Severe Obstetric Haemorrhage

A population-based study

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ABSTRACT

Background: As maternal mortality is very low in high resource settings, a complimentary indicator to assess obstetric care is needed. Severe maternal morbidity is suggested as a useful indicator as it occurs more frequently. Severe obstetric haemorrhage is the main cause of severe maternal morbidity and mortality worldwide. Norway is characterised by a low maternal mortality and a well established registry of all births. However, large population-based studies on the proportion, causes and risk factors of severe obstetric haemorrhage are lacking. Uterine rupture, one of the causes of severe haemorrhage, is expected to rise due to the increased rates of caesarean section (CS). Yet, we do not have documentation of the proportion and impact of uterine rupture after previous CS in Norway. Information about severe obstetric haemorrhage and uterine rupture is warranted for both preventive and curative health services.

Aims: to determine the proportion, risk factors, causes and maternal outcome of severe obstetric haemorrhage with emphasis on the role of increasing obstetric procedures as induction and CS. Another aim was to determine the proportion, risk factors and maternal and perinatal outcome of uterine rupture after previous CS.

Materials and Methods: We used data from the Medical Birth Registry of Norway on all women giving birth after 16 weeks gestations in 1999-2004 for the study of severe obstetric haemorrhage (307 415 mothers). Data on mothers with gestations ≥28 weeks, giving birth after previous CS in 1999-2005, were used for the study of uterine rupture (18 794 mothers). The main outcome measures included severe obstetric haemorrhage (blood loss >1500 ml/need for blood transfusion) and uterine rupture. Secondary maternal outcomes were maternal death, peripartum hysterectomy, admission to intensive care unit, acute renal failure, and postpartum sepsis. Serious perinatal outcomes included perinatal death, post hypoxic encephalopathy and severe asphyxia. The explanatory variables consisted of demographic and medical variables, pregnancy and labour complications, and delivery mode variables. Cross tabulations and multiple logistic regressions were used and associations were measured as relative risks (estimated odds ratios).

Results:

- Severe obstetric haemorrhage occurred in 1.1% of all mothers. Uterine atony was the main cause. One third of cases has unidentified causes, especially at caesarean section. Mothers with severe obstetric haemorrhage had significantly higher risk for serious maternal outcome.
- The mode of delivery was the most important risk factor for severe obstetric haemorrhage, especially emergency CS, followed by elective CS. Other important risk factors included multiple pregnancy, von Willebrand's disease, HELLP syndrome, anaemia during pregnancy and macrosomia.
- Prelabour CS and induction significantly increased the risk for severe postpartum haemorrhage (PPH) compared with spontaneous labour onset.
- Vaginal deliveries halved the risk of severe PPH compared with prelabour CS even in mothers with previous CS.
- Emergency CS after labour onset had the highest risk for severe PPH in all mothers, but especially after induction in women with previous CS.
- Operative vaginal delivery after induction significantly increased severe PPH risk in primiparas.
- Uterine rupture occurred in 5/1000 of mothers with previous CS. The highest risk was for induced labour, especially with prostaglandins, and for emergency prelabour CS, while the lowest risk was for repeated elective CS.
- Uterine rupture after trial of labour was significantly associated with serious maternal and perinatal outcome.
- Older age and ethnicity were significant risk factors for both severe obstetric haemorrhage and uterine rupture.

Conclusion:

For every 100 women giving birth in Norway, one woman develops severe obstetric haemorrhage, with a higher risk of adverse outcome. Severe haemorrhage was in a major part related to obstetric procedures and labour management indicating that induction and prelabour CS should be practiced with caution. However, prelabour CS might be a better option for mothers with previous CS if the probability of emergency CS is high. Uterine rupture after trial of labour carried a greater risk of adverse maternal and perinatal outcome compared with elective repeated CS, although the absolute risks were low.

LIST OF PAPERS

1. Al-Zirqi I, Vangen S, Forsén L, Stray-Pedersen B. Prevalence and Risk Factors of Severe Obstetric Haemorrhage. BJOG 2008; 115: 1265–1272.

2. Al-Zirqi I, Vangen S, Forsén L, Stray-Pedersen B. Effects of Onset of Labor and Mode of Delivery on Severe Postpartum Hemorrhage. Am J Obstet Gynecol 2009; 201:273.e.1–9.

3. Al-Zirqi I, Stray-Pedersen B, Forsén L, Vangen S. Uterine Rupture after Previous Caesarean Section. BJOG 2010; DOI: 10.1111/j.147-0528.2010.02533.x.

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DEFINITIONS AND ABBREVIATIONS

Definitions:

Macrosomia (applied only for this study): Birth weight ≥ 4.5 kg.

Maternal death: The death of a woman while pregnant or within 42 days of termination of pregnancy, from any cause related to or aggravated by pregnancy or its management, but not from accidental or incidental causes.

Maternal Mortality Ratio: Maternal deaths per 100 000 live births.

Mechanical induction methods: Amniotomy alone or other non-medical induction methods.

Moderate postpartum haemorrhage: Visually estimated blood loss 500-1500 ml, within 24 hours postpartum.

Perinatal death (applied only for this study): Sum of Intrapartum fetal deaths ≥ 28 weeks gestation, and neonatal deaths ≤7 days after birth, not related to congenital causes. Antepartum stillbirths were excluded in the present study since they were not delivery-related.

Perinatal mortality rate: Sum of stillbirths at ≥22 weeks and deaths of live born infants within the first seven days after birth per 1000 total births.

Post hypoxic encephalopathy: Defined clinically as cerebral irritation, cerebral depression, or seizures in the presence of severe asphyxia.

Severe Obstetric Haemorrhage: Visually estimated blood loss of >1500 ml intrapartum and within 24 hours post-partum, or the need for blood transfusion postpartum regardless of the amount of blood loss.

Severe postpartum haemorrhage: Defined as severe obstetric haemorrhage, excluding haemorrhages due to placenta previa and abruption.

Abbreviations:

CI: Confidence interval.

CS: Caesarean section.

DIC: Disseminated intravascular coagulation.

EUPHRATES: The **EU**ropean **P**roject on obstetric **H**aemorrhage **R**eduction: **A**ttitudes, **T**rial and **E**arly warning **S**ystem.

FIGO: International Federation of Gynaecology and Obstetrics.

HELLP syndrome: Haemolysis elevated liver enzymes & low platelets.

ICD-10: The International statistical classification of diseases and related health problems, 10th revision.

ICU: Intensive care unit.

NICU: Neonatal intensive care unit.

IMC: International Confederation of Midwives.

MBRN: The Medical Birth Registry of Norway.

MMR: Maternal Mortality Ratio.

MOMS: **MO**thers **M**ortality and **S**evere **M**orbidity. A European initiative.

NOMESCO: The Nordic Medico-Statistic Committee.

NCSP: NOMESCO Classification of Surgical Procedures.

OR: Odds Ratio.

PHE: Post hypoxic encephalopathy.

PPH: Postpartum haemorrhage.

TOL: Trial of labour.

UKOSS: The **UK O**bstetric team **S**urveillance **S**ystem.

WHO: World Health Organisation.

INTRODUCTION

For every minute of every day worldwide, a woman dies due to pregnancy and childbirth.[1] The majority of deaths are from severe obstetric haemorrhage. Most of these deaths could have been prevented[1–3] if only sufficient resources had been available during childbirth. Most deaths occur in low resource settings. In high resource settings, with few fatalities from haemorrhage, severe obstetric haemorrhage stands as the main severe maternal morbidity.[4–9]
The main focus of the current thesis was to study the proportion, causes, risk factors, and outcome of severe obstetric haemorrhage in a high resource setting with adequate registration of births. The emphasis was placed on factors increasingly applied in obstetric practice, such as delivery by caesarean section (CS), and induction of labour. As CS rate is increasing worldwide, special emphasis was placed on uterine rupture after previous CS.[10] Uterine rupture is an important cause of severe obstetric haemorrhage and is associated with both serious perinatal and maternal outcome.[11, 12] Increasing knowledge on severe obstetric haemorrhage may reduce its occurrence and its impact on maternal health. It may also contribute toward lower maternal mortalities in low resource settings.

Why focus on severe obstetric haemorrhage?

From ancient times, obstetric haemorrhage has remained a major killer of mothers. It stands behind the shadows of the Taj Mahal in India. The Taj Mahal was built by the grieving Emperor Shah Jehan in the memory of his wife Empress Mumtaz Mahal, who died in 1630 from postpartum haemorrhage after delivering her 14th child.[13] Severe obstetric haemorrhage is also behind the Triple Tragedy in England in 1817.[14] At the age of 21, Princess Charlotte, George IV only child, went into labour with her first baby. She delivered a stillborn boy after 50 hours of labour. Six hours later, she died from postpartum haemorrhage. The obstetrician, who was widely criticised, shot himself few months later. King George was left without an heir, and the throne passed first to his brother and then to his niece, who became Queen Victoria.

We chose to concentrate on the epidemiology of severe obstetric haemorrhage for the following reasons:

1. Severe obstetric haemorrhage is the main cause of maternal deaths.[1–3, 15]

2. Severe obstetric haemorrhage is the most common severe maternal morbidity in high- and low- resource settings. [4–9] It may result in serious physical and psychological short-term and long-term disability.[2] It has grave consequences that affect not only the mother, but also the newborn, other family members and society at large.
3. Severe obstetric haemorrhage is the most preventable severe maternal complication, and suboptimal obstetric care was identified in more than half the deaths due to haemorrhage, even in high resource settings[16, 17]

Obstetric haemorrhage is the most feared obstetric emergency that can occur to any woman at childbirth. If unattended, haemorrhage can kill even a healthy woman within two hours.[19, 20] The global estimate of deaths due to haemorrhage is 150 000 per year.[3] Haemorrhage accounts for nearly one quarter of all maternal deaths, and for almost half of all postpartum deaths in low-income countries.[3, 20, 21] If we manage to reduce severe obstetric haemorrhage, a major reduction of maternal mortality and morbidity would be achieved worldwide.
Recent studies in high resource settings[18] including Canada,[22] USA,[23]
Australia,[24] and UK[25] indicate an unexpected and unexplained increase in obstetric haemorrhage over the last ten years. Although maternal deaths are extremely rare in high resource settings, the morbidity associated with severe haemorrhage is still a major problem.[6, 8, 25–27] Many more women survive, but suffer serious illness as a result, not only from the effects of acute hypo-perfusion and anaemia, but also from the interventions which severe haemorrhage may necessitate.[28, 29] It can furthermore affect the health of the newborn through weakening of mother's health and subsequent reduced bonding.[20, 30] All factors considered, severe haemorrhage also poses substantial costs to the health care system and to society in general. It is therefore suggested as a complimentary indicator for the assessment of the quality of obstetric care.[32–33] This necessitates the performance of large population studies in order to determine the proportion and risk factors of severe obstetric haemorrhage.

Norway is a high resource country, characterised by a low maternal mortality ratio (MMR) of 4.1-5.5/ 100 000[34,35], and a well established registry of all births. Few maternal deaths from severe obstetric haemorrhage were detected according to a study review of case records in 1976-1995.[35] However, deaths from haemorrhage were all found to be avoidable. In addition, large population-based studies on the proportion and risk factors of severe obstetric haemorrhage are lacking. Such information is warranted for both preventive and curative health services. The data in the Medical Birth Registry of Norway (MBRN), established since

1967, is a relevant source of data for such a study.[36, 37] As of 1999, severe obstetric haemorrhage is recorded in specific ticked boxes in the MBRN registration forms.

Severe maternal morbidity: an important indicator of obstetric care

Each year, more than half a million women die from causes related to pregnancy and childbirth: 99% of the deaths occur in poor countries, with the majority in sub-Saharan Africa and South Asia.[1, 15] The risk of a woman dying as a result of pregnancy or childbirth during her lifetime is about one in six in the poorest parts of the world, compared with one in 30 000 in Northern Europe.[1, 15]

One hundred and fifty years ago, the rate and causes of maternal deaths in Scandinavia were similar to those observed in the least developed world today.[38, 39] Maternal deaths were mainly due to obstetric haemorrhage, infections, eclampsia, prolonged or obstructed labour and complications of abortion. Significant reductions in MMR were accomplished first in North-western Europe in the mid- to late 19th century.[40] This was mainly due to the increased coverage of deliveries by skilled professional midwives, established first in Scandinavia during 1860-1900.[41–43] In the 1940s, obstetric haemorrhage was the most common cause of maternal mortality in UK[44] and the USA.[45]The most dramatic reduction in MMR in the industrialized world occurred after the Second World War. This was due to the improved health and nutrition of women and universal access to modern obstetric medicine,[40] comprising the introduction of antiseptics, improving operative deliveries, anaesthesia, antibiotics, blood transfusion and the use of uterotonics against postpartum haemorrhage. The MMR remained generally static at 8 per 100,000 live births between 1990 and 2005.[15]

As maternal death is becoming rare in the industrialized world, the safety of childbirth is generally taken for granted. Services are encouraged to provide choice, including home or hospital delivery, epidurals, or water births. A growing number of women opt for planned caesarean section without real indication. As a result, the CS rate is increasing in many countries with consequent increased short- and long- term complications.[28, 29, 46–48] However, the sharpest increase in CS rates is found in fact in urban areas of South-America, Asia and Africa.[49]

By looking only at maternal deaths, we may overlook other major problems in obstetric care.[50] Maternal deaths are only the tip of the iceberg; severe maternal morbidity is a huge burden on women and their families. Mantel, et al[31] defined woman with severe maternal morbidity as ‘a very ill pregnant or recently delivered woman who would have died had it not

been but that luck and good care was on her side'. In industrialised countries, the rates range from 0.05 to 1.7%, depending on the definition used.[51, 52]

Analysis of severe maternal morbidities is a new area of research as they can be used as a complementary indicator of obstetric care. The case fatality ratio (Death/Severe morbidity) is an objective indicator of obstetric care, with very low ratio in high resource countries, and very high ratio in countries with low resources.[9] The demographic and other characteristics as well as management aspects can be compared between mothers who survived a severe maternal morbidity and mothers who died from the same severe morbidity. Regular audits of severe morbidity cases may improve the quality of obstetric care.

History of obstetric medicine in Norway

Women in the 19th century could have contractions for days. Nothing was usually done before the infant was dead or the mother was seriously ill.[38,42] The first dramatic reduction of maternal mortality, observed in Norway from the second half of the 19th century (6.7/1000 in 1860 to 3.3/1000 in 1900), was due to the increased numbers of professional midwives and decreased puerperal fever.[41-43] The increased use of Simpson's forceps contributed to a dramatic reduction of prolonged labour and postpartum haemorrhage.[107] It was used initially to save mothers life, but fetal indications became more frequent towards the end of the 19th century.[108] The first CS in Norway resulting in a living child, was performed in 1849, but no mother survived the operation before 1890.[109] In the 19th century, CS was performed rarely due to high mortalities from CS related to infection and haemorrhage. The mortality from CS was reduced dramatically through the 20th century due to developments in surgical technique, introduction of antibiotics, blood transfusion, improvement in postoperative care, and epidural anaesthesia. CS became more frequent as a result, especially after the 2nd World War.[109] This contributed to less obstetric haemorrhage from placenta previa, abruption and uterine atony. In 1915, Christian Kjelland (1871-1941), a Norwegian obstetrician from Rikshospitalet, designed rotational forceps.[110] Kjelland forceps were used internationally for extraction of the incompletely rotated head from the upper pelvis, and for deep transverse arrest of the head, avoiding emergency CS in late stage of labour.

The second dramatic reduction in MMR in Norway was after the Second World War.[34] MMR in Norway was 2.34/1000 in 1936-1940, but dropped to 0.74/1000 in 1951-1956 (Figure 1),[111] due to universal access to modern obstetric medicine and immediate emergency care. From 1976 to 2000, the MMR was 4.1-5.5/100 000 live births with preeclampsia as the main cause of maternal deaths[34, 35]

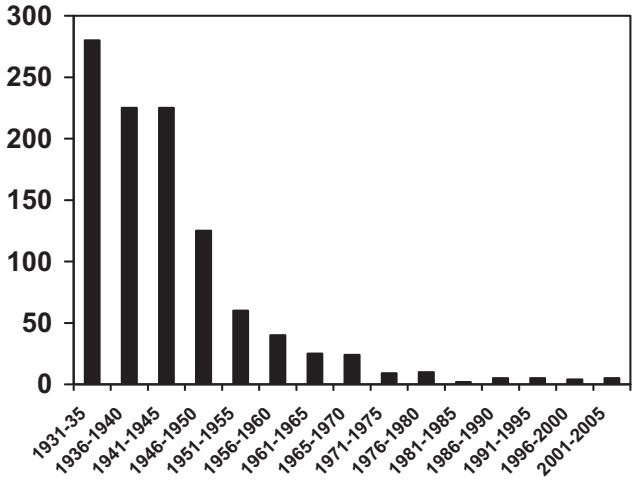

Figure 1. Maternal Mortality Ratio per 100 000 in Norway 1931-2005

Perinatal mortality dropped from 35/1000 in 1901[112] to 4.3/ 1000 in 2008.[85] The vacuum extractor, invented by Tage Malmstrøm of Sweden, was used for the first time in Norway in 1960.[113] The vacuum does not need a very high level of skill, unlike Kjelland's forceps, but nonetheless has a higher failure rate. Vacuum deliveries increased gradually in contrast to forceps, which started declining from the eighties.[113] The maximum rate of forceps usage was 4.5% in 1986, declining thereafter until it reached 1.8% in 2008. In contrast, use of vacuum delivery increased from 1.2% in 1967 to 7.9% in 2008. The rate of CS increased from 1.8% in 1967 to 17.1% in 2008.[85] Ironically, this dramatic growth in the rate of CS might increase severe haemorrhage due to both surgery complications and reduced skills in performing instrumental vaginal delivery. The CS rate of 17.1% in Norway today is however, still lower than in many other countries.

Challenges in epidemiological studies on severe obstetric haemorrhage

1. Problems in defining severe obstetric haemorrhage

Obstetric haemorrhage refers to excessive blood loss from the genital tract, occurring antepartum, intrapartum, or in the postpartum period. The most common type of obstetric haemorrhage is postpartum haemorrhage (PPH), mainly primary PPH, occurring within 24 hours postpartum. Primary PPH has been the focus of this thesis. Secondary PPH is less

common, occurring between 24 hours and 6 weeks postpartum, most likely due to infection secondary to retained placental products.[53]

Any review on obstetric haemorrhage is complicated by the lack of agreement on what constitutes excessive blood loss. Primary PPH is defined according to WHO (World Health Organisation) as blood loss > 500 ml in the first 24 hours postpartum.[54] This is debatable, because nearly half of all women who are delivered vaginally shed that amount of blood, or more, when measured objectively. Blood loss of more than 500 ml is not necessarily unusual for vaginal delivery.[55] Furthermore, women with low body mass index have usually low blood volume, and women who are anaemic or having severe preeclampsia might have fewer physiological reserves to withstand blood loss. Hence, these patients might not be able to tolerate even 500 ml of blood loss, and will therefore decompensate sooner.[56, 57]

Other proposed definitions of haemorrhage include a 10% decrease in haemoglobin or hematocrit level, or the need for blood transfusion.[58] Given the delay in obtaining laboratory values, this information would not reflect the patient's current hemodynamic status. The change in hematocrit depends on the timing of the test and the amount of fluid previously administered.[59] It could also be affected by extraneous factors such as prepartum hemoconcentration, which may exist in conditions such as preeclampsia. [57] Any definition based on the need for blood transfusion is problematic and may reflect differences in provider practice patterns rather than patient clinical status.[60]

In an attempt to combine clinical presentation with objective data, obstetric haemorrhage may best be defined as excessive bleeding that makes the patient symptomatic (light-headedness, syncope) and/or results in signs of hypovolemia (hypotension, tachycardia, or oliguria)[61] (Table 1).

Table 1. Symptoms and signs related to blood loss with obstetric haemorrhage

Blood loss		Systolic blood pressure (mmHg)	Signs and symptoms
%	*ml*		
10–15	500–1000	normal	palpitations, dizziness, tachycardia
15–25	1000–1500	slightly low	weakness, sweating, tachycardia
25–35	1500–2000	70–80	restlessness, pallor, oliguria
35–45	2000–3000	50–70	collapse, air hunger, anuria

Adapted from Bonnar J. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000; 14:1[61]

We used a combination of blood loss or need for blood transfusion to identify severe haemorrhage. Blood transfusion is rarely given to mothers with haemoglobin ≥7gm/dl in Norway.[62] It is given only to mothers with a clinical picture of acute anaemia.

Classifying haemorrhage according to severity is another problem. There is a lack of agreement on a reproducible clinical definition of severe obstetric haemorrhage that can be identified easily and accurately. Some researchers have used a strict definition including only women admitted to an intensive care unit (ICU).[63–69] This however, underestimates the real proportion, since only one third of cases of severe morbidity are transferred to ICU.[7] Others included only those who required hysterectomy[7] resulting in considerable variations due to different management policies. Even those who used clinical definitions based on the amount of blood loss have used different limits, varying from >1000 ml[70] to ≥ 2500 ml.[7, 25]

It has been suggested that the definition should take into account any blood loss that causes a major physiological change which threatens mother's life.[61] This is especially important in cases of concealed intra-abdominal bleeding. The combination of blood loss ≥1500 ml or the transfusion of > 4 units of blood postpartum or drop of haemoglobin by 4 gm was used as a definition of severe obstetric haemorrhage in certain studies.[6, 8]

In the present thesis severe obstetric haemorrhage was defined as a visually estimated blood loss of >1500 ml intrapartum and within 24 hours postpartum, or the need for blood transfusion postpartum, regardless of the amount of blood loss. We used a cut-off for severe haemorrhage of >1500 ml representing 25% of the blood volume, since blood loss of such an amount would lead to hemodynamic decompensation.[71]

2. Estimation of blood loss

Visual estimation is the most universal method used to assess blood loss at delivery. It is relatively straightforward and requires no expenditure.[72] Visual estimation is the standard method in Norway. The major advantage of this method is that it is a real time assessment. It enables the birth attendant to correlate findings, on an individualized basis, with the clinical presentation. However, visual estimation of blood loss is known to underestimate the actual loss by 30–50%.[55, 73]

Standardized visual estimation is an attempt to rectify this error, based on training of providers and standardization of the size and quality of the pads used during delivery. Instruction in this method has significantly reduced the error in blood loss estimation for inexperienced as well as experienced clinicians.[74]

Direct collection of blood into bedpan or plastic bags immediately after the delivery of the newborn and clamping the cord, is another method used in some studies.[72] This method has errors arising from failure to collect all the blood in stained linen or within the placenta, mixing of blood with amniotic fluid, and technical inaccuracies. Acid hematin method and measurement of tagged erythrocytes were referred to in earlier studies.[55, 76] However, they were not used in practice as they require larger resources and consist of several impractical procedures.

BRASSS-V DRAPE is a special drape which has a calibrated and funnelled collecting pouch, incorporated within a plastic sheet that is placed under the woman's buttocks, immediately after delivery of the baby. This simple, practical tool has the potential for a more accurate detection of blood loss and would lead to earlier interventions contributing to reduction of both mortality and severe morbidity.[77]

A study using collector bags for measuring blood loss at delivery was performed by The EUPHRATES group (**EU**ropean **P**roject on obstetric **H**aemorrhage **R**eduction: **A**ttitudes, **T**rial and **E**arly warning **S**ystem. The group performed a multi-centre European study to determine whether severe postpartum haemorrhage would occur less if blood loss was measured objectively by collector bags.[78] Severe PPH was defined as a composite of one or more of: blood transfusion, intravenous plasma expansion, arterial embolisation, surgical procedure, admission to ICU, treatment with recombinant factor VII, and death. In 2006-2007, maternity units, including two units from Norway were randomly assigned to systematic use of collector bags or to continue to visually assess postpartum blood loss after vaginal delivery.[78] The results showed that the use of collector bags did not reduce the rate of severe PPH compared with visual estimation. This indicates that the management of postpartum haemorrhage was not improved by objective measurement of blood loss without specific guidelines on threshold and action.

3. The use of different methods in conducting third stage of labour

Active management of the third stage of labour as recommended by FIGO (International Federation of Gynaecology and Obstetrics) and IMC (International Confederation of Midwives) involves the use of prophylactic uterotonics such as syntocinon or syntometrine with the delivery of the fetal anterior shoulder clamping of the umbilical cord once pulsations stopped, controlled cord traction using the Brandt-Andrews technique once uterine contraction is achieved.[79] In contrast, expectant management involves waiting for spontaneous separation of the placenta from the uterine wall and avoidance of synthetic

uterotonics. A meta-analysis indicated that active management of the third stage resulted in reduction in maternal blood loss, and a reduction in the risks of PPH.[80] Clearly, the reported incidence of PPH in any population is influenced by the conduct of the third stage. As active management is not homogeneously performed, even across Europe,[81] this must be taken into consideration when making comparisons of severe PPH incidence in different studies.

4. The proportion of severe obstetric haemorrhage

4.a Denominator data

Studies that attempt to quantify the proportion and impact of severe obstetric haemorrhage need a denominator value over a specified time period. Common denominators are maternities or live births, and these can include early gestations from 16 weeks, as in our present study. Most of the previous studies included pregnancies from 24 weeks or even later gestations. High resource settings in contrast to low resource settings have the advantage of accurate denominator data, including both live births, still births and late miscarriages. When the denominators represent the total pregnant population, the estimate would be more reliable.

4.b Impact of population characteristics and study design

The proportion of severe obstetric haemorrhage is influenced by the study design and population characteristics as well as obstetric management. A systematic review of international studies was performed covering the period 1997-2006 of 120 data sets reporting PPH (blood loss >500 ml), and 70 data sets reporting severe PPH (blood loss > 1000 ml).[82] The percentage of PPH and severe PPH was approximately 6% and 1.86% of all deliveries, respectively. The proportion of severe PPH was 3.04% when the outcome was measured objectively and 1.68% when it was assessed subjectively. The incidence was 1.67% and 2.95%, in population-based and institution-based studies respectively. The percentage was 3.75% when the sample size was ≤ 1000 women and 1.78% for those studies with > 1000 women. It was 3.84% for expectant management and 2.99% for active management of third stage of labour. Severe PPH for vaginal deliveries was 2.94%, and 6.38% for caesarean section. The incidence of severe PPH across global regions was 2.21% in Africa, 1.78% in Asia, 1.75% in Europe, 5.33% in Latin America and 4.33% in Oceania. However, there was small number of data sets in the latter two regions.

The incidence of severe haemorrhage varies considerably, even between countries with high resources. This can be partly due to the use of different definitions as well as differences in

registration methods or management aspects. However, other factors as different population characteristics may contribute to such variations. The MOMS (**MO**thers **M**ortality and **S**evere **M**orbidity) Survey[8] was conducted during the 1990s by an international team which spanned 11 European countries. Using unified clinical definitions of severe obstetric haemorrhage (blood loss ≥1500 ml or blood/plasma expanders transfusion, or death), the survey found a total incidence of severe haemorrhage of 4.6/1000 deliveries. However the incidences varied widely from 0.7/1000 in Austria to 8.8/1000 in Finland.[8] The survey established that MMR were not higher in the countries with the highest severe haemorrhage rates, i.e. Belgium, Finland and the UK. This suggests either that ascertainment of cases in these three countries is more complete, or that haemorrhage is not a major cause of death, or that the low mortality rate is due to proper management of severe obstetric haemorrhage. The geographical areas chosen in different countries had very different demographics (age and ethnic origin), and this also may have affected the rates of severe haemorrhage. In both the UK and Belgium, the study covered areas with larger percentages of immigrants. Genetic profiles vary between different populations, as certain populations have increased hereditary coagulation disorders, or increased severe preeclampsia, predisposing to increased severe obstetric haemorrhage. The Finnish population for example, has a higher occurrence of placental abruption compared with other populations.[83]

5. Causes and risk factors of severe obstetric haemorrhage

The most common causes of obstetric haemorrhage are those related to primary PPH, (The Four Ts: Tone, Trauma, Tissue, and Thrombin) (Table 2). Uterine atony accounts for more than 70% of cases, retained placental products accounts for approximately 10%, genital-tract trauma (uterine rupture and inversion, cervical and perineal injuries) accounts for 20%, and pre-existent or acquired coagulation disorders and platelets dysfunction account for 1% of cases.[84] Ante/intra-partum haemorrhage was reported to occur in about 3%-4% of pregnant population.[85], of which 30% was due to placental abruption, and 20% was due to placenta previa. Both are associated with increased risk for postpartum haemorrhage.[86] Placenta previa may be associated with abnormal adherent placenta (placenta accrete/increta or percreta), especially in the presence of uterine scar.

Uterine rupture is one of the causes of severe obstetric haemorrhage. We focused on uterine rupture as it is associated with severe maternal haemorrhage and adverse fetal outcome. Uterine rupture is expected to increase due to increasing rates of CSs.[11, 12, 88]

Table 2. Etiology and risk factors for the 4Ts processes involved in postpartum haemorrhage[87]

Process	Etiology	Risk factor
Tone	Uterus over-distension	Multiple pregnancy; Macrosomia, Polyhydramnios; Fetal abnormalities
	Uterine muscle fatigue	Prolonged/precipitate labour. High parity; Previous pregnancy with PPH
	Uterine infection/chorioamnionitis	Prolonged SROM; Fever
	Uterine distortion/abnormality	Fibroid uterus; Placenta previa
	Uterine relaxing drugs	Anaesthetics; beta-mimetics; MgSO4
Tissue	Retained placenta/membranes	Incomplete placenta at delivery, esp. < 24weeks: Previous uterine surgery; Abnormal placenta on ultrasound
	Abnormal placenta-succinturiate /accessory lobe	
Trauma	Cervical/vaginal/perineal tears	Precipitous delivery; manipulations at delivery Operative delivery; Episiotomy
	Extended tear at CS	Malposition; Fetal manipulation, e.g., version of second twin; Deep engagement
	Uterine rupture	Previous uterine surgery
	Uterine inversion	High parity; Fundal placenta Excessive traction of cord
Thrombin	Pre-existing clotting abnormality e.g., hemophilia/ vWD/	History of coagulopathy/liver disease
	Acquired in pregnancy ITP; PET with thrombocytopenia (HELLP); DIC from PET, IUD, abruption, AFE, severe infection.	High BP, bruising Fetal death Fever, raised WCC APH, sudden collapse
	Dilutional coagulopathy from massive transfusions	
	Anticoagulation	History of DVT/PE; Aspirin, heparin

PPH: postpartum haemorrhage; SROM: spontaneous rupture of membranes; CS: Caesarean section; vWD: von Willebrand's disease; ITP: idiopathic thrombocytopenic purpura; BP: blood pressure; PET: preeclampsia; WCC: white cell count; HELLP: hemolysis, elevated liver enzymes, and low platelets; APH: antepartum haemorrhage; DIC: disseminated intravascular coagulation; IUD: intrauterine death; AFE: amniotic fluid embolism; DVT/PE: deep vein thrombosis/pulmonary embolism.

Identifying exact causes of severe haemorrhage may be challenging in the presence of multiple causes or clinically unrecognised or undocumented causes. Different etiologies may have common risk factors. This is especially true for uterine atony and trauma of the lower genital tract being both increased by prolonged labour or macrosomia.

Risk factors are important and should be studied even though up to 2/3 of cases had no identifiable risk factors.[89] With changes in the obstetric population (e.g., increased mean maternal age at childbirth, increasing number of women with complex medical disorders becoming pregnant, increasing maternal obesity and macrosomic infants) and advances in technology (e.g., assisted reproduction leading to an increased rate of multiple pregnancy, increasing caesarean section rates leading to placenta previa and its sequelae), some of these risk factors may become more important and others less so, in the future.[6,16,71, 86, 90 7]

Grand multiparas were traditionally thought to be at high risk of PPH, but some studies suggest that their risk may be no greater than that of women of lower parity.[91]

In the past, most cases of intractable PPH followed vaginal delivery and were due to uterine atony; however, more recent reports show that more cases are now associated with caesarean delivery. Caesarean delivery for placenta previa increased the risk for peripartum hysterectomy by 100-fold, with many patients having a diagnosis of placenta accrete.[92] Higher risk for hysterectomy was found for emergency CS at full dilatation due to failed progress in labour or failed delivery using instruments.[28] Recent audits showed that CS, even if planned, was associated with severe postpartum haemorrhage. [93, 94]

The complex interrelation between different risk factors is important to remember when determining their independent contribution to severe haemorrhage risk.

Maternal mortality due to severe obstetric haemorrhage

Rapidly progressing hypovolemic shock is the major cause of death from obstetric haemorrhage.[19,20] Inadequately treated, it can result in prolonged tissue hypoxia and damage with consequent release of thromboplastin from damaged tissue, leading to disseminated intravascular coagulation (DIC), and finally cardiac failure, where death is imminent.[95] The risk of mother dying from severe haemorrhage is dependent on her previous health and the presence of anemia, but most importantly on the availability of an immediate access to high quality emergency obstetric care. Although MMR from haemorrhage has been dramatically reduced in the industrialized world, severe obstetric haemorrhage usually ranks among the top

three causes of maternal death, along with embolism and hypertension.[16, 96, 97] The recent Confidential Enquiries into Maternal and Child Health report in the UK concluded that suboptimal care was found in 58% of maternal deaths from haemorrhage.[16] There were questions concerning the most appropriate management of women with placenta percreta. There were apparent failures in recognising the signs and symptoms of intra-abdominal bleeding, especially after CS. Failure to assess the clinical picture, underestimating blood loss, delayed treatment, lack of multidisciplinary teamwork and failure to seek timely senior staff help are some of the issues highlighted in the British report.[16] Among maternal deaths due to haemorrhage in the USA, placental abruption was the most common cause, followed by lacerations/uterine rupture, uterine atony and coagulopathy.[96] Placental abruption was associated with MMR of 38.8/100 000 (7 times higher than the overall MMR) in Finland.[83]

Capturing maternal deaths statistically is not straightforward, even in high income countries.[34, 105] Maternal deaths by nature are prone to underreporting due to misclassification of causes and the absence of a diagnosis of pregnancy, especially at early gestations.

Maternal morbidity due to severe obstetric haemorrhage

Severe obstetric haemorrhage is associated with increased risks for postpartum sepsis, [29,48,100,101] acute renal failure,[102] and anaemia.[103] Iron deficiency anaemia is strongly linked with postpartum fatigue and depression.[104] Many women who needed hysterectomy suffer from serious complications related to the operation as injuries to other organs and infection.[29,47,48,101] Depression can be the consequence of loss of reproductive capacity or perceived loss of femininity and cessation of menstruation.[105] The UK Obstetric Team Surveillance System (UKOSS) showed a rate of peripartum hysterectomy due to haemorrhage of 41/100 1000 maternities. This suggests that more than 60 women undergo a peripartum hysterectomy for every woman who dies from haemorrhage.[28]

Women with severe morbidities suffered from poorer health with statistically significant increases in urgent admissions to hospitals, sexual problems, and outpatient visits within 6-12 months of follow up.[106]

AIMS OF THE STUDY

The main purpose of this study was to increase our knowledge of severe obstetric haemorrhage, a major maternal complications at childbirth. Shedding the light on the epidemiology of severe obstetric haemorrhage in high resource setting with adequate birth registration might contribute into reducing maternal mortality and severe morbidity. The underlying general research questions were:

1. What is the proportion and risk factors of severe obstetric haemorrhage in a high resource setting and what is the impact of such complication on maternal and perinatal outcome?
2. Is there significantly higher risk of severe postpartum haemorrhage at caesarean section compared with spontaneous and induced labour onset?

These issues were explored through a series of works designed to address the following aims:

1. Determine the proportion, risk factors, causes and maternal outcome of severe obstetric haemorrhage.
2. Determine the role of obstetric procedures as induction and caesarean section on the risk of severe postpartum haemorrhage.
3. Determine the proportion, risk factors and maternal and perinatal outcome of uterine rupture after previous caesarean section.
4. Determine the effect of spontaneous and induced labour compared with repeated elective caesarean section on the impact of uterine rupture on maternal and perinatal outcome.
5. Determine the effect of different induction methods on the risk of uterine rupture after previous caesarean section.

Components influencing severe obstetric haemorrhage

The study concentrated on identifying risk factors that might increase the risk of severe obstetric haemorrhage. These included demographic, medical, pregnancy and labour variables predisposing to or exaggerating the main causes and mechanisms of severe obstetric haemorrhage (Figure 2).

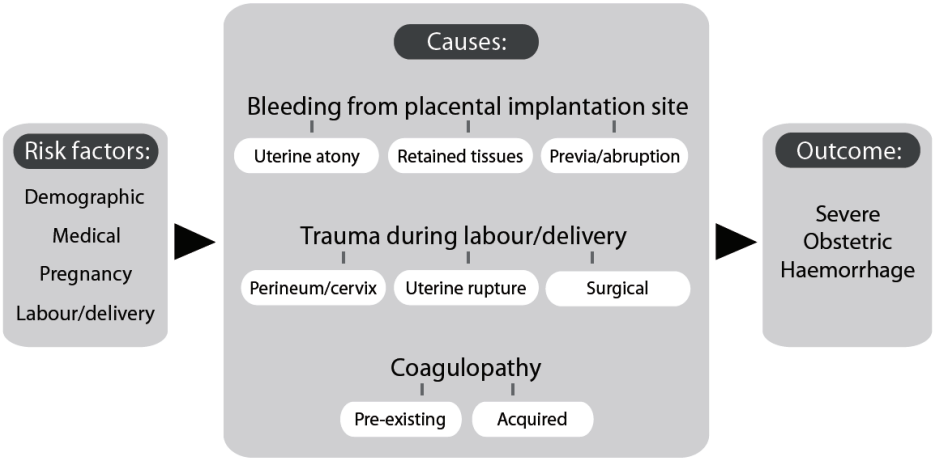

Figure 2. A model illustrating components influencing the occurrence of severe obstetric hemorrhage

MATERIALS AND METHODS

Data Source: The Medical Birth Registry of Norway (MBRN)

The source of data in this thesis was the Medical Birth Registry of Norway (MBRN). The Medical Birth Registry of Norway was established in 1967 for surveillance of perinatal health and to establish a basis for epidemiological research.[36, 37] It is a complete nationwide registry with consecutive registration of all births after 16 weeks of gestation, containing information on the mother, her pregnancy and delivery and the neonate. Information is based on three elements: 1) a standardised form used during pregnancy by the mother's physician, 2) information given by the mother when admitted to the hospital and 3) information from the physician and midwife about the actual delivery and the neonate. Complete ascertainment of

births is ensured through linkage of records with the National Population registry run by Statistics Norway,

It is compulsory to notify the MBRN of all births in Norway, and midwives or physicians attending the delivery complete a standardized form within seven days after delivery. The form contains information on maternal health before and during pregnancy, detailed information about delivery and complications occurring intrapartum or postpartum, and also information about the newborn (see appendix). Paediatricians complete a standardised form for neonates admitted to neonatal intensive care unit (NICU).[33, 35] The data of each mother is linked through a unique personal number to The Cause of Death Registry in order to detect any maternal or perinatal death. For the purpose of the current study, data in the MBRN file was additionally linked to Statistics Norway, in order to obtain information on education level and mother's country of birth.

In response to the MOMS studies, it has been possible since 1999 to use ticked boxes in the registration forms when recording severe obstetric haemorrhage and the majority of variables included in this study. These variables included the demographic, major medical diseases and most complications occurring during pregnancy, labour and postpartum. We believe that this change contributes to facilitating case ascertainment.[36, 37] The remaining medical diseases and surgical procedures such as hysterectomy were identified by using International Classification of Diseases, 10th revision (ICD-10),[114] and the Norwegian edition of The NOMESCO Classification of Surgical Procedures (NCSP) 2006[115] respectively.

Study design

The studies were all population-based registry studies. We analysed the registered data of population based maternity cohorts. The row data file was converted through several syntaxes into readable and feasible data for analysis.

Study population:

The study population in papers I and II comprised all women giving birth after 16 weeks of gestation from 1st January 1999 to 31st April 2004 (307 415 mothers). We included pregnancies from the 16th week of gestational age as severe haemorrhage can occur due to miscarriages and extra uterine pregnancies. The study population in paper III comprised 18 794 mothers with births ≥28 weeks gestation after previous CS, from 1st January 1999 to 30th June 2005. We included births ≥ 28 weeks as no ruptures occurred < 28 weeks. Only mothers with previous CS were studied as previous CS is the main risk factor of uterine rupture in high resource settings.[10]

Table 3. Overview of study populations and main variables in papers I–III.

	Paper I	Paper II	Paper III
Study population	307 415 mothers ≥16 gest. weeks	307 415 mothers ≥16 gest. weeks	18 794 mothers with previous CS ≥28 gest. weeks
Sub-populations		- No previous CS = 291604 - Previous CS = 15 811	- Repeated elective CS = 5442 - Emergency prelabour CS = 1398 - Trial of labour = 11 954
Study period	January 1999 - April 2004	January 1999 - April 2004	January 1999 - June 2005
Main outcome	Severe obstetric haemorrhage	Severe postpartum haemorrhage	Uterine rupture
Secondary outcome	1. Hysterectomy 2. ICU admission 3. Postpartum sepsis 4. Acute renal failure 5. Maternal death		<u>Maternal outcome</u> 1. Hysterectomy 2. Severe PPH 3. Moderate PPH 4. General anaesthesia <u>Perinatal outcome</u> 1.Perinatal death 2. Post hypoxic encephalopathy 3. Severe asphyxia 4. Other complications
Explanatory variables	• Demographic factors • von Willebrand's disease • Cardiac disease • Anaemia during pregnancy • HELLP syndrome • Previous CS • Multiple pregnancy • Induction • Prolonged labour • Macrosomia • Delivery mode: 1. Spont. vag. delivery (ref.) 2. Forceps delivery 3. Vacuum delivery 4. Elective CS 5. Emergency CS 6. Assisted breech delivery	• Onset of labour: 1. Spontaneous onset (ref.) 2. Induced onset 3. Prelabour CS • Mode of delivery 1. Prelabour CS (ref.) 2. Spontaneous vaginal delivery 3. Operative vaginal delivery 4. Emergency CS after labour start	<u>A. All mothers</u> • Maternal age • Ethnicity • Parity • Gestational age • Start of birth: 1. Repeated elective CS (ref.) 2. Emergency prelabour CS 3. Spont. labour 4. Induced labour <u>B. Attempting trial of labour</u> • Induction method: 1. No induction (ref.) 2. Prostaglandin± amniotomy 3. Oxytocin± amniotomy 4. Prostaglandins+ oxytocin + amniotomy 5. Mechanical methods
Confounding variables		Demographic, medical diseases, preeclampsia, HELLP syndrome, gestational diabetes, gestational age, multiple pregnancy, prolonged labour, macrosomia, polyhydramnios, intrapartum pyrexia, uterine rupture (only for CSs)	Gestational age in B

CS: Caesarean section; ICU: Intensive care unit; PPH: Postpartum haemorrhage; HELLP syndrome: haemolysis elevated liver enzymes & low platelets; Gest.: gestational ; Spont.: spontaneous; Vag.: vaginal

Variables (Table 3)

Main outcome variables:

- ***Severe obstetric haemorrhage*** was defined as a visually estimated blood loss of >1500 ml intrapartum and within 24 hours post-partum, or the need for blood transfusion postpartum regardless of the amount of blood loss. Blood transfusion was added to the definition so as to avoid missing cases when using visual estimation.[52, 70] For severe haemorrhage a specific box is ticked off by the attending midwife.
- ***Severe postpartum haemorrhage (severe PPH)*** was defined as severe obstetric haemorrhage, excluding haemorrhages due to placenta previa and abruption.
- ***Uterine rupture*** was identified through diagnostic code ICD-10: O71.0 (uterine rupture prior to labour start) and O71.1 (uterine rupture during labour) in the registration form. The ICD coding does not differentiate between complete or incomplete uterine rupture.[114]

Secondary outcome measures

Maternal outcome

Only the short-term postpartum complications were available. The association between each of severe obstetric haemorrhage and uterine rupture with serious maternal outcomes was assessed.

Maternal death: Maternal death was defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, from any cause related to or aggravated by pregnancy or its management, excluding accidental or incidental causes.[15]

Peripartum hysterectomy**:** Hysterectomy indicates the severity of estimated outcome measure and its impact on the fertility and future health of women.[28, 29, 47, 48, 101, 103]

Intensive care unit (ICU) admission: Severe obstetric haemorrhage is the most common cause of maternal admission to ICU.[116]

Acute renal failure: Is an indicator of serious hypoperfusion, and carries a risk of dialysis and renal transplantation.[102]

Postpartum sepsis: Is usually increased after severe haemorrhage due to pre-existing infection,[70,87,117] or to increased risk of ascending infection following procedures as manual removal of placenta or hysterectomy.[29, 48,100,101] In addition, increased infection risk is associated with anaemia due to reduced immunity.[100,104]

Moderate postpartum haemorrhage: Moderate PPH was defined as blood loss 500-1500 ml, visually estimated within 24 hours postpartum. It was used as an indicator of the seriousness of the identified uterine rupture.

Exposure to general anaesthesia is an indicator of a high grade of urgency required to save the mother or the infant. It indicates a catastrophic nature of the outcome measure (uterine rupture).

All maternal outcomes studied were identified through ticked boxes, except for acute renal failure, and hysterectomy identified through international diagnostic and surgical procedures coding.

Perinatal outcome

We studied perinatal outcomes after uterine rupture. They were categorised into four mutually exclusive groups as follows:

Perinatal deaths*,* defined as intrapartum fetal deaths ≥ 28 weeks gestation, and neonatal deaths ≤7 days after birth, not related to congenital causes. Antepartum stillbirths were excluded in the present study since they were not delivery-related. Stillbirths and neonatal deaths within 24 hours are recorded directly in the MBRN form. Information on late neonatal deaths and infant deaths is obtained through linkage with the Cause of Death Registry in Statistics Norway, ensuring ascertainment close to 100%.[36, 37]

S***evere asphyxia***, defined by diagnostic coding ICD-10: P21.0, excluding encephalopathy.

Post hypoxic encephalopathy -PHE, defined clinically as cerebral irritation, cerebral depression, or seizures in the presence of severe asphyxia. There was no specific box identifying PHE. Only cerebral irritation, cerebral depression, and seizures were identified through ticked boxes. Therefore, a new variable (PHE variable) was computed where both severe asphyxia and any of the neurological signs mentioned were present.

Other complications*,* defined as any neonatal problem with or without admission to neonatal intensive care unit (NICU), excluding perinatal deaths, severe asphyxia, and PHE described above.

Explanatory variables

The explanatory and confounding variables for severe obstetric and postpartum haemorrhage and uterine rupture each are shown in table 3.

Demographic factors: These comprised maternal age, parity, ethnicity, education level, and smoking. *Older maternal age* is shown to be associated with increased risk of severe obstetric

haemorrhages in previous studies.[6, 117, 118] Placenta previa, placental abruption and uterine rupture significantly increase with older maternal age.[119–121] *Primiparity* is associated with uterine atony and perineal trauma due to increased risk of prolonged labour and operative deliveries.[118,122] Immigrant mothers from non-Western background were associated with significantly higher risks for maternal mortality and adverse maternal outcome according to several studies.[16,123,124] *Asian mothers* were shown in previous studies to have a higher risk for severe haemorrhage.[70] *Smoking* is known to increase placental abruption.[120] *Education level* was used as an indicator of socioeconomic status. Low socioeconomic status is associated with increased risk for severe obstetric haemorrhage and other adverse maternal and perinatal outcomes.[6, 16]

Medical factors: *von Willebrand's disease* is the most common inherited blood disorder, and is associated with increased risk for severe obstetric haemorrhage due to coagulopathy.[125] Mothers with pre-existent *cardiac disease* are increasing due to recent advances in surgical correction of congenital heart diseases. Mothers with these diseases were shown to have increased risk for PPH in a previous study.[126]

Pregnancy/labour factors: *Multiple pregnancy* increases the risk of severe haemorrhage due to uterine overdistension, resulting in uterine atony.[6, 70, 86] *HELLP syndrome* increases the risk of coagulopathy and placental abruption.[86, 120] *Anaemia* during pregnancy increases maternal decompensation due to small blood reserve.[56, 120] *Previous CS* increases the risk for placenta previa, abnormally adherent placenta, and uterine rupture.[28, 48, 86-88, 128] *Macrosomia* increases uterine atony by uterine overdistension and uterine exhaustion, in addition to increasing genital trauma.[70, 87, 90] *Induction* and, *prolonged labour* increase both of uterine exhaustion and uterine rupture.[70, 87, 128]

Mode of delivery: Compared with spontaneous vaginal delivery, *operative vaginal delivery* increases uterine atony and perineal trauma.[70, 83, 94,120] Both *Emergency CS* and *elective CS* increase the risk for uterine atony and surgical haemorrhage.[87, 93, 94,120]

Start of birth was the main explanatory variable in paper II and III. In paper II, It was categorised into three groups: 'Spontaneous labour onset', 'Induced labour onset' and 'Prelabour CS'. The group of 'prelabour CS' comprised both elective CS (16 315 mothers) and emergency CS performed prior to established labour (6770 mothers). In this paper, we focused on determining the risk of severe PPH at prelabour CS with no underlying placenta previa or placental abruption, regardless of the emergency element included in the procedure.

Start of birth in paper III was categorised into four groups: 'Elective prelabour CS' (reference), defined as planned CS performed before onset of labour, 'Emergency prelabour

CS', defined as emergency CS before onset of labour, 'Spontaneous labour onset', and 'Induced labour onset'. Information about birth start was complete.

Induction method: Categorised into: 'No induction: spontaneous labour onset' (reference), induction by 'Prostaglandins with or without amniotomy', 'Prostaglandins, amniotomy & oxytocin', 'Oxytocin with or without amniotomy', and 'mechanical methods' defined as amniotomy alone or other non-medical induction methods.

Gestational age: Calculated by ultrasound at 18 weeks and categorized into: '24–36', '37–40' (reference), and '≥41' weeks.

All variables were identified through ticked boxes except for von Willebrand's disease. As they are not routinely recorded in the MBRN registration form, variables such as previous obstetric haemorrhage, prophylactic use of oxytocin in third stage, maternal body mass index, number of previous CSs, and indications of previous CS were not available

Statistical analyses

Proportion of the outcome measure

The occurrence measure of an outcome in perinatal and maternity cohorts can be expressed by the terms: risk, cumulative incidence, or proportion.[129] We will be using the term ''proportion'' to describe the occurrence measure of the outcome. This term was used to describe the occurrence of uterine rupture in paper III. Unfortunately, we used the term ''prevalence'' in paper I and II. ''Prevalence'' was frequently used to describe severe obstetric haemorrhage in previous studies in international obstetric journals. As severe obstetric haemorrhage is an acute morbidity and not a chronic disease, we believe that it is incorrect to use ''prevalence'', and therefore, we will be using ''proportion'' in this thesis. Frequency analysis and cross tabulations were used to measure the proportion of primary and secondary outcomes. The proportions of different causes of severe obstetric haemorrhage were calculated using cross tabulations.

Choosing the explanatory variables in analytic models

We studied the train of events where risk factors (the starters) lead to the different causes of severe obstetric haemorrhage (Figure 2). In doing that, the explanatory variables were chosen based on their clinical relevance and evidence from previous studies.[6,16, 28, 48, 56,70, 83, 86-88, 93, 94, 117–128] Risk factors might start prior to pregnancy as demographic factors, pre existing medical diseases, or previous obstetric history. They might start during pregnancy, as multiple

pregnancy, and might as well start during labour, as induction or prolonged labour or even later at delivery. We have tried different models including explanatory variables at different levels. Medical pre-existing variables were controlled for demographic factors as age, parity, and ethnicity in one model. Several models were tried so as to analyse pregnancy complications controlled for relevant confounders prior to pregnancy. Other models were tried to analyse labour variables, controlled for confounders prior to labour. This process of analysing was continued until we reached the final model where delivery mode variable was the main explanatory variable. The mode of delivery variable was controlled for confounders prior to delivery. Confounders included clinically relevant demographic, medical, pregnancy and labour risk factors that preceded the delivery (Figure 3).

We avoided using variables that constitute parts of the outcome measure (severe obstetric haemorrhage) as early gestational age and manual removal of placenta. Early gestational age was not included as a risk factor although it is known to be associated with severe haemorrhage. This association is in a major part due to placenta previa or abruption, causing severe haemorrhage as well as precipitating to premature delivery. Manual removal of the placenta was not included either as it is a known consequence of retention of placenta, another main cause of severe haemorrhage. Shoulder dystocia was not included in the model as it followed the delivery mode. Even when considered as the actual explanatory variable in a separate model, shoulder dystocia lost its significance after adjusting to macrosomia.
All variables were handled as categorical. The category with the lowest risk or the largest number of mothers included was used as the reference group in logistic regression analysis.
In paper III , we limited the number of explanatory variables to avoid overfitting or inflation of the model, as the events (uterine rupture) were of small size due to rarity.[130]

Stratification

Stratification is an important analytical approach. It involves preparing separate analyses within subgroups of the study population. This allows one to examine the relationship between the outcome and the explanatory variables in subsets in which the relationship may be simpler and clearer.[131]

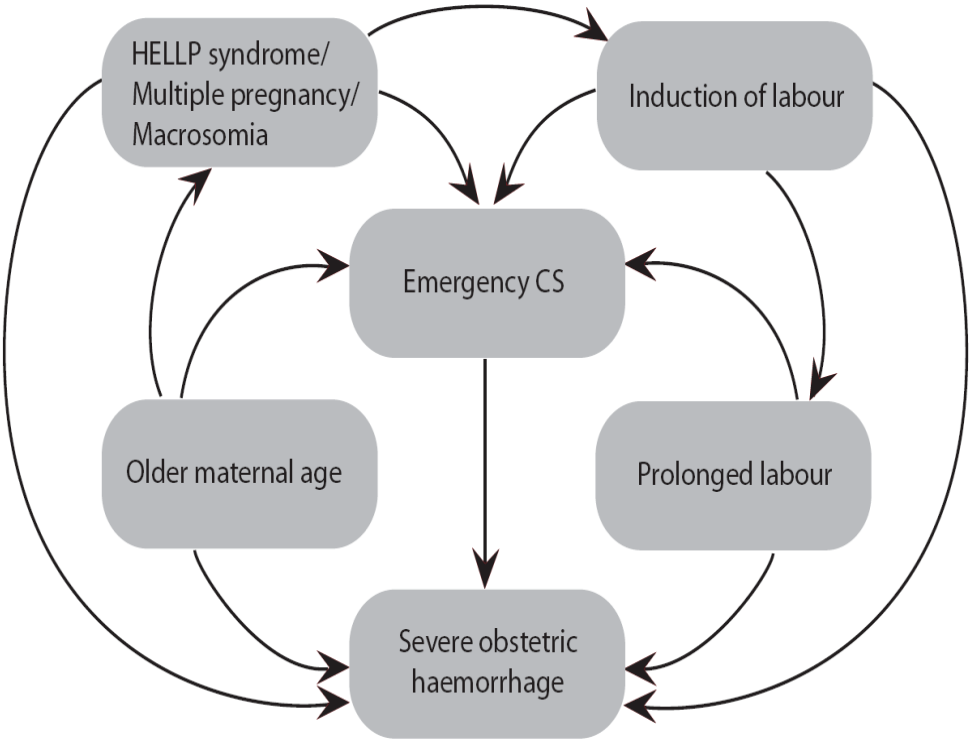

Figure 3. Interrelation between risk factors of severe obstetric haemorrhage

The association between the delivery mode for example and severe obstetric haemorrhage was assessed while stratified into different groups with or without other explanatory variables. This stratification revealed no interaction between the explanatory variables but showed the presence of confounding. A covariate was considered as a confounder when its addition to the model, resulted in a change of the estimate (odds ratio) of at least > 10%.[132] These tests are not shown in the papers, but were performed as preliminary steps to design the final model.

Univariate and bivariate analysis

To examine the risk of outcome related to certain explanatory variables, we started first with cross tabulations/logistic regressions of each explanatory variable and the main outcome. This reveled the absolute risk of the outcome in the group exposed to the studied variable, expressed in percentage (univariate analysis), and the relative risk of the same variable, expressed in odds ratio and 95% confidence interval (bivariate analyisis). The Chi-square test was used for hypothesis testing. The P-value was interpreted as the probability of observing our data when the null hypothesis is true.[133] The level of significance was $P<0.05$. In

interpretation, the emphasis was on confidence intervals rather than p-value, as confidence interval reflects the precision of the results more than P-value. Fishers exact test was used to assess the significance when the size of the outcome (the events) was small as in paper III studying uterine rupture and its serious maternal and perinatal outcomes.

The relative risk after bivariate analysis describes the effect of the risk factor studied, but does not determine if this effect is real or specific as it does not adjust for the effects of other interelated risk factors (Confounding).

Multivariate analysis

Multiple logistic regressions were used as many risk factors of obstetric morbidities are inter-related (Figure 3). Multiple logistic regressions are used in order to assess the relationship between the explanatory variables and the dichotomous outcome, allowing for adjustment for other independent variables (confounding).[134] We used multiple logistic regressions to control for these confounding factors to avoid a 'false positive' conclusion that the dependent variables are in a causal relationship with the independent variable (a spurious relationship). We chose the confounding variables that satisfied all these following three criteria in each model: (1) it must have an association with the outcome, (2) it must be associated with the exposure, and (3) it must not be an effect of the exposure; this also means that it may not be part of the causal pathway. We tried to avoid adjusting for highly correlated variables (i.e. avoiding the problem of multicollinearity).[135] In the presence of multicollinearity, the estimate of one variable's impact on the outcome, while controlling for the others, tends to be less precise than if the predictors in the model were less correlated with one another.

The factors of clinical relevance, and factors with level of significance of $P<0.20$ were taken into account, adding one variable at a time in two variables models first. The effect is based on the change in the odds ratio calculated and the 95% confidence intervals and the p-value (<0.05). The fitness of the model was assessed using Hosmer-Lameshow goodness of the fit in logistic regression in SPSS programme, version 15.

In paper III on uterine rupture, the influence of single observations on the fit of the model was tested for each coefficient in the final models by using the influence test DfBeta (Difference in Beta values) in the logistic regression in SPSS.[136]

Ethical Consideration

The study was approved by the Regional Ethical Committee for Medical Research, The Norwegian Data Inspectorate, and the Norwegian Directorate of Health.

SUMMARY OF PAPERS

Paper I: Prevalence and Risk factors of Severe Obstetric Haemorrhage

Objective: To determine the proportion, causes, risk factors and maternal outcome of severe obstetric haemorrhage in all pregnant women giving birth after 16 weeks in 1999-2004 (N=307 415).

Main outcome measure: Severe obstetric haemorrhage (blood loss of > 1500 ml, or blood transfusion).

Methods: Cross-tabulation and multiple logistic regressions were used to determine proportion, causes, risk factors, and acute maternal complications of severe obstetric haemorrhage.

Results: Severe obstetric haemorrhage occurred in 1.1% of mothers. Uterine atony was the main identified cause (30.1%), while no cause was identified in 30.8% of cases (Figure 4). The risk factors with the highest odds for severe haemorrhage were emergency CS, von Willebrand's disease, elective CS, multiple pregnancy, anemia, macrosomia and HELLP syndrome. Other risk factors included operative vaginal delivery, older age, South East Asian origin, induction, previous CS and prolonged labour. Severe haemorrhage was associated with higher risks for maternal death, hysterectomy, ICU admission, postpartum sepsis and acute renal failure.

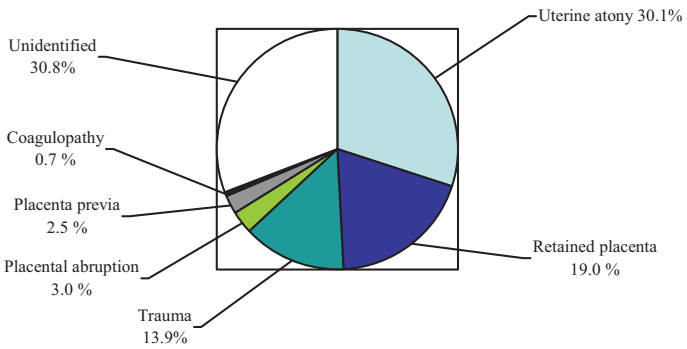

Figure 4. Causes of severe obstetric haemorrhage

Conclusion: A relatively high rate of severe obstetric haemorrhage was detected, with a large percentage of unidentified causes. Many of the significant risk factors can be influenced by reviewing labour management and protocols.

Paper II: Effects of Onset of Labor and Mode of Delivery on Severe Postpartum Hemorrhage

Objective: To study the impact of labour onset and delivery mode on the risk of severe postpartum haemorrhage in total mothers of 307 415, and in the two subgroups of mothers without previous CS (291 604), and mothers with previous CS (15 811).
Main outcome measure: severe postpartum haemorrhage
Method: The association between severe postpartum haemorrhage and labour onset was analyzed using three logistic regression models: (1) Spontaneous labour onset (reference) versus Induced labour onset, (2) Spontaneous labour onset (reference) versus Prelabour CS, and (3) Induced labour onset (reference) versus Prelabour CS. The association between severe postpartum haemorrhage and mode of delivery was analysed using four logistic regression models with prelabour CS as reference. Finally, the association between severe postpartum haemorrhage and delivery mode after both spontaneous and induced labour was analyzed using logistic regression in three separate groups: 1. primiparas, 2. multiparas without previous CS, and 3. mothers with previous CS. Cross tabulations were used to identify causes of severe postpartum haemorrhage at different delivery modes.
Results: Compared with spontaneous labour, haemorrhage risk was higher for induction (OR: 1.71; 95% CI: 1.56– 1.88) and prelabour CS (OR: 2.05, 95% CI: 1.84–2.29). The risk was 55% higher for emergency CS, and halved for vaginal deliveries (OR: 0.48; 95% CI: 0.43-0.53), compared with prelabour CS (Figure 5). The highest risk was observed for emergency CS after induction in mothers with previous CS (OR: 6.57; 95% CI: 4.25–10.13), compared with spontaneous vaginal delivery in mothers without previous CS. Mothers with previous CS had significantly higher proportion of severe PPH (2.1 %), versus mothers without previous CS (1%). The largest percentage of unidentified causes was found in mothers with severe PPH after CS (more than 60%).

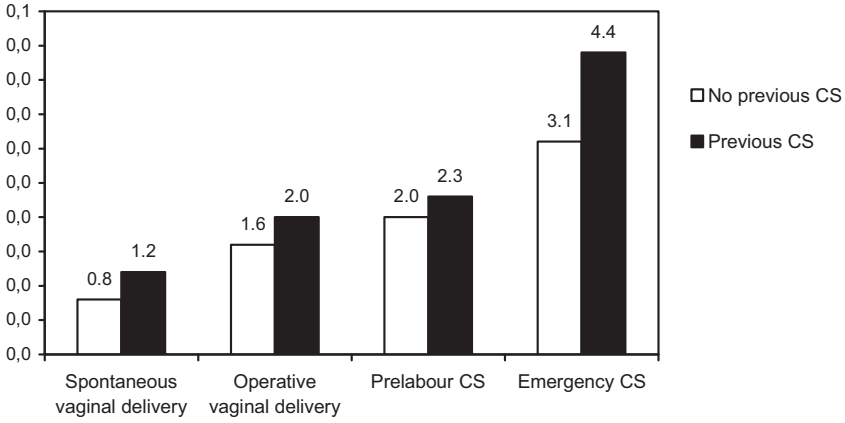

Figure 5. Severe haemorrhage percentage at different delivery modes

Conclusion: Induction and prelabour CS should be practiced with caution due to the increased risk of severe postpartum haemorrhage. Prelabour CS might be a better option if the probability of emergency CS is high. Large-scale prospective studies are needed to objectively document the amount and precise causes of blood loss at CS.

Paper III: Uterine Rupture after Previous Caesarean Section

Objective: To determine the risk factors, proportion, and maternal and perinatal outcomes of uterine rupture among mothers giving birth ≥ 28 weeks subsequent to previous CS (N= 18794) during six years. A further aim was to study the impact of different induction methods on uterine rupture.

Main outcome measure: Uterine rupture.

Method: The association between different explanatory variables and uterine rupture risk was assessed using cross tabulations and multiple logistic regressions.

The medical records of eleven mothers with uterine ruptures at prelabour CS were studied. The association between uterine rupture and serious maternal and perinatal outcomes was assessed in all mothers, in mothers having prelabour CS and mothers attempting trial of labour (TOL).

Results: A total of 94 uterine ruptures were identified (5.0/1000 mothers). Compared with elective prelabour CS, the odds of rupture increased for emergency prelabour CS (OR: 8.63;

95% CI: 2.6–28.0), spontaneous labour (OR: 6.65; 95% CI: 2.4–18.6) and induced labour (OR: 12.60; 95% CI: 4.4–36.4). The odds were increased for maternal age ≥40 vs. <30 years (OR: 2.48; 95% CI: 1.1–5.5), non-Western origin (OR: 2.87; 95% CI: 1.8–4.7) and gestational age ≥41 weeks vs. 37-40 (OR: 1.73; 95% CI: 1.1–2.7). Uterine rupture after TOL significantly increased severe postpartum haemorrhage (OR: 8.51; 95% CI: 4.6–15.1), general anaesthesia exposure (OR: 14.20; 95% CI: 9.1–22.2), hysterectomy (OR: 51.36; 95% CI: 13.6–193.4), and serious perinatal outcome (OR: 24.51 (95% CI: 11.9–51.9). The highest percentages of rupture-related serious maternal and perinatal outcome were observed when ruptures followed TOL (Figure 6). Serious perinatal outcomes were highest when ruptures followed induction of labour. Induction by prostaglandins significantly increased the odds for uterine rupture compared with spontaneous labour (OR: 2.72; 95% CI: 1.6–4.7). Prelabour ruptures were detected after latent uterine activity or abdominal pain among mothers with multiple or longitudinal uterine scars.

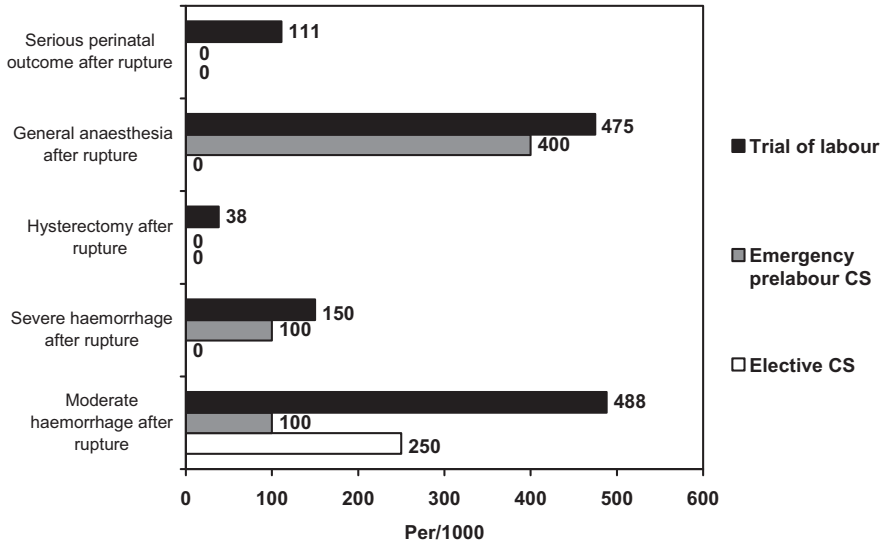

Figure 6. Proportion of rupture-related maternal and perinatal outcome at different birth starts

Conclusion: Trial of labour carried greater risk and graver outcome of uterine rupture vs. elective repeated CS, although absolute risks were low. A review of labour management and induction protocol is needed.

DISCUSSION

Main results

Severe obstetric haemorrhage occurred in 1.1% of all mothers. Uterine atony was the main identified cause, representing 30%, while no cause was identified in almost one third of the cases. Cases of Severe haemorrhage at CS had in a major part unidentified cause. The mode of delivery was the most important risk factor, especially emergency CS, followed by elective CS when compared with spontaneous vaginal deliveries. Other important risk factors included multiple pregnancy, von Willebrand's disease, HELLP syndrome, anaemia during pregnancy and macrosomia. Mothers with severe obstetric haemorrhage had significantly higher risk for severe postpartum morbidity as peripartum hysterectomy and maternal mortality.

Prelabour CS and induction significantly increased the risk for severe postpartum haemorrhage (PPH) compared with spontaneous labour onset in mothers with or without previous CS, even after adjusting for underlying indications. There was no significant difference in severe PPH risk between prelabour CS and induction. Vaginal deliveries halved the risk of severe PPH compared with prelabour CS even in mothers with previous CS. Operative vaginal deliveries after induction significantly increased haemorrhage risk in primiparas. Emergency CS after labour onset had the highest risk for severe PPH in all mothers, but especially after induction in women with previous CS. Thus, elective CS might be a better option among mothers with previous CS if the probability for emergency CS after trial of labour is high.

Uterine rupture occurred in 5/1000 of all mothers with previous CS. The highest risk was for induced labour and emergency prelabour CS, while the lowest risk was for repeated elective CS. Uterine rupture was significantly associated with both severe and moderate PPH, peripartum hysterectomy, exposure to general anaesthesia, and serious perinatal outcome, but only if occurring after trial of labour. Induction by prostaglandins carried significantly greatest odds for uterine rupture. Prelabour ruptures were detected after latent uterine activity or after abdominal pain in mothers with multiple or longitudinal uterine scars. Older age and ethnicity were significant risk factors for both severe obstetric haemorrhage and uterine rupture.

Methodological consideration

Methodological questions have been discussed in the individual papers. The aim of this section is to summarize the methodological limitations and advantages of the study, and to assess to what extent the limitations may have influenced the results. The interpretation of the results obtained will be then discussed.

Advantages and limitations of the study

The methodological strength of the current study is the population-based design including a large sample of mothers. This gives the opportunity to study the total population without selection bias. It allows also for studying rare events like uterine rupture, and severe complication as severe obstetric haemorrhage. The large sample size provided sufficient power to estimate associations in subgroups of women, even for small effects. Information on many covariates contributed to controlling for many potentially confounding variables. An important advantage in our population is the presence of a high rate of trial of labour after previous CS (around 61%).[137] This allowed us to study the association of different onsets of labour and modes of deliveries with the risk of severe haemorrhage and uterine rupture after previous CS.

The disadvantages lie in lack of specific details of labour and induction due to the nature of register, and inherent inadequate registration of diagnosis and/or procedures. Details of obstetric history as previous obstetric haemorrhage or previous retention of placenta, etc. was not available through the data file used in this study. This could be achieved if we had a sib ship file that follows the different pregnancies of each mother. Case records would provide us with information not available in the registry, such as the duration of labour, the dosage of specific induction agents, or causes of haemorrhage at CS, etc. Information bias could be reduced in this study by using clearer definitions of variables, better measuring methods, standardized procedures and quality control. Certain variables like prolonged labour need a clearer definition. Ticked boxes should be used to record uterine rupture, placenta accreta and hysterectomy. Visual estimation of blood loss should be standardised in order to get valid results. Quality control can be achieved by performing validity study of MBRN registration of severe obstetric haemorrhage and uterine rupture. MBRN has generally adequately high registration quality as documented by several validity studies.[138–143]

Do the results of this study truthfully reflect the reality? To answer this question, it is necessary to assess the possible sources of error. In principle, the reliability of the measurement may be reduced due to random error, while the validity of the results may be reduced due to systematic error (bias).

Reliability consideration: Random errors

Random error is due to chance or insufficient information, and leads to loss of precision. Precision in an estimator (i.e. an odds ratio OR) can be improved by increasing the sample size or by increasing the efficiency with which information on the individual level is obtained. In epidemiological studies, the principle way to increase precision is usually by increasing the sample size.[144] Our study sample covering all maternities over a five years period, was large enough for analysis in paper I & II. This was also reflected in the narrow confidence intervals achieved indicating precision. However, the sample of mothers with previous CS over a six years period was not large enough to measure the association between exposures and the rare event of uterine rupture with high a high degree of precision, as seen in the wide confidence intervals of the odds ratios. This was particularly the case when measuring the association between uterine rupture (only 94 rupture) and the secondary maternal and perinatal outcomes, and also between specific induction methods and uterine rupture.

Validity considerations (bias)

The validity of any epidemiological study is influenced by systematic error (bias). We can say that our study was valid if our design and methods provided unbiased estimates of the parameters studied.

Sources of systematic errors (bias) include selection / sample bias, information bias and confounding.[144]

1. Selection bias

Selection bias occurs as a result of non representative samples, often resulting from the use of convenience samples and other non-probability methods. As our sample size represents the total population of pregnant women, selection bias does not affect the internal validity of this study. However, selection bias may be a problem concerning the external validity of the study if the results are generalized beyond the target population. The pregnant population in Norway may not share the general demographic, genetic, and management factors as the pregnant populations in other high resource settings as for example in the UK.

2. Information bias

There is a probable information bias in this study as it is based on population registry data. Information bias is due to misclassification of study factors: Either of the exposure /explanatory variable), of the outcome (severe obstetric haemorrhage/ uterine rupture), or of the confounding variables. As the old saying goes, the quality of the study is limited by the quality of the measurements ("garbage in, garbage out").

Briefly, information bias can be either differential or non-differential.[144] The former is a systematic misclassification occurring at different rates in the groups being compared, resulting in a particular group or groups of individuals having a greater chance of being misclassified than do others in the sample. This is of concern since it leads to either inflated or deflated estimates of associations. Non-differential misclassification is random misclassification where all individuals for whom we have the data are equally likely to be misclassified. In general, the non-differential misclassification is preferred, as the resulting bias will bring estimation toward the null hypothesis. These errors tend to deflate associations with the outcome in the case of dichotomous exposures.

As the details of each mother are routinely registered by birth attendant within very short time postpartum, systemic misclassification due to recall bias or differential recording of the events would be uncommon in this study. In contrast, non- differential misclassification tends to be more common in the MBRN, leading generally to deflated estimations in this study.

a. Information bias in explanatory variables

In general, the explanatory variables that are identified through ticked boxes are less frequently to be misclassified than those identified through diagnostic coding as demonstrated in a validating study of the Swedish Birth Registry.[145]

The majority of explanatory variables, including demographic, pregnancy and labour factors, were identified through ticked boxes in this study.

Maternal age is likely to have essentially no errors while parity and birth weight may have a small amount of error that is essentially negligible due to the large size of the sample. Education level, though identified through ticked boxes, was missing in a good proportion of mothers. This might have resulted in lack of association with severe obstetric haemorrhage.

Delivery modes and onset of labour tends to be most accurate as they are straightforward and registered within short time after delivery. However, it is difficult to use a unified concrete definition of prolonged labour. The definition varies due to differences in subjective individual assessments as well as maternal factors like parity and use of epidural anaesthesia.

Moreover, there is no specific box for prolonged first stage or prolonged second stage of labour in the registration form. Misclassification can occur when documenting the specific induction method, especially if induction was followed by augmentation with oxytocin. These errors might have resulted in underestimated associations with severe obstetric haemorrhage or uterine rupture. The validating study from the Swedish registry found generally the same errors that we are concerned with such as using the codes instead of ticked boxes, inadequate transfer of information from the case records, misclassified clinical diagnosis.[145] On the other hand, even with errors occurring at different stages of registration, the data set is so large, that it compensates for relatively small margin of errors.

b. Information bias in outcome variables

An Australian study assessing the quality of data based on hospital discharge registry found that when compared with a recorded diagnosis of postpartum haemorrhage (PPH) in the medical records, the discharge data had a sensitivity of 73.8% and a positive predictive value (PPV) of 83.9%. However, when defined by either a recorded diagnosis of PPH or amount of blood loss, the hospital discharge data had a sensitivity of 50.3% and PPV of 91.0%. The findings of this validating study imply that it is important to be aware of the definition used to code the diagnosis or procedure as opposed to the clinical definition.[146] This strengthens the validity of our estimations in this study as we used the amount of blood loss in the recorded definition as well as the clinical definition. The amount of blood loss however could be misclassified clinically as visual estimation underestimates the actual amount. We tried to minimise this underestimation of blood loss by adding the need for blood transfusion in the definition.

Sensitivities in the Australian study ranged from 28.3% for the reporting of peripartum hysterectomies to 100% for placenta previa and repair of cervical laceration or perineal lacerations. Misclassification of hysterectomy was also found in our study. In paper I, we reported only eight hysterectomies in the target population where we related this to underreporting resulting from using procedure codes. These figures were revised while writing paper III and we found that one of the hysterectomy codes was not used while calculating hysterectomies. Being used, this resulted in increasing hysterectomies to 47 (40 in mothers with obstetric haemorrhage). The calculated increased risk of hysterectomy after severe obstetric haemorrhage should accordingly be 500-fold instead of 115-fold.

One of the challenges in identifying causes of obstetric haemorrhage through registered data worldwide is the lack of separate ICD codes for specific causes like the different types of

placenta accrete/percreta/increta. In addition, there are no separate codes for atonic PPH and PPH immediately following childbirth due to other causes. In this study, uterine atony, placenta previa, placental abruption and retained placenta were identified through specific ticked boxes, ensuring better reporting.

Uterine rupture, however was identified through international coding, not differentiating between incomplete and complete ruptures (symptomatic ruptures). Mixing would most probably result in deflated association between risk factors and actual complete ruptures. Risk factors for complete ruptures might be different from those affecting dehiscences. This problem could be avoided if ticked boxed were used for each of complete and incomplete rupture. We discussed this problem in details in paper III. Post hypoxic encephalopathy and severe asphyxia are also likely to be underreported.

3. Confounding

Confounding (from the Latin confundere: to mix together) is a systematic error in which lack of control for a third variable may distort an association between an exposure and an outcome. All efforts were focused on minimising multicollinearity by avoiding adjusting for intermediate events or events in the casual pathway between exposure variable (delivery mode) and the outcome measure (severe haemorrhage).

Residual confounding means the presence of confounding variables that were not controlled in models measuring association parameter.[144] Previous obstetric haemorrhage and maternal obesity were not available, and thus their contribution into haemorrhage risk could not be measured. Confounding variables as multiple previous CS, indication of previous CS, and other types of uterine scars were not available when measuring the effect of start of birth on uterine rupture. This issue is of great importance especially that we found such risk factors in mothers with prelabour ruptures through studying their case records. Information on cervical ripeness/duration of induction was not available. Therefore their confounding on induction method could not be controlled.

Interpretation of the results

The proportion of severe obstetric haemorrhage

The proportion of severe obstetric haemorrhage of 11.38/1000 (95% CI: 11.3-11.5)[147] was relatively higher than other studies in high resource settings (Table 4). MOMS-B study used the same clinical definition of blood loss>1500 ml or need for blood transfusion as ours, but only from 24 weeks gestations, covering only certain regions in each European country included in one year interval.[8] The proportion of severe obstetric haemorrhage in each country involved was lower than our figure. The highest proportions of 8.8/1000 was found in Finland (65% of all maternities), followed by 6.8/1000 in UK (only South East Thames region). These figures are still lower than ours as was discussed in paper I. This could be partly explained by our larger denominator of gestations after 16 weeks, in addition to including cases of placenta previa and abruption. However, even if we removed these cases (total of 221), we are still having a proportion of 10/1000.

Studies from Canada and USA had very low figures as they used stricter inclusion criteria of severe haemorrhage (ICU admission/ hysterectomy).[63–67]

There are several probabilities underlying our relatively higher proportion of severe haemorrhage compared with the figures reported in MOMS study. These include the following: 1. Norway has a real higher proportion of severe obstetric haemorrhage than these countries, 2. Better ascertainment of our study, or 3. We have overestimated the actual proportion of severe haemorrhage.

We might have better case ascertainment than other studies as we used data of the total population through five years (307 415 mothers), and not only selected regions in limited time. In spite of generally narrow confidence intervals in previous studies (Table 4) our confidence interval is even much narrower, reflecting higher precision of our estimate due to larger sample size.[147]

Norway participated in MOMS study, with data from two hospitals in Oslo. Mothers referred to these hospitals with severe complications from areas outside Oslo were excluded. This might have contributed to the low reported rate of severe haemorrhage of 2.7/1000 among a sample of 3010 mothers.[8] Eggebø et al performed a hospital-based study in Stavanger University Hospital over three years, and reported a higher proportion of severe haemorrhage of 8.5/1000.[148, 149] This might be due to a larger representative sample of mothers in this study

or a restricted use of prophylactic oxytocin in the third stage of labour during a certain period covered by this study .

Table 4. Severe obstetric haemorrhage reported in different studies

Author/Country	Study years	No. of deliveries	Proportion/1000	Definition criteria
Basket and Sternadel,[63] Canada	1980-1993	76 119	0.16 (0.1–0.2)	ICU admission
Lapinsky et al,[64] Canada	1990-1994	25 000	0.4 (0.3–0.5)	ICU admission
Mahutte et al[65] Canada	1991-1997	44 340	0.8 (0.7-0.9)	ICU admission
Monaco et al,[66] USA	1983-1999	15 323	0.2 (0.1–0.3)	ICU admission
Murphy and Charlette,[67] USA	2002-2002	51 576	0.2 (0.16–0.23)	ICU admission
Hazelgrove et al,[68] UK	1994-1996	122 850	0.6 (0.56–0.64)	ICU admission
Bewley and Creighton,[69] UK	1991-1992	6039	2.3 (1.9–2.7)	ICU admission
Brace et al,[7] Scotland	2004-2004	51 165	1.9 (1.8–2.0)	Blood loss ≥ 2500 ml, or blood transfusion >5 units, or treatment for coagulopathy
Brace et al,[25] Scotland	2003-2005	155 820	3.7 (3.4–4.0)	Blood loss ≥ 2500 ml, or blood transfusion >5 units, or treatment for coagulopathy
Zhang et al (MOMS-B), [8] Europe	1995-1998	182 734	4.6 (4.3–5.0)	Blood loss ≥ 1500ml, or transfusion (blood/expanders)
1. Austria	9/1996-8/1997	6022	0.7 (0.2–1.8)	
2. Belgium	1/1996-12/1996	17042	6.0 (5.0–7.4)	
3. Finland	5/1996-9/1996	17249	8.8 (7.5–10.4)	
4. France	1/1995-12/1995	71909	3.1 (2.7–3.5)	
5. Hungary	1/1995-12/1995	13 667	1.6 (1.0–2.5)	
6. Ireland	1/1996-12/1996	1800	1.1 (0.2–4.5)	
7. Italy	3/1996-2/1997	3170	1.3 (0.4–3.5)	
8. Norway (Oslo)	1/1995-12/1995	3010	2.7 (1.2–5.2)	
9. UK	1/1997-2/1998	48865	6.8 (6.1–7.5)	
Eggebø and Gjessing,[148,149]Norway	1/1997-1/2000	12659	8.5 (8.0–8.9)	Blood loss > 1500 ml
Al-Zirqi et al,[147] Norway, 2008	1/1999-3/2004	307415	11.4 (11.3–11.5)	Blood loss > 1500ml, or need of transfusion.

ICU: intensive care unit

The data used in our present study is routinely registered according to Norwegian law. We are not dependent on response rate or motivation of participants, and thus selection bias is avoided. We therefore hypothesise that using a similar population- based study would increase the proportion of severe haemorrhage in other settings, and allow the results from different countries to be comparable.

Could it be possible that we have in fact a higher proportion of severe obstetric haemorrhage than other countries? If this was true, this might be explained by different characteristics of our population, or different management or procedures. Generally, Our CS rate of 17.1% is lower than other countries with similar resources such as 30.8% in USA,[150] 24% in UK[151], and 38.3%in Italy.[152] The global increase in mean maternal age and maternal obesity is also seen in Norway, but the figures in our population are not higher than in other countries.[153, 154] The induction and multiple pregnancy rates are increasing in our population,[85] as in other populations.[158] Our population is more homogenous than other populations with higher percentages of immigrants with higher risk for adverse maternal outcome.[155] We can not omit, however the possibility of an underlying genetic predisposition to haemorrhage in Norwegian mothers.

Inadequate management of the third stage might be contributing to the high proportion of severe haemorrhage in our study. According to a European survey, [81] among 83.6% of responding maternity units in Norway, only 11% were using active management of third stage as FIGO recommended. In addition only 39% of these units used controlled cord traction, while only 72% used oxytocin as prophylaxis. However, this was not only the case for Norway, as the survey showing that only 3–20% of the responding obstetric units in Austria, Denmark, Finland, France, Hungary, Italy, and Portugal actively managed the third stage. Among 68.4% responding units in the UK, prophylactic oxytocin and controlled cord traction were used in 96% and 87% of these units respectively. However, severe haemorrhage was reported to be much more frequent in the South East Thames region in UK (6.8/1000) than in upper Austria (0.7/1000).[8] In Austria, oxytocin prophylaxis and controlled cord traction were used in only 52% and 21% of the units respectively. However only 31.7% of units in Austria responded to the survey.[81] It is important to mention that the Norwegian study by Eggebø et al demonstrated that severe haemorrhage increased when prophylactic use of Oxytocin was restricted during a certain period.[148]

In Norway, manual removal of retained placenta is not performed in the majority of units before 60 minutes after birth. One may speculate whether this may have contributed to our relatively high proportion. However, the same policy is practiced in the Netherlands, Denmark and Finland.[156] The majority of units in France and Belgium remove the placenta at or before 30 minutes, but they do not have the lowest rates of severe haemorrhage (Table 4). Moreover, there is no evidence that artificial reduction of the length of the third stage by manually removing placentas that have not been spontaneously expelled will reduce the risk of PPH. Retained placenta may be the consequence of an impaired uterine contractility that will also lead to PPH. In that case, a long third stage would be a more risk marker than a cause of PPH.

As discussed earlier in introduction, the different protocols regarding blood transfusion and other procedures contribute to the variation in reported rates of severe haemorrhage despite using the same definition.

The third probability behind our figure lies in an overestimation, or false positive cases. This might be due to misclassification in registration. This is highly unlikely as discussed in methodology that such random misclassification would result in underestimation rather than overestimation. Measuring haemorrhage depending on visual estimation would most likely result in underestimation. We do not think that adding blood transfusion is a reason of overestimation, as the policy of blood transfusion is very strict.

Using a broad definition may capture larger number of cases at an earlier stage in the train of events prior to near miss or death. If we included only those with hysterectomy, or those admitted to ICU, the proportion of severe haemorrhage would be 0.12/1000 and 0.8/1000 respectively. This is as low as in studies using strict criteria (Table 4). Using ICU admission criteria would capture only 7% of mothers reported with severe haemorrhage in our study.

The seriousness of severe obstetric haemorrhage would be better assessed in our population if we could identify mothers with blood loss >2500 ml, and if we knew the number of blood units transfused. This could contribute to establishing a scoring system of severe obstetric haemorrhage prior to hysterectomy or other serious outcomes. We can thus estimate the association of certain risk factors with more serious degree of severe haemorrhage.

Causes of severe obstetric haemorrhage

The finding that uterine atony was the main cause of severe haemorrhage is consistent with the reports in the literature.[81] It also reflects the main mechanism of postpartum haemorrhage:

failure of uterus to contract. The relaxed myometrium will fail to constrict the blood vessels, thereby allowing haemorrhage. Since up to one fifth of cardiac output, or 1000ml/min, enters the uteroplacental circulation at term, postpartum haemorrhage is capable of exsanguinating the mother within a short time. As uterine atony can result in retained placenta, the contraction failure often becomes self perpetuating. Uterine atony should be presenting in at least 70% of mothers with severe obstetric haemorrhage, but it was detected only in 30% in the current study. Uterine atony was identified in only 48% in a Scottish audit.[25] The inclusion of early gestations may explain our higher percentage of retained placenta of 19% compared with reported figures of 10%.

A larger percentage of unidentified causes might be due to the lack of either documentation or clinical recognition of uterine atony. This reflects the lack of being precise and specific when assessing severe obstetric haemorrhage. It seems that the inaccuracy in estimating blood loss and identification of causes of bleeding reflects the general management attitude towards severe postpartum haemorrhage. This inaccuracy might be one of the main underlying causes of inadequate management of severe PPH.

The finding that the 60% of those who had caesarean delivery had no identified cause of associated severe haemorrhage indicates a difficulty in identifying exact causes of haemorrhage at CS. CS is associated with higher risk for uterine atony, and surgical bleeding related to hysteretomy sites. Surgical bleeding is usually underreported due to lack of coded diagnosis even if recognised clinically. It is important to mention that placenta previa had the second highest risk for hysterectomy after uterine rupture in our population (Data not shown in papers). This may indicate the presence of placenta accreta, which is not specifically coded internationally.

Although special ticked boxes contribute to better identification of causes than ICD codes, complete identification of causes is difficult to achieve. There would be still unidentified causes of haemorrhage even through following the case records, due to inadequate clinical recognition or documentation. A French study of obstetric haemorrhage based on case records found that uterine atony and retained placenta accounted for 80% of PPH after vaginal deliveries, while the cause remained unknown in 20% of PPH and 12% of severe PPH. Among haemorrhages at CSs, uterine atony was the most frequent cause, followed by hystertomy bleeding and placental abruption. In almost 50% of cases detected after CSs, no cause was identified.[157] This is consistent with the results of our study.

Proportion of uterine rupture

The proportion of uterine rupture was consistent with that in other countries,[158] despite uncertainty due to including both incomplete and complete ruptures. This may indicate that the majority of ruptures estimated in our study are complete ruptures. This hypothesis is strengthened by the finding that 73% of prelabour ruptures were complete ruptures after reviewing the case records as shown in paper III.

Risk factors

The final model in paper I determined the adjusted haemorrhage risk for delivery mode. We will be referring to the unadjusted OR of the other risk factors, as the delivery mode was an intermediate variable between these risk factors and severe obstetric haemorrhage.

Demographic factors

The risk of severe haemorrhage increased as maternal age was increasing. Mothers older than 40 years old had the highest risk for severe haemorrhage and also for uterine ruptures in agreement with previous studies.[6, 118-120,149] Studies suggested that older age is associated with increased risk for dysfunctional labour and deficient healing of uterine scar, contributing to increased risk for severe haemorrhage and uterine rupture.[159] Mothers ≥40 years old had 4.5 times increased risk for peripartum hysterectomy in our study. These results should be used in the debate against postponing childbearing to older age in modern societies.

Grandmultiparity was not a risk factor for severe haemorrhage, probably due to few numbers of women with actually higher number of deliveries as 10 or more. In addition, this group is usually treated as high risk in labour, and thus the risk might be minimised by the vigilant obstetric care. In fact the primiparas were more at risk as they were predisposed to prolonged labour, operative vaginal deliveries and perineal trauma, consistent with recent studies.[91, 122, 148] Primiparas should have more attention during labour as they constitute potential candidates for CS on mother request in future pregnancies as a result of traumatic experience at childbirth.

Immigrant women from non-Western background were shown in previous studies to have significantly higher mortality rate and adverse maternal outcomes.[6, 16] This was attributed to their limited access to emergency and regular obstetric care compared with other women. Language barrier and communication difficulties contributed to suboptimal care provided for these mothers. In our population, there was generally no significant difference in the risk for severe obstetric haemorrhage between mothers of Western and non-Western origin. This may

indicate equality in obstetric care. However, mothers of non-Western origin had significantly higher risk for uterine rupture in our population. This may be due to inadequate information on the obstetric history of these women, especially regarding the number and type of previous uterine scars.

Women from South East Asia had the highest risk of severe obstetric haemorrhage, in contrast to women from the Middle East in our population. Both groups usually have severe haemorrhage as the leading cause of maternal deaths in their countries of origin.[1–3] Why did the women from the Middle East have less risk for severe haemorrhage in Norway than in their original countries? This could be attributed to different characteristics of these women as compared with women in their original countries, or that they are getting better obstetric care in Norway. We found in further analysis that immigrant women from the Middle East were youngest at childbirth, had the fewest elective CSs, and the highest vaginal delivery rates. In addition, they had lowest induction rate, lowest placenta previa or abruption and previous CS, and the lowest risk of perineal trauma, uterine atony and retained placenta.

Mothers from South East Asia had the opposite characteristics and about 60% of them had a Norwegian partner. South East Asian mothers with Norwegian partner had significantly higher risk of severe obstetric haemorrhage than other South East Asian women. The former group had significantly higher percentage of infants with birth weight >3500 gm, fetopelvic disproportion, prolonged labour, shoulder dystocia, and operative deliveries. These results were not shown in tables in paper I.

Previous CS

Mother with previous CS had doubled risk of severe obstetric haemorrhage. They had higher risk than primiparas in our population. Having a previous CS is shown in several studies to increase severe haemorrhage and peripartum hysterectomy risk.[47, 48] Even after excluding placenta previa and placental abruption, mothers with previous CS had significantly higher risk for severe haemorrhage than mothers without previous CS in our population.

As the CS rate is increasing, uterine rupture is expected also to increase. The risk of uterine rupture depends on the number of uterine scars, and the type of previous uterine incision. The reported risk ranges from 4% to 9% for prior classical and T-shaped incision, whereas that reported for low vertical and low transverse ranges from 1% to 7% and 0.2% to 1.5%, respectively.[160] Reviewing the case records demonstrated the importance of number and types of previous uterine scars in predicting uterine rupture even at latent uterine activity. Using ultrasound in such mothers might serve in reducing the number of ruptures occurring while waiting for planned repeated CS.[161]

Medical and pregnancy factors

Our finding of increased risk for severe haemorrhage among mothers with cardiac disease was shown in a previous study suggesting association with uterine atony and operative vaginal deliveries.[126] We need further studies on these women as there are increasing numbers who reach childbearing age. Clinical studies are warranted to find whether the use of anticoagulation or inadequate prophylaxis with oxytocin in third stage of labour are contributing to this increase in haemorrhage risk

von Willebrand's disease, the commonest hereditary blood disorder, needs special attention as it had the highest odds for severe haemorrhage (4-fold increase) among pregnancy and medical complications. These mothers should have conjoined planning and management of delivery by haematologist, obstetrician, and anaesthetist prior to labour. The significant increase of severe haemorrhage by HELLP syndrome suggests coagulopathy as the underlying cause of haemorrhage. Coagulopathy in the form of disseminated intravascular coagulation is among the most common causes of fatality due to haemorrhage.[96] The doubled risk carried by anaemia was shown in previous studies, with greatest impact in low resource settings.[56, 120] The low reserve of blood volume in anaemic mothers leads to quicker decompensation than other women with similar blood loss. Anaemia during pregnancy can be treated easily, and consequent prevention of chronic anaemia due to severe obstetric haemorrhage can be achieved.

Multiple pregnancy and macrosomia were shown to increase severe haemorrhage in agreement with previous studies.[6,70,86,87,90,148,149] This shows how certain risk factors are becoming more important due to changes in population demographics. The rate of multiple pregnancy is increasing due to increased assisted reproduction in increasing numbers of older women seeking pregnancy. Macrosomia is increasing partly as a result of increasing obesity and sedentary life style.

Among mothers with previous CS, advanced gestational age increased the risk for uterine rupture in our population. This was in major part due to the higher induction rate at advanced gestational age. We believe that we need a larger sample to determine the effect of gestational age on uterine rupture. Previous studies with larger samples showed that gestational age was not a significant risk factor for uterine rupture.[162]

Labour factors

Prolonged labour was a significant risk factor that almost doubles the risk for severe haemorrhage, when controlled for relevant confounders prior to labour in agreement with

previous studies.[70, 87, 163] However, it was not shown to increase the risk of uterine rupture after previous CS in our population.

On the other hand, induction significantly increased the risk for both severe haemorrhage and uterine rupture as shown previously.[6,70, 87, 128, 148] Prostaglandins had specifically significant risk for uterine rupture as shown in several studies.[128, 164]

The finding that induction increased severe haemorrhage at all delivery modes reflects a pharmacological effect on uterine contractility and suggests uterine muscles exhaustion in the third stage as a consequence. Induction rate have increased in Norway up to 15% in 2008. The greatest increase was in the use of prostaglandins.[85]. Compared with other countries, we in Norway are using a higher dose of prostaglandin and oxytocin in mothers with previous CS. As mechanical induction was shown to be relatively safer than other induction methods in our study, more efforts should be made toward using mechanical method instead of medical induction.

The finding of uterine ruptures at emergency prelabour CS showed that uterine rupture can not be prevented even in the absence of established labour. However, the absence of serious maternal or perinatal outcomes after such ruptures showed that labour is the actual risk factor of catastrophic ruptures, and consequent prolonged intrapartum hypoxia.

Delivery factors

The finding that delivery by emergency CS carried the highest risk for severe obstetric haemorrhage (> 3-fold higher) was confirmed in several studies.[6, 23, 28, 149, 165, 166] Uterine atony and surgical bleeding are expected to be the highest at emergency CS, especially CS in late labour. A previous Norwegian population-based cohort study showed that cervical dilatation, particularly one of 9–10 cm at the time of operation, was an independent risk factor for a blood loss of ≥1000 ml, transfusion and other complications[166]. That study found that an unexpectedly high number of caesareans were performed in the late stages of labour. Moreover, a UK study showed that 10% of emergency peripartum hysterectomies were performed after caesarean section at full dilatation due to failed progress in labour or failed delivery using instruments.[28] This emphasizes the importance of performing emergency caesareans with the correct timing and for the correct indications.

Our results confirmed that emergency CS after labour start had the highest risk for severe postpartum haemorrhage especially after induction. We analysed mothers with elective and emergency prelabour CS together in one group as prelabour CS in paper II. However, separate analysis performed by the author (not included in tables), showed that emergency prelabour CS had significantly lower risk for severe postpartum haemorrhage than emergency CS after

labour onset. This implies that labour especially in late stages is a detrimental factor in increasing severe haemorrhage. The risk of labour was at its maximum when it was performed after induction, ending in emergency CS in mothers with previous CS.

We found that elective CS had higher risk for severe haemorrhage (2-fold higher) compared with spontaneous vaginal deliveries. Even operative vaginal deliveries carried lower risk than elective CS. This finding and the finding that prelabour CS had significantly higher risk for haemorrhage compared with spontaneous labour, were not detected in previous studies.[165] A recent study from Finland found similar results to ours.[94] The increased risk for haemorrhage found at operative vaginal delivery was reported previously.[70, 94, 120, 148] Our findings suggest an anticipation of increased severe haemorrhage at operative vaginal deliveries after induction among primiparas, mainly due to perineal trauma.

Maternal outcomes

Seven maternal deaths were identified after severe obstetric haemorrhage, representing a proportion of 2 /100 000 during our study interval from 1999-2004. This is much higher than the proportion of 0.6/100 000 reported previously in a review of maternal death in 1976-1995.[35] Our results might be less accurate as we relied solely on the registered data in MBRN, linked to the Registry of Causes of Death. In addition, the underlying causes of death were coded.

The death/severe haemorrhage ratio in our population was 1: 500, based on the current study. This ratio is an indicator of our obstetric care. The satisfying case fatality estimate could be a result of an overestimation of haemorrhage cases leading to falsely low death/sever haemorrhage ratio. However, our ratio was lower than 1: 327 reported in a UK study using same inclusion criteria of severe haemorrhage as ours.[6] The ratio of hysterectomy: severe obstetric haemorrhage was 1:100 in our study population.

Hysterectomy is a major operation that saves lives, but is associated with major maternal morbidity and mortality**.** Many studies have found high complication rates
for emergency peripartum hysterectomy, mainly due to the need for massive blood transfusion, coagulopathy, injury to the urinary tract, need for re-exploration because of persistent bleeding or complications caused by the hysterectomy itself, and febrile morbidity.[28,29,47,48,101,103] After the correction we made, hysterectomy risk was 500 –fold increased after

severe haemorrhage. The most common cause of hysterectomy was uterine atony followed by placenta previa, retained placenta and uterine rupture.

The majority of hysterectomies occurred at emergency CS after induction especially among mothers with previous CS (not shown in paper). This again indicates the severity of haemorrhage occurring as a result of emergency CS following induction.

In spite of the few cases identified with acute renal failure, the increased risk for this serious complication indicates the serious degree of hypoperfusion caused by obstetric haemorrhage.[102] Our finding of increased risk for postpartum sepsis was found in previous studies.[29, 48,100,101,104] Although only 7% of mothers with severe haemorrhage were admitted to ICU, severe obstetric haemorrhage represented the most common cause of maternal admissions to ICU (30%) in agreement with previous studies.[117]

Perinatal outcome

The same obstetric haemorrhage that threatens women' survival can also cause death and disability in the newborns. In this study, mothers with severe haemorrhage had significantly larger proportion of serious perinatal outcome as perinatal death and post hypoxic encephalopathy compared with mothers without such complication. The highest odds for serious perinatal outcome were observed at very premature deliveries. The complication associated with the highest odds for serious perinatal outcome was uterine rupture, followed by placenta abruption in our study. The underlying risk factor of severe haemorrhage as prolonged labour was associated with increased risk for serious perinatal outcome due to increased risk for intrapartum hypoxia.

Serious perinatal outcome after uterine rupture, though low in absolute number, resulted only if rupture occurred after trial of labour in this study. This indicates that avoiding prolonged duration of intrapartum hypoxia once rupture is suspected is the key for favourable perinatal outcome. The highest percentage of perinatal outcomes occurred when uterine rupture followed induction, reflecting the significant risks of induction in mothers with previous CS.

Increasing trend of severe obstetric haemorrhage

A disturbing trend of an unexplained and unexpected increased incidence of postpartum haemorrhage and severe postpartum haemorrhage was shown in recent studies in the developed world, including Canada, UK, Australia, and USA in last ten years.[18] Maternal mortality from haemorrhage, however, remained static. At the same time, there was an increased incidence of certain risk factors in the pregnant populations in these countries such

as increased CS rate, increased maternal age and immigrant mothers in addition to increased multiple pregnancy and induction. However, the changes in these risk factors could not explain the rise in PPH rates. It was postulated that other risk factors that are not easily identified or recorded in hospital data could be underlying causes of such increase in PPH. These factors include a more liberal approach to duration of labour, increases in obesity, or changes in management of third stage of labour, induction agents used or more complex interaction between different risk factors. Performance of large population studies in different countries was suggested in order to determine the incidence of severe obstetric haemorrhage, and whether this incidence is increasing, and to identify underlying risk factors contributing to such increases.[18]

We tried to find out whether there is an increase in severe haemorrhage (>1500 ml) through the years of this study. We did not find, however any trend of increased incidence as we had a short interval of time.

According to data from MBRN, there is a significant increase of obstetric haemorrhage >500ml from 1998 at 5.5% up to 16.8% in 2008.[85] (Table 5). Table 5 shows the increase in certain procedures and events during labour especially prolonged labour, induction with prostaglandins and CS rate.[85] The reported increase in obstetric haemorrhage might be partly due to a better case ascertainment as ticked boxes were introduced in 1999.[35]

Table 5. Percentage (%) of different events during labour in 1998 and 2008 in Norway[85]

	1998 (%)	2008 (%)
Obstetric haemorrhage >500 ml	7.7	16.5
Induction of labour	11.2	15.2
Induction with prostaglandins	2.2	9.3
Prolonged labour; FPD; Augmentation with oxytocin	10.8	32.4
Caesarean section (CS)	13.5	17.1
Epidural anaesthesia during labour (excluding CS)	12.0	23.3
Multiple pregnancy	1.6	1.8

FPD:Feto-pelvic disproportion

IMPLICATIONS FOR LOW RESOURCE SETTINGS

The significant risk of severe haemorrhage associated with CS is of particular importance in low resource settings. A sharp increase in CS has been observed in urban regions of countries in Asia, Africa and South-America,[49] The use of operative vaginal delivery is low in these settings. High fertility, increasing numbers of women with previous CS and increasing numbers of previous CSs in each mother might contribute a further increase in severe obstetric haemorrhage and case fatality due to severe haemorrhage. Anaemia is widespread among women of fertile age in low resource settings. In accordance with previous studies, we found a significant association of anaemia and severe haemorrhage. Such association might also play an important role in obstetric haemorrhage and its outcomes in low resource settings. Improving surgical skills to perform operative vaginal deliveries by childbirth attendants is a necessary task that should be achieved in these settings. All efforts should be directed toward implementing active management of the third stage of labour. This procedure, though simple, is of great importance for the prevention of atonic postpartum haemorrhage, especially when immediate access to emergency obstetric care is difficult.

SUGGESTIONS FOR FUTURE STUDIES

There are still several unresolved questions regarding severe obstetric haemorrhage. Important research questions for future research include:

1) Is there an increasing temporal trend in the incidence of severe obstetric haemorrhage and uterine rupture and their outcomes such as peripartum hysterectomy and maternal deaths?

Population-based studies covering a longer interval of time and using MBRN would be a valuable data source for such research. Additional review of case records would provide us with information on the third stage management, maternal body mass index, and induction details, and eventually causes of maternal deaths. A validity study of MBRN regarding case ascertainment of severe haemorrhage or uterine rupture is needed to secure results with high reliability.

2) What are the causes of haemorrhage at CS? A review of case records could determine the exact causes, especially those related to surgical bleeding, intra-abdominal bleeding and placenta accreta.

3) What are the most important late maternal and perinatal consequences of severe obstetric haemorrhage? We suggest a study assessing the fertility and subsequent pregnancy outcome

in mothers with severe haemorrhage and uterine rupture. Additionally, studies assessing the long term effects of severe obstetric haemorrhage on the general health of both mother and infant are needed

4) How can we improve obstetric care in cases of severe haemorrhage and uterine rupture? A clinical audit study is recommended to assess the quality of obstetric care given for mothers identified with such complications. Case records of all mothers identified with severe obstetric haemorrhage/uterine rupture in MBRN data in the last 5 years could be reviewed so as to assess the management of individual cases. In addition, a prospective clinical audit should be established through risk management teams. The components of clinical management that would be assessed include mainly: *communication, resuscitation, monitoring and investigation, and arresting the bleeding*.[25]

Our National Guidelines in Obstetrics and international guidelines from the Royal College and the American College of Obstetricians & Gynaecologists would be used as standards.

CONCLUSION

This study showed that severe obstetric haemorrhage is a relatively frequent complication in Norway. The frequency and impact of severe haemorrhage can be effectively reduced by removing avoidable risk factors. Our findings call for reviewing labour management, particularly with regard to the use of CS and induction of labour. Our results indicate that mothers with previous CS constitute a high-risk risk group that should be managed with vigilance during pregnancy and labour. Careful selection of mothers with previous CS for trial of labour should be continued, and induction of labour with prostaglandins in mothers with previous CS should be questioned, with more effort toward using mechanical induction methods. Counselling of mothers with previous CS should include explanation of short and long term risks for both trial of labour and elective repeated CS. The finding that trial of labour carries greater risk and graver consequences of uterine rupture, compared with elective repeated CS, should be included in counselling. However, we should emphasize that the absolute number of such consequences is very low. Among mothers with previous CS, planned repeated CS is a better option than trial of labour if the chances of emergency CS are high. Other risk factors not amenable to change as age and ethnic origin can be minimised by extra vigilance.

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ERRATA

The following errors were detected while writing this thesis:

Paper I

Table 2:

Percentage with severe haemorrhage for cardiac disease should be 1.9%, not 1.1%.

Table 3:

Hysterectomy after severe haemorrhage should be 40 (114.2/10000), not 6 (17/10000)

Hysterectomy without severe haemorrhage should be 7 (0.23/10000), not 1 (0.0/10000).

Odds ratio for hysterectomy:

The correct odds ratio (OR) is: 501.76; 95% CI: 224.6–1120.8, not OR: 115.87; 95% CI: 25.92–517.92.

Paper II

Correct references:

13. Pritchard JA, Baldwin RM, Dickey JC, Wiggins KM. Blood volume changes in pregnancy and the puerperium. II. Red blood cell loss and changes in apparent blood volume during and following vaginal delivery, cesarean section, and cesarean plus total hysterectomy. *Am J Obstet Gynecol* 1962;84:1271–82.

Paper III

-In page 3, line 23 under subheading 'Perinatal outcome', perinatal death was defined as intrapartum fetal deaths ≥28 weeks of gestation, and neonatal deaths seven or more days after birth, not related to congenital causes. The correct definition should be as follows: Intrapartum fetal deaths ≥28 weeks of gestation, or neonatal deaths seven or less days after birth, not related to congenital causes.

The journal will be sent a written correction of this accidental error.

In Table 5; page 9: OR values presented in the table were accidently exchanged between each of 'Prostaglandins, amniotomy and oxytocin' and 'Oxytocin +/- amniotomy'; As can be seen, these results were statistically insignificant and have no impact on the overall results; The results should be as follows:

Prostaglandins, amniotomy and oxytocin:

OR (95% CI): 2.17 (0.5–8.9); OR** (95% CI): 2.01 (0.5–8.3).

Oxytocin +/) amniotomy:

OR (95% CI): 1.30 (0.5–3.6); OR** (95% CI): 1.22 (0.4–3.4).

The journal will be sent a written correction of these accidental errors.

APPENDIX

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus: ☐ Gift ☐ Samboer ☐ Ugift/enslig ☐ Skilt/separert/enke ☐ Annet

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja — Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn | **Mors fødselsnr:**

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag | ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte: Levendefødte | Dødfødte (24. uke og over) | Spontanabort/Dødfødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja — UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet:
☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon ☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom ☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei — Før sv.sk. / I sv.sk.
Multivitaminer ☐ ☐
Folat/Folsyre ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet:
☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom ☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B» ☐ Annet, spesifiser i «B»

Legemidler i svangerskapet: ☐ Nei ☐ Ja – spesifiser i «B»

Røyking og yrke
Forutsetter mors samtykke – se rettledning på baksiden
☐ Skriftlig orientering gitt til mor
☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til — Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til — Ant. sig. dagl.:

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon:
☐ Normal bakhode
☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart:
☐ Spontan
☐ Indusert ☐ Sectio

Ev. induksjonsmetode: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon
☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak
☐ Ingen
☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

Komplikasjoner
☐ Ingen
☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning ☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4) ☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intrauterin asfyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi:
☐ Ingen
☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta:
☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter
☐ Koagler ☐ Utskrapning ☐ Manuell uthenting
Placenta-vekt

Navlesnor
☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier
☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute
Navlesnor-lengde:

Fostervann
☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel
☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | **Klokken**

Pluralitet: ☐ Enkeltfødsel ☐ Flerfødsel — For flerfødsel: Nr. | Av totalt

Kjønn: ☐ Gutt ☐ Pike — Ved tvil spesifiser i «D» — For dødfødte: ☐ Usikkert kjønn

Barnets vekt: | Hode-omkrets:

Total lengde: | Eventuelt sete–issemål:

Apgar score: 1 min | 5 min

Barnet var:
☐ Levendefødt
☐ Dødfødt/sp.abort — Oppgi dødsårsak i «D»

For dødfødte: ☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også: ☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer: Livet varte: Timer | Min.

Død senere (dato): | **Klokken**

Overfl. barneavd.
☐ Nei ☐ Ja — Dato:

Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater)
☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder:
☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet:
☐ Lysbehandlet ☐ Utskifting

Årsak:
☐ AB0 uforlik. ☐ RH immunisering ☐ Fysiologisk ☐ Annen årsak

Tegn til medfødte misdannelser:
☐ Nei ☐ Ja

D — Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato
Mor:
Barn:

Protokollnr.: /

IS-1002 23011. 07.06. Andvord Grafisk.

REPORT ON COMPLETED PREGNANCY AFTER 12 WEEKS
BIRTHS, STILLBIRTHS, MISCARRIAGES

A – Civil information

Institution no: A01 Institution name A02		**Birth outside institution** A03 ☐ At home, planned A04 ☐ At home, not planned A05 ☐ During transportation A06 ☐ Elsewhere	Mother's full name and address A09
Mother's marital status	A11 ☐ Married A13 ☐ Unmarried/single A15 ☐ Others A12 ☐ Cohabitant A14 ☐ Divorced/separated/widow		Maiden name (Surname) A10
Are parents related A16 ☐ No ☐ Yes If yes, how? A18		**Mother's municipality** A21	A22
Father's date of birth A19	Father's full name A20	**Mother's National ID no. (11 digits)** A07 A08	

Autorisert

Dato: 23/8-2007

Signatur:

B –About the pregnancy and mother's health

Last menstrual period:

1st day of bleeding B01

B02 ☐ Certain
☐ Uncertain

Mother's previous pregnancies/births

Live births	Stillborn (24 wks or more)	Miscarriages / stillborn (12-23 wks)	Miscarriages (under 12 wks)
B04	B05	B06	B07

Ultrasound performed? B08 ☐ No ☐ Yes

Ultra-sound due date B10

Other prenatal diagnostics? B11 ☐ No ☐ Yes, specify: B13

Pathological findings at prenatal diagnostics? B14 ☐ No ☐ Yes, if confirmed – specify

Special conditions before pregnancy:

B16 **None**

B17 Asthma
B18 Allergy
B19 Previous caesarean
B20 Recurring urinary tract infection
B21 Chronic renal disease
B22 Chronic hypertension
B23 Rheumatoid arthritis
B24 Heart disease
B25 Epilepsy
B26 Diabetes type 1
B27 Diabetes type 2
B49 other, specify in "B"

Regular dietary supplement:

B70 ☐ No

	Before pregn.	During pregn.
Multi vitamins	B28	B29
Folic acid	B30	B31

Specification of conditions before or during pregnancy

B

B66

Special conditions during pregnancy:

B32 **None**

B33 Bleeding< 13 wk
B34 Bleeding 13-28 wk
B35 Bleeding> 28 wk
B36 Glycosuria
B37 Gestational diabetes
B38 Hypertension only
B39 Preeclampsia light
B40 Preeclampsia severe
B41 Preeclampsia<34wks
B42 HELLP syndrome
B43 Eclampsia
B44 Hb< 9.0 g/dl
B45 Hb > 13.5 g/dl
B46 Thrombosis, treated
B48 Infections, specify in "B"
B47 Other, specify in "B"

Medication during pregnancy

☐ No
B50 ☐ Yes – specify in "B"

Smoking and Occupation
Conditioned on mother's consent – see instructions on reverse.

B52 ☐ Written info given to mother
B53 ☐ Does not consent to smoking info

Did mother smoke at start of pregnancy? B54 No B55 Sometimes B56 Daily **No. of** cigs. daily: B57

- at the end of of pregnancy? B58 No B59 Sometimes B60 Daily **No. of** cigs. daily: B61

Mother's occupation B62 **Does not consent to employment info**

B63 Not emplyed
B64 Employed fulltime
B65 Employed part time

Mother's occupation:

Business, trade, line etc.:

B67

C – about birth

Presentation

C01 **Normal cephalic**

C02 Breech

C03 Transverse

C04 Cephalic, abnormal

C05 Other, specify in "C"

Inception of labour

C06 **Spontaneous**

C07 Induced

C08 Caesarean

Induction method

C09 C10 Prostaglandin

C11 Oxytocin

C12 Amniotomy

Others, specify in "C"

Indication for intervention and/or induction

C13 Complications, as described below

C14 Birth defects

C15 Postterm

C16 Other, specify in "C"

Intervention

C17 **None**

C18 Low forceps, cephalic

C19 Other forceps, cephalic

C20 Vacuum extractor

C21 Episiotomy

Assistance at breech delivery:

C22 Usual procedure

C23 Extraction

C24 Forceps on head

Caesarean section

Was the section planned prior to delivery?

No C27 Yes

C25 Performed elective section

Performed emergency section

Specification of conditions during delivery / other complications

C C84

Complications

C29 **None**

C30 Rupture of membrane 12-24 hours

C31 Rupture of membrane >24 hours

C32 Mechanical obstruction

C33 Complicated shoulder delivery

C34 Placenta previa

C35 Abruptio placentae

C36 Perineal rupture (degree 1-2)

C37 Sphincter ruptur (degree 3-4)

C38 Haemorrhage >1500 ml, transf

C39 Haemorrhage 500-1500 ml

C40 Eclampsia during delivery

C41 Prolaps of cord

C42 Threatening intrauterine asphyxia

C43 Reduced contractions - stimulated

C44 Slow progress

C45 Uterine atony

C86 Other:

Anaesthetics / analgesic

C46 **None**

C47 Nitrous oxide

C48 Pethidine

C49 Epidural

C50 Spinal

C51 Pudendal

C52 Infiltration

C53 Paracervical block

C54 General anaesthetics

C87 Other:

Placenta

C55 **Normal**

C56 Membranal residue

C57 Incomplete

C58 Infarction

C59 Blood clots

C60 Curettage

C61 Manual extraction

Weight of Placenta: C62

Umbilical cord

C63 **Normal**

C64 Velamentous attachment

C65 Peripheral attachment

C66 Vessel anomalies

C67 Coiled round neck

C68 Other form of coiling

C69 Genuine knot

Length of umbilical cord: C85

Amniotic fluid

C70 **Normal**

C71 Polyhydramnion

C72 Oligohydramnion

C73 Discoloured

C74 Malodorous, infected

C75 Bloodstained

After-delivery complications - mother

C76 **None**

C77 Fever >38.5 C

C78 Thrombosis

C79 Eclampsia postpartum

C80 Mother transferred

C81 Mother intensive care

Sepsis C82

C83 Other, specify

D – About the child

Date of Birth: D01

Time: D02

Plurality

D03 **Single delivery**

D04 Multiple birth

For multiple birth:

No.: D05

Of total: D06

Sex

D07 Male D08 Female

If uncertain, specify in "D"

For stillborn: D09 Uncertain sex

Child's weight: D10

Total length: D12

Head circumference: D11

Buttocks-vertex length: D13

Apgar score:

1 min: D14

5 min: D15

The child was:

D16 **Live born** D17 Stillborn/miscarriage

Specify cause of death in "D"

For stillborn: D18 Died before labour

D19 Died during labour

D20 Time of death unknown

For stillborn, note also:

D21 Dead before arrival

D22 Dead after arrival

Live birth, died within 24 hours

Life lasted:

Hours: D23 Mins.: D24

Died later:

Date: D25

Time: D26

Transferred to neonatal unit:

☐ **No** D27 ☐ Yes

Date: D29

Transferred to (name of unit): D30

Indication for transfer:

D31 Respiratory problems

D32 Pre-mature

D33 Birth defects

D34 Perinatal infections

D35 Other, specify

Neonatal diagnoses: (To be completed by physician / pediatrician)

D36 **None**

D37 Hypoglyco. (<2 mmol/l)

D38 Cong.anaemia (Hb<13.5 g/dl)

D39 Hip joint dysplasia treated with pillow

D40 Transit. tachypnea

D41 Resp. distress syndrome

D42 Aspiration syndrome

D43 Intracranial hemorrhage

D44 Cerebral irritation

D45 Cerebral depression

D46 Abstinence

D47 Neonatal fits

D48 Conjunctivitis treated

D49 Navel/dermal infection treated

D50 Perinatal infections, bacterial

D51 Perinatal infections, other

D52 Fract. claviculae

D53 Other fracture

D54 Facial paresis

D55 Plexus injury

Treatment codes:

D56 Systematic antibiotics

D57 Respiratory treatment

D58 CPAP treatment

Icterus, treated:

D59 Light treatment

D60 Transfusion

Icterus, cause:

D61 ABO incompatible

D62 RH immunization

D63 Physiological

D64 Other cause

Signs of birth defects:

☐ No D65 ☐ Yes

Specification of injuries, neonatal diagnoses and birth defects – to be completed by physician:

D D67

Record no: D68 / D69

Physician:

Maternity ward / Pediatric ward:

Discharged date:

Mother: D70 **Child:** D71

I

II

III