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MATERNAL-FETAL MEDICINE

The increasing role of a retained placenta in postpartum blood loss: a cohort study

Hellen McKinnon Edwards[1] · Jens Anton Svare[1] · Anne Juul Wikkelsø[2] · Jeannet Lauenborg[1] · Jens Langhoff-Roos[3]

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Abstract

Purpose To describe the association between quantity of blood loss, duration of the third stage of labour, retained placenta and other risk factors, and to describe the role of a retained placenta depending on the cutoff used to define postpartum haemorrhage.

Methods Cohort study of all vaginal deliveries at two Danish maternity units between 1 January 2009 and 31 December 2013 ($n = 43{,}357$), univariate and multivariate linear regression statistical analyses.

Results A retained placenta was shown to be a strong predictor of quantity of blood loss and duration of the third stage of labour a weak predictor of quantity of blood loss. The predictive power of the third stage of labour was further reduced in the multivariate analysis when including retained placenta in the model. There was an increase in the role of a retained placenta depending on the cutoff used to define postpartum haemorrhage, increasing from 12% in cases of blood loss ≥ 500 ml to 53% in cases of blood loss ≥ 2000 ml

Conclusion The predictive power of duration of the third stage of labour in regard to postpartum blood loss was diminished by the influence of a retained placenta. A retained placenta was, furthermore, present in the majority of most severe cases.

Keywords Postpartum haemorrhage · Retained placenta · Third stage of labour · Pregnancy blood loss

Introduction

It is well-known worldwide that the leading direct cause of maternal morbidity and mortality in both developing and developed regions is postpartum haemorrhage (PPH) [1]. In recent years, the awareness towards PPH has increased further due to a rising incidence in developed regions [2–4]. This rise has not only been seen in cases of mild PPH, but also in more severe cases [5, 6]. The major cause of PPH has typically been attributed to lack of tone in the uterus, i.e., atony, with the remainder of causes associated with either trauma to the birth canal, retained tissue, or coagulopathy [7]. However, the cutoff used to define PPH and the distribution of causes varies between studies, leaving us unsure whether it is the different cohorts or the different definitions that cause the variation in distribution [5, 8–10].

Prolonged duration of the third stage of labour has been identified as one of the risk factors for PPH, leading to most national guidelines recommending active management of the third stage of labour and manual removal of the placenta if this exceeds 30 min or if there is bleeding [5, 11–13]. Recent studies have, however, reported that the increased risk of PPH already exists if the third stage of labour exceeds 15–20 min, suggesting that manual removal of the placenta should be performed early on regardless of blood loos [14–16]. Up to 90% of placentas are delivered within 10 min [15, 17], with the majority of remaining cases having a prolonged duration of the third stage of labour due to a placenta that is trapped, adherent, or even abnormal invasive (AIP) [18, 19]. These disorders are all risk factors for PPH

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✉ Hellen McKinnon Edwards
dochellen@gmail.com

[1] Department of Obstetrics and Gynaecology, Copenhagen University Hospital Herlev, Herlev Ringvej 75, 2730 Herlev, Denmark

[2] Department of Anaesthesia and Intensive Care Medicine, Copenhagen University Hospital Herlev, Herlev Ringvej 75, 2730 Herlev, Denmark

[3] Department of Obstetrics, Juliane Marie Centre, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark

and often require manual removal of the placenta irrespective of the length of the third stage of labour. However, the majority are difficult to diagnose before manual removal has taken place [19], with the exception of trapped placenta that sometimes can be diagnosed by postpartum ultrasound. The question is, therefore, whether some placentas removed manually could have been delivered spontaneously without an increased risk of PPH regardless of the length of the third stage of labour.

In the present study, we analysed data from a large regional birth cohort to investigate the association between the duration of the third stage of labour, a retained placenta, other risk factors, and quantity of postpartum blood loss. Furthermore, we investigate whether the proportion of cases with retained placenta depended on the cutoff used to define PPH.

Methods

Study population

This retrospective cohort study is based on data from the Copenhagen Obstetric Database, where all births in the Capital Region of Copenhagen are registered. Data from 01 January 2009 until 31 December 2013 were retrieved. We acquired permission from the Danish Data Protection Agency (ID HEH-2014-078). No permission was required from the Danish Ethics Committee according to Danish legislation.

The Obstetric Database includes data on maternal demographics, parity, labour, and delivery, and holds a high internal validity with kappa coefficients from 0.7–1.0 [20]. Midwives register baseline data and interventions both during and after labour, while obstetricians or senior midwives supply specialist diagnosis after the patients have been discharged from hospital [20]. Estimations of blood loss at the hospitals are based primarily on weighing of pads, collector bags, and collection during peripartum surgery. Combined weighing of standard pads and the content of collector bags are used as a standard to determine blood loss on all labour beds at the included hospitals. The Danish national guideline recommends routine administration of 10 IU of oxytocin at delivery, and manual removal of the placenta within 30 min or immediately if there is active bleeding [11]. Inclusion criteria were all vaginal births (singleton and multiple pregnancies) from 22 to 43 weeks of gestation, as the majority of cases with GA >43 + 6 were interpreted as faulty registration. All cases with missing data on blood loss (897 deliveries), or postpartum blood loss lower than 50 ml (68 deliveries) were excluded, due to the assumption that all women bleed at least 50 ml. Due to some hospitals only reporting to the registry for less than 1 year of the study period, we excluded these hospitals (3 centres/4591 deliveries).

Variables

The following variables from the database were included in this study: maternal age, parity, previous caesarean section, singleton or multiple pregnancy, hypertensive disorders of the mother, antepartum haemorrhage, placenta praevia, abnormal invasive placenta, presentation of the foetus, amniotic fluid abnormalities, preterm premature rupture of membranes (PPROM), premature rupture of membranes (PROM), date and time of delivery, hospital, gestational age at delivery, induction of labour, augmentation of labour, fever during labour, mode of delivery, episiotomy, genital tract lacerations, epidural analgesia, uterine rupture, placental abruption, shoulder dystocia, uterine inversion, quantity of postpartum blood loss (ml), duration of labour (min), duration of expulsive efforts (min), time of delivery or removal of the placenta, retained placenta, and manual removal of tissue or placenta. The diagnosis "retained placenta" is used in the registry when it is removed manually, regardless of the length of the third stage of labour. Abnormal invasive placenta, retained placenta, and manual removal of placental tissue were grouped together as "retained placenta" for our study. Cases with missing or invalid durations of labour, expulsive efforts, and third stage of labour were excluded from the linear regression model. We were not able to retrieve sufficient data on the previous PPH, BMI, and birthweight. Uterine atony is not coded in our database. Outcome of quantity of postpartum blood loss was not only analysed as a continuous variable, but also using four different definitions of PPH with cutoffs of: ≥ 500 ml, ≥ 1000 ml, ≥ 1500 ml, and ≥ 2000 ml. Duration of the third stage of labour was calculated from the time of delivery of the neonate until the time of delivery of placenta —either spontaneously or by manual removal.

Statistical analysis

All data analyses were carried out using SPSS 22.0 (SPSS, Chicago, IL, USA). Quantity of postpartum blood loss and durations are presented as medians and interquartile ranges (IQR) due to their non-parametric distribution. Quantity of postpartum blood loss was logarithmic transformed (log10) due to substantially skewed distribution. Risk factors for quantity of postpartum blood loss were analysed using univariate and multivariate linear regression analyses presented as β-coefficients and 95% confidence intervals (CI). Due to the logarithmic transformation of quantity of postpartum blood loss, β values need to be back-transformed by raising 10 to the power of each value and subtracting one (10^{x}-1); and can then be interpreted as percent change in

the predicted quantity of postpartum blood loss. Thereby, the predicted mean blood loss can be calculated for each risk factor using the constant β and the percent change. The predicted mean blood loss for a combination of risk factors can be calculated by adding the β coefficient for each risk factor to the β coefficient of the constant, before "back-transforming". All variables extracted from the database were included in the multivariate linear regression model stepwise with model 1 only including variables known before and during pregnancy, model 2 including variables arising during labour and delivery, and finally model 3 including a retained placenta. All variables were tested for correlation using Pearson's correlation in the linear regression analysis, and there were no significant correlations between any two variables. Chi-square test was used to analyse postpartum blood loss as a categorical variable. Data are presented as proportions and percent (%), means and standard deviations (SD), or medians and interquartile ranges (IQR) for normally and non-normally distributed data. A two-tailed p value of less than 0.05 was considered statistically significant.

Results

We identified 43,357 vaginal deliveries from the Copenhagen Obstetric Database from 2009 until 2013 (Fig. 1). The majority of deliveries were by nulliparous women (53.9%) between 20 and 34 years of age (75.6%) without any hypertensive disorders (95.5%). A total of 92.2% gave birth at term with a median duration of the third stage of labour of 8 min [IQR 5–12] and a median blood loss of 300 ml [IQR 200–400] (Online Resource 1).

Prediction of quantity of postpartum blood loss

Duration of the third stage of labour was identified as a significant but weak predictor of quantity of postpartum blood loss in the univariate linear regression analysis $\beta = 0.0046$ ($p < 0.005$), equivalent to a predicted increase in postpartum blood loss of 10.7% for every prolonged 10 min (Table 1). The multivariate linear regression analysis predicted the mean blood loss to 224 ml (95% CI 219–229, $\beta = 2.350$) for a delivery without the presence of any of the included risk factors. The predictive power of the duration of the third stage of labour remained unchanged after adjusting for the majority of variables in the multivariate analysis ($\beta = 0.004$, $p < 0.005$) (Table 1, model 2). However, the effect of duration of the third stage of labour decreased substantially after inclusion of retained placenta in the model to $\beta = 0.001$ (95% CI 0.001–0.001), equivalent to a predicted increase in postpartum blood loss of 2.9% for every 10 min increased duration of the third stage of labour (Table 1, model 3). A full list of all variables investigated in the univariate and multivariate analyses can be seen in Online Resources 1 and 2.

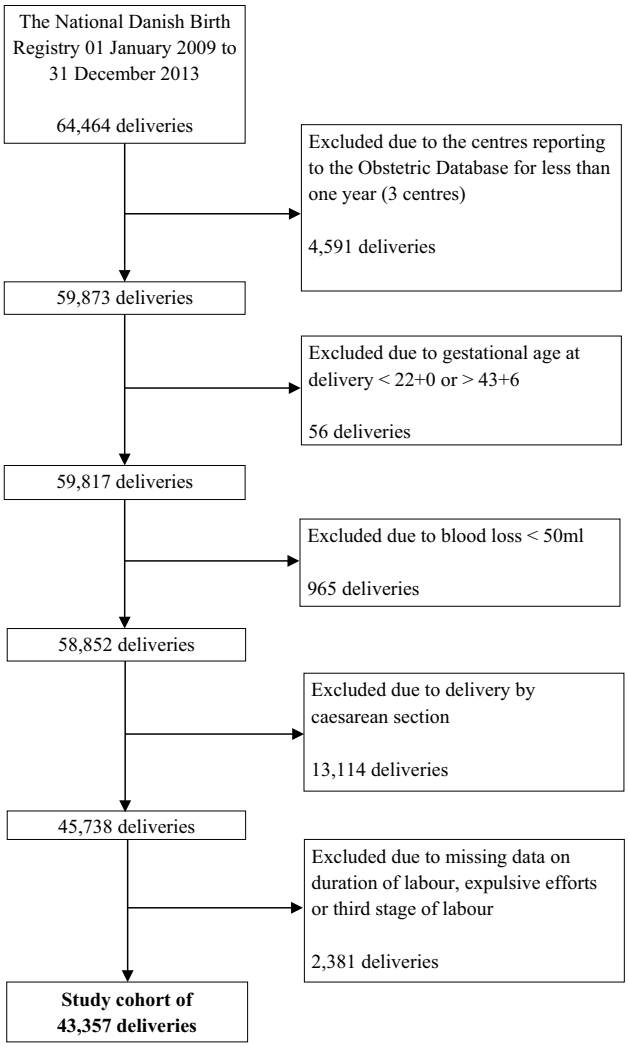

Fig. 1 Flow chart of excluded deliveries for the analysis of risk factors for quantity of postpartum blood loss

The majority of placentas were delivered within 15 min, with the majority of these being delivered spontaneously. However, the more prolonged third stage of labour, the less likely spontaneous delivery of the placenta (Table 2). We have plotted the median quantity of postpartum blood loss for different time intervals of the third stage of labour to illustrate the effect of duration of the third stage of labour (Fig. 2). However, as we have identified retained placenta or tissue as a major contributor to a decrease in effect size, we have also stratified the cohort and illustrated them independently. The graph illustrates that for all vaginal births, there is a rise in median quantity of blood loss if the length of the third stage exceeds 60 min. After stratification, however, there is minimal change in the median blood loss for retained placenta; regardless of the length of the third

Table 1 Univariate and multivariate linear regression analyses of risk factors for quantity of postpartum blood loss after vaginal delivery [proportions and percent (%) are depicted for categorical data and medians and interquartile ranges (IQR) for non-normally distributed data]

Variables	*N* (%) or median [IQR]	Univariate linear regression		Model 2		Model 3		Percent change in outcome (%)**
		β	*p* value	*β*	95% CI	*β*	95% CI	
Constant				**2.325**	2.315;2.334	**2.350**	2.341;2.360	
Duration of third stage of labour (minutes)	8 [5–12]	**0.0046***	< 0.005	**0.004**	0.004;0.004	**0.001**	0.001;0.001	**2.9*****
Before and during pregnancy								
Previous caesarean section	1649 (3.8)	**0.060**	< 0.005	**0.057**	0.044;0.069	**0.054**	0.042;0.065	**13.2**
Hypertensive disorders:								
None	41,419 (95.5)	Ref						
Gestational hypertension	783 (1.8)	**0.050**	< 0.005	0.016	0.000;0.033	0.015	− 0.001;0.031	
Mild/moderate preeclampsia	957 (2.2)	**0.073**	< 0.005	**0.026**	0.011;0.042	**0.020**	0.005;0.035	**4.7**
Severe preeclampsia	143 (0.3)	**0.151**	< 0.005	**0.091**	0.053;0.130	**0.081**	0.045;0.118	**20.5**
Eclampsia	4 (0.0)	0.240	0.057	**0.242**	0.015;0.470	**0.254**	0.037;0.472	**79.5**
HELLP	51 (0.1)	**0.140**	< 0.005	**0.087**	0.023;0.150	0.054	− 0.007;0.115	
During labour and delivery								
Induction of labour:								
None	31,770 (73.3)	Ref		Ref				
Medical	8739 (20.2)	**0.044**	< 0.005	**0.021**	0.015;0.027	**0.018**	0.012;0.024	**4.2**
Artificial rupture of membranes	4687 (10.8)	**0.041**	< 0.005	**0.025**	0.018;0.025	**0.025**	0.017;0.032	**5.9**
Balloon dilation	74 (0.2)	0.048	0.105	− 0.027	− 0.081;0.027	− 0.018	− 0.069;0.033	
Augmentation of labour	14,382 (33.2)	**0.080**	< 0.005	**0.025**	0.019;0.031	**0.024**	0.019;0.030	**5.7**
Fever during labour	1186 (2.7)	**0.120**	< 0.005	**0.037**	0.023;0.051	**0.035**	0.022;0.048	**8.4**
Episiotomy	1793 (4.1)	**0.086**	< 0.005	**0.073**	0.062;0.085	**0.071**	0.060;0.082	**17.8**
Outlet operative vaginal delivery	2871 (6.6)	**0.085**	< 0.005	0.009	0.000;0.019	0.006	− 0.003;0.016	
Low/mid cavity operative vaginal delivery	2206 (5.1)	**0.120**	< 0.005	**0.031**	0.020:0.041	**0.026**	0.016;0.036	**6.2**
Genital tract lacerations:								
None	19,714 (45.5)	Ref		Ref				
Perineal 1st/2nd	20,710 (47.8)	**0.065**	< 0.005	**0.055**	0.051;0.060	**0.056**	0.051;0.061	**13.8**
Perineal 3rd/4th	1610 (3.7)	**0.189**	< 0.005	**0.146**	0.134;0.158	**0.141**	0.129;0.153	**38.4**
Upper vaginal	1137 (2.6)	**0.170**	< 0.005	**0.147**	0.133;0.161	**0.140**	0.126;0.153	**38.0**
Cervical	186 (0.4)	**0.700**	< 0.005	**0.632**	0.598;0.665	**0.497**	0.465;0.529	**214.1**
Uterine rupture	2 (0.0)	**0.701**	< 0.005	**0.630**	0.307;0.953	**0.625**	0.317;0.934	**321.7**
Placental abruption	116 (0.3)	**0.093**	< 0.005	**0.092**	0.046;0.137	**0.088**	0.044;0.131	**22.5**
Shoulder dystocia	507 (1.2)	**0.119**	< 0.005	**0.081**	0.061;0.102	**0.075**	0.056;0.095	**18.9**
Uterus inversion	5 (0.0)	**0.457**	< 0.005	**0.395**	0.191;0.598	**0.024**	0.046;0.434	**5.7**
Postpartum								
Retained placenta	964 (2.2)	**0.642**	< 0.005			**0.544**	0.527;0.560	**250.0**

Values are *β* coefficients and 95% confidence intervals (CI). Bold *β* indicates $p < 0.05$. A 1 min increase in the three duration variables represents a unit change in log10 of quantity of postpartum blood loss. Model 2 is a multivariable linear regression of all variables listed in the table apart from retained placenta. In addition adjusted for maternal age, parity, multiple pregnancy, antepartum haemorrhage, non-cephalic presentation, amniotic fluid abnormalities, preterm premature rupture of membranes, premature rupture of membranes, year of delivery, time of day, hospital, induction of labour, mode of delivery, duration of labour, duration of expulsive efforts, and fever during labour. Model 3: all variables in model 2 + retained placenta

**β* coefficient for duration is the change per minute

***Percent change in outcome: The percentage each variable increases or decreases the predicted blood loss in model 3

****Percent change in the outcome with a 10 min change in duration

Table 2 Total number of placental deliveries for each time interval, divided into retained placentas and placentas delivered spontaneously

	< 15 min	15–29 min	30–44 min	45–59 min	60–74 min	75–89 min	>89 min	Total
Spontaneous delivery	36,765	5211	930	405	233	55	49	43,648
Retained placenta	315	113	69	70	86	111	243	1007
Total	37,080	5324	999	475	319	166	292	44,655

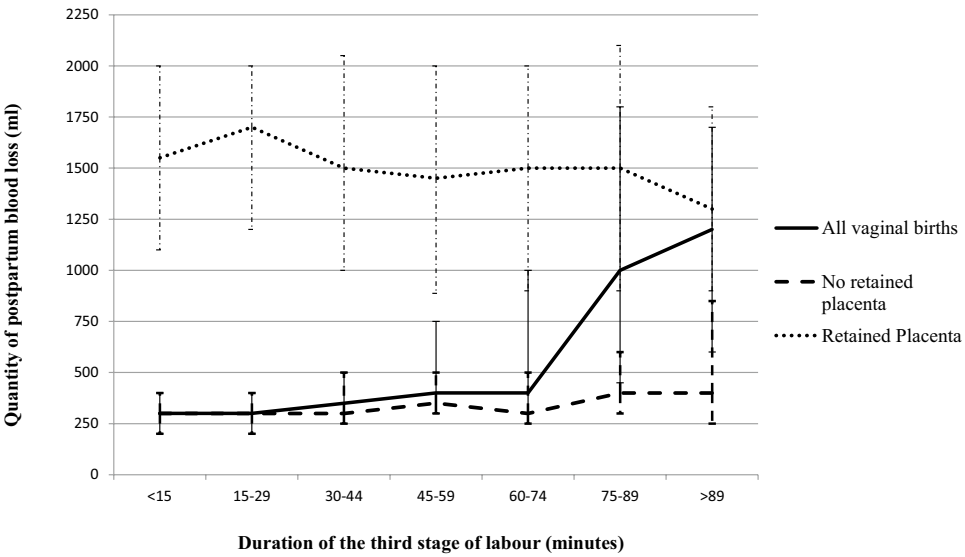

Fig. 2 Median quantity of postpartum blood loss in relation to duration of the third stage of labour. All vaginal deliveries, and also stratified for retained placenta. Whiskers indicating interquartile range

stage, they all have a median blood loss of approximately 1500 ml. Likewise, for women with spontaneous delivery of an intact placenta, there is no change in the median blood loss (Fig. 2).

The multivariate linear regression model also identified other predictors of blood loss (Table 1). Uterine rupture had the highest effect on prediction of blood loss in our multivariate linear regression model ($\beta = 0.625$), but was only seen in two cases in this cohort of vaginal deliveries and with a blood loss of 800 ml and 3000 ml, respectively (Table 1). The remaining variables with the highest significant effect in the multivariate analysis were: retained placenta ($\beta = 0.544$), cervical lacerations ($\beta = 0.497$), eclampsia ($\beta = 0.254$), placenta praevia ($\beta = 0.144$), 3rd- and 4th-degree perineal lacerations ($\beta = 0.141$) and upper vaginal lacerations ($\beta = 0.140$) (Table 1). Overall, the predictors in the final model accounted for 23.2% of the variability in quantity of postpartum blood loss ($R^2 = 0.232$). The proportion of cases without any predictors of blood loss was, therefore, also high, comprising 20.6% ($n = 8936$) of all vaginal deliveries including women with blood loss < 500 ml. However, the proportion of cases without any risk factors decreased significantly the higher cutoff used to define PPH from 11% ($n = 806$) of cases with a postpartum blood loss ≥ 500 ml, 7% ($n = 151$) of cases ≥ 1000 ml, 5% ($n = 52$) of cases ≥ 1500 ml, and 4% ($n = 22$) of cases ≥ 2000 ml.

Causes of postpartum blood loss

Postpartum blood loss of ≥ 500 ml was seen in 7541 women (17% of all vaginal deliveries) of which 12% ($n = 886$) were caused by retained placenta. The proportion of cases with retained placenta increased significantly, the higher the cutoff for postpartum blood loss, from 12% ($n = 886$) of women with a postpartum blood loss of > 500 ml to 53% ($n = 288$) of women with a postpartum blood loss of > 2000 ml (Fig. 3).

Discussion

Main findings

In this retrospective cohort study of 43,357 vaginal deliveries, we found that the duration of the third stage of labour was associated with the quantity of postpartum blood loss, but that the effect size of this association diminished after adjusting for retained placenta. Furthermore, we found that a retained placenta played an increasing role the higher the cutoff used to define PPH.

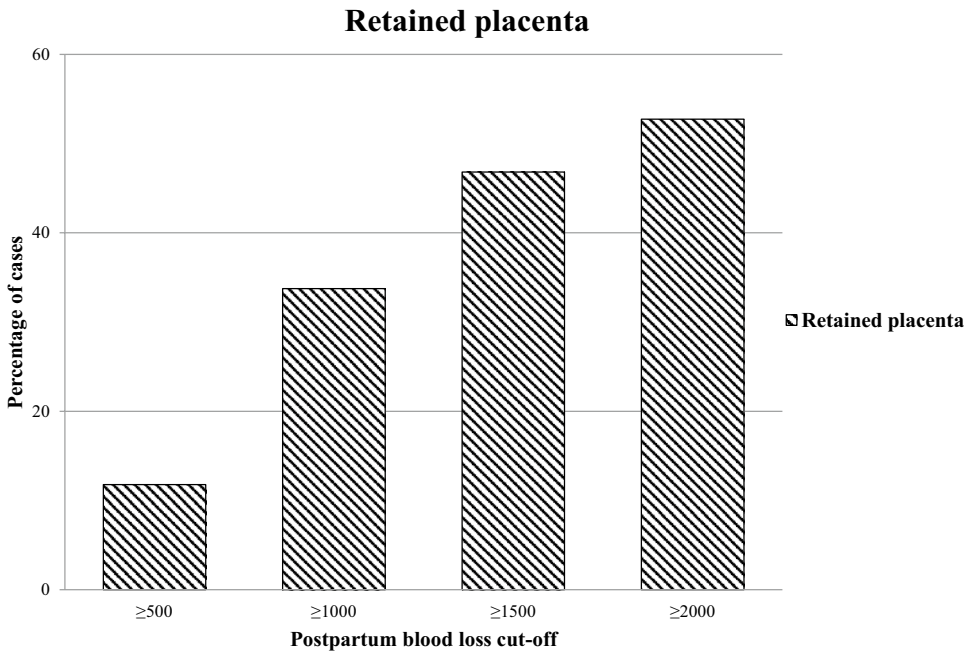

Fig. 3 Proportion of deliveries with retained placenta for different definitions of postpartum blood loss (number of deliveries in each category: ≥ 500 ml: 7514, ≥ 1000 ml: 2198, ≥ 1500 ml: 1113, ≥ 2000 ml: 546)

Strengths and limitations

The main strength of this study is the large cohort size and the known high validity of the Obstetric Database [20]. Furthermore, the data are from two large university hospitals in the capital region of Denmark representative of the Danish population, due to the known substantial sociodemographic and healthcare homogeneity with the remaining four regions of Denmark [21]. Most other studies investigating risk factors for PPH have dichotomised postpartum blood loss into values above or below a certain threshold, thereby facilitating logistic regression analysis and results in odds ratios [10, 13, 22–24]. Overall, we have identified many of the same risk factors, but interpretation of the results is more challenging. An odds ratio can only describe the odds of blood loss more than, e.g., 500 ml compared to less than 500 ml, thereby not differentiating between 550 ml or 2000 ml. By analysing quantity of postpartum blood loss as a continuous outcome, we were able to identify the effect on quantity of each variable.

Limitations of this study are mainly attributed to this study being a cohort study and the fact that we were not able to include uterine atony as a diagnosis. The latter can affect the distribution of causes of PPH. Further limitations are related to the missing information on some risk factors such as previous PPH, birthweight, and BMI. The few studies that included data on BMI or previous PPH have shown either non-significance or low odds ratios of 1.5–2.2 [25–27]. Macrosomia is a well-known risk factor for PPH with odds ratios of 1.4–3.5 [5, 13, 28] and, therefore, a possible confounder in our study. We have, however, been able to include shoulder dystocia in our analyses, which is a proxy variable for macrosomia. Furthermore, the cohort was sufficient in size to test for all included risk factors without overfitting. The main limitation of this study in regard to the association between the length of the third stage of labour and quantity of postpartum blood loss relates to the observational design. Women with "retained placenta" are a heterogeneous group, as some women in this group might not have needed manual removal of placenta as many factors can influence this decision. Factors that can prolong the time to manual remove the placenta include availability of obstetricians and operating theatre, whereas the severity of bleeding can reduce the time to manual remove the placenta.

Interpretation

The minimal effect, the duration of the third stage of labour had on quantity of postpartum blood loss in our study contradicts the majority of other research to date. One of the reasons for these conflicting findings is the role of the retained placenta. Retained placenta is a risk factor often identified after delivery and a known cause for PPH. Apart from uterine rupture, it was the variable with the highest impact on prediction of quantity of blood loss, in accordance with other studies [3, 13, 23, 28]. In our analyses, it was comprised of several different diagnoses, most of which were made after delivery (e.g., manual removal of placenta and tissue), which could explain some of the disparities. The majority of studies have not included retained placenta in their analyses and are thereby not comparable [14, 15]. However, a large study investigating the risk of postpartum

blood transfusions and duration of the third stage of labour excluded all women in need of manual removal, and still found that a third stage longer than 17 min was associated with an increased risk of blood transfusion [17]. A Dutch study investigating risk factors for standard (> 500 ml) and severe (> 1000 ml) PPH included duration of the third stage of labour (> 30 min) and retained placenta in their multivariate logistic regression analysis [28]. They found an odds ratio of 2.61 if the third stage of labour was > 30 min for PPH > 500 ml and 4.90 for PPH > 1000 ml. Interestingly, their multivariate logistic analysis, including only five other variables alongside retained placenta, decreased the odds ratios from the univariate analysis substantially from 4.07 to 2.61 for PPH > 500 ml, and from 11.9 to 4.90 for PPH > 1000 ml, in accordance with our findings. One could argue that retained placenta was the cause of a prolonged third stage, but the data in Fig. 2 also suggest that a woman could have a prolonged third stage and have spontaneous delivery of an intact placenta, but no increase in blood loss. Therefore, it seems evident to focus on identifying women requiring manual removal, to be able to initiate removal as soon as possible after delivery of the neonate, to prevent further postpartum blood loss. Today up to 50% of abnormal invasive placenta cases can be diagnosed before delivery by ultrasound and magnetic resonance imaging [29, 30], compared to only some cases of trapped placenta postpartum and hardly any cases of adherent placenta [18, 31]. Therefore, identification of all women requiring manual removal is as yet not possible, but could be improved by advances in ultrasound or use of biomarkers that are involved in placental implantation [32].

This is the first study investigating the change in proportion of cases with retained placenta using different cutoffs to define PPH in the same cohort. We chose to use cutoffs as this gives a different clinical perspective than using bands to group the quantity of PPH. In a clinical setting, we are interested in identifying and preventing the most severe cases, thereby it seems relevant to look at all cases with PPH above a certain limit such as above 1500 ml and not cases with PPH 1000–1500 ml or 1500–2000 ml.

Other studies have shown changes in the distribution of causes, but have only compared PPH with severe PPH [13, 27, 28]. A study from Israel defined the severity of PPH not by quantity but by different interventions [23]. They found that the rate of retained placenta increased from 0% of women with PPH and no need for intervention to 1.8% of women with PPH in need of revision of the uterus and 4.5% of women with PPH requiring blood transfusions. Similarly, a Dutch study found an increase in retained placenta 7.4% in PPH>500 ml to 25.5% in PPH>1000 ml [28]. Both these studies had lower rates of retained placenta than in our study. A study from Turkey analysed the different causes of PPH in women with PPH > 500 ml and women with severe PPH (PPH ≥ 2000 ml, Haemoglobin decrease ≥2 g/dl, transfusion of ≥ 4 packed red blood cells, and haemostatic intervention or death) [27]. They found an increase in atony (40.4–62.4%), and an increase in retained placenta including abnormal placentation (11.6–16.0%), but still with a smaller proportion of cases of retained placenta compared to our study. These discrepancies in the role of a retained placenta could be explained by how the different studies defined this. We defined a retained placenta as all cases with the need for removal of any placental tissue, thereby perhaps including cases caused by other causes. We did not include atony in our study, as it is not included as a diagnosis in our database. Atony as a diagnosis is often used when no other cause is obvious or in cases of PPH, where bleeding from the uterine cavity is misinterpreted as atony, but is in fact bleeding from the placental site due to AIP or coagulopathy developed later on in the course of events.

Conclusion

Duration of the third stage of labour was a weak predictor of quantity of blood loss, while retained placenta was a much stronger predictor. The predictive power of the duration of the third stage of labour was further reduced when considering the influence of a retained placenta. There was a significant difference in the distribution of causes depending on the cutoff used to define PPH, with a retained placenta present in an increasing number of cases the higher the blood loss. However, uterine atony as a diagnosis was not included and poses a limitation in our study.

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Author contributions HME: project development, data collection, data analysis, and manuscript writing. JL-R: project development, data collection, data analysis, and manuscript editing. AJW: project development and manuscript editing. JAS: project development and manuscript editing. JL: project development and manuscript editing.

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Compliance with ethical standards

Conflicts of interest HE, JL, AW, JS, and JLR declare that we have no conflicts of interest or financial ties to disclose.

Ethical approval This study fulfils all Danish ethical standards and was approved by the Danish Data Protection Agency (No. 2012-58-0004).

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