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Postpartum hemorrhage: from insight to action

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CHAPTER 3

WOMEN RECEIVING MASSIVE TRANSFUSION DUE TO POSTPARTUM HEMORRHAGE: A COMPARISON OVER TIME BETWEEN TWO NATIONWIDE COHORT STUDIES

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ABSTRACT

Introduction

Incidence of massive transfusion following childbirth was high in the Netherlands between 2004 and 2006 compared to other high-income countries. This study investigated incidence, causes, management and outcome of women receiving massive blood transfusion due to postpartum hemorrhage in the Netherlands in more recent years.

Material and methods

Data for all pregnant women who received eight or more units of packed red blood cells from a gestational age of 20 weeks and within the first 24 hours after childbirth, during the period 2011 and 2012, were obtained from a nationwide retrospective cohort study, including 61 hospitals with a maternity unit in the Netherlands.

Results

Incidence of massive transfusion due to postpartum hemorrhage decreased to 65 per 100 000 births (95% Confidence Interval: 56–75) between 2011 and 2012, from 91 per 100 000 births (95% Confidence Interval: 81–101) between 2004 and 2006, while median blood loss increased from 4500mL (Interquartile Range: 3250–6000) to 6000mL (Interquartile Range: 4500–8000). Uterine atony remained the leading cause of hemorrhage. Thirty percent (53/176) underwent peripartum hysterectomy between 2011 and 2012, versus 25% (83/327) between 2004 and 2006. Case fatality rate for women who received massive transfusion due to postpartum hemorrhage was 2.3% (4/176) between 2011 and 2012, compared to 0.9% (3/327) between 2004 and 2006.

Conclusions

The incidence of postpartum hemorrhage with massive transfusion decreased in the Netherlands between both time frames, but remained an important cause of maternal mortality and morbidity, including peripartum hysterectomy. National surveillance of maternal morbidity and mortality due to postpartum hemorrhage through an improved and continuous registration with confidential enquiries may lead to the identification of clear improvements of maternal care.

INTRODUCTION

Postpartum hemorrhage is a serious obstetric complication and a major contributor to maternal morbidity and mortality worldwide.¹ Its incidence seems to be increasing in high-income countries accompanied by increasing rates of severe adverse outcomes.² In obstetrics, massive transfusion (defined as eight or more units of packed red blood cells transfused) after birth is associated with high rates of morbidity and hysterectomy.^{3, 4} Incidence of massive transfusion due to postpartum hemorrhage was notably high in the Netherlands between 2004 and 2006 (91 per 100 000 births) compared with the United Kingdom (UK) between 2012 and 2013 (23 per 100 000 births) and with the state of New York between 1998 and 2007 (60 per 100 000 births).³⁻⁵

A nationwide study based on the national perinatal database in the Netherlands showed an increased incidence of postpartum hemorrhage (defined as ≥ 1000 mL blood loss following the first 24 hours after birth) between 2004 and 2013 (from 4.1% to 6.4% of women giving birth), but a decreased incidence of any number of obstetric-related transfusion of packed red blood cells (from 23% to 3.9% of all women with postpartum hemorrhage).⁶ It is unknown whether the number of women receiving massive transfusion due to postpartum hemorrhage followed this same decreasing pattern. Assessing such a pattern and discerning possible differences over time in incidence, causes, management and outcome of postpartum hemorrhage leading to massive transfusion could help evaluate maternity care. Moreover, identifying antepartum risk factors may also raise awareness for women at high risk of receiving massive transfusion after birth.

The aim of this study was to describe incidence, causes, management and outcome of women who received massive transfusion due to postpartum hemorrhage in the Netherlands between 2011 and 2012 and compare these to the same parameters previously described in the Netherlands between 2004 and 2006 and to the Dutch general pregnant population of 2012.³

MATERIAL AND METHODS

Study design

We performed a secondary analysis of women who received massive transfusion due to postpartum hemorrhage as part of the *Transfusion strategies in women during Major Obstetric Haemorrhage* study (TeMpOH-1). TeMpOH-1 is a nationwide retrospective cohort study in 61 hospitals in the Netherlands (71% of all hospitals in the country at the time) that collected data from women of at least 18 years old, who received four units of packed red blood cells or any transfusion of fresh frozen plasma and/or platelets in addition to packed red blood cells because of obstetric hemorrhage (≥ 1000 mL blood loss during pregnancy or the first 24 hours following childbirth) between January 1st, 2011 and January 1st, 2013.

Population

For the present analysis, women were selected from the TeMpOH-1 cohort who had experienced postpartum hemorrhage and received massive transfusion at a gestational age of at least 20 weeks. Massive transfusion was defined as eight or more units of packed red blood cells transfused within the first 24 hours after childbirth. All results were compared to our previous observations from the LEMMoN cohort (Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland) between 2004 and 2006, and nationwide statistics obtained from the Netherlands Perinatal Registry (PRN, 2012) were used as national reference values.^{3, 7, 8}

Data collection

The TeMpOH-1 study identified eligible women by cross-referencing data from hospitals' blood transfusion services with local birth registers in participating hospitals. Trained medical students and research nurses obtained available data from maternity units, operating theatres and intensive care units. We recorded the following parameters: maternal age at time of birth, body mass index (BMI) at the beginning of pregnancy, parity, ethnicity (Caucasian/non-Caucasian), obstetric medical history (previous cesarean section and/or previous postpartum hemorrhage), gestational age, mode of birth (vaginal birth, instrumental vaginal birth, elective cesarean section or emergency cesarean section), induction of labor, multiple pregnancy, pre-eclampsia in current pregnancy, blood loss (measured by weighing gauzes and by use of a suction system in the operating theatre), number of packed red blood cells transfused, cause of hemorrhage (uterine atony, uterine rupture, placental pathology [including retained placenta, placental remnants, placenta previa,

abnormally invasive placenta and placental abruption], laceration of the birth canal, uterine inversion and clotting disorder with or without amniotic fluid embolism) and management of obstetric hemorrhage (uterotonic agents [oxytocin, sulprostone, ergometrine, misoprostol], non-uterotonic agents [tranexamic acid], intrauterine balloon tamponade, surgical interventions [B-Lynch sutures, uterine artery ligation, peripartum hysterectomy] and uterine artery embolization). Furthermore, since severe postpartum hemorrhage can be the result of concurrent causes, we re-examined all cases of massive transfusion due to postpartum hemorrhage within the TeMpoH-1 cohort, and only included multiple causes for an individual woman if those causes contributed significantly to the bleeding, as was previously done in the LEMMoN study.³ Causes of postpartum hemorrhage in women who received massive transfusion were further analyzed by mode of birth and the number of packed red blood cells transfused, using the same cut-off points described by Green et al.⁴ in the UK: 'moderate' (8–12 units of packed red blood cells), 'high' (13–20 units of packed red blood cells) and 'immense' (more than 20 units of packed red blood cells). Adverse maternal outcome was defined as the need for hysterectomy, admission to an intensive care unit and/or maternal death.

Statistical analyses

All statistical analyses were performed with IBM SPSS Statistics (version 22.0). Categorical data were presented as frequencies with percentages and continuous data as medians with the 25th and 75th interquartile ranges (IQR). The association between possible risk factors and occurrence of postpartum hemorrhage leading to massive transfusion was analyzed by comparing available characteristics from the TeMpoH-1 cohort to characteristics of the general pregnant population in 2012, as obtained from the PRN database.⁸ Given that the PRN database only has summary denominator data, odds ratios (OR) were calculated by means of univariate logistic regression models, resulting in crude odds ratios with 95% confidence intervals (CI).⁸ Women with missing values for a specific parameter were excluded from analyses that required that parameter. The number of births of the TeMpoH-1 cohort comprised women who gave birth under guidance of obstetricians, but did not include women with low risk pregnancies who had given birth under guidance of their midwives or family physicians (primary care), which represented about 29% of all births in the Netherlands between 2011–2012.^{8,9} To estimate a population-based incidence of massive transfusion due to postpartum hemorrhage, number of births in the TeMpoH-1 study was multiplied by 100/71 to represent all births, including those under guidance of primary care.

Ethical approval

The TeMpOH-1 study was approved by the ethics committee of the Leiden University Medical Centre on January 31, 2013 (P12.273) and by the institutional review board of each participating hospital. The study was registered in the Netherlands Trial Register (NTR4079). Need to obtain informed consent was waived by the ethics committee.

RESULTS

The TeMpoH-1 source population comprised 270 101 births (including births under guidance of primary care) in the Netherlands during the two-year inclusion period. A total of 176 women experienced postpartum hemorrhage and received transfusion of eight or more units of packed red blood cells, making the incidence of massive transfusion due to postpartum hemorrhage in the Netherlands 65 per 100 000 births (95% CI; 56 to 75) between 2011 and 2012 (Figure 1)³⁻⁵.

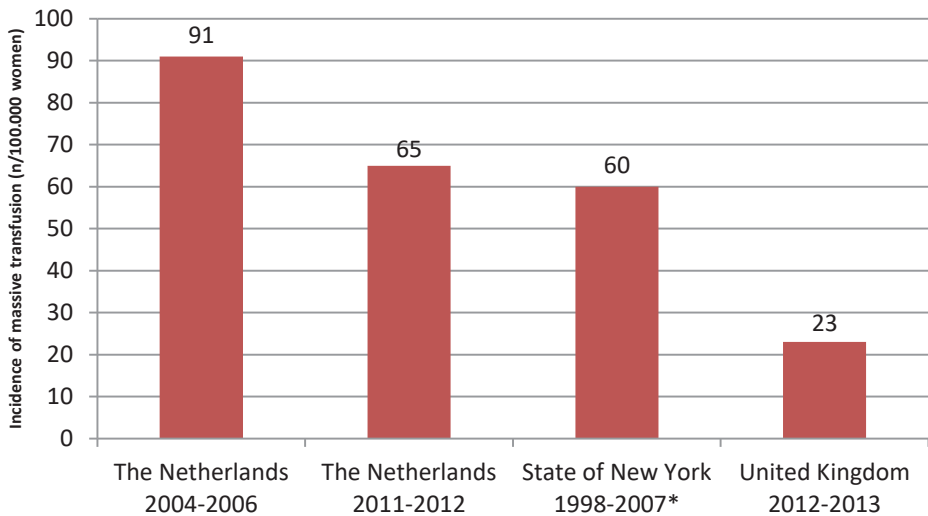


Figure 1. The incidence of women requiring massive transfusion due to postpartum hemorrhage.

*Defined massive transfusion as ≥ 10 packed cells and included all pregnancy-related hemorrhage.⁵

Characteristics of women and bleeding

Women who received massive transfusion due to postpartum hemorrhage had a median (IQR) age of 32 years (29–37), BMI of 23 kg/m² (21–26) and a gestational age of 39 weeks (37–40). The characteristics of women, pregnancy and birth are presented in Table 1 and juxtaposed to the characteristics of women who experienced postpartum hemorrhage and received massive transfusion between 2004 and 2006 in the Netherlands and to the Dutch general pregnant population in 2012.^{3, 8, 10, 11} The median (IQR) estimated blood loss was 6000mL (4500–8000).

Table 1. Characteristics of the women, pregnancy and birth

	2004-2006 ³	2011-2012	General pregnant Dutch population
	N=327	N=176	
	N (%)	N (%)	N (%)
Age (years)			
<20	0 (0)	2 (1)	2257 (1.3) ⁸
20-34	208 (63)	114 (65)	135.406 (78.2) ⁸
35-39	94 (29)	44 (25)	29.562 (17.1) ⁸
≥40	25 (8)	16 (9)	5860 (3.4) ⁸
BMI (kg/m²)			
<18.5	15 (5)	6 (3)	N/A (N/A)
18.5-24.9	137 (42)	84 (48)	N/A (N/A)
25.0-29.9	39 (12)	30 (17)	N/A (N/A)
≥30	24 (7)	10 (6)	N/A (N/A)
Missing	112 (34)	46 (26)	N/A (N/A)
Ethnicity			
Caucasian	N/A (N/A)	109 (62)	N/A (N/A)
Non-Caucasian	N/A (N/A)	51 (29)	N/A (N/A)
Missing	N/A (N/A)	16 (9)	N/A (N/A)
Parity			
0	158 (48.3)	82 (47)	77.647 (44.9) ⁸
1-2	145 (44.3)	83 (47)	93.454 (49.1) ⁸
≥3	24 (7.3)	11 (6)	1998 (6.0) ⁸
Previous CS	66 (20)	45 (26)	1068 (10.9) ¹⁰
Previous PPH*	40 (12)	15 (9)	N/A (N/A)
Gestational age			
20-24	6 (2)	1 (1)	N/A (N/A)
24-32	18 (5)	10 (6)	N/A (N/A)
32-37	62 (19)	24 (13)	N/A (N/A)
≥37	241 (74)	141 (80)	N/A (N/A)
Mode of birth			
Vaginal	131 (40)	64 (36)	131265 (74.5) ⁸
Instrumental	43 (13)	37 (21)	16.210 (9.2) ⁸
Cesarean section	151 (46)	75 (43)	28.680 (16.3) ⁸
Elective	46 (14)	36 (21)	12.280 (7.1) ⁸
Emergency	105 (32)	39 (22)	16.400 (9.2) ⁸
Induction of labor	100 (31)	61 (35)	37.510 (21.7) ⁸
Multiple pregnancy	37 (11)	11 (6)	2992 (1.7) ⁸
Pre-eclampsia	54 (17)	23 (13)	31.560 (2.2) ¹¹

CS: Cesarean section, PPH: postpartum hemorrhage, N/A: data not available.

*Data about previous experienced PPH were missing for 82 women (47%).

Risk factors and causes of hemorrhage

Women with postpartum hemorrhage leading to massive transfusion were more likely to be aged over 35 years (OR 2.01, 95% CI; 1.47 to 2.74), had a previous cesarean section (OR 2.81, 95% CI; 2.00 to 3.95), suffered from preeclampsia (OR 6.71, 95% CI; 4.33–10.41), had a multiple pregnancy (OR 3.86, 95% CI; 2.10 to 7.12), had induced labor (OR 1.92, 95% CI; 1.41 to 2.62), had an instrumental vaginal birth (OR 2.63, 95% CI; 1.83 to 3.78), or had an elective (OR 3.37, 95% CI; 2.34 to 4.86) or emergency (OR 2.82, 95% CI; 1.97 to 4.02) cesarean section. In figure 2 the proportion of causes of postpartum hemorrhage that led to massive transfusion in 2004 to 2006 and in 2011 to 2012 in the Netherlands are compared.³ The commonest cause of postpartum hemorrhage leading to massive transfusion remained uterine atony, followed by retained placenta and placenta previa. Compared with 2004 to 2006, it appears that a larger proportion of women between 2011 and 2012 sustained postpartum hemorrhage due to placenta previa (17% [29/176] vs 11% [37/327]), abnormally invasive placenta (13% [22/176] vs 10% [32/327]) and uterine rupture (11% [19/176] vs 6% [20/327]).³ For 67 women (38%), two causes were registered with uterine atony and placental remnants (N=12) being the commonest combination. The most frequent combination of women with three causes (N=12) was uterine atony with placental remnants and laceration of the birth canal (N=5). The ‘other causes’ as mentioned in Figure 2 were primary clotting disorder (N=4), amniotic fluid embolism (N=1), uterine inversion (N=1) and liver capsule rupture with uterine atony (N=1). Categorising the top three causes of according to the mode of birth showed no noticeable differences over time with placenta previa (22/36; 61%) remaining the commonest cause during elective cesarean section and uterine atony in other modes of birth (Supporting Information Table S1). Uterine atony also remained a leading cause when causes were grouped by the total units of packed red blood cells transfused: ‘moderate’ (8–12 units, N=113), ‘high’ (13–20 units, N=49) and ‘immense’ (≥20 units, N=14).

Management of postpartum hemorrhage

Median (IQR) number of units of packed red blood cells transfused was 11 (9–16). Distribution of obstetric interventions per cause of hemorrhage in 2004 to 2006 and in 2011 to 2012 are summarized in Table 2.³ Compared with 2004 to 2006, it seems that proportionally more women received sulprostone between 2011 and 2012 (82% vs 70%), and sulprostone became the most frequent uterotonic drug administered during postpartum hemorrhage leading to massive transfusion.³ Misoprostol (34% vs 11%) and tranexamic acid (74% vs 22%) were seemingly administered more often as well, while it appears that ergometrine (10% vs 18%) and (non-prophylactic) oxytocin (64% vs 87%) were used less frequently over time.³

Table 2. Distribution of obstetric interventions by cause of postpartum hemorrhage

	Uterine atony		Uterine rupture	
	2004- 2006 ³ N=179	2011- 2012 N=105	2004- 2006 ³ N=20	2011- 2012 N=19
Oxytocin*	94% (N=168)	66% (N=69)	70% (N=14)	47% (N=9)
Sulprostone	87% (N=156)	88% (N=92)	50% (N=10)	84% (N=16)
Tranexamic acid	33% (N=59)	71% (N=74)	5% (N=1)	74% (N=14)
Ergometrine	23% (N=41)	12% (N=12)	15% (N=3)	11% (N=2)
Misoprostol	16% (N=29)	37% (N=39)	5% (N=1)	37% (N=7)
Intrauterine balloon	32% (N=58)	59% (N=62)	10% (N=2)	16% (N=3)
Uterine artery ligation	6% (N=10)	7% (N=7)	5% (N=1)	5% (N=1)
Uterine artery embolization	29% (N=52)	49% (N=51)	10% (N=2)	37% (N=7)
B-Lynch suture	5% (N=8)	18% (N=19)	0% (N=0)	11% (N=2)
Hysterectomy	27% (N=48)	24% (N=25)	70% (N=14)	63% (N=12)

*Prophylactic oxytocin after childbirth excluded.

Thirty-six women with uterine atony did not receive postpartum oxytocin infusion and of those who gave birth vaginally (N=12), all received sulprostone. Of those women without postpartum oxytocin infusion and who gave birth by cesarean section (N=24), 17 received sulprostone. Among these 24 women, uterine atony co-occurred frequently with placenta previa (N=8), uterine rupture (N=6) and abnormally invasive placenta (N=4), and the hysterectomy rate was considerably high (10/24; 42%). Furthermore, it appears that proportionally more women between 2011 and 2012 received intrauterine balloon tamponade (56% vs 23% between 2004 and 2006), B-Lynch suture (14% vs 2% between 2004 and 2006) and embolization of uterine arteries (48% vs 22% between 2004 and 2006).³ Hysterectomy rate among all women receiving massive transfusion due to postpartum hemorrhage was allegedly higher in 2011 to 2012 compared with 2004 to 2006 (30% [53/176] vs 25% [83/327])³, with highest rates among women who endured bleeding due to abnormally invasive placenta (N=18/22), placenta previa (N=20/29) and uterine rupture (N=12/19).

Placenta previa		Invasive placenta		Placental abruption		Total	
2004- 2006 ³ N=37	2011- 2012 N=29	2004- 2006 ³ N=32	2011- 2012 N=22	2004- 2006 ³ N=20	2011- 2012 N=5	2004- 2006 ³ N=327	2011- 2012 N=176
87% (N=32)	38% (N=11)	91% (N=29)	55% (N=12)	70% (N=14)	40% (N=2)	84% (N=275)	64% (N=112)
54% (N=20)	66% (N=19)	72% (N=23)	73% (N=16)	55% (N=11)	40% (N=2)	70% (N=228)	82% (N=145)
19% (N=7)	62% (N=18)	13% (N=4)	77% (N=17)	5% (N=1)	60% (N=3)	22% (N=72)	74% (N=130)
14% (N=5)	7% (N=2)	19% (N=6)	9% (N=2)	20% (N=4)	0% (N=0)	18% (N=60)	10% (N=18)
3% (N=1)	21% (N=6)	3% (N=1)	18% (N=4)	20% (N=4)	20% (N=1)	11% (N=36)	34% (N=60)
14% (N=5)	45% (N=13)	28% (N=9)	36% (N=8)	5% (N=1)	20% (N=1)	23% (N=75)	56% (N=99)
8% (N=3)	3% (N=1)	3% (N=1)	9% (N=2)	5% (N=1)	0% (N=0)	5% (N=17)	5% (N=9)
19% (N=7)	35% (N=10)	19% (N=6)	32% (N=7)	5% (N=1)	40% (N=2)	22% (N=71)	48% (N=84)
3% (N=1)	21% (N=6)	3% (N=1)	9% (N=2)	10% (N=2)	0% (N=0)	2% (N=8)	14% (N=25)
38% (N=14)	69% (N=20)	66% (N=21)	82% (N=18)	5% (N=1)	0% (N=0)	25% (N=83)	30% (N=53)

Adverse maternal outcome

Of all women, 146 (83%) were admitted to an intensive care unit and 53 (30%) underwent hysterectomy as a last resort to stop bleeding. Four women died (three due to exsanguination caused by uterine atony and one due to liver capsule rupture accompanied by uterine atony), of whom two after hysterectomy. Case fatality rate of postpartum hemorrhage with massive transfusion was 1 in 44 women (2.27%) and case fatality rate of women who underwent peripartum hysterectomy due to major postpartum hemorrhage was 2 in 53 women (3.77%).

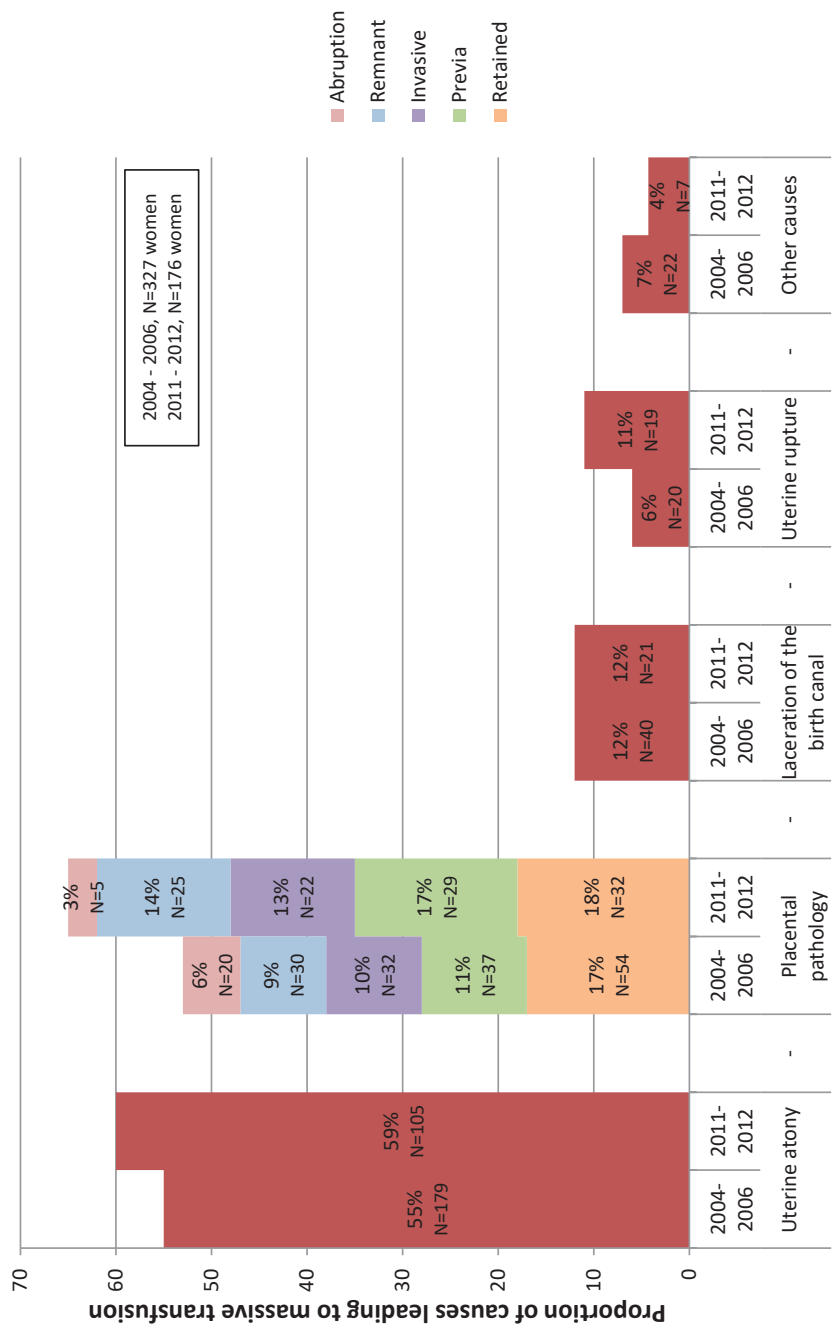


Figure 2. Proportion of causes leading to postpartum hemorrhage with massive transfusion.

DISCUSSION

The incidence of massive blood transfusion due to postpartum hemorrhage decreased in the Netherlands from 91 per 100 000 births (95% CI; 81 to 101) between 2004 and 2006 to 65 per 100 000 births (95% CI; 56 to 75) between 2011 and 2012, while the median (IQR) blood loss increased from 4500mL (3250–6000) to 6000mL (4500–8000).³ The leading cause of postpartum hemorrhage with massive blood transfusion remained uterine atony. Sulprostone was the most administered uterotonic agent and almost one-third (30%) underwent hysterectomy with highest rates among women with abnormally invasive placenta, placenta previa and uterine rupture. Case fatality rate was 0.9% (3/327) between 2004-2006 vs 2.27% (4/176) between 2011-2012.³

Key strengths of this study are that our results are based on a nationwide cohort study (the 71% of the Dutch obstetric units that participated in the TeMpOH-1 were a representative distribution of all obstetric units in the Netherlands at the time, thereby reflecting the general pregnant population in the Netherlands) and that we included all women with postpartum hemorrhage who received massive transfusion by cross-referencing data from hospitals' blood transfusion services with birth registers in local participating hospitals. Additionally, by using the same inclusion criteria and definition of massive transfusion as our previous cohort and the study conducted in the UK, results are directly comparable.^{3, 4} However, in applying eight or more units of packed cells as definition of massive transfusion, it must be noted that these numbers can be influenced by clinical decision making. There is still no definite consensus in the literature as to which definition of massive transfusion should be applied.¹²⁻¹⁴ Furthermore, number of births used as denominator for calculation of incidence of massive transfusion due to postpartum hemorrhage was estimated by multiplying the number of hospital births in the TeMpOH-1 study by the proportion of births under guidance of primary care. However, since coverage of the PRN registry was about 99% of all births in the Netherlands and all women with hemorrhage receiving massive transfusion will eventually have been referred to a maternity unit, we believe that this estimate of incidence is reliable.⁸

The decreased incidence of postpartum hemorrhage leading to massive transfusion along with an observed increase in median blood loss reflects the more restrictive blood transfusion policy in the Netherlands over time.⁶ This gradual change followed, among other things, after the introduction of the '4-5-6 rule' (depending on the presence of co-morbidity, the threshold for transfusion of

packed cells varies between 4.0 mmol/L [6.5 g/dL] and 6.0 mmol/L [9.7 g/dL]) in the Dutch national guideline on blood transfusion in 2004, which implementation probably took time before the effect on the number of blood transfusions became visible.¹⁵ At the same time, the finding that proportionally more women appear to have had peripartum hysterectomy and uterine artery embolization in the recent time frame could either reflect a larger proportion of high-risk pregnancies due to a more restrictive blood transfusion policy, or a more aggressive management of postpartum hemorrhage. Nonetheless, the incidence of massive transfusion due to postpartum hemorrhage in the Netherlands between 2011 and 2012 became comparable to the state of New York between 1998 and 2007 (notwithstanding the higher threshold of 10 or more units of packed cells applied to define massive transfusion in that setting). The incidence, however, remained considerably higher than in the United Kingdom between 2012 and 2013 (23 per 100 000 births, 95% CI; 19 to 26), even though median blood loss in women receiving massive transfusion due to postpartum hemorrhage was similar between the UK and the Netherlands.^{4,5}

Of the women receiving massive transfusion after birth in the Netherlands between 2011 and 2012, there appears to be an increase in the proportion of women who experienced hemorrhage due to placenta previa, abnormally invasive placenta and uterine rupture, and it seems that proportionally more women underwent hysterectomy to control hemorrhage. Although the cesarean section rate remained relatively stable around 16% in the Netherlands^{8,16}, these seemingly increased proportions are partly explained by the fact that a larger proportion of women with a prior cesarean birth were present in the TeMPOH-1 cohort (26% compared to 20% between 2004 and 2006).³ This is known to be associated with increased risks of placenta previa, abnormally invasive placenta and uterine rupture in subsequent pregnancies.¹⁷⁻¹⁹ Furthermore, studies showed that the risk of peripartum hysterectomy increased with the number of prior cesarean births and in presence of an abnormally invasive placenta.²⁰⁻²² Other countries have reported increasing prior cesarean birth rates with an increasing trend in incidence of placenta previa, abnormally invasive placenta and uterine rupture, which may suggest that more countries experience the high burden of hysterectomy because of severe postpartum hemorrhage.²³⁻²⁵

Nevertheless, the hysterectomy rate in the Netherlands remained substantially lower than in the United Kingdom, where the overall rate was 45%.⁴ This difference could be explained by the lower rates of women with previous cesarean births in the Netherlands (26% vs 40% in the UK) and higher rates of embolization

(48% vs 16% in the UK), which may avert hysterectomy in most cases.⁴ The national guideline from the Netherlands Society of Obstetrics and Gynecology (NVOG) states that in case of an ongoing hemorrhage, embolization and/or surgical interventions should not be postponed, while the national guideline in the UK made by Royal College of Obstetricians and Gynaecologists (RCOG) specifically recommends to ‘resort to hysterectomy sooner rather than later’ without explicitly mentioning the option of trying embolization first.^{26, 27} This difference could lead to a more restrictive policy of peripartum hysterectomy in the Netherlands.

Furthermore, the incidence of postpartum hemorrhage also depends on prevalence of risk factors in the population. Our findings confirm previous observations that increased maternal age (≥ 35 years), previous cesarean birth, multiple pregnancy, pre-eclampsia, labor induction, and instrumental or cesarean birth are associated with postpartum hemorrhage leading to massive transfusion.^{5, 11, 28, 29} These antepartum risk factors were only present in a certain number of women enduring severe hemorrhage. Considering that uterine atony remained the leading cause of postpartum hemorrhage that required massive transfusion, demonstrates that all obstetric caregivers should acknowledge the possible severity of uterine atony despite absence of risk factors. In this respect, the substantial decrease of oxytocin use among women with postpartum hemorrhage with massive transfusion due to uterine atony is striking, considering that the Dutch national guideline specifically recommends oxytocin as uterotonic agent of first choice.²⁶ Although our findings rely on the accuracy of data entered into the TeMpoH-1 database, such a decrease is worrying and should be reported to all obstetric caregivers by emphasizing the importance of oxytocin in the Dutch national guideline on the management of postpartum hemorrhage, which may reduce the need to resort to massive transfusion following childbirth.

Despite all changes over time, the maternal mortality ratio (MMR) in women with postpartum hemorrhage leading to massive transfusion in the Netherlands was 1.48 deaths per 100 000 live births between 2011 and 2012 vs 0.84 deaths per 100 000 live births between 2004 and 2006.³ These results should be viewed with caution, given the substantial uncertainty surrounding these estimates due to the small number of deaths. However, the MMR of postpartum hemorrhage requiring massive transfusion was considerably higher than reported in the United Kingdom between 2012 and 2013 (0.23 deaths per 100 000 live births)⁴, and this finding is worrying and merits closer analysis. Our findings are of utmost importance to other high-income countries, where similar patterns may have

occurred. Maternal mortality has become a very rare outcome in these countries, which hampers comparisons over time and between settings. Our findings should encourage researchers in other high-income settings to critically evaluate their clinical management and maternal mortality because of severe postpartum hemorrhage.

National surveillance of maternal morbidity and mortality due to postpartum hemorrhage through improved continuous registration with confidential enquiries and multidisciplinary simulation training of postpartum hemorrhage-related emergencies could improve the quality of maternal care. The MBRRACE-UK reports (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) are likely to have contributed to a steady fall of obstetric hemorrhage-related deaths in the United Kingdom and provides a rational framework for how national surveillance may be applied by other countries.^{30, 31} Nevertheless, the escalating rates of postpartum hemorrhage in other high-income countries emphasizes the importance of nationwide studies into obstetric hemorrhage-related maternal morbidity and mortality.^{29, 32, 33} International comparison of data regarding postpartum hemorrhage that led to massive blood transfusion could reveal variations in the management and outcome between countries, and consequently lead to improvements in maternal care. Collaboration such as the International Network of Obstetric Survey Systems could help facilitate population-based studies.³⁴

CONCLUSION

The incidence of postpartum hemorrhage leading to massive blood transfusion decreased in the Netherlands, but continues to be an important cause of maternal morbidity and mortality. Improved continuous registration of severe postpartum hemorrhage with confidential enquiries to identify substandard factors could lead towards better maternal care and may prevent severe maternal outcome from postpartum hemorrhage in the Netherlands. International comparison of our findings could provide high quality evidence for the best management practices of severe postpartum hemorrhage.

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SUPPLEMENTALS

Table S1. Top three causes of postpartum hemorrhage categorized by mode of birth

2004–2006 ³			2011–2012		
	N	(%)		N	(%)
Vaginal birth (N=131)			Vaginal birth (N=64)		
1. Uterine atony	84	(64)	1. Uterine atony	32	(50)
2. Retained placenta	40	(31)	2. Retained placenta	21	(33)
3. Placental remnant	20	(15)	3. Placental remnant	18	(28)
Instrumental birth (N=43)			Instrumental birth (N=37)		
1. Uterine atony	26	(60)	1. Uterine atony	24	(65)
2. Retained placenta	14	(33)	2. Retained placenta	10	(27)
3. Placental remnant	6	(14)	3. Laceration birth canal	10	(27)
Elective cesarean section (N=46)			Elective cesarean section (N=36)		
1. Placenta previa	24	(52)	1. Placenta previa	22	(61)
2. Uterine atony	17	(47)	2. Uterine atony	21	(58)
3. Abnormally invasive placenta	13	(28)	3. Abnormally invasive placenta	13	(36)
Emergency cesarean section (N=105)			Emergency cesarean section (N=39)		
1. Uterine atony	51	(49)	1. Uterine atony	28	(72)
2. Uterine rupture	13	(12)	2. Uterine rupture	11	(28)
3. Iatrogenic during cesarean	9	(9)	3. Placenta previa	5	(13)

