance of needing a red blood cell transfusion on second instance.


7

Chapter 7
Summary

The aim of this thesis was to study variation in the incidence of postpartum hemorrhage in the Netherlands, adherence to active third stage management and treatment of women with acute anemia after postpartum hemorrhage with red blood cell transfusion.

This thesis describes a large cohort study investigating variation in postpartum hemorrhage incidence across regions in the Netherlands, a cross-sectional study investigating implementation of active third stage management of labor in daily clinical practice and a multicenter randomized controlled trial studying red blood cell transfusion policy in acutely anemic women after postpartum hemorrhage. Alongside this trial, a cost-effectiveness analysis of red blood cell transfusion versus non-intervention was performed. At last, determinants of health-related quality of life in the postpartum period were studied in a large cohort created by merging data of three randomized controlled trials.

The incidence of postpartum hemorrhage across regions in the Netherlands in 2000 to 2008 was determined. A large cohort based on the Dutch Perinatal Registry, including almost 2 million Dutch deliveries, was used. Incidence of postpartum hemorrhage was determined for each province and for the four largest cities (Amsterdam, Rotterdam, Utrecht, The Hague). Within the two largest cities, Amsterdam and Rotterdam, variation in incidence across neighborhoods was also examined. The incidence of postpartum hemorrhage in the Netherlands during the study period was 4.5% while variation in incidence across regions ranged from 1.8 to 8.1%. The four largest cities had a relatively high incidence of postpartum hemorrhage (4.9% compared to 4.4% in the provinces ($p < 0.001$). Variance across neighborhoods in the two largest cities was, as incidence across regions nationwide, large. Adjustment for maternal characteristics, pregnancy characteristics, medical interventions and health care setting did not account for variation across regions. Regional variation is either unavoidable or subsequent to regional variation of a yet unregistered variable.

Implementation of the FIGO/ ICM guideline on active third stage management of labor, recommending administration of uterotonic medication, controlled cord traction and uterine massage, was studied in an observational prospective setting. Birth attendants completed a case record form after every vaginal delivery and registered which interventions, recommended in the guideline, had been performed. Results of this study showed low adherence to the guideline: in less than 50% of the deliveries in our study, all three interventions were performed. Prevention of postpartum hemorrhage becomes even more important considering the increasing incidence that has been observed in several developed countries. The results of this study address the requisite for

a training program to enhance adherence to the ICM/ FIGO guideline.

The WOMB trial (Well-being of Obstetric patients on Minimal Blood transfusions) is a non-inferiority trial that included women with acute anemia after postpartum hemorrhage (Hb concentration 4.8 to 7.9 g/dL [3.0 to 4.9 mmol]), without severe anemic complaints, to either red blood cell transfusion or non-intervention. Primary outcome was physical fatigue, measured by the Multidimensional Fatigue Inventory, at day three postpartum.

Prior beliefs in daily clinical practice, collected using an inventorial survey, regarding the WOMB trial are presented. With regard to WOMB trial results, 91% of respondents declared to be prepared to adjust their current red blood cell transfusion policy if trial results would indicate so.

Results of the WOMB trial demonstrate that red blood cell transfusion mildly improved physical fatigue. Non-inferiority of a non-intervention policy could not be proven. However, the difference in physical fatigue was small and clinical significance of the difference is doubtful. Complication rate and length of hospital stay were comparable between study arms though women allocated to non-intervention, had a 10-15% chance of receiving an escape transfusion. In the light of these results, we believe that a non-intervention policy is safe and without disadvantages for women when proper counseling is provided.

Prediction models on the need for escape red blood cell transfusion in women with acute anemia after postpartum hemorrhage that were initially treated with a non-intervention policy were created. Several clinical variables (primiparity, multiple pregnancy, total blood loss during delivery and Hb concentration postpartum) were identified to predict the need for escape red blood cell transfusion. Addition of health-related quality of life-scores improved the prediction model that was created. After external validation, the extended model and its formula (to calculate an individual's probability of needing an escape red blood cell transfusion after non-intervention) may be an important tool for counseling and decision making in clinical practice.

A cost-effectiveness analysis on the WOMB trial is presented, using a direct medical perspective to estimate costs for both treatment strategies. Costs for women in the red blood cell transfusion arm were significantly higher than costs in the non-intervention arm (respectively €1957 versus €1707). Results of this economic analysis strengthen our recommendation for a non-intervention strategy in women with acute anemia after postpartum hemorrhage.

Finally, we merged data of three randomized controlled trials to create a large cohort: the DIGITAT, the HYPITAT and the WOMB trial. The DIGITAT trial included women with intra-uterine growth restriction and the HYPITAT included women with a hypertensive disorder. Both trials randomized patients to either induction of labor or expectant management. The protocol of the WOMB trial was previously described in detail. We aimed to investigate determinants of physical and mental health, measured by the SF-36, at six weeks postpartum. The physical component score (PCS) and mental component score (MCS) were studied to assess respectively physical health and mental health.

Physical health at six weeks postpartum was negatively influenced by pregnancy-induced hypertension, delivery by elective or emergency cesarean section, delivery at a tertiary hospital and neonatal admission. A non-Dutch birth country and induction of labor negatively influenced mental health, while surprisingly postpartum hemorrhage had a positive influence. However, all women in the study population suffered from an obstetric complication; postpartum hemorrhage apparently results in better mental health than intra-uterine growth restriction and hypertensive disorders. Awareness of parameters that influence health-related quality of life postpartum, can improve counseling of women and health care.

Postpartum hemorrhage was, is and remains a topic that requires continuous alertness. Results presented in this thesis will promote prevention and optimize treatment of women after postpartum hemorrhage.

Samenvatting

Het doel van dit proefschrift is om de incidentie van fluxus postpartum in Nederland in kaart te brengen, om na te gaan of de richtlijn van de FIGO/ ICM omtrent het actief nageboortetijdperk wordt nageleefd en om de optimale behandeling van kraamvrouwen met een acute anemie, na fluxus postpartum, middels erytrocytentransfusie te onderzoeken.

In dit proefschrift beschrijven we een grote cohort studie waarin de regionale variatie (en mogelijke determinanten hiervan) van de incidentie van fluxus postpartum in Nederland werd onderzocht. Verder worden een cross-sectionele studie, die de naleving van actief nageboortetijdperk in de dagelijkse praktijk in kaart bracht, en een multicentrum gerandomiseerde studie naar het transfusiebeleid in kraamvrouwen met een acute anemie na een fluxus postpartum beschreven. Parallel aan deze laatste studie werd een kosteneffectiviteitsanalyse verricht. Tot slot werden de determinanten van kwaliteit van leven onderzocht in een cohort dat was gebaseerd op data van drie multicenter gerandomiseerde studies.

De incidentie van fluxus postpartum in verschillende regio's in Nederland werd onderzocht in een dataset die beschikbaar was gesteld door de Perinatale Registratie Nederland. Dit cohort omvatte bijna 2 miljoen bevallingen; 96% van alle bevallingen in Nederland in de jaren 2000 tot en met 2008. De incidentie van fluxus postpartum in elke provincie en de vier grootste steden (Amsterdam, Rotterdam, Utrecht en Den Haag) werd onderling vergeleken. Van Amsterdam en Rotterdam werd de variatie in kaart gebracht van de incidentie van fluxus postpartum tussen wijken. De Nederlandse incidentie van fluxus postpartum bedroeg 4,5% in de studieperiode; variatie tussen regio's en steden was groot met incidenties die varieerden tussen 1,8% en 8,1%. De vier grootste Nederlandse steden hadden een relatief hoge incidentie van fluxus postpartum. Ook tussen wijken van zowel Amsterdam als Rotterdam was de variatie van de fluxus incidentie, net als bij regionale variatie, groot. Na correctie voor maternale karakteristieken, zwangerschapskarakteristieken, medische interventies en zorginstelling bleef deze variatie bestaan. De regionale variatie van de incidentie van fluxus postpartum lijkt derhalve onvermijdbaar of is gebaseerd op de regionale variatie van een nog niet geïdentificeerde variabele.

Implementatie van de FIGO/ ICM richtlijn werd onderzocht in een observationele prospectieve setting. Deze richtlijn adviseert een actief nageboortetijdperk toe te passen middels toediening van uterotonica, gecontroleerde tractie aan de navelstreng en uterusmassage. Na elke bevalling werd een case record form ingevuld: zodoende werd geregistreerd welke handelingen, beschreven in de richtlijn, accuraat verricht waren. Deze studie toonde aan dat de richtlijn niet goed wordt nageleefd: in minder dan 50% van de bevallingen werden alle drie de voorgeschreven handelingen uitgevoerd.

De preventie van fluxus postpartum wordt meer en meer van belang gezien de toenemende incidentie in verschillende westerse

landen. Deze studie toont de noodzaak aan van trainingsprogramma's om de naleving van de richtlijn te optimaliseren.

De WOMB studie ('Well-being of Obstetric patients on Minimal Blood transfusions') is een gerandomiseerde studie waarin kraamvrouwen met een acute anemie na fluxus postpartum, zonder ernstige anemische klachten, werden geïncludeerd. Het doel was om aan te tonen dat een expectatief beleid niet slechter is dan het geven van een erytrocytentransfusie; de primaire uitkomstmaat was fysieke vermoeidheid, gemeten met de Multidimensional Fatigue Inventory, op dag drie postpartum.

De hedendaagse overtuigingen in de dagelijkse praktijk betreffende erytrocytentransfusies in het kraambed werden geïnventariseerd met behulp van een enquête die naar alle opleiders gynecologie werd verzonden. Uit deze enquête bleek dat 91% van de respondenten bereid zou zijn om het huidige transfusiebeleid in het kraambed aan te passen indien de WOMB resultaten hierop aan zouden sturen.

De resultaten van de WOMB studie toonden aan dat een erytrocytentransfusie bij een acute anemie, na een fluxus postpartum, de fysieke vermoeidheid in het kraambed licht verbetert; de hypothese dat expectatief beleid niet slechter is dan erytrocytentransfusie, kon echter niet worden bewezen. Het gevonden verschil in fysieke vermoeidheid tussen studie armen was echter klein en de klinisch relevantie ervan dubieus. Het optreden van fysieke complicaties en de opname duur in het ziekenhuis verschilden niet tussen de studie armen. Vrouwen die werden gerandomiseerd voor een expectatief beleid, kregen in 10-15% in tweede instantie alsnog een erytrocytentransfusie, in de meeste gevallen wegens anemische klachten. Gezien de resultaten van de WOMB studie lijkt een expectatief beleid veilig en zonder nadelen voor de kraamvrouw wanneer adequate counseling wordt gegeven.

Naar aanleiding van de WOMB studie werden bij anemische kraamvrouwen met een initieel expectatief beleid, de determinanten van de noodzaak tot een transfusie in tweede instantie onderzocht. Door de ontwikkeling van een predictiemodel, werden verschillende klinische variabelen (primipariteit, meerling zwangerschap, hoeveelheid bloedverlies tijdens de bevalling en Hb concentratie postpartum) als determinanten geïdentificeerd. Toevoeging van kwaliteit van leven scores verbeterde het ontwikkelde predictiemodel. Op basis van de beschreven determinanten werd een formule gecreëerd die de individuele kans op noodzaak tot transfusie kan berekenen. Na externe validatie, kan het predictiemodel en de bijbehorende formule een belangrijke rol gaan spelen bij zowel counselen als besluitvorming in de dagelijkse praktijk.

De kosteneffectiviteitsanalyse, welke parallel aan de WOMB studie werd verricht, maakt gebruik van een direct medisch perspectief om de kosten voor beide behandelingsopties te schatten. Kosten voor vrouwen in de transfusie arm waren significant hoger dan kosten voor vrouwen in de expectatieve arm (€1957 versus €1707, respectievelijk). Resultaten van deze economische analyse onderschrijven een expectatief beleid in acuut anemische kraamvrouwen, zonder ernstige klachten, na fluxus postpartum.

Tot slot werden data van drie gerandomiseerd gecontroleerde studies samengevoegd om een groot cohort te creëren. Hiervoor werd gebruikt gemaakt van data van de DIGITAT, HYPITAT en WOMB studie. De DIGITAT studie includeerde vrouwen met een intra-uteriene groeirestrictie en de HYPITAT studie includeerde vrouwen met een hypertensieve aandoening in de zwangerschap. Beide studies randomiseerden vrouwen voor inleiding van de baring dan wel een expectatief beleid. Het protocol van de WOMB studie is in dit proefschrift in detail beschreven. Het doel van deze cohortstudie was om determinanten van fysieke en mentale gezondheid, zes weken postpartum te identificeren. De fysieke component score (PCS) en de mentale component score (MCS), gemeten met de SF-36 vragenlijst, werden bestudeerd om de fysieke en mentale gezondheid in kaart te brengen.

Resultaten van deze cohort studie toonden aan dat de fysieke gezondheid op zes weken postpartum negatief werd beïnvloed door de factoren zwangerschapshypertensie, bevalling middels primaire en secundaire sectio cesarea, bevalling in een academisch ziekenhuis en opname van de neonaat. Een niet-westers geboorteland en inleiding van de baring beïnvloedden de mentale gezondheid negatief, terwijl fluxus postpartum verassend genoeg een positieve invloed op de mentale gezondheid liet zien. Doordat alle zwangerschappen in deze studie werden gecompliceerd door een obstetrische complicatie, kunnen we hieruit herleiden dat vrouwen na een fluxus postpartum een relatief betere mentale gezondheid ervaren dan na intra-uteriene groeirestrictie of een hypertensieve aandoening van de zwangerschap.

Bewustzijn van parameters die de kwaliteit van leven in het kraambed beïnvloeden, kan leiden tot betere counseling en zorg in het kraambed.

Fluxus postpartum was, is en blijft een obstetrische complicatie die alertheid vereist. Resultaten in dit proefschrift moedigen aan tot preventie en bieden mogelijkheden tot het optimaliseren van de zorg voor vrouwen na fluxus postpartum.

Addendum

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Manuscripts
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Manuscripts

Manuscripts related to this thesis

Reasons for regional differences in severe postpartum hemorrhage: a nationwide comparative study of 1.6 million deliveries.
B.W. Prick, J.F. von Schmidt auf Altenstadt, C.W.P.M. Hukkelhoven, G.J. Bonsel, E.A.P Steegers, B.W. Mol, J.M. Schutte, K.W.M. Bloemenkamp, J.J. Duvekot
Manuscript submitted

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Cost-effectiveness of red blood cell transfusion versus non-intervention in women with acute anaemia after postpartum haemorrhage.
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Manuscript submitted

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Gynaecongres 2012, Den Haag, Netherlands: 3rd price.

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Rubriek afgeronde studie: WOMB.
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Babette Wilhelma Prick werd geboren op 14 juli 1983 te Breda.
Na het behalen van haar gymnasium diploma in 2001 aan het Mencia de Mendoza Lyceum te Breda, begon zij met haar studie Geneeskunde aan de Erasmus Universiteit te Rotterdam.

Babette is reislustig: haar keuze onderwijs in het tweede jaar volgde zij bij de spoedeisende hulp afdeling op Malta en in haar vierde jaar vertrok zij naar Peru waar zij onderzoek deed naar ondervoeding bij kinderen in de leeftijd 0-3 jaar in een academisch ziekenhuis in Lima en een ziekenhuis in de Amazone. Na een actief studentenleven en diverse commissies begon zij in 2006 aan haar co-schappen. Haar vakantie tijdens de co-schappen besteedde ze aan een extra-curriculaire stage bij een borstkankerscreening organisatie in Ghana.

Met veel enthousiasme maakte zij tijdens de co-schappen kennis met de gynaecologie en dit was aanleiding om in oktober 2007 te starten met een literatuurstudie naar de neonatale gevolgen van phenylketonurie tijdens de zwangerschap, o.l.v. Hans Duvekot. Dit onderzoek bleek de basis voor een verdere samenwerking: na haar afstuderen in 2008 werkte Babette als ANIOS in het Erasmus MC te Rotterdam en startte gelijktijdig als arts-onderzoeker van de WOMB studie, o.l.v. Hans Duvekot. Door het verwerven van een tweetal fondsen, Landsteiner Stichting voor Bloedtransfusie Research en Vrienden van de Bloedtransfusie, kreeg zij de mogelijkheid om ruim 2 jaar fulltime onderzoek te doen om dit proefschrift te schrijven. In november 2012 startte zij met de opleiding tot gynaecoloog in het Maasstad ziekenhuis te Rotterdam.

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General courses		
How to conduct a systematic review	2009	0.3
Quality of Life measurement	2010	1.0
Methodology course	2010	1.0
SPSS course	2010	0.3
Clinical Decision Analysis	2010	1.0
Conceptual Foundation of Epidemiologic Study Design	2010	1.0
Classic methods for Data Analysis	2010	6.0
Biomedical English Writing	2010	4.0
Endnote course	2010	0.1
Literature search	2010	0.1
Methodology course	2012	1.0
Seminars and workshops		
Meeting Obstetric Consortium	2008	0.3
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Meeting Obstetric Consortium	2009	0.3
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Meeting Obstetric Consortium	2009	0.3
Mini symposium PPROMEXIL	2009	0.3
Meeting Obstetric Consortium	2009	0.3
Educational meeting Obstetric Consortium	2010	1.0
Gynaecongres	2010	0.6
Meeting Obstetric Consortium	2011	0.3
Gynaecongres	2013	0.6

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Presentations at seminar	2008	0.5
Stan symposium: WOMB trial	2009	0.5
Midwivery conference Amphia Hospital	2009	0.5
DIGITAT symposium: WOMB trial	2009	0.5
Introduction WOMB trial Elisabeth Hospital	2009	0.5
Introduction WOMB trial Jeroen Bosch Hospital	2009	0.5
Introduction WOMB trial Gemini Hospital	2010	0.5
Midwivery conference Hogeschool Rotterdam	2011	1.0
WOMB symposium	2011	0.5
Bella Obstetrica: WOMB trial	2012	0.5
Research meeting, Amphia Hospital	2013	0.5
Research meeting, Maasstad Hospital		
Presentations at (inter)national conferences		
Society of Maternal and Fetal Medicine, Dallas, US	2012	1.0
Wladimiroff researchmeeting, Rotterdam, NL: *1st Award*	2012	1.0
Gynaecongres, Den Haag, NL: *3rd Award*	2012	1.0
Obstetrie & Neonatologie congres, Veldhoven, NL	2012	1.0
TRIP symposium, Ede, NL	2012	1.0
International Society Blood Transfusion, Cancun, MX	2012	1.0
Pijlerdag Foetomaternale Geneeskunde Den Bosch, NL	2013	1.0
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