Full length article

Incidence and recurrence rate of postpartum hemorrhage and manual removal of the placenta: A longitudinal linked national cohort study in The Netherlands

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ABSTRACT

Objective: We studied the incidence of postpartum hemorrhage and manual removal of the placenta and their recurrence rate in a subsequent pregnancy. We hypothesized that the risk of recurrence was dependent on the gestational age at first birth and whether or not a manual removal of the placenta was necessary. Knowledge on this subject can potentially improve counselling, prevention and management in obstetric care for women at risk for PPH or identify women at low risk for recurrence.
Study design: This was a retrospective national cohort study consisting of women with two consecutive singleton deliveries between 1999 and 2009 in the Netherlands.
A longitudinal linked national cohort with information on subsequent singleton deliveries in the Netherlands was used. Main outcome measures were: postpartum hemorrhage (defined as $\geq$1000 mL after vaginal delivery or Caesarean section) and manual removal of the placenta. We calculated incidence and recurrence rates of postpartum hemorrhage and manual removal of the placenta for all women and stratified by gestational age.
Results: After application of in- and exclusion criteria 359 737 women were studied. A total of 5.4% women experienced postpartum hemorrhage in the first pregnancy and 2.7% of women had a manual removal of the placenta. The risk of postpartum hemorrhage in a subsequent pregnancy was significantly higher in women with a history of postpartum hemorrhage compared to women without a previous postpartum hemorrhage (18% vs 3.9%, adjusted odds ratio 4.5; 95% confidence interval 4.3–4.7). The risk of manual removal of the placenta in the second pregnancy was only 1.4% in women without a previous manual removal compared to 17% of women with a previous manual removal of the placenta. Women with a manual removal of the placenta in the first pregnancy between 32 and 37 weeks were most at risk for recurrence (adjusted odds ratio 8.9; 95% confidence interval 7.2–11).
Conclusion: Women with a previous delivery complicated by postpartum hemorrhage or manual removal of the placenta are at increased risk for recurrence. The magnitude of this risk is highest in women with deliveries beyond 32 weeks in the first pregnancy.

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Introduction

Postpartum hemorrhage (PPH) is still one of the leading causes of maternal morbidity and mortality in developed and third world countries, despite improvements in prevention and management

[1,2]. Recent studies on PPH in developed countries report an increasing incidence over time [3–5].

PPH is associated with uterine atony, genital tract lesions and manual removal of the placenta (MRP) [6]. Risk factors for PPH have been established in several studies and are among others; increased maternal age, multiple pregnancy, fibroid tumors, placenta previa or accreta, macrosomia, prolonged third stage of labor, instrumental vaginal delivery, caesarean delivery and genital tract lesions [3,7,8,2].

Previous research showed an increased risk of MRP in case of preterm delivery [9]. The hypothesis behind this is that defective or impaired deep placentation can lead to enhanced oxidative stress

and apoptosis in the placenta and thereby increase the risk of retained placenta [10–12].

Women with a previous PPH are considered to be at high risk for recurrence, and therefore in their next delivery preventive measures are often taken. It is unknown whether the gestational age of the previous delivery influences the recurrence risk.

We aimed to calculate the incidence and recurrence rate of PPH and MRP. We hypothesized that the risk of recurrence was dependent on the gestational age at first birth and whether or not a manual removal of the placenta was necessary. Knowledge on this subject can potentially improve counselling, prevention and management in obstetric care for women at risk for PPH or identify women at low risk for recurrence.

Materials and methods

We performed a nationwide retrospective cohort study using data from the Netherlands Perinatal Registry (PERINED). The PERINED registry consists of prospectively collected data containing information on pregnancies, deliveries and neonatal (re) admissions. The database is constructed by a validated linkage of three separate registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) [13,14].

Approximately 96% of all deliveries in the Netherlands are documented in the PERINED registry. The PERINED registry is primarily designed and used for annual assessment of the quality indicators of obstetric care. Standard quality checks are performed by the PERINED registry yearly after the data is supplied by the individual caregivers. In addition, changes have been made over the years to improve the electronic data transfer, which is an ongoing process.

Since all records in the PERINED registry are entered at child's level there is no unique maternal identifier. To link records of children of the same mother, a mother identifier was created by a longitudinal probabilistic linkage procedure. Details on this linkage procedure are described elsewhere [15]. So far only records up till 2009 have been linked.

In and exclusion criteria

We selected all women that delivered between Jan. 1, 1999 and Dec. 31, 2009. For both pregnancies, women with a multiple gestation or with a gestational age at delivery <24 + 0 weeks or > 42 + 6 weeks were excluded. Furthermore, we excluded all women with a placental abruption, since the etiology of this blood loss is different from the postpartum hemorrhage of interest in our study.

Outcomes

Our main outcomes were postpartum hemorrhage (PPH $\geq$ 1000 mL after vaginal delivery or Caesarean section) and/or manual removal of the placenta. We selected all women that were registered with a code for PPH or MRP in the PERINED registry. Diagnosis codes are assigned and registered by midwives, residents and gynecologists present at the delivery. A diagnosis of PPH is assigned with a minimum amount of blood loss of 1000 mL, independently of execution of interventions because of PPH. The amount of blood loss is judged by the individual care giver. In addition, we labelled all women with a positive history of documented PPH at the beginning of their second pregnancy as cases of PPH in the first pregnancy.

Statistical analyses

We divided the cohort in four groups; no PPH and no MRP, no PPH but MRP, PPH without MRP and no PPH but MRP. Demographic and first pregnancy and delivery baseline characteristics between the four subgroups of women were compared with the ANOVA test or chi-square test. All tests were two-sided with a p-value of 0.05 as the threshold for statistical significance.

The incidence of PPH was calculated for first and second pregnancies by dividing the number of deliveries complicated by PPH by the total number of vaginal and caesarean deliveries. The total number of MRP was divided by the total number of vaginal deliveries.

To estimate the effect of a previous PPH and/or MRP on the recurrence of these complications in a subsequent pregnancy

Table 1
Baseline characteristics of the complete linked cohort (N = 359 737).

Maternal characteristics	First pregnancy								p-value
	No PPH, no MRP (n = 337 229)		PPH with MRP (n = 4 302)		PPH without MRP (n = 14 972)		MRP without PPH (n = 3 234)		
	n	%	n	%	n	%	n	%	
Maternal age, years ± SD	28.5 (± 4.2)		30.2 (± 3.7)		28.8 (± 4.1)		29.8 (± 4.0)		<0,001
Maternal age <25 y, n (%)	57 490	17	303	7.0	2 099	14	311	9.6	<0,001
Maternal age ≥35 y, n (%)	23 843	7.1	514	11	1 093	7.3	362	11	<0,001
Non-Caucasian ethnicity, n (%)	39 270	12	214	5.0	1 492	10	253	7.8	<0,001
Low socioeconomic status, n (%)	75 301	22	739	17	3 065	21	652	20	<0,001
Hypertensive disorder, n (%)	41 001	12	686	15	2 134	14	609	19	<0,001
Fibroid tumors	637	0.20	20	0.46	51	0.34	5	0.15	<0,001
Delivery characteristics									
Mean gestational age, wk ± SD	39w1d (± 2w0d)		39w1d (± 2w4d)		39w4d (± 2w0d)		38w1d (± 3w6d)		<0,001
Premature birth <37wk	24 544	7.3	473	11	786	5.2	659	20	<0,001
Spontaneous start of labor, n (%)	195 284	58	1 885	43	8 052	54	1 303	40	<0,001
Perineal or labial tear*	103 454	37	1 372	32	4 659	36	828	28	<0,001
Episiotomy*	143 687	52	2 644	61	7 846	61	1 650	56	<0,001
Fetal characteristics									
Male, n (%)	173 669	52	2 049	47	7 335	49	1 623	50	<0,001
Mean birthweight (grams ± SD)	3358 (± 582)		3369 (± 649)		3576 (± 579)		3056 (± 879)		<0,001
Macrosomia >4000	38 333	11	619	14	3253	22	264	8.2	<0,001
Macrosomia >4500	5 514	1.6	121	2.8	623	4.2	40	1.2	<0,001

*% of vaginal deliveries PPH postpartum hemorrhage MRP manual removal of placenta.

logistic regression modelling was used and was expressed as odds ratio (OR) with a 95% confidence interval (CI). To account for the effect of potential confounders we used a multivariate logistic regression analysis to adjust for confounders. In addition a subgroup analysis was performed including only vaginal deliveries.

To determine whether gestational age at delivery in the first pregnancy was associated with the recurrence rate, we stratified women by gestational age at first delivery (early preterm 24+^{0} - 31+^{6} weeks gestation, late preterm 32+^{0} - 36+^{6} weeks gestation and term 37+^{0} - 42+^{6} weeks gestation). The effect of gestational age at first occurrence of PPH on the recurrence rate was estimated and expressed as odds ratio with 95% CI, comparing women with a history of PPH (regardless of MRP) to women without PPH in the first pregnancy.

We did the same analysis for the recurrence risk of MRP (regardless of PPH) in women with two subsequent vaginal deliveries.

Data were analyzed with the SAS statistical software package (version 9.4; SAS Institute Inc, Cary, NC, USA).

Ethical approval

The data in the PERINED database are anonymous so no ethical approval was needed. The Netherlands Perinatal Registry gave their approval for the use of the data for this study (approval no. 14.01).

Results

Between Jan. 1, 1999 and Dec. 31, 2009, a total of 359 737 singleton-singleton pregnancies met all inclusion criteria and were included in our study. A total number of 10 800 (2.8%) multiple gestations, 2,754 (0.7%) pregnancies with a gestational age at delivery <24 + 0 weeks or > 42 + 6 weeks and 335 (0.1%) pregnancies complicated by a placental abruption were excluded. For the calculation of recurrence of MRP only women with 2 vaginal deliveries (N = 281 806) were included.

The baseline characteristics of our linked cohort are listed in Table 1. Women with a PPH and/or MRP after their first delivery were older, more often of Caucasian ethnicity and had more often hypertensive disorders and a macrosomic infant compared to women without PPH or MRP in their first pregnancy (*P* < 0.0001).

A total of 19 274 (5.4%) women had PPH in their first pregnancy. The total number of MRP was 7 536 (2.7%) in the first pregnancy. The overall incidences of PPH (with and without MRP) and MRP in the first pregnancy per gestational week are shown Fig. 1a and b. The incidences of PPH in the first pregnancy per gestational age shows a marked increase of PPH in early (24–26 weeks) and late gestation (42 weeks) Fig. 1a. The incidence of MRP on the other hand decreases with increasing gestational age, Fig. 1b.

The recurrence rates of PPH and/or MRP are shown in Table 2, as well as the corresponding odds ratios. The majority of women without a previous PPH or MRP delivered without PPH or MRP the second time (96%). Women with a history of PPH and MRP were at increased risk of recurrence of PPH and MRP in the second pregnancy. The magnitude of the risk depends on characteristics of the first delivery with an aOR varying from 18; 95%CI; 16–19 for women with previous PPH and MRP compared to an aOR of 4.8; 95%CI; 4.4–5.3 for women with PPH without MRP (Table 2)).

The total recurrence rate irrespective of gestational age is 18% (Table 3). In addition, Table 3 shows the gestational age at first delivery complicated by PPH (both with and without MRP) and the corresponding recurrence rate in a subsequent pregnancy (ranging from 7.7 to 18% depending on the gestational age). The recurrence
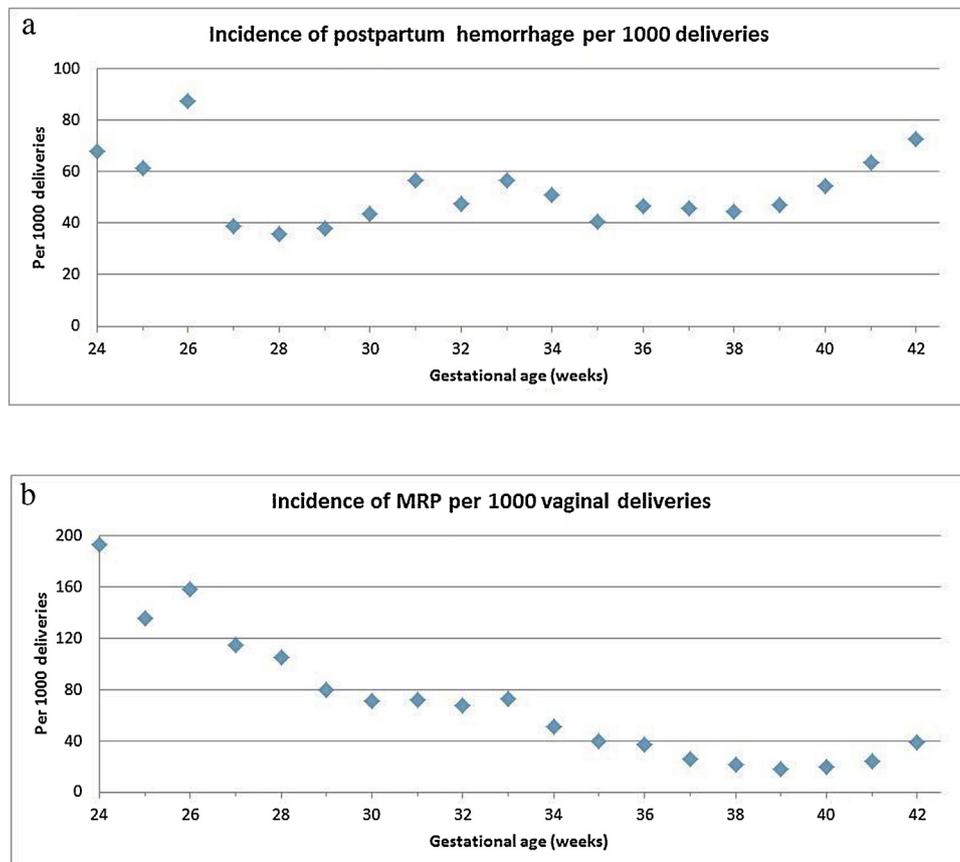
Fig. 1. (a) Incidence of PPH by gestational age. (b) Incidence of MRP by gestational age.

Table 2
(a) and (b) Percentages of recurrence and adjusted odds ratios.

2a. Percentages of recurrence

| Characteristics of first delivery: | Second delivery | | | | | | | |
| | No PPH, no MRP (n = 340,619) | | PPH and MRP (n = 4,132) | | PPH without MRP (n = 12,680) | | MRP without PPH (n = 2,306) | |
	n	%	n	%	n	%	n	%
No PPH, no MRP (n = 337,229)	322476	96	2761	0.82	10181	3.0	1811	0.5
PPH and MRP (n = 4,302)	3066	71	586	14	472	11	178	4.1
PPH without MRP (n = 14,972)	12378	83	582	3.9	1856	12	156	1.0
MRP without PPH (n = 3,234)	2699	84	203	6.3	171	5.3	161	5.0

2b. Adjusted odds ratios [A]

| Characteristics of first delivery: | Second delivery | | | |
	No PPH, no MRP (n = 340,619)	PPH and MRP (n = 4,132)	PPH without MRP (n = 12,680)	MRP without PPH (n = 2,306)
No PPH, no MRP (n = 337,229)	Reference	Reference	Reference	Reference
PPH and MRP (n = 4,302)	0.12 (0.11-0.13)	18 (16-19)	3.8 (3.5-4.2)	7.3 (6.2-8.6)
PPH without MRP (n = 14,972)	0.22 (0.21-0.23)	4.8 (4.4-5.3)	4.4 (4.2-4.7)	1.9 (1.6-2.3)
MRP without PPH (n = 3,234)	0.24 (0.22-0.27)	7.5 (6.5-8.7)	1.8 (1.5-2.0)	8.6 (7.2-10)

PPH postpartum hemorrhage MRP manual removal of placenta.
[A] Adjusted for maternal age, ethnicity, hypertension, gestational age, induction of labor, genital tract lesions, fetal presentation, fetal sex, macrosomia.

Table 3
PPH in a subsequent pregnancy in total and by gestational age of delivery in the first pregnancy.

| First pregnancy | | PPH second pregnancy | | Odds ratio (95% CI) | |
	Total	n	%	Crude	Adjusted
Women without PPH	340 463	13 316	3.9	Reference	
Women with PPH	19 274	3 496	18	4.9 (4.6-5.1)	4.5 (4.3-4.7)[A]
Gestational age at delivery:					
<**32 weeks**	208	16	7.7	2.1 (1.2-3.4)	1.4 (0.84-2.4)[B]
32-37 weeks	1 051	183	17	5.2 (4.4-6.1)	4.0 (3.4-4.7)[B]
>**37 weeks**	18 015	3 297	18	5.5 (5.3-5.7)	4.6 (4.4-4.8)[B]

[A] Adjusted for manual placental removal, maternal age, ethnicity, hypertension, gestational age, induction of labor, genital tract lesions, fetal presentation, fetal sex, macrosomia.
[B] Adjusted for manual placental removal, maternal age, ethnicity, hypertension, induction of labor, genital tract lesions, fetal presentation, fetal sex and macrosomia.

rate was increased for women with a history of PPH following a delivery in the term period (aOR 4.6; 95% CI; 4.4–4.8) and late preterm period (aOR 4.0; 95% CI; 3.4–4.7) compared to women without a history of PPH.

A subgroup analysis including only two subsequent vaginal deliveries showed comparable results (supplemental Table 1).

Table 4 shows that among women without a MRP in the first pregnancy only 1.4% needed a MRP in the second pregnancy. In women with a MRP in the first pregnancy 17% needed a MRP in the second pregnancy. The increased risk of recurrence after a MRP in the first pregnancy is present irrespective of gestational age of the first pregnancy. Even though the odds of recurrence in women with a late preterm MRP was significantly higher compared to women with an early preterm or term MRP in their first pregnancy (aOR late preterm 8.9; 95%CI 7.2–11, aOR early preterm 4.6 ;95%CI 2.9–7.2, aOR term 5.9; 95%CI 5.3–6.5, Table 4).

Comment

In this linked cohort study we investigated the incidence and recurrence rate of PPH and MRP among singleton pregnancies in the Netherlands. In addition, we investigated

Table 4
MRP in a subsequent pregnancy by gestational age of delivery in the first pregnancy.

| First pregnancy | | MRP second pregnancy | | Odds ratio (95% CI) | |
	Total	n	%	Crude	Adjusted
Women without MRP	275 424	3990	1.4	Reference	
Women with MRP	6 382	1100	17	14 (13-15)	6.1 (5.6-6.7)[A]
Gestational age at delivery:					
<**32 weeks**	220	22	10	7.6 (4.9-12)	4.6 (2.9-7.2)[B]
32-37 weeks	653	133	20	17 (14-21)	8.9 (7.2-11)[B]
>**37 weeks**	5509	945	17	14 (13-15)	5.8 (5.3-6.5)[B]

[A] Adjusted for PPH, maternal age, ethnicity, hypertension, gestational age, induction of labor, genital tract lesions, fetal presentation, fetal sex, macrosomia.
[B] Adjusted for PPH, maternal age, ethnicity, hypertension, induction of labor, genital tract lesions, fetal presentation, fetal sex and macrosomia.

the effect of gestational age and mode of first delivery on the recurrence rate.

Main findings

The incidence of PPH in first pregnancies was 5.4% and the incidence of MRP was 2.7% in first pregnancies with a decreasing incidence with increasing gestational age. The recurrence rate of PPH in a subsequent pregnancy was 18% in our study. The risk of PPH in a subsequent pregnancy was significantly higher in women with a previous PPH compared to women without a history of PPH, the same applies to MRP.

Importantly, this study shows that the recurrence rate of PPH and MRP in a subsequent pregnancy is mildly associated with the gestational age of the first delivery that was complicated by PPH. Women with a history of MRP after a late preterm delivery are even more at risk of recurrence compared to women with a history MRP after an early preterm or term delivery.

Strengths and limitations

This study comes with both strengths and limitations. One of the strengths of this study is that it is performed with data from a large national registry with prospectively collected data thereby minimizing recall and reporting bias. We needed to rely on the information that was available in the perinatal registry thus we cannot rule out misclassification and potential under registration. However, since a history of PPH or MRP is a well-known indication for hospital delivery in a subsequent pregnancy in the Netherlands, we do not expect that a significant amount of cases of PPH and MRP have not been registered. Furthermore, PPH and MRP are clinical outcomes which are caused by multifactorial aetiologies such as atony, trauma, surgery, retained placenta, trapped placenta or partial accreta. These factors are not separately documented in our database and provide a limitation of our study, as well as the lack of data on other possible confounders and potential risk factors for PPH as body mass index, tobacco use and bleeding disorders. In addition, the total amount of blood loss is not registered in the PERINED registry which made it impossible to account for the degree of severity of PPH. One could argue that we should not have excluded women with a placental abruption since it could be of interest to know if abruption increases the risk for PPH and MRP in forthcoming pregnancies. However, since the number of women with placental abruption was so low (0.1%), it was not possible to draw any definite conclusions about whether placental abruption increases the risk of recurrent PPH.

Interpretation

The incidence of PPH in literature varies between 2.3 and 10%. But since the definition of PPH is not uniform and the incidence of PPH appears to follow an increasing trend over time, exact comparison is difficult. Numerous studies used a total amount of blood loss of 500 mL as cut-off for PPH whereas in the Netherlands a cut- off of 1000 mL is used. Since blood loss of 500 mL rarely comprises maternal condition we think our definition is clinically more relevant. [8,16] When we compare our data to studies with data from a similar study period and definition, we find comparable incidences, varying between 5.1 and 6.8% [4,5,17]. The incidence in our study is slightly higher than the incidence calculated in studies based on data before the year 2000, which was on average 4.0% [5,18]. This is in line with the increasing trend on PPH incidence described in previous studies [3,4,19]. The incidence of MRP in our study is comparable to the incidences reported in literature, between 0.5 and 3.0%. [6,9,20–23].

In our study we found a recurrence rate of PPH in a subsequent pregnancy of 18% which is comparable with previous documented recurrence rates [5,19]. Potentially, the recurrence rate is even higher than reported since it is known that women with a history of PPH are less likely to conceive again [18]. Knowledge on a history of PPH in prenatal care may alter the obstetric care for women that do conceive again. A previous study of Oberg et al. found that the risk of recurrence of PPH was significantly increased nonetheless the cause of the first episode of PPH. They found that women with a vaginal delivery complicated by PPH because of retained placental tissue were more at risk for recurrence of PPH than women with PPH because of atony or genital tract lacerations, which is in line with our results that women with PPH and MRP are more at risk for recurrence than women with PPH without MRP [19].

In our study we extended the findings of previous studies on the recurrence rate by investigating the effect of gestational age at delivery at first episode of PPH. Although a higher incidence of PPH in term deliveries beyond 40 weeks of gestation has been reported in literature before, comparison with preterm deliveries or the recurrence rate in subsequent pregnancies haven't been studies before [24]. To our knowledge, our study is the first to stratify recurrence rate of PPH and MRP by gestational age of the first episode of PPH or MRP. Women with a late preterm delivery complicated by MRP have the highest risk of occurrence of MRP in a subsequent pregnancy compared to women with an early preterm or term MRP. We hypothesize that the limited development of preterm myometrial tissue may explain why cases of early preterm MRP recur less in a subsequent pregnancy than cases of late preterm MRP [20]. Thus, although preterm delivery is known to increase the initial risk of PPH and MRP [20,21,25,26], the consequences for a potential future pregnancy depend on the gestational age.

Conclusion

Women with a previous delivery 32–37 weeks complicated by MRP are most at risk for recurrence compared to women without a history of MRP. Longitudinal linked cohort studies with complete information on type of PPH, gestational age at delivery and total amount of blood loss are needed to develop prediction models to further stratify low- and high risk women for PPH and or MRP. These models will help in counselling and individualization of prenatal and peripartum care in women with a history of PPH/MRP in order to decrease the recurrence of these serious complications.

Conflict of interest

The authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.05.022.

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