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Maternal morbidity and mortality in the Netherlands and their association with obstetric interventions

Kallianidis, A.F.

Citation

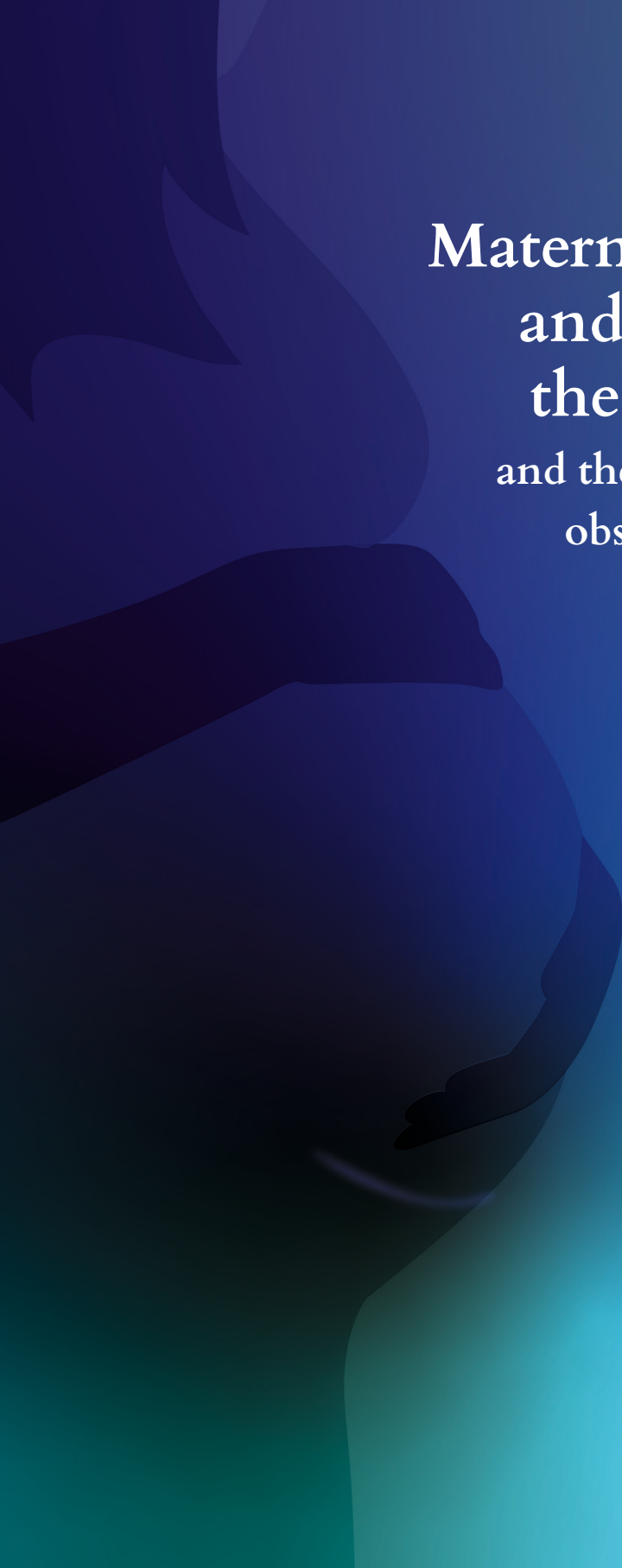
Kallianidis, A. F. (2023, March 16). *Maternal morbidity and mortality in the Netherlands and their association with obstetric interventions. Safe Motherhood*. Retrieved from <https://hdl.handle.net/1887/3571872>

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A stylized, dark blue silhouette of a pregnant woman is positioned on the left side of the cover. The silhouette is composed of several overlapping, rounded shapes that suggest the form of the body and the protruding belly. The background is a gradient of blue, transitioning from a darker shade on the left to a lighter, teal-like shade on the right.

Maternal morbidity and mortality in the Netherlands

and their association with
obstetric interventions

A.F. Kallianidis

**Maternal morbidity and mortality
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ISBN: 978-94-6458-746-3

Cover design and layout: Elisa Calamita, www.elisacalamita.com

Printing: Ridderprint, www.ridderprint.nl

Financial support for the publication of this thesis was kindly provided by: Stichting Oranjekliniek, Chipsoft, Bridea Medical, Department of Obstetrics of the Leiden University Medical Centre, Gedeon Richter, Hellp Stichting, Canon Medical Systems Nederland, Walaeus University Library, Alexandra Houps

Maternal morbidity and mortality in the Netherlands and their association with obstetric interventions

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 16 maart 2023
klokke 16.15 uur

door

Athanasios Franciscus Kallianidis
Geboren te Thessaloniki, Griekenland
in 1990

Promotores:

Prof. dr. T.H. van den Akker

Prof. dr. J.M.M. van Lith

Leden promotiecommissie

Prof. dr. K.W.M. Bloemenkamp

Prof. dr. M. Knight

Prof. dr. O.M. Dekkers

Prof. dr. J.C. Kiefte-de Jong

Dr. M.L.P. van der Hoorn

University Medical Center Utrecht, the Netherlands

Oxford University, United Kingdom

Υγιείας νόσος γὰρ γείτων ομότοιχος

"Sickness and health are neighbors with a common wall"
Aeschylus, 525-456 BC, Ancient Greek tragedian

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General Introduction



INTRODUCTION

A 30-year-old woman, Mrs H, with a previous caesarean section, this time around hoped for an uncomplicated pregnancy. She was healthy and pregnant with a singleton. At the screening ultrasound at 20 weeks' gestation, complete placenta previa was diagnosed. Ultrasonographic follow-up at 32 weeks did not reveal signs of invasive placentation with the placenta in a low anterior position. Therefore, at early term, a planned repeat caesarean section was performed. The obstetricians were confronted with an undiagnosed abnormally invasive placenta, invading into the uterine serosa. After extracting the foetus from a uterine incision higher up in the uterus, massive haemorrhage occurred following efforts to remove the placenta. Oxytocin, sulprostone, tranexamic acid, calcium gluconate and surgical ligation of the internal iliac arteries were unsuccessful in stopping the bleeding. There was no time left for additional uterus-sparing interventions, such as radiological uterine artery embolization. In an ultimate attempt to control the haemorrhage, emergency peripartum hysterectomy was performed, with the woman in severe hypovolaemic shock. Post-operatively she was admitted in the intensive care unit (ICU) for haemodynamic support and treatment of the coagulopathy secondary to the massive blood loss. Perioperative severe hypovolaemia resulted in irreversible cerebral damage and the woman died a few days later, without ever having seen her newborn baby, leaving behind her partner, family and friends. (Reported case of maternal mortality from the Dutch Audit Committee Maternal Mortality and Morbidity - Anonymised and modified in order not to be identifiable)

Death during childbirth is a devastating event. Many questions will arise among those confronted with this tragedy. Was the death of this woman preventable? Would the outcome have been different had the invasive placenta been diagnosed on forehand? What would have been the optimal management of the acute, massive obstetric haemorrhage? Would management have been different in another hospital or country? To what extent is this death attributable to the previous caesarean section? Which lessons can be learned in order to prevent similar calamities from happening to other women?

The importance of maternal deaths in the history of mankind is signified by Greek mythology describing maternal death and birth by what we nowadays know to be caesarean section. Striking is the mythological description of Asclepius' birth, the God of medicine and healing, which was by 'peri-' or 'post-mortem' caesarean section. Asclepius was the son of Apollo, the god of the sun, and Coronis, a mortal woman. During her pregnancy, Coronis fell in love with Ischys, a mortal man. Once Apollo learned of her infidelity, he killed Coronis, with the help of his sister Artemis. Out of remorse, when the dead body of the pregnant Coronis lay on the funeral fire, Apollo extracted Asclepius from the womb (Figure 1).



Figure 1. Woodprint from 1549 edition of Alessandro Benedetti's *De Re Medica*. The Birth of Asclepius. (Source: Cesarean Section - birth of Aesculapius - Benedetti, A. *De re medica*, Venice, 1533, Digital Collection of U.S. National Library of Medicine <http://resource.nlm.nih.gov/101450734>)

PART 1 - MATERNAL MORTALITY - IN THE NETHERLANDS

During the course of uncomplicated pregnancies, women and their families look forward to what usually results in a joyful life event, childbirth. For the vast majority, the course of pregnancy will indeed be uneventful and uncomplicated. However, for a small number of women this will not be the case as unforeseen complications can always occur. Even in healthy women, pregnancy and childbirth can lead to complications, ranging from minor, self-limiting conditions mainly causing discomfort to life-threatening conditions with life-long sequelae or even death. Such complications can arise from obstetric conditions but may also be the result of the physiological adaptation of the female body to the pregnancy, during which previously 'hidden' underlying and undiagnosed conditions can come to light, or arise from the deterioration of mild, pre-existing conditions.

According to the World Health Organization (WHO) maternal mortality is defined as 'the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes'.¹ It is an important indicator of the quality of obstetric care and, in essence, can be seen as the uttermost form of maternal morbidity. (Figure 2) Reduction of maternal mortality by 75% by the year 2015, was

one of the eight Millennium Development Goals proposed in 2000. Notwithstanding some astonishing progress, this target remained far from achieved, with the global reduction stabilising at 45% from the 1990-level.² This was followed up by the Sustainable Development Goals in 2015, in which further reduction of maternal mortality to less than 70 per 100,000 live births was again prioritised.

Most women die in low-income countries, which carry the largest burden of maternal morbidity and mortality. But also in several middle- and high-income countries, maternal health is under pressure. This pressure has been compounded by the recent COVID-19 pandemic, which indirectly affected maternal health tremendously, with resources being diverted away from maternity services and restricted access to emergency care. As a result, considerable increases in maternal and perinatal mortality and severe morbidity have been witnessed, due to disruption of routine health care and increases of patient and facility delays, in health systems that were often already failing at the onset of the pandemic.³

The frequency of maternal deaths in populations is expressed as the maternal mortality ratio (MMR): the number of maternal deaths per 100,000 livebirths. Traditionally, causes of maternal mortality are divided into direct and indirect causes. The former result directly from obstetric disease or pregnancy complications and the latter from non-obstetric - usually pre-existing- disease, aggravated by the physiological effects of pregnancy. Non-pregnancy related 'fortuitous' deaths due to traffic accidents or violence are excluded from calculations of the MMR.

The dichotomous classification into direct and indirect, however, has started to lose its meaning in recent times.⁴ During past decades, non-obstetric conditions have become more prevalent, at least in the more privileged parts of the world, leading to increasing incidence of indirect as well as direct complications. For instance, morbidly obese women are at higher risk of cardiological 'indirect' complications (such as arrhythmia) as well as 'direct' obstetric complications such as pregnancy-related thrombo-embolism or postpartum haemorrhage. In this way, an increase of the MMR related to direct causes of death may not necessarily reflect poor management of obstetric haemorrhage but could also represent changing risk profiles. Moreover, classification of death by suicide during pregnancy and the postpartum period also changed following the introduction of the new ICD-MM classification of maternal deaths.⁵ Previously, suicide was generally classified as 'indirect', with pregnancy seen to aggravate pre-existing psychiatric conditions, or even as 'fortuitous' when no pre-existing psychiatric conditions were present. This categorization is often difficult and arbitrary, and in order to highlight maternal deaths due to suicide as one clear entity, these are nowadays uniformly classified as a direct deaths.⁶

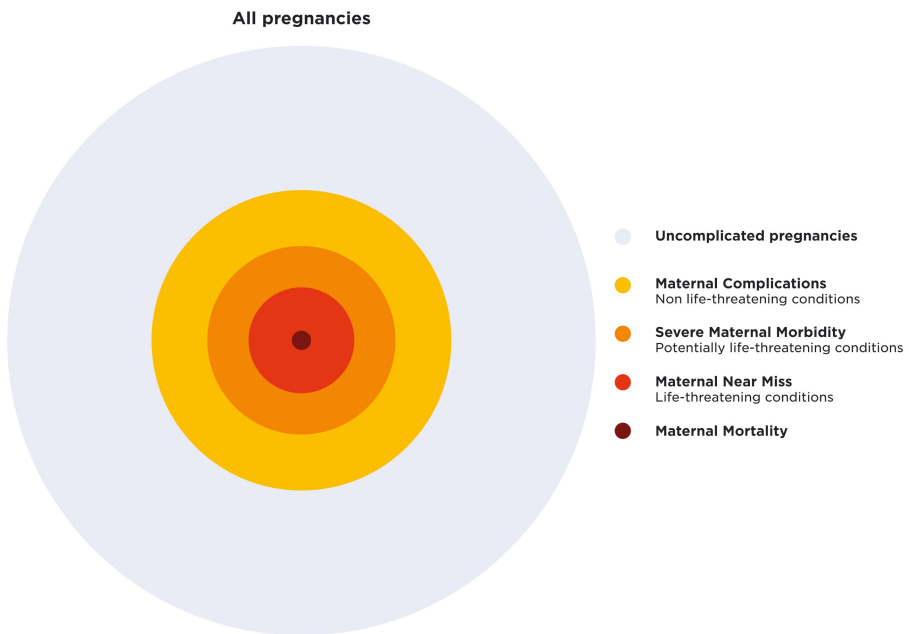


Figure 2. The circle of disease. From uncomplicated pregnancy to maternal mortality. Adapted from the Pyramid of Disease.

Maternal mortality has been registered in The Netherlands since 1950 by Statistics Netherlands (*Centraal Bureau voor de Statistiek*), where all vital statistics of the country are registered. However, use of vital statistics only, based on information from death certificates is known to give substantial underestimation of maternal deaths.⁷ In 1981, the Maternal Mortality Committee (MMC) was installed, a committee of the Netherlands Society of Obstetrics and Gynaecology (*Nederlandse Vereniging van Obstetrie en Gynaecologie*). Aim of the committee is systematic registration and classification of maternal deaths, and -by means of confidential enquiry- identification of lessons learned from each death. Confidential enquiry is a multi-disciplinary anonymous investigation of all maternal deaths, by means of which numbers and causes of deaths, as well as improvable factors in care are identified.⁸ Being relatively labour-intensive, it can only be performed for small numbers of maternal deaths at a time, and is usually done on a nationwide scale in high-income countries as well as some middle-income countries such as South Africa and Namibia. Basis of the enquiry forms full accessibility to medical reports, maternity registers, theatre charts and laboratory results, as well as anonymity of women and health workers to overcome barriers to reporting. Improvable factors, previously called 'substandard care factors', are identified after examining the care given during pregnancy and childbirth and the events leading to death. Improvable factors can be identified in any aspect of care which might have had a negative

effect, even if it had no major impact on the final outcome. Standards of care are informed by national guidelines and, in their absence, best available evidence. Explicitly, the purpose of confidential enquiries is to operate outside the medico-legal realm. Rather, its aim is educational: to draw lessons from each woman's death, and feed these lessons back to professionals to avoid future deaths. After incorporation of the Netherlands Obstetric Surveillance System (NethOSS) into the MMC in 2016, the committee became the Dutch Audit Committee Maternal Mortality and Morbidity (*Auditcommissie Maternale Sterfte en Morbiditeit, AMSM*). Since 2019, the AMSM has been comprised of eight senior consultants in obstetrics and gynaecology, one obstetric anaesthesiologist, one midwife and two registrars in obstetrics and gynaecology.

In The Netherlands, registration of maternal mortality relies on reporting of deaths during pregnancy, and up to one year after birth or termination of pregnancy to the AMSM. Reporting is described as mandatory in the national guideline on maternal mortality. Any failure to do so is considered substandard.⁹ Midwives, obstetricians, general practitioners and any other medical specialists may report the death of a woman. Until 2011, unreported maternal deaths were identified after annual cross-checking with Statistics Netherlands. Data reported to Statistics Netherlands about maternal deaths, however, rely on vital information recorded on death certificates, which is neither exhaustive in identifying all maternal deaths up to one year postpartum, nor specific enough to identify the cause of death in a majority of cases. Relying on routine vital statistics as reported to Statistics Netherlands resulted in an estimated level of underreporting of maternal deaths of around 26-33%. Crosslinking death and birth registries resulted in an estimated level of underreporting to the AMSM of 11%.¹⁰ After 2011, no more cross-check took place as Statistics Netherlands considered that anonymity of reported cases could not be guaranteed, due to small numbers, with information potentially traceable to individual women.

An overview of the MMR in The Netherlands for the years 2000-2016, by use of data from Statistics Netherlands only -as reported to the WHO, is presented in Figure 3. Causes and frequency of maternal mortality in the Netherlands have been assessed twice before by means of confidential enquiry into maternal deaths. Schuitemaker et.al., for the years 1983 – 1992, identified 192 maternal deaths, leading to an MMR of 9.7 per 100,000 live births.¹¹ Leading cause of death was (pre-)eclampsia (n=51, 27%) followed by thromboembolism (n=21, 11%) and cerebrovascular conditions (n=19, 10%). The authors underlined the importance of being aware of risk factors for maternal mortality such as maternal age, parity and migrant status. In this study, medical records for one in five of the reported deaths were unavailable for confidential enquiry, which was significantly higher than reported in other countries with comparable enquiry systems such as the UK. In addition, the authors called for increasing the autopsy rate in maternal deaths, which stood at only 57% at the time. The most recent report on maternal mortality

in the Netherlands, before the report presented in this thesis, is that by Schutte et.al., which included the years 1993-2005.⁽¹⁰⁾ With a total of 309 deaths, the MMR increased from 9.7 to 12.1 per 100,000 live births. Commonest cause of death remained (pre-)eclampsia (n=93, 30%) followed by cardiovascular disorders (n=45, 15%) and thromboembolism (n=44, 14%). This rise in MMR was attributed to better reporting of cases and demographic changes such as increases in the average age of pregnant women, and the proportions of non-native women and pregnant women with underlying conditions.

Around the same time, the 2010 *EuroPeristat* report on health and care of pregnant women and babies, listed the Netherlands below average in terms of perinatal mortality compared to other European countries.¹² This led to action across the country to improve the quality of maternal and perinatal health. Audit of perinatal death was implemented nationwide, led by Perinatal Audit Netherlands, later combined with the Perinatal Birth Registry into Perined.¹³ The relatively high perinatal mortality rate in the Netherlands generated considerable media attention and led to important changes in the organization of the maternity care system and clinical practice, such as improvements in the collaboration between primary midwifery practices and secondary obstetric care. How come that these results regarding perinatal mortality led to such important policy changes, whilst the increasing maternal mortality ratio, reported around the same time, drew much less public attention?

The Netherlands has a relatively low MMR compared to other European countries, which all have ratios much below those of middle- and low-income countries.¹⁴ Dutch maternal mortality ratios are usually compared to other European high-income countries like the UK, which has a longstanding history of a renowned system of confidential enquiry. Using relatively high numbers of maternal deaths and livebirths (approximately 200 maternal deaths and 2.2 million livebirths every 3 years), the MBRRACE-UK programme (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiry across the UK) of the national perinatal epidemiology unit in Oxford (NPEU) publishes robust annual reports on mortality rates and tri-annual reports on causes of death and trends in maternal mortality, as well as an in-depth analysis of risk factors. In the UK, the MMR has remained stable throughout recent years (2009-2017), around 9-10 per 100,000 livebirths.

For the years 2015-2017, the commonest causes of death in the UK were cardiac disease (23%), thromboembolism (16%) and cerebrovascular conditions (13%) while pre-eclampsia accounted for only 2%. This presents a striking difference with the Netherlands, where direct causes of death, foremost pre-eclampsia, have always been most frequent. There is worry that identification of indirect causes of deaths in the Netherlands might not be exhaustive. A particular question arising is: do we miss (late) maternal deaths, in particular of women who are managed by other medical specialists and who are not yet or not anymore under obstetric care, so particularly during early pregnancy or in the (late) postpartum period? Differences

in categorisation of causes of death could also explain some of the observed differences. For example, a woman with pre-eclampsia followed by severe obstetric haemorrhage during birth is classified as death due to haemorrhage in the UK but due to pre-eclampsia in the Netherlands.¹⁵ However, even the combined proportion of pre-eclampsia and haemorrhage deaths in the UK does not even reach half the proportion of 35% of deaths due to (pre-)eclampsia in the Netherlands.

Maternal mortality trends in France, another high-income European country with an enhanced maternal mortality surveillance system, also differ from the Netherlands. While, for the years 1998 – 2007, direct causes of death also outnumbered indirect causes (66.2% vs 30.8%), haemorrhage has always been the leading cause (16%), followed by amniotic fluid embolism and thromboembolism (both 12%).¹⁶ A comparison between the Netherlands and Italy reveals similar differences. In the Italian report on maternal mortality, conducted after crosslinking hospital discharge databases and death registries, commonest cause of death was 'non-pregnancy related causes', which included malignancies (39%) followed by violent deaths (17%) which both mostly occurred beyond the traditional 42-day postpartum interval. Regarding pregnancy-related causes, the most prevalent were haemorrhage, hypertensive disorders of pregnancy and cardiac disease, which are generally classified as 'indirect' pregnancy-related deaths.¹⁷

According to the concept of 'obstetric transition', as proposed by Souza et.al., during the process of maternal mortality reduction, countries progress through five stages. Starting with high maternal mortality ratios (MMR>1000), mostly due to direct obstetric causes, high fertility rates and high numbers of communicable diseases, progress occurs with improvement of infrastructure, equity in access to healthcare and eventually implementation of prevention strategies and better maternal and neonatal health care. In the latest stage of the obstetric transition (MMR <50 maternal deaths per 100 000 live births), indirect causes of maternal mortality and noncommunicable diseases become more prominent than direct causes.¹⁸ In light of this obstetric transition, the question arises how the Netherlands, with an MMR around 10 per 100,000 live births, still finds its proportion of direct mortality exceeding that of indirect mortality.^{10, 19}

While globally the ratios of maternal mortality show a steady decline, recent results from the United States, one of eight countries with a considerable rise in maternal mortality, come as a true wake-up call.²⁰ Figure 3, presents maternal mortality estimates for 2017 as well as trends since 2000, collected by the WHO and is based on vital statistics. Here the increase in the US can be clearly visualised. In a report from 2016, the MMR increased by 23% from 18.8 in 2000 to 23.8 per 100,000 live births in 2014. Reasons for this increase are still under debate. Much attention was directed to the newly added pregnancy checkbox to the standard death certificate, which was introduced in 2013, aiming for better ascertainment of maternal deaths. However, it was demonstrated that this improvement had only a limited effect on improved registration of maternal deaths and even led

to considerable ratios of false positives. Strikingly, racial-ethnic disparities remain extreme, with black women having a three times higher mortality risk compared to white women. This once more underlines the importance of regular quality assessment of maternal health outcomes and maternity care, also in high-income countries.

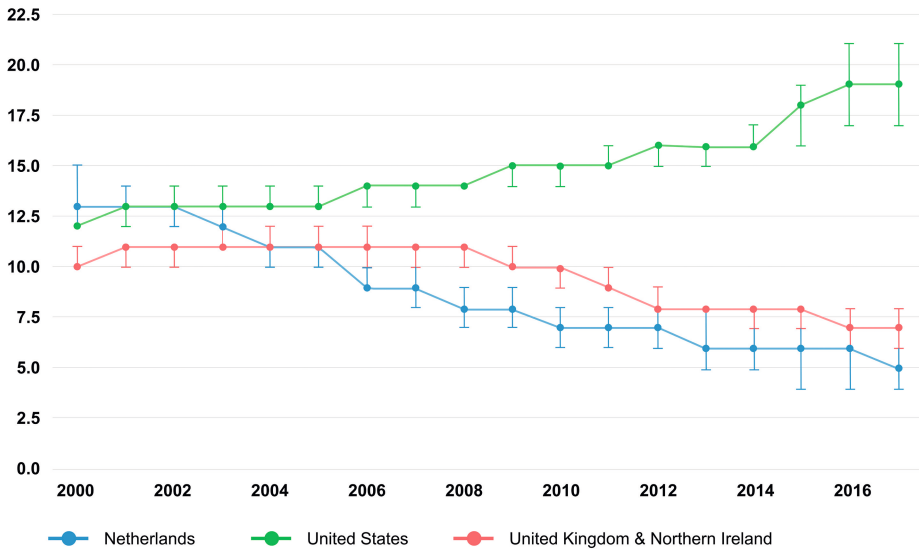


Figure 3. Maternal mortality ratios in the UK, US and the Netherlands, 2000 – 2017. (Source: MMR2017.srhr.org, WHO)

A decrease in mortality does not come by itself. Overtime, the prevalence of risk factors at the population level may change and so does medical practice, based on forthcoming evidence and insight. Most high- and upper middle-income countries progress or have progressed through the later stages of obstetric transition achieving lower MMRs with a concomitant higher prevalence of indirect causes of mortality. More women give birth in obstetric facilities and have access to obstetric interventions like caesarean section, induction and augmentation of labour. Availability and accessibility of medical interventions to assist during labour in case of complications are important, but optimal use might become overuse, referred to as “Too much too soon”.²¹ Every intervention comes with possible complications and therefore close monitoring of the association between interventions and adverse maternal outcome should not be neglected.²⁰

Caesarean section is one of the interventions of which use has seen an unprecedented rise between 2000 and 2015, with the global rate having almost doubled from 12.1% to 21.1%.²² Until the late 19th century, it was performed only after maternal death to extract the foetus, like Asclepius from the dead body of Ischys

and only in very rare cases were mothers reported so survive. In presence of modern anaesthesia, fine-tuned surgical procedures and post-operative care, caesarean section is considered a generally relatively safe procedure in high-income settings, for which the indications have become broader. When performed on evidence-based indications, it can be a lifesaving procedure for woman and foetus. However, rates of caesarean sections performed for non-medical indications, even at maternal request only, increase dramatically and this increase has downsides for maternal and perinatal health.²³

A caesarean section rate of 9%-16% on a nationwide scale is considered optimal by the WHO and there appears to be no benefit above this rate on maternal and perinatal outcome.^{24, 25} Availability and accessibility of caesarean section are considered necessary.²⁶ In some low-income countries, rates are still very low at the population level, leading to preventable maternal and foetal morbidity and mortality from impaired access to caesarean section. On the other hand, *at the facility level* in other low-, and middle-income countries and in many middle- and high-income countries even *at the population level*, overuse has become part of the caesarean pandemic.²² For example, rates below 5% are observed in a few African countries while rates far exceeding 50% or even much higher are not uncommon in private healthcare facilities in China, Brazil and South Africa.^{22, 27} In the Netherlands, caesarean section rates are relatively low compared to the rest of Europe, but have not escaped from the global increase, rising from 10% in 2000 to 14.9% in 2018.²⁸ (Figure 4)

Mode of birth and maternal outcome are closely linked. Caesarean section can be the result of unsuccessful vaginal birth or worsening pregnancy related or non-pregnancy related morbidity such as hypertensive disorders or cardiac disease leaving no window of opportunity for vaginal birth. At the same time, these women more often experience complications of the surgical procedure, ultimately even leading to maternal mortality, which can be regarded as the most extreme form of morbidity. (Figure 2) As such, the association of maternal death with caesarean section is even more pressing in light of the ever rising global caesarean section rates.²² From an epidemiological perspective, it is challenging to measure the extent to which caesarean section contributes to a woman's death. Firstly, the initial events leading to death could have been present before surgery. Secondly, caesarean section might have been unavoidable, or even the best choice for the woman to give birth at that moment. And, last but not least, surgery itself can be the direct cause of death, or even totally unrelated to death. As such, confounding by indication hampers studies of causality or association in the retrospective design. In attempts to perform comparisons between vaginal birth and caesarean section, previous studies excluded women with pre-existing morbidity or even twin pregnancies.²⁹ Although this might facilitate comparisons, even in women with pre-existing morbidities and other risk factors the indication may be more or less evidence-based, and substantial variations exist between countries for these indications.

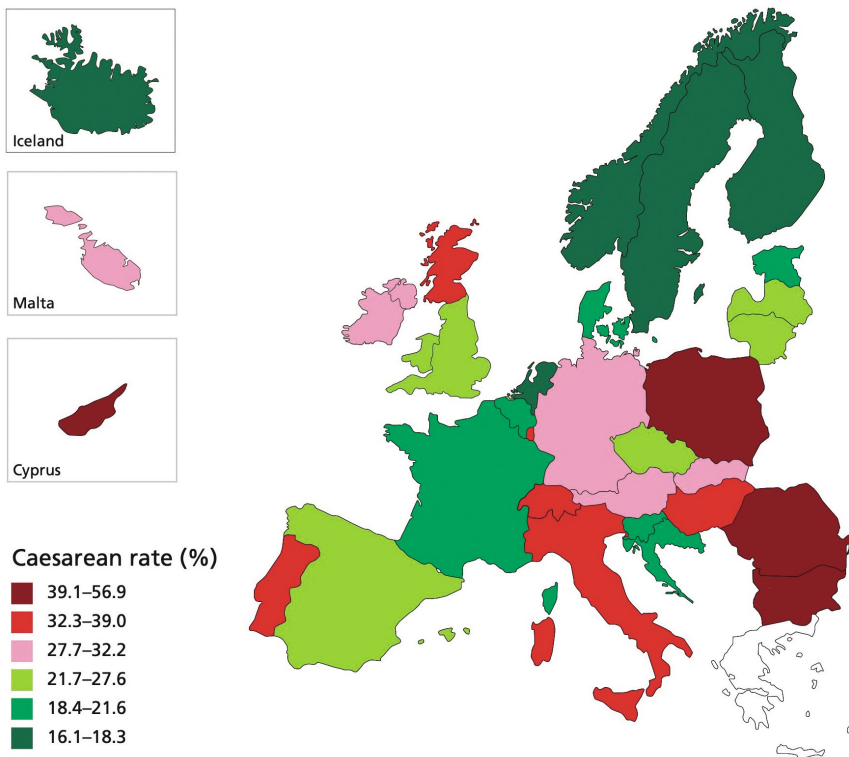


Figure 4. Caesarean section percentages in European countries. Figure from the European Perinatal Health report 2015 12

PART 2 - MATERNAL MORBIDITY

Maternal complications are unintended outcomes of pregnancy and childbirth resulting in negative short- or long-term outcomes for women. While maternal mortality can be seen as only the inner circle of maternal complications, a significant burden of disease is sustained by women with (potentially) life-threatening diseases. (Figure 2) Therefore, maternal morbidity has been added as a condition for audit in order to improve maternal health. Though the concept of maternal morbidity is not a new one, a discussion which definition best captures morbidity has been ongoing for a long time.^{30, 31} In 2009, the WHO suggested the *maternal near miss* (MNM) approach to identify women with life-threatening conditions who survived: "a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy".³²

Identification of women with 'potentially life threatening conditions' may use one of the following approaches:

- 1) clinical criteria (e.g. eclampsia);

2) intervention or treatment criteria (e.g. mass transfusion, admission to ICU, hysterectomy);

3) organ system disfunction criteria.

MNM is based on the concept of organ dysfunction and a core set of 25 “life-threatening conditions” is currently used.^{32, 33}

As a result of improved maternity care, global ratios of maternal mortality had been declining up to the COVID-pandemic.³⁴ In a country like the Netherlands, usually between 10-20 maternal deaths are reported each year to the AMSM, including non-pregnancy related deaths as well as (extremely) rare pregnancy complications. Lessons can be drawn from each woman’s death and maternal mortality will remain an undisputable quality indicator of healthcare. Given the small numbers of maternal deaths, it takes, however, decades before trends are detectable, and feedback aiming for improvement might be outdated already at the time more substantial numbers are collected. Therefore, focus has been shifted to maternal near misses, enabling more rapid collection of larger numbers, identification of risk factors at the population level and comparisons of maternal outcome between countries.

Combining maternal mortality and MNM forms the concept of severe maternal outcome (SMO). This concept stems from the common pathophysiology underlying all life threatening conditions: while some women will survive thanks to adequate and timely use of knowledge and care, others will die, sometimes only due to bad luck. The study of severe maternal outcome from obstetric complications such as severe postpartum haemorrhage or severe hypertensive disease of pregnancy is the cornerstone in improving management and thus maternal outcome. Rare pregnancy-related conditions, such as amniotic fluid embolism or acute fatty liver of pregnancy, are associated with high rates of mortality and morbidity. To acquire better data about such rare diseases and to arrive at clues for improved management, larger nationwide and internationally pooled studies are required.

In the Netherlands, the first nationwide registration of severe acute maternal morbidity and mortality (SAMM) was conducted in the years 2004-2006. Conceptually, SAMM differs from MNM, since SAMM can be seen to include also *potentially* life-threatening events. The LEMMoN study (*Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland*) aimed to assess incidence and determinants of SAMM in The Netherlands.³⁵ During this two-year period, women with SAMM were reported from all hospitals with a maternity unit. SAMM encompassed women with ICU admission, eclampsia or HELLP syndrome complicated by liver haemorrhage, uterine rupture, major obstetric haemorrhage (transfused with ≥ 4 units of blood) and other serious complications according to the local clinician. The results of the study were of invaluable importance, revealing rates of adverse maternal outcomes, options for prevention and improved management, and specific populations at risk such as women with a migration background.³⁵ The results contributed to improved clinical management, with emphasis given to the

management of hypertensive disorders, improved registration of risk categories and support of local audit.

Following the LEMMoN study, the importance of systematic, continued nationwide obstetric surveillance became clear. In 2013, a follow-up national obstetric surveillance system was set up, the NethOSS. The first set of outcomes consisted of eclampsia, cardiac arrest in pregnancy and amniotic fluid embolism.³⁶ ³⁷ A decline in the incidence of eclampsia following the LEMMoN-period was demonstrated and thought to result from prompter management of hypertensive disorders following updated national guidelines. NethOSS contributed to new recommendations for clinical practice in relation to eclampsia, cardiac arrest, amniotic fluid embolism and management of COVID-19.^{36,37,41,46}

Internationally, there are several other countries conducting national or multi-regional obstetric surveillance studies, with an aim to improve the quality of maternity care. Amongst others, UKOSS in the UK, B.OSS in Belgium, ItOSS in Italy, SOSS in Slovakia and NOSS in Denmark, Finland, Iceland, Norway and Sweden. The International Network of Obstetric Survey System (INOSS) is a collaborative platform of national and multi-regional obstetric survey systems.³⁸ INOSS aims to increase the knowledge of uncommon obstetric diseases and allows for comparisons of incidence, management and outcomes of therapeutic interventions between countries. Differences between countries may contribute to identification of improved management strategies. By pooling data from national surveillance systems, more robust conclusions can be drawn about pathophysiology and outcomes of rare pregnancy-related illness. Harmonization and use of common definitions is necessary.⁴⁷ Prior to this thesis, INOSS had conducted studies on eclampsia, uterine rupture and amniotic fluid embolism.³⁹⁻⁴¹ The next step should now be further research into peripartum hysterectomy and massive obstetric haemorrhage.

Peripartum hysterectomy

Following birth, surgical intervention by means of laparotomy is sometimes performed for severe unforeseen complications. It is a critical intervention that may be required in the management of women with life-threatening events. Incidence is usually low and mostly done to perform additional interventions or re-laparotomy after caesarean section. Interventions performed during (re-)laparotomy are directed to resolve haemorrhagic or septic complications. Women undergoing laparotomy, irrespective of mode of birth, will be at high risk for short- of long-term complications, including MNM and maternal death. Although laparotomy itself is not included in the MNM criteria as proposed by WHO, women who undergo laparotomy will have severe bleeding or infectious complications or undergo major surgery such as peripartum hysterectomy and could therefore be regarded as MNM. Women who underwent (re-)laparotomy certainly belong to the red MNM circle of maternal outcomes.(Figure 2)

Peripartum hysterectomy refers to removal of the uterus during pregnancy or shortly after birth. Different terms are used in the literature such as emergency peripartum hysterectomy, post-partum hysterectomy, obstetric hysterectomy or pregnancy-related hysterectomy. Most frequently, this procedure is performed for uncontrollable bleeding complications from atony, abnormally invasive placenta, but it is sometimes also done to manage uterine rupture, sepsis and first-trimester complications such as caesarean scar pregnancies. Therefore, these hysterectomies are an outcome of interest in studies of adverse maternal outcome in general and management of major obstetric haemorrhage in particular. Incidence was previously shown to differ between poorer (low- and lower middle-income) and richer settings (upper middle- and high-income): 28 vs. 7 per 10,000 births.⁴² It may be considered as the most invasive surgical procedure in obstetrics, can be surgically challenging and is usually performed in emergency settings. At the same time, it is non-reversible in terms of permanently disabling fertility.

Management of massive postpartum haemorrhage requires acute intervention. Main pillars in clinical management are controlling the bleeding, haemodynamic blood and volume replacement, and correction of secondary coagulopathy. First interventions are usually performed in the labour room. These consist of uterine massage, administration of uterotonics and crystalloid fluids. When haemorrhage persists or is very severe, scaling up to mechanical and/or surgical intervention in the operating room is the next step. Depending on the mechanism or underlying cause of bleeding, interventions such as manual removal of the placenta, intrauterine balloon tamponade or restoring tissue damage are considered. A multidisciplinary approach with skilled anaesthesiologic support and prompt access to transfusion products as well as an intensive care unit is essential in such a life-threatening complication. Further management will consist of surgical intervention, which may require laparotomy following vaginal birth or additional interventions during caesarean section. Alternatively, radiological interventions like temporary iliac artery balloon occlusion or selective embolization of the uterine blood supply have made their entrance in obstetrics.

The plethora of possible interventions, lack of robust data and differences in management of massive obstetric haemorrhage between doctors and countries render it difficult to stipulate the optimal sequence or hierarchical order. Attempts have been made to compare the efficacy of different interventions, e.g. balloon tamponade vs. radiological embolization or balloon tamponade vs. uterine compression sutures. However, meta-analyses are hampered by wide variations in study design and randomised controlled trials are methodologically difficult given the low frequency and the acute setting in which interventions take place.⁴³

Last resort intervention to stop uterine bleeding is inevitably hysterectomy itself. Due to its nature and association with postoperative complications, this procedure is sometimes seen as an adverse outcome in itself. Any delay, posing women at even higher risk due to severe hypovolaemia and coagulopathy, may

contribute to poor surgical outcome. On the other hand, removing the uterus in too early a stage in absence of alternative management options also exposes women to unnecessary risks. Can we define an optimal moment, in the cascade of blood loss, where extra delay in attempts of potentially unsuccessful interventions will be worse than resorting to hysterectomy? How far are clinicians inclined to go in order to preserve the womb? And is there any correlation with access to alternatives?

A major risk factor for hysterectomy is birth in the setting of one or more previous caesarean sections.⁴⁴ A scarred uterus is the main risk factor for an abnormally invasive placenta, which in turn, either diagnosed antenatally or not, leads to a very high risk of hysterectomy as was seen earlier in the case of *Mrs H*. If known antenatally, birth by caesarean section with planned caesarean hysterectomy is often the preferred management option, although conservative management or limited surgery are also practiced.⁴⁵ Many questions remain. How will the ever rising rates of caesarean sections impact on the national rates of hysterectomy? Will knowledge gaps related to the management of massive obstetric haemorrhage lead to differences in management between countries?

With trends of maternal mortality ratios showing remarkable differences, even between high-income countries, it is now time to provide an update of the MMR and causes of death in The Netherlands, and present the latest work of the AMSM. In light of the global caesarean section pandemic, The Netherlands is not an exception, although caesarean sections are increasing at a slower pace than in other parts of the world. We nevertheless hypothesise that the steady increase will have an impact on maternal outcomes and, as such, will take a closer look into causes of death following caesarean section, and compare the MMR following caesarean section to that of vaginal birth.

It must be noted, however, that maternal death is only the inner circle of morbidity, and zooming out, as we do in this thesis, is important to obtain a more complete view on maternal morbidity. With obstetric interventions so readily available, which is of course an important asset, there is a risk of these interventions being overused. Combined with increases in risk factors for adverse maternal outcomes in the general population, it is possible that larger numbers of women will experience severe adverse pregnancy outcomes. Both postpartum laparotomy and peripartum hysterectomy, mostly for bleeding complications, are likely to continue to be performed as management options for women with severe morbidity. The lack of international guidelines with regard to the management of life threatening obstetric haemorrhage might translate in differences in prevalence, indications and outcomes of peripartum hysterectomy. Platforms such as INOSS enable more robust analyses of such infrequent interventions on national and international scale, as we aim to show in this thesis.

OUTLINE OF THIS THESIS

First, the most recent MMR and causes of maternal mortality in The Netherlands for the years 2006-2018 are described in **Chapter 2**. A comparison is made with the previous studies of maternal mortality in the Netherlands. Lessons learned from the national confidential enquiry are presented.

Chapter 3 then zooms in on the association between maternal mortality in The Netherlands and mode of birth. The extent to which surgery was associated with maternal death, was evaluated by means of confidential enquiry into all deaths reported between 2006 and 2013. In addition, causes of death following caesarean section are presented and compared to previous studies in the Netherlands.

The second part of this thesis explores issues pertaining to maternal morbidity. Hysterectomy, laparotomy or re-laparotomy after birth are rare but potentially life-saving surgical procedures in obstetrics. In **Chapter 4**, a secondary analysis of the nationwide LEMMoN cohort, we identified national incidence rates for postpartum laparotomy related to SAMM in the Netherlands. Building on the previous chapter, hypothesis was that risk of postpartum laparotomy differed by mode of birth.

Focus then shifts to peripartum hysterectomy worldwide and in Europe. In **Chapter 5**, we present an update on prevalence, indications and outcomes of peripartum hysterectomy worldwide. In this literature review and meta-analysis, prevalence is compared between low-, middle- and high-income countries. Indications and outcomes are pooled to give estimates and insight into associated factors around the world.

Subsequently, we narrow down this exploration of peripartum hysterectomy to nine European countries. **Chapter 6** describes differences in prevalence between these member states of the International Network of Obstetric Survey Systems (INOSS). Data were pooled, and correlations between rates of peripartum hysterectomy and national (previous) caesarean section rates analysed. **Chapter 7** is a continuation of the same INOSS hysterectomy project, describing differences in management interventions, and maternal and neonatal outcomes in women who underwent peripartum hysterectomy. Given the lack of guidance in the literature on management of severe obstetric haemorrhage, we postulated that big differences would be observed in the management of postpartum haemorrhage leading up to hysterectomy.

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PART 1

Maternal mortality

Confidential enquiry into maternal deaths in the Netherlands, 2006–2018

A.F. Kallianidis*, J.M. Schutte*, L.E.M. Schuringa, I.C.M. Beenackers, K.W.M. Bloemenkamp, B.A.M. Braams-Lisman, J. Cornette, S.M. Kuppens, A.L. Rietveld, T. Schaap, J. Stekelenburg, J.J. Zwart, T. van den Akker

* The authors contributed equally to the manuscript

Acta Obstetricia et Gynecologica Scandinavica. 2022;101(4):441-449.



ABSTRACT

Introduction: To calculate the maternal mortality ratio (MMR) for 2006-2018 in the Netherlands and compare with 1993-2005. Describe women's characteristics, causes of death and improvable factors.

Methods: We performed a nationwide, cohort study of all maternal deaths between January 1st, 2006, and December, 31st, 2018 reported to the Audit Committee Maternal Mortality and Morbidity. Main outcome measures were the national MMR and causes of death.

Results: Overall MMR was 6.1 per 100,000 livebirths, a decrease from 12.1 in 1993-2005 (Risk Ratio (RR) 0.5). Women with non-Western ethnic background had an increased MMR compared to Dutch women (MMR 6.5 vs 5.0, RR 1.3). The MMR was increased among women with a background from Surinam/Dutch Antilles (MMR 14.7, RR 2.9). Half of all women had an uncomplicated medical history (79/161, 49.1%). Of 171 pregnancy-related deaths within one year postpartum, 102 (60%) had a direct and 69 (40%) an indirect cause of death. Leading causes within 42 days postpartum were cardiac disease (n=21, 14.9%), hypertensive disorders (n=20, 14.2%) and thrombosis (n=19, 13.5%). Up to one year postpartum, commonest cause of death was cardiac disease (n=32, 18.7%). Improvable care factors were identified in 76 (47.5%) of all deaths.

Conclusions: Maternal mortality halved in 2006-2018 compared to 1993-2005. Cardiac disease became the main cause. In almost half of all deaths improvable factors were identified and women with a background from Surinam/Dutch Antilles had a threefold increased risk of death compared to Dutch women without migration background.

INTRODUCTION

In 2017, 295,000 women worldwide died during pregnancy or postpartum, over 90% in low- and middle-income countries.¹ However, also in high-income countries, reporting and reviewing maternal deaths remains important: from every death, lessons can be drawn to improve obstetric care and prevent future deaths. The national maternal mortality ratio (MMR) is an important healthcare indicator. To further unravel reasons why women die, several countries have established systems of confidential enquiry into maternal deaths.^{2,3}

While the global rate of maternal mortality dropped by 43% between 1990 and 2015, in some high-income countries, like the United States, the MMR rose.^{4,5} In the Netherlands, the MMR increased from 9.7 in 1982-1992 to 12.1 per 100,000 livebirths in 1993-2005.⁶⁻⁸ This was attributed to demographic changes, upcoming risk factors like obesity and chronic hypertension, and reduced underreporting.⁶ In light of these trends, an updated national maternal mortality report was deemed necessary.

In 1993-2005, the commonest cause of death was (pre-)eclampsia, accountable for almost one in three deaths. In 2013, the Netherlands Obstetric Surveillance System (NethOSS) was introduced for nationwide registration of severe maternal morbidity (and later also mortality). Results showed a 70%-reduction in eclampsia rates comparing timeframes 2004-2006 and 2013-2016.⁹ This was attributed to increased awareness of the hypertension-related risk, combined with improved management (earlier treatment with magnesium sulphate and antihypertensives, early term induction) and obstetric emergency training.^{10, 11} It is not yet known whether this decline in eclampsia incidence is also reflected in the number of hypertension-related deaths.

Primary aim was to calculate the MMR for 2006-2018, and compare it to 1993-2005. Secondary aims were to describe women's and obstetric characteristics, causes of deaths and improvable factors.

METHODS

This was a nationwide cohort study of maternal deaths between January 1st, 2006 and December 31st, 2018.¹²

Maternal mortality is the death of a woman during pregnancy, childbirth, or within 42 days postpartum or after termination of pregnancy. Death after 42 days up to one year postpartum is defined as late maternal mortality.¹³ In the Netherlands, maternal deaths until one year postpartum are reported to the Audit Committee Maternal Mortality and Morbidity (*Auditcommissie Maternale Sterfte en Morbiditeit*, AMSM) as stated in a national guideline by the Netherlands Society of Obstetrics and Gynecology.¹⁴ The AMSM consists of eight consultant obstetrician-

gynecologists, one obstetric anesthesiologist and two registrars in obstetrics and gynecology, employed at academic and non-academic teaching hospitals.

Deaths are reported to the AMSM by medical specialists, midwives or general practitioners using a case report form, requesting basic pregnancy and birth data.¹⁴ Starting from 2016, electronic reporting of deaths was also available through NethOSS. A monthly email is sent out to assigned clinicians in every hospital with a maternity ward requesting to report cases meeting inclusion criteria or declare 'nothing to report'.⁹ Thereafter, the AMSM requests all medical records necessary for external audit.

To ensure completeness of reporting, a cross-check with Statistics Netherlands, the national authority collecting vital statistics, was performed annually until December, 31st, 2011. After 2011 Statistics Netherlands did not allow further cross-checking, since anonymity of data was considered to be potentially compromised due to small numbers. Statistics Netherlands relies on information from death certificates, including only cause of death and women's age.¹⁵ Postpartum deaths identified from cross-checking were included as non-late deaths to avoid underestimation.

Main outcome was the MMR for 2006-2018, compared with that of 1993-2005. A sensitivity analysis was conducted for the absence of cross-checking after 2011, comparing the MMR with and without additional deaths from Statistics Netherlands. Maternal and obstetric characteristics are presented alongside those of the general pregnant population that were extracted from the Netherlands Perinatal Registry.¹⁶ For parity, age groups and ethnic background groups an MMR was calculated, with the number of livebirths obtained from Statistics Netherlands.¹⁷

We analyzed underlying causes of death, as described by the confidential enquiry. A cause-specific MMR was calculated and compared with 1993-2005. Underlying cause is defined as the disease or condition that initiated the morbid chain of events.¹ Causes are classified as 'direct', 'indirect', or 'non-pregnancy-related' according to the WHO classification.¹ Non-pregnancy-related deaths, e.g. traffic accidents, non-pregnancy-related malignancies and violence, were excluded from further analyses. Late maternal deaths were excluded from calculations of the MMR, but included in other analyses. According to the tenth revision of the International Classification of Diseases to deaths during pregnancy, childbirth, and the puerperium (ICD-MM), with regard to the classification of suicide as a direct cause of death, all suicide deaths were re-classified into that category.¹⁸ Deaths due to malignancy were categorised as non-pregnancy related unless disease course, treatment or diagnosis were affected or delayed by the pregnancy.

Causes of death were categorised according to the classification applied by 'Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries in the UK' (MBRRACE-UK), which is based on the ICD-MM, but has more extensive subclassifications. In the previous national maternal mortality report, a classification that differed from international standards had been applied.⁶ To compare our

results with those from 1993-2005, whilst still seeking international uniformity, the previous time period was reclassified according to the MBRRACE-UK categories. (Supplementary material 1)

In all deaths available for enquiry, quality of care was assessed with regard to possible improvable factors. These refer to events that may have contributed to the death, but do not necessarily imply that it could have been avoided. Care received was compared with the standard of care, laid out in national guidelines or -in case these were absent- determined by best available evidence. To overcome possible information bias, considerable effort was put into collecting all information necessary for enquiry, from all levels of care, both information documented in the medical records and additional information collected over the phone through contacting involved care givers. Improvable factors could be patient-, primary obstetric care- (general practitioner or midwife) or hospital care-related (obstetricians and other medical specialists).⁶ Additionally, lessons learned were proposed by the AMSM, translating improvable factors into generalised clinical recommendations, aiming to promote care improvements at all levels. Lessons were categorised in a manner similar to that of the national perinatal mortality audit, with regard to guidelines, communication and training of health professionals.¹⁹

We compared improvable factors for women with different ethnic backgrounds. Ethnic background was based on medical records, without further information available as to whether women were native or foreign-born. Categorization into Western and non-Western, was based on definitions of Statistics Netherlands. Western women were those originating from Europe (excluding Turkey), North-America, Oceania, Indonesia and Japan, and non-Western women those from Africa, Latin-America, Turkey and the remainder of Asia.²⁰ Dutch women were natives without a migration background. Dutch women and Western women were grouped together for comparison with non-Western women, due to the very small proportion of non-Dutch women with a Western ethnic background. This is in line with studies from the US, where the risk of maternal death was comparable for US-native white and foreign-born white women, but much lower than that of black women, born in the US or elsewhere.²¹

The MMR is defined as the number of maternal deaths during pregnancy or within 42 days postpartum per 100,000 livebirths.¹ Livebirths were collected from Statistics Netherlands.¹⁷ Obesity was defined as a body mass index (BMI) of ≥ 30 kg/m² at booking, or when obesity was explicitly mentioned in medical records. Caesarean sections are classified into 'planned' in case vaginal birth was never intended, even if the woman presented in labor, and 'unplanned' when decision for caesarean section was made during labor. In the Netherlands, "low risk" women receive maternity care and give birth in midwife-led primary care, or are referred to hospital obstetrician-led care if assessed as being "high-risk" at booking or if complications arise according to national guidelines.²²

Risk ratios (RR) were calculated to compare the MMR between groups. Statistical analyses were performed using IBM SPSS for Mac (SPSS Inc., Chicago, IL, USA).

Ethical approval

In the Netherlands, ethical approval is not required for confidential enquiry, which is considered an essential element to improve birth care. Data collected in the database are strictly de-identified and none of our published outcomes can be traced back to individual patients or health workers. Therefore, approval of the Ethics Committee was previously waived.

RESULTS

A total of 206 maternal deaths were reported to the AMSM during the thirteen-year period. After cross-checking with Statistics Netherlands for 2006-2011, 11 additional mortalities were identified. In 46 women, death was classified as non-pregnancy-related. They were excluded from further analysis (Supplementary material 2). In 30/171 (17.5%), death occurred after 42 days postpartum. In 94.5% of all deaths (205/217), medical records were available for enquiry. Statistics Netherlands documented 83 deaths in 2006-2018, compared to 206 reported to the AMSM, amounting to 60% underreporting in routine vital statistics.

The MMR for 2006-2018 was 6.1 per 100,000 livebirths (141/2,304,271), lower than 12.1 for 1993-2005 (RR 0.5). Excluding deaths identified after cross-checking with Statistics Netherlands did not substantially alter the reduction (MMR 5.7 vs 10.4 per 100,000 livebirths, RR 0.5). Considerable decreases were seen in both direct and indirect deaths (Table 1). When excluding numbers from Statistics Netherlands these decreases remained similar: 3.6 vs 7.2 per 100,000 livebirths for direct deaths (RR 0.5) and 2.1 vs 3.2 per 100,000 livebirths for indirect deaths (RR 0.7).

Of the 130 maternal deaths within 42 days postpartum (excluding numbers from Statistics Netherlands), 62 (47.7%) were in nulliparous women. Nulliparous women and women of higher parity had a higher risk of death compared to women with a second ongoing pregnancy, who had the lowest MMR: RR 1.5 and 2.2 respectively (Table 2). Mean age was 31.9 years (range 17 - 53). Compared to Dutch women, women with a non-Western ethnic background had an increased MMR (6.5 vs 5.0 per 100,000; RR 1.3). Compared to Dutch and Western women, women with a non-Western ethnic background more often had pre-existing medical conditions (23/41 vs 33/119, RR 2.0), obesity (13/41 vs 19/119, RR 2.0) and teenage pregnancies (4/41 vs 0/119, RR 25.7) (Supplementary material 3). Women with a background from Surinam and the Dutch Antilles (n=13) had a considerably increased MMR (14.7 per 100,000).

Table 1. Maternal mortality ratio and underlying causes of death in the Netherlands, 2006-2018 vs 1993-2005. Classified according to MIBRRACE-UK classification.

	1993-2005			2006-2018		
	Livebirths: 2,557,208			Livebirths: 2,304,271		
	≤ 1 year (n)	≤ 42 days (n)	MMR	≤ 1 year (n)	≤ 42 days (n)	MMR
All maternal deaths	333	309	12.1	171	141	6.1
Direct deaths	236	224	8.8	102	90	3.9
Indirect deaths	97	85	3.3	69	51	2.2
Underlying cause of death	n (%)^a	n (%)	MMR	n (%)^a	n (%)	MMR
Cardiac disease	45 (13.5)	40 (12.9)	1.6	32 (18.7)	21 (14.9)	0.9
Hypertensive disorders of pregnancy	99 (29.7)	95 (30.7)	3.5	21 (12.3)	20 (14.2)	0.9
Thrombosis	44 (13.2)	42 (13.6)	1.6	19 (11.1)	19 (13.5)	0.8
Neurological - indirect	17 (5.1)	17 (5.5)	0.7	19 (11.1)	15 (10.6)	0.7
Unascertained - direct	22 (6.6)	21 (6.8)	0.9	14 (8.2)	14 (9.9)	0.6
Haemorrhage	25 (7.5)	25 (8.1)	1.0	13 (7.6)	13 (9.2)	0.6
Suicide	7 (2.1)	4 (1.3)	0.3	19 (11.1)	8 (5.7)	0.3
Amniotic fluid embolism	11 (3.3)	11 (3.6)	0.4	8 (4.7)	8 (5.7)	0.3
Sepsis – non obstetric	10 (3.0)	10 (3.2)	0.4	9 (5.3)	8 (5.7)	0.3
Pregnancy-related infection	20 (6.0)	19 (6.1)	0.7	6 (3.5)	6 (4.3)	0.3
Other indirect	15 (4.5)	13 (4.2)	0.5	6 ^b (3.5)	5 ^b (3.5)	0.2
Early pregnancy death	7 (2.1)	7 (2.3)	0.3	2 (1.2)	2 (1.4)	0.1
Indirect malignancy	3 (0.9)	1 (0.3)	0.0	3 ^c (1.8)	2 ^c (1.4)	0.1
Anaesthesia	2 (0.6)	2 (0.6)	0.1	0	0	0
Other direct	6 (1.8)	2 (0.6)	0.3	0	0	0

^a Late deaths, up to 1 year postpartum, included^b Other indirect within 42 days: systemic lupus erythematosus (1), antiphospholipid syndrome (1), upper gastrointestinal bleeding (1), relapsing polychondritis (1), pheochromocytoma (1). After 42 days: aplastic anaemia (1)^c Indirect malignancy within 42 days: brain tumour (1), cervix carcinoma (1). After 42 days: melanoma (1)

RR= Risk Ratio, MMR= Maternal Mortality Ratio (≤42 days postpartum).

Table 2. Maternal mortality ratio for parity, age and ethnic background. Numbers from Statistics Netherlands excluded for age and ethnic background.

	N	Livebirths	MMR	RR
Parity				
0	62	1,052,002	5.9	1.5
1	34	844,224	4.0	Ref
2	23	293,585	7.8	1.9
3+	10	114,460	8.7	2.2
Missing	1			
Age ^a (years)				
15-19	3	19,562	15.3	3.9
20-24	13	190,412	6.8	1.8
25-29	25	642,711	3.9	Ref
30-34	50	886,680	5.6	1.4
35-39	36	469,620	7.7	
40-44	9	90,656	9.9	2.6
≥45	1	4,630	21.6	5.6
Missing	4			
Ethnic background				
Dutch native	83	1,644,594	5.0	Ref
Western ^b	9	231,180	3.9	0.8
Non-western ^c	38	588,888	6.5	1.3
Surinam/Dutch Antilles	13	88,581	14.7	2.9
African	11	156,741	7.0	1.4
Turkey	5	79,453	6.3	1.3
Morocco	4	99,750	4.0	0.8
Asian	3	133,116	2.3	0.6

a Numbers from Statistics Netherlands included

b Western: European (5), Indonesian (3), Japanese (1)

c Non-western: additionally Syrian (1), South American (1)

MMR= Maternal Mortality Ratio, RR = Risk Ratio

Of 160 women who died up to one year postpartum, 60 (37.5%) were booked as “high-risk” and received antenatal care in secondary or tertiary obstetrician-led care. Eighty-seven (54.4%) were initially booked at primary care, nine (5.6%) received no antenatal care at all. Sixty-five women (40.6%) were referred from primary care to secondary or tertiary care during pregnancy (n=52, 80%), childbirth (n=5, 7.7%) or postpartum (n=5, 7.7%). A total of 119 women (74.4%) died postpartum, of whom 13 had given birth at home (10.9%). Caesarean section was performed in 60 (50.4%) women: 40 were unplanned (66.7%) and 14 (2.3%) were perimortem caesarean sections during resuscitation. Autopsy was performed in 68 women (42.5%) (Table 3).

Table 3. Pregnancy, birth and obstetric care characteristics of all deaths up to one year postpartum.

	Maternal deaths n (%)	General population ^a (%)
Initial antenatal care	N=160	84.6
Primary maternity care	87 (54.4)	15.4
Obstetrician	60 (37.5)	
Not (yet) under obstetric care	9 (5.6)	
Unknown	4 (2.5)	
Referral by primary care giver	N=65	61.8
During pregnancy	52 (80.0)	35.9
During birth	5 (7.7)	2.2
Postpartum	5 (7.7)	
Unknown	3 (4.6)	
Time of death	N=160	
During pregnancy	38 (23.8)	
Postpartum	119 (74.4)	
Within 1 day	27 (22.7 ^b)	
Between 1-7 days	28 (23.5 ^b)	
Between 8-42 days	33 (27.7 ^b)	
Late death (>42 days)	30 (25.2 ^b)	
Unknown	1 (0.8 ^b)	
1 st trimester pathology ^c	3 (1.9)	
Place of death	N=160	
At home	37 (23.1)	
In hospital	119 (74.4)	
Start lethal event out of hospital	43 (36.1 ^b)	
Unknown	4 (2.5)	
Twin pregnancy	3 (1.9)	1.6
Birth	N=119	15.9
At home	13 (10.9)	82.7
In hospital	97 (81.5)	
During transport	1 (0.8)	
Unknown	8 (6.7)	
Mode of birth	N=119	80.6
Vaginal	51 (42.9)	6.9
Instrumental	8 (6.7)	14.9
Caesarean section	60 (50.4)	
- Planned	6 (10.0 ^b)	
- Unplanned	40 (66.7 ^b)	
- Perimortem	14 (2.3 ^b)	
Autopsy performed	N=160	
Yes	68 (42.5)	
Unknown	3 (1.9)	

Table 3. Continued.

	Maternal deaths n (%)	General population ^a (%)
Intrauterine foetal death	N=160	
< 24 weeks	27 (16.9)	
≥ 24 weeks	6 (3.8)	
Perinatal death ^d	24 (14.9)	0.4 ^e
Smoking	N=160	24.9
Yes	38 (23.8)	
Unknown	36 (22.5)	12.0
Obesity	37 (23.1)	

^a National reference values from *Perinatal Registry the Netherlands (Perined)*, 2006-2018

^b Percentages of their subheading

^c Women who died shortly after miscarriage (2) or abortion (1)

^d Perinatal death defined as stillbirth with birthweight ≥ 1000g or ≥28 weeks of gestation, or neonatal death in the first 7 days postpartum.

^e Only numbers until 2016 available.

Medical history was uncomplicated in 79/160 (49.4%) women before conception. Thirteen (8.1%) women had a previous thromboembolic event, 20 (12.5%) were known to have a cardiovascular condition and 12 (7.5%) a mental health condition (Supplementary material 4).

Following confidential enquiry of all 171 deaths within one year postpartum, 102 (59.6%) were categorised as direct and 69 (40.4%) as indirect. For 141 maternal deaths within 42 days postpartum, leading causes were cardiac disease (n=21, 14.9%), hypertensive disorders of pregnancy (n=20, 14.2%) and thrombosis (n=19, 13.5%). Up to one year postpartum, cardiac disease (n=32, 18.7%) and hypertensive disorders (n=21, 12.3%) remained the commonest causes (Table 1). For late deaths, cardiac disease and suicide were commonest (n=11, 13.3%) (Supplementary material 5).

Assessment of quality of care for cases available for enquiry up to one year postpartum (n=160) identified improvable factors in 76 women (47.5%) (Table 4). The majority of these pertained to secondary or tertiary care (n=46, 28.8%), mostly due to inadequate management (n=27, 16.9%) and delay in diagnosis (n=18, 11.3%), followed by delay in diagnosis in primary care (n=14, 8.8%). Lessons learned during audit are presented in Box 1.

Table 4. Improvable factors in care, compared between women with different ethnic background. Late deaths included.

	Dutch and Western women (N= 119)	Non-Western women (N= 41)	Total (N=160)
Improvable factors in care	55 (46.2)	21 (51.2)	76 (47.5)
Patient			
Delay consulting doctor	7 (5.9)	2 (4.9)	9 (5.6)
Refusing medical advice	9 (7.6)	2 (4.9)	11 (6.9)
Communication difficulties	1 (0.8)	5 (12.2)	6 (3.8)
Primary obstetric care*			
Delay in diagnosis	12 (10.1)	2 (4.9)	14 (8.8)
Delay in referral to hospital	2 (1.7)	2 (4.9)	4 (2.5)
Inadequate referral to perinatal centre	0	1 (2.4)	1 (0.6)
Secondary or tertiary care **			
Inadequate antenatal visits	0	1 (2.4)	1 (0.6)
Delay in diagnosis	15 (12.6)	3 (7.3)	18 (11.3)
Inadequate management	19 (16.0)	8 (19.5)	27 (16.9)

*Primary midwifery care and/or general practitioner, ** Obstetricians and/or other medical specialists.

Box 1. Lessons learned as deduced from the improvable factors formulated by the AMSM during audit of maternal deaths in the Netherlands, 2006-2018.

Guidelines and obstetric care

- Generate awareness among pregnant women for alarm symptoms in pregnancy especially for hypertensive disorder and cardiac symptoms. Every woman should be encouraged to seek medical advice in case of new symptoms without experiencing any barriers in terms of communication or other. Maternity care givers should invest time and effort in overcoming language barriers with women of non-native ethnic background.
- Manage hypertensive diseases timely and appropriately with administration of magnesium sulphate and antihypertensive medication. Plan adequate or more frequent antenatal visits for woman at risk of hypertensive disorders or monitor more intensively at home or in hospital.
- Implement screening methods at booking, to identify women at risk of developing perinatal depression, such as the Edinburgh Postnatal Depression Scale. For women with estimated high risk of mental problems, organise a multidisciplinary care pathway in pregnancy and postpartum.
- Implement obstetric early warning scores for monitoring and early detection of critically ill or deteriorating women, especially post-operatively.
- Stabilise critically ill women, before proceeding to birth or transportation to another facility/department. Maximise the use of multidisciplinary expertise when caring for critically ill pregnant women.
- Consider timely postpartum hysterectomy in the management of major haemorrhage, especially in women refusing blood transfusion. Delay due to applying serial conservative options might lead to adverse outcome.

Communication

- Women with severe pre-existing medical conditions require a timely multidisciplinary approach and preferably even pre-conceptual counselling.
- Improve communication, collaboration and comprehension between obstetricians and anesthesiologists by joint team training sessions in obstetric emergencies.

Training

- Be aware of non-specific complaints in the postpartum period. Shortness of breath should not be attributed to hyperventilation without further analysis, but prompt medical evaluation including vital parameters, especially oxygen saturation.

DISCUSSION

Maternal mortality decreased by 50% in the Netherlands in 2006-2018 compared to 1993-2005. This trend was contrary to the previous increase in maternal deaths, though changes in case ascertainment method might have contributed to the observed differences. Improvable factors in care were identified in nearly half of all deaths. Women with a background from Surinam and the Dutch Antilles had an almost threefold higher MMR, remarkably higher than other women with a non-Western background. Commonest causes of death were cardiac disease, hypertensive disorders and thromboembolism.

Compared with other high-income countries, the Netherlands has one of the lowest MMRs, although differences in case ascertainment must be considered. In the UK, the MMR was 9.8 in 2015-2017, which has remained stable in the last decade. In contrast with the Netherlands, indirect causes of death have been more prevalent than direct causes ever since 2003.²³ In France, the MMR was 10.3 in 2010-2012, the commonest cause being obstetric haemorrhage with double the haemorrhage-related MMR compared to the Netherlands (1.6 vs 0.6 per 100,000 livebirths).²⁴ In Italy, the MMR was 9.2 per 100,000 livebirths in 2006-2012 with obstetric haemorrhage being the leading cause (1.9 per 100,000 livebirths).^{25, 26} Differences in rates of deaths caused by obstetric haemorrhage and hypertensive disorders might partly be explained by classification differences, which were previously demonstrated between the UK and the Netherlands.²⁷ However, such differences are unlikely to substantially impact on these comparisons.

Leading cause of death has become cardiac disease, in line with the UK and the US.^{4, 23} However, in the UK rates of mortality due to cardiac disease, are more than twice as high as in the Netherlands (MMR 2.1 vs 0.9 per 100,000 livebirths), accounting for 23.0% of deaths. In the US, cardiovascular diseases account for 15.5% of maternal deaths. Possible explanations for the growing contribution of cardiac disease are changes in risk profiles with more pregnant women being older, obese and having pre-existing cardiac conditions. Some women with congenital heart defects now reach fertile age due to improved care, and have increased risk of adverse outcome.^{28, 29}

We recommend that women with pre-existing conditions including cardiac disease access pre-conception counselling and multidisciplinary care by a dedicated team of obstetricians and other specialists. In-depth analysis of cardiac deaths may help identify additional lessons. Our findings stress the importance of efforts to stop smoking and reduce obesity.

In 1993-2005, hypertensive disorders accounted for one third of maternal deaths, compared to 14% in 2006-2018 and a dramatic decrease in MMR from 3.5 to 0.9.^{6, 7} This is in line with the demonstrated decline in incidence of eclampsia, related to more timely management of hypertensive disorders following an updated national guideline.^{9, 11} Nevertheless, the proportion of hypertensive disorders-related

deaths remains considerable, with improvable factors still present with regard to frequency of antenatal monitoring and timely treatment of severe hypertensive disorders.

Suicide was one of the commonest causes of death up to one year postpartum, more than twice as many as reported in 1993-2005. This rise is in line with other high-income countries. In Austria and Italy, suicides represented 11% and 12% of maternal deaths up to one year postpartum respectively.^{30, 31} The increased suicide rate in the Netherlands may also be partly explained by better reporting of suicides and late maternal mortality. According to Statistics Netherlands, a similar trend was observed in the general Dutch population with suicide rates dropping from 1991 to 2007, but then showing a steady increase until 2017.³² We endorse recommendations of implementing methods to identify women at risk of depression during pregnancy or postpartum, promote joint efforts between obstetric care and mental health professionals for pregnancy-related mental health matters and increase awareness among women and their families to timely recognise symptoms and seek care. Also, the number of suicide-related maternal deaths, most of which occur after 42 days postpartum, underlines the importance of addressing late deaths.

The number of autopsies performed hardly changed compared to 1993-2005 (40%) and in 8% of all deaths cause of death remained unascertained. We believe that in a large proportion of these deaths, a cause could have been identified had autopsy been performed. Therefore, we underline the importance of autopsy, especially in women without apparent pre-existing or obstetric disease, also in case of death at home. In these cases, we recommend consultation of a forensic pathologist.

Although outcomes of women with a non-Western ethnic background appear to have improved, women from Surinam and the Dutch Antilles continue to lag behind. In this group of second or third generation migrants, risk factors for adverse outcome appear to be more common, with almost double the rate of obesity during pregnancy, around 40%.³³ Previously this group was also found to have higher rates of severe acute maternal morbidity.³⁴ They require particular vigilance from health professionals.³⁵

Major strength of this study is its nationwide character, with collection of data over thirteen years. Based on the systematic confidential enquiry performed in all reported deaths, we were able to distil lessons for care based on access to actual medical records. We adjusted categorization of deaths to that used by the MMBRACE-UK, which is based on the ICD-MM, to conform with international literature, enabling future comparisons.²³

Although it appears that deaths during pregnancy and up to 42 days postpartum are reported to the AMSM with great compliance, the relatively low number of late maternal deaths compared to other enhanced maternal mortality systems suggests possible underreporting. Compared to the previous Dutch maternal mortality report where 23/333 (12%) of pregnancy-related deaths were

late, the reporting of late deaths seems to have increased to 30/171 (17.5%), which is still low compared to for instance Italy (>40%).²⁵ Besides cross-checking with Statistics Netherlands, there is no way to identify unreported maternal deaths. Therefore, re-establishing such cross-checking, or including a pregnancy-checkbox in the death certificates has been prioritised by the AMSM.⁶

CONCLUSION

The MMR in the Netherlands is among the lowest in the world and the decline of maternal mortality implies improvements in quality of obstetric care, particularly with regard to management of hypertensive disorders. The decrease, however, should not be taken for granted, as risk factors for developing pregnancy-related complications increase nationally and globally. Effort should be made to optimise care for women at higher risk of mortality such as women from Surinam and the Dutch Antilles and women with pre-existing conditions. Maternal mortality should not be seen as a mere obstetric problem given the latest trends in causes of mortality with increases in cardiac and mental health related deaths.

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SUPPORTING INFORMATION

Supplementary material S1. Reclassification of deaths from the categories used by Schutte et al to the categories used by MBRRACE-UK

Schutte et. A.	MBRRACE-UK
Direct causes of death	
Hypertensive disorders of pregnancy	Hypertensive disorders of pregnancy
Acute fatty liver of pregnancy	
Complications of abortion	Early pregnancy death
Ectopic pregnancy	
Obstetric haemorrhage	Haemorrhage
Genital tract trauma	
Complications of caesarean section	
Miscellaneous-direct	Other direct
Indirect causes of death	
Cerebrovascular accidents (not related to hypertensive disorders)	Indirect neurological
'Other neurological disorders' from the miscellaneous category	
'HIV' Form the miscellaneous category	Sepsis – non obstetric
Infectious diseases	
'Miscellaneous'	Other indirect
- Steinert disease,	
- Systemic lupus erythematosus,	
- Liver cirrhosis,	
- Renal disorders	
Diseases of blood forming organs	
Endocrine diseases	
Pulmonary disorders	

Supplementary material S2. Causes of non-pregnancy related deaths in the Netherlands, 2006-2018.

Cause of death	N
Malignancies	28
Neurological	6
Breast	4
Gastrointestinal	4
Melanoma	4
Gynaecological	2
Haematological	2
Liver	2
Vestibular	1
Lung	1
Liposarcoma	1
Adrenal	1
Violence	4
Accidents	4
Unknown	3
Neurological	2
Infectious^a	2
Other	3
Total	46

a Including cardiac ischemia, (1) Thromboembolic event, 330 days postpartum (1), Wegener vasculitis.

Supplementary material S3 . Risk factors compared between different ethnic background groups. Including late deaths. Values denoted as n (%). RR = Risk Ratio, CS = Caesarean Section, BMI = Body Mass Index

	Dutch and Western women (N = 119)	Non-Western women (N = 41)	RR
Pre-existing medical conditions	33 (27.7)	23 (56.1)	2.0
Previous CS	8 (6.7)	5 (13.2)	1.8
BMI $\geq$ 30	19 (16.0)	13 (34.2)	2.0
Parity			
0	50 (42.0)	12 (31.6)	0.7
1+	40 (33.6)	26 (63.4)	1.9
Age			
15-19	0	4 (10.5)	25.7
20-29	26 (21.8)	9 (22.0)	1.0
30-39	59 (49.6)	22 (53.7)	1.1
>40	6 (5.0)	3 (7.3)	1.5

Supplementary material S4. Pre-existing medical conditions of women who died up to one year postpartum.

Pre-existing medical conditions (N = 160)	
Uncomplicated medical history	79 (49.4)
Thrombosis	13 (8.1)
Cardiovascular	20 (12.5)
Hypertension	9 (5.6)
Valvular disease	4 (2.5)
Cardiomyopathy	2 (1.3)
ASD/VSD	2 (1.3)
Other ^a	3 (1.9)
Mental	12 (7.5)
Depression	6 (3.8)
Neurological	14 (8.8)
Epilepsy	10 (6.3)
CVA	4 (2.5)
Pulmonary	9 (5.6)
COPD	5 (3.1)
Asthma	4 (2.5)
Haematological	
Inherited blood disorders	4 (2.5)
Malignancies	4 (2.5)
Haematological	2 (1.3)
Cervical	1 (0.6)
Astrocytoma	1 (0.6)
Other	
Hepatitis B/C	5 (3.1)
SLE	3 (1.9)
Renal disorders	3 (1.9)
Bariatric surgery	2 (1.3)
Diabetes Mellitus	1 (0.6)

Multiple conditions per woman possible, thus sum is more than 161. Values denoted as n (%).

^a Other cardiovascular diseases: ischaemic event (1), heart failure (1), aortic bifurcation graft (1)
 ASD = atrial septal defect, VSD = ventricular septal defect, CVA = cerebrovascular accident,
 COPD = Chronic obstructive pulmonary disease

Supplementary material S5. Late maternal deaths and underlying causes of death in the Netherlands, 2006-2018. Classified according to MBRRACE-UK classification.

	>42 days (n)
Late maternal deaths	30
Direct deaths	12
Indirect deaths	18
Underlying cause of death	n (%)
Cardiac disease	11 (36.6)
Hypertensive disorders of pregnancy	1 (3.3)
Thrombosis	0 (0)
Neurological - indirect	4 (13.3)
Unascertained - direct	0 (0)
Haemorrhage	0 (0)
Suicide	11 (36.6)
Amniotic fluid embolism	0 (0)
Sepsis – non obstetric	1 (3.3)
Pregnancy-related infection	0 (0)
Other indirect	1 (3.3)
Early pregnancy death	0 (0)
Indirect malignancy	1 (3.3)
Anaesthesia	0 (0)
Other direct	0 (0)

MMR= Maternal Mortality Ratio (≤ 42 days postpartum).

Maternal mortality after caesarean section in the Netherlands

A.F. Kallianidis, J.M. Schutte, J. van Roosmalen, T. van den Akker

On behalf of the Dutch Audit Committee Maternal Mortality and Morbidity

European Journal of Obstetrics Gynecology and Reproductive Biology.
2018;229:148-152.



ABSTRACT

Objectives: Maternal mortality is rare in high-resource settings. This hampers studies of the association between maternal mortality and mode of birth, although this topic remains of importance, given the changing patterns in mode of birth with increasing caesarean section rates in most countries. Purpose of this study was to examine incidence of caesarean section-related maternal mortality in the Netherlands and association of surgery with the chain of morbid events leading to death.

Study Design: We performed a retrospective cohort study using the Confidential Enquiry into Maternal Deaths, including all 2,684,946 maternities in the Netherlands between January 1st, 1999, and December 31st, 2013, registered in the Dutch Perinatal Registry. All available medical records of cases reported to the Dutch Maternal Mortality and Severe Morbidity Audit Committee were assessed by two researchers, and one or two additional experts in case of contradicting opinions, based on a set of pre-identified clinical criteria. Main outcome measures were (1) incidence and relative risk of maternal death following caesarean section and vaginal birth and (2) incidence of death directly related to caesarean section and death in which caesarean section was one of the contributing factors.

Results: Risk of death after caesarean section was 21.9 per 100,000 caesarean sections (86/393,443) versus 3.8 deaths per 100,000 vaginal births (88/2,291,503): Relative Risk (RR) 5.7 (95% Confidence Interval [CI] 4.2–7.7). Death directly related to complications of caesarean section occurred in 8/86 women: 2 per 100,000 caesarean sections. With addition of 43 women in which caesarean section did not initiate, but contributed to the chain of events leading to mortality, risk of death increased to 13 per 100,000 caesarean sections (51/393,443; RR 3.4; 95%CI 2.4–4.8). At the start of caesarean section, pre-existing morbidity was present in 70/86 women (81.4%).

Conclusions: Compared to vaginal birth, maternal mortality after caesarean section was three times higher following exclusion of deaths that had no association with surgery. In approximately one in ten deaths after caesarean section, surgery did in fact initiate the chain of morbid events.

INTRODUCTION

Caesarean section rates have increased worldwide, despite several recommendations by the World Health Organization (WHO) to curb this increase.^{1,2} A WHO ecological study found that rates above 10% are not associated with reduction of maternal and perinatal mortality.^{3,4} Caesarean sections carry short- and long-term risks for index and subsequent births.^{5–8}

Death of a woman during pregnancy, childbirth or puerperium has become a rare event in high-resource settings.^{9,10} This makes examining the association between maternal mortality and mode of birth difficult. Previous facility-based studies comparing maternal mortality after caesarean and vaginal birth have shown inconsistent results. Comparisons are hampered by indication bias, limited power and absence of uniform categorization of caesarean sections. Only few studies have assessed caesarean section-related mortality on a nationwide scale.^{11–16}

The Netherlands have seen an increase in caesarean section rate from 10.8% in 1999 to 16.6% in 2015, although still lower than in almost any other high-income country at that time.^{10,17} Confidential Enquiries into Maternal Deaths revealed that the maternal mortality ratio (MMR) rose from 9.7 to 12.1 per 100,000 live births between the time frames 1983–1992 and 1992–2005. This rise was attributed to a changing risk profile, since advanced maternal age, pre-existing medical conditions and non-resident status increased among pregnant women.^{18,19} In 1983–1992, maternal mortality was found to be seven times higher following caesarean section compared to vaginal birth.¹⁴

Aim of this study was to investigate risk of maternal mortality following caesarean section and vaginal birth in the Netherlands in more recent times, and assess to what extent surgery contributed to the chain of events that ultimately leading to maternal death.

MATERIALS AND METHODS

This was a nationwide retrospective cohort study, including all maternal deaths reported to the Dutch Maternal Mortality and Severe Morbidity Audit Committee (MMSMAC) between January 1st, 1999, and December 31st, 2013.

In the Netherlands, all maternal deaths are voluntarily reported to the MMSMAC by specialists, general practitioners and midwives. The MMSMAC consists of eleven obstetricians and one obstetric anesthetist. All members are employed at either non-university teaching hospitals or university hospitals. Deaths were cross-checked with maternal mortality data from Statistics Netherlands (CBS) up to 31st December 2011. Thereafter, cross-check did not happen due to very small numbers of maternal deaths that CBS feared individual cases could have become recognizable, putting confidentiality at risk.²⁰

After a case is reported, all medical records are requested to be sent to the MMSMAC. These include antenatal charts, microbiology and laboratory results, theatre records, autopsy reports and local maternal death reviews. The MMSMAC classifies underlying causes of death, mode of death and audits substandard care factors. All patient records are anonymised and kept in a secured database that can only be accessed after approval by MMSMAC.

Records for all maternal deaths following caesarean section were accessed and information about maternal history and current pregnancy extracted. Maternal death was defined according to the WHO's International Classification of Diseases, tenth revision (ICD- 10).²¹ Late maternal deaths – occurring longer than 42 days but within one year after delivery - and deaths unrelated to pregnancy, e.g. traffic deaths were excluded from calculations and analysis. After in-depth examination of case files, deaths were categorised according to relation with mode of delivery as directly related, associated and not associated with caesarean section. A pre-specified set of criteria was used to categorise deaths according to relation with surgery. Death was defined to be directly related to surgery if the chain of events leading to death started during or within 24 h after surgery and the cause or mode of death were the direct result of surgical or anesthetic complications. In addition, a death was also categorised as directly related to surgery, if the chain of morbid events started with uterine scar rupture resulting from previous caesarean section. Deaths were categorised to be associated with surgery, if caesarean section was assessed to have contributed to the chain of morbid events that had already started prior to surgery. Such deaths 'associated with caesarean section' occurred in women with already complicated pregnancies or labor, but in whom surgery or anesthesia was deemed to have contributed to the fatal outcome, as assessed by the audit panel. Deaths were categorised as not associated with caesarean section, if surgery had not contributed. These deaths included women who had given birth by perimortem caesarean section during cardiopulmonary resuscitation and women with advanced stages of obstetric or non-obstetric illness, in whom caesarean section was done to save the life of the fetus with poor chances of a woman's survival. Categorization was done by two investigators (AK and TA) in the following manner: in a first round both investigators independently examined and categorised all maternal deaths according to the above definition. AK is a registrar who had no previous knowledge of the cases. TA is a consultant obstetrician who has been a member of the MMSMAC for seven years and was involved in obstetric audit in other settings even before that time.²²⁻²⁴ For deaths in which there was discrepancy between these two investigators, a second round was conducted after additional inquiry into the woman's medical records. In this round, a third (JR, previous chair of the MMSMAC with ample experience in audit^{25,26}) and/or fourth investigator (prof. K. Bloemenkamp, current chair of the MMSMAC) were consulted and consensus was needed for eventual categorization.

We calculated the overall MMR for the study period and risk of death following caesarean section and vaginal birth before and after excluding cases with no association between surgery and mortality. MMR was defined as the number of maternal deaths per 100,000 live births. Caesarean sections were classified into 'primary or elective' in cases where vaginal birth had never been intended even if the woman presented in labor, and 'secondary' when decision for caesarean section was made during labor. This classification is not meant to reflect sense of emergency surrounding the procedure and is based on the intention to treat principle. Pre-existing morbidity was defined as any medical or obstetric condition, or any pregnancy-related complication present before birth, which had a significant impact on the pathophysiological pathway leading to death. Often, these complications were the indication for caesarean section. Obesity was defined as a body mass index of 30 kg/m² or more, or when body mass index was unknown, when obesity was explicitly stated in the maternal charts.

The total number of live births, for calculation of MMR, was extracted from Statistics Netherlands.²⁰ National numbers for caesarean sections and vaginal births were collected from the Dutch Perinatal Registry, in which approximately 95.5% of all births with gestational age of at least 22 weeks were recorded before 2011, and since that year more than 99%.¹⁷

Statistical analyses were performed using IBM SPSS for Windows version 21 (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

The MMSMAC is authorised and mandated by the Netherlands Society of Obstetrics and Gynaecology for collection and analysis of maternal mortality in the Netherlands. Members are appointed by the Society. Confidential Enquiry into Maternal Deaths involves the assessment of anonymised reported data. In the Netherlands, ethical approval is not required for confidential enquiry.

No funding was received for this study.

RESULTS

Over the fifteen-year study period, 269 deaths (excluding deaths unrelated to pregnancy) were reported to the MMSMAC. Of these 269 deaths, 32 were late deaths and therefore excluded, leaving 237 maternal deaths for further analysis. Eighty-six women (36.3%) died following caesarean section, 88 (37.1%) following vaginal birth, 55 (23.2%) undelivered and eight (3.4%) following complications of abortion, miscarriage or ectopic pregnancy. Overall MMR was 8.3 per 100,000 live births (237/2,841,663). Risk of maternal mortality following caesarean section was 21.9 per 100,000 caesarean sections (86/393,443) versus 3.8 per 100,000 vaginal births (88/2,291,503) (Relative Risk [RR] 5.7; 95% Confidence Interval [CI] 4.2–7.7).

In the categorization of deaths according to the relation with surgery the two investigators agreed in 76/86 cases (kappa for agreement 0.8), a second round was needed in ten cases and a third round in only one. In eight women (9.3%), death was categorised as directly related to caesarean section, giving a case fatality rate of 2 per 100,000 caesarean sections (Box 1). In addition, in 43 women (50%), death was categorised to be associated with caesarean section. This gives a combined case fatality rate of 13 per 100,000 caesarean sections (51/393,443) and a RR for caesarean section of 3.4 (95%CI 2.4–4.8) compared to vaginal birth. There was no association between caesarean section and death in 34 women (39.5%). One maternal death could not be categorised due to missing medical records.

Women who died after caesarean section had a mean age of 31.9 years (standard deviation 5.6). The majority ($n = 59$; 68.6%) had preterm births. Twenty-four women (27.9%) were of non-Dutch origin. Eleven (12.8%) had a caesarean section in a previous pregnancy. At their initial antenatal visit, 50 women (58.1%) were booked as 'high-risk' for obstetric care, while 36 (41.9%) started as 'low-risk' in primary midwifery care and were referred during pregnancy or labor (Table 1). At the time of surgery, 70 women (81.4%) had one or more pre-existing morbidities: 32 (37.6%) hypertensive disorders of pregnancy, 11 (12.8%) cerebrovascular disorders (meningitis, encephalitis, epilepsy, neurological tumor, intracranial haemorrhage), ten (11.6%) cardiovascular disorders (severe hypertension, dilated aorta, aortic dissection, cardiomyopathy or mechanical heart valve), ten (11.6%) sepsis and ten (11.6%) other obstetric and non-obstetric conditions (liver cirrhosis, psychiatric conditions, morbid obesity, abnormally invasive placenta, history of severe thromboembolism, acute fatty liver of pregnancy).

Of all caesarean sections, 58 (67.4%) were 'primary or elective' and 28 (32.6%) 'secondary'. Most frequent indications for caesarean section were hypertensive disorders in 30 women (34.9%), followed by 'severe non-obstetric medical condition' in 22 (25.6%) and fetal distress in 12 (14%) (Table 2). Commonest underlying causes of death were hypertensive disorders ($n = 25$; 29%), cardiovascular disease ($n = 11$; 128%) and cerebrovascular disease ($n = 10$; 116%) (Table 3).

Compared to 1983–1992, combined risk of maternal mortality directly due to or associated with caesarean section decreased from 28 to 13 per 100,000 operations (RR 0.47; 95%CI 0.3–0.74).¹⁴ Risk of maternal mortality directly related to surgery or anesthesia decreased considerably from 13 to 2 per 100,000 (RR 0.16; 95%CI 0.07–0.38). Deaths due to anesthesiology-related complications decreased from 3.7 to 0.3 per 100,000 surgeries (RR 0.07; 95% CI 0.008–0.62) (Table 4).

Table 1. Maternal characteristics of women who died after caesarean section

Maternal characteristics	
	N (%)
Ethnicity	
Dutch native	62 (72.1%)
Black African	12 (14%)
Surinam/Dutch Antilles	6 (7%)
Asian	3 (3.5%)
Turkish	1 (1.2%)
Missing	2 (2.3 %)
Age (years)	
<20	2 (2.3%)
20-24	10 (11.6%)
25-29	18 (20.9%)
30-34	28 (32.6%)
35-39	20 (23.3%)
≥ 40	7 (8.1%)
Missing	1 (1.2%)
Parity (n)	
0	48 (55.8%)
≥ 1	38 (44.2%)
Gestational age (weeks ^{+days})	
Term (≥37)	27 (31.4%)
32 - 36 ⁺⁶	41 (47.7%)
24 - 31 ⁺⁶	18 (20.9%)
Multiple gestation	
Singleton	78 (90.7%)
Multiple	8 (9.3%)
Previous caesarean section	11 (12.8%)
Pre-existing morbidity	70 (81,4%)

Table 2. Indications of Caesarean Section

	Primary N=58 (67.4%)	Secondary N=28 (32.6%)	Total N=86
Hypertensive disorder	24 (41.4%)	6 (21.4%)	30 (34.9%)
Preeclampsia	18 (26,3 %)	6 (21.4%)	24 (27.9%)
HELLP	4 (6.9 %)	0	4 (4.7%)
Eclampsia	2 (3.4 %)	0	2 (2.3%)
Non-obstetric medical condition ^a	20 (34.5%)	2 (7.1%)	22 (25.6%)
Fetal distress	1 (1.7%)	11 (39.3%)	12 (14%)
Prolonged labor	0	8 (28.6%)	8 (9.3%)
Perimortem	5 (8.6 %)	1 (3.6%)	6 (7%)
Non-vertex presentation	4 (6.9 %)	0	4 (4.7%)
Previous caesarean section	2 (3.4 %)	0	2 (2.3%)
Other ^b	2 (3.4 %)	0	2 (2.3%)

^a Six cases of deteriorating heart disease, eight cases of non-obstetrical sepsis, five cases of cerebrovascular haemorrhage, two cases of respiratory failure due to pneumonia and one due to cystic fibrosis.

^b One case of uterine leiomyoma and one with previous uterine surgery.

Table 3. Underlying causes of maternal mortality according to association with caesarean section.

	Direct (n=8)	Association (n=43)	No association (n=34)	Total (n=86)^a
Obstetric causes				
Hypertensive disorders	0	17	7	25 (29%) ^a
Preeclampsia	0	10	2	12 (14%)
Eclampsia	0	3	3	6 (7%)
HELLP	0	4	2	7 (8.1%) ^a
Obstetric sepsis	2	5	0	7 (8.1%)
Obstetric haemorrhage	5	2	0	7 (8.1%)
Thromboembolism	0	5	0	5 (5.8%)
Acute Fatty Liver of Pregnancy	0	3	0	3 (3.5%)
Amniotic Fluid Embolism	0	2	0	2 (2.3%)
Anesthesiological complication	1	0	0	1 (1.2%)
Unknown	0	4	1	5 (5.8%)
Non obstetric causes				
Cardiovascular disease	0	3	8	11 (12.8%)
Cerebrovascular disease	0	0	10	10 (11.6%)
Non-obstetric sepsis	0	0	5	5 (5.8%)
Mental disorders	0	0	2	2 (2.3%)
Other	0	2	1	3 (3.5%)

^a One case of maternal death due to HELLP could not be categorised due to missing information but was taken into account for totals of underlying cause of death.

Table 4. Women with hypertensive disorders of pregnancy, by primary or secondary caesarean section.

	Primary 27 (81.8%)	Secondary 6 (18.2%)	Total (N=33)
Pregnancy induced hypertension ^a	1 (100%)	0	1
Pre-eclampsia ^b	12 (70.6%)	5 (29.4%)	17
Eclampsia ^c	6 (85.7%)	1 (14.3%)	7
HELLP-syndrome ^d	8 (100%)	0	8

^a Mode of death: epilepsy.

^b Mode of death: Hypovolemic shock (5), Intracerebral haemorrhage (3), Multiorgan failure (2), Acute Respiratory Distress Syndrome/respiratory failure (3), Sepsis (2), Thromboembolism (1), Suicide (1).

^c Mode of death: Intracerebral haemorrhage (4), post anoxic encephalopathy (2), respiratory failure (1).

^d Mode of death: Intracerebral haemorrhage (5), Multi-organ failure (2), Unknown

DISCUSSION

Caesarean section in the Netherlands was associated with a three-fold increase in risk of maternal death compared to vaginal birth, which is in line with literature from other settings.^{11–13} Impact of surgery on the chain of events varied, and in most women pre-existing morbidity was present at the start of surgery, hampering differentiation between contribution of surgery and other morbid factors. In approximately one in ten deaths, caesarean section initiated the chain of events, and in half of deaths the operation contributed. At the same time, our findings indicate that the risk of caesarean section has decreased significantly in this period compared to the previous period of investigation.¹⁴

The decrease in anesthesiology-related deaths is in line with results from the United Kingdom and may be due to improved care and procedures for women before, during and after surgery.²⁷ Hypertensive disorders remain the predominant underlying cause of death in our study.^{14,18} This underlines the fact that preeclampsia poses women at increased risk of haemorrhage and that caesarean section may contribute to this risk.²⁸ Finally, even though the percentage of women with a non-native background is comparable to the general population during the study period (19.5% in 2006 increasing to 25.7% in 2013), this does not apply to women from sub-Saharan Africa and Suriname or the Dutch Antilles, who were over-represented.²⁹ This supports previous literature that non-native background or immigrant status is a risk factor for maternal mortality and morbidity and that risk factors differ importantly between different non-native groups.^{18,30,31}

Comparison with previous studies from France and Brazil is hampered by variations in study design and setting.^{13,32} Maternal deaths with obstetric or non-

obstetric morbidity present before birth and multiple gestations were excluded in those studies in order to correct for indication bias. We purposely did not exclude women with pre-existing maternal morbidity or multiple gestation because also in these women, mode of birth may contribute to the chain of events leading to death. Only by including these cases can the actual incidence of surgery-related death be calculated. Accuracy of comparisons of underlying causes of death between different countries has been questioned, since classification is not uniform.²²

Major strength of our study is its nationwide coverage. Categorization of association of caesarean section with maternal death was performed by two independent investigators, and in multiple rounds in case of discrepancy in order to minimise interpretation bias. We excluded cases in which caesarean section did not contribute to death, avoiding overestimation. Completeness of case files was exceptionally high for a retrospective study covering 15 years and allowed categorization in all but one woman.

Reporting maternal deaths in the Netherlands is based on voluntary reporting and cross-check with Statistics Netherlands took place up to December 2011, leaving 22 cases in our cohort that could not be cross-checked. Guidelines of the Netherlands Society of Obstetrics and Gynaecology describe failure of reporting maternal deaths as substandard care. For the period 1993–2005, we found that cross-checking revealed an additional 11% of unreported maternal deaths.¹⁸

Main limitations are inherent to the retrospective design. Indication bias is unavoidable, since women with severe morbidity before birth are at higher risk of caesarean section. A threefold higher risk, however, does not differ from previous studies in the Netherlands and other settings.^{8,12,13} Since we had to rely on case notes, we were also confronted with variations in quality of documentation. A significant time frame was necessary to achieve sufficient numbers of deaths, but obstetric practice will have changed over time. Perimortem caesarean sections are performed more frequently since the introduction of the “Managing Obstetric Emergencies and Trauma” course in 2004 and hypertensive disorders are treated more aggressively.^{33,34}

Finally, considering rising rates of caesarean section, obstetric caregivers should realise that risk of maternal death following caesarean section in high-income countries, even though small, remains threefold higher than after vaginal birth. Especially in women with severe non-obstetric morbidity and hypertensive complications of pregnancy, vaginal birth should be considered, maternal and fetal condition permitting. Ensuring that caesarean sections are performed when medically necessary remains an important cornerstone to avoid unnecessary maternal deaths.

Box 1. Cases in which maternal mortality was a direct consequence of caesarean section or anesthesia.

Case 1: G1P0, 25 years, previously healthy, breech presentation, failed external cephalic version, elective caesarean section at term, fever post-partum, antibiotics given, paralytic bowel obstruction, septic shock, re-laparotomy with no abnormalities, progressive septic shock, maternal death six days post-partum due to obstetric sepsis.³⁵

Case 2: G4P2, 29 years, previously healthy, twin gestation, elective caesarean section due to breech lie of first child at term, first postoperative day cardiac arrest and death. Postmortem: severe intra-peritoneal haemorrhage.

Case 3: G2P1, 39 years, Asian, history of caesarean section and pre-existing hypertension; current pregnancy: placenta praevia, mild pre-eclampsia and intrauterine growth restriction. Elective caesarean section at 35+1 weeks, due to suspicion of fetal distress. Perioperative: covered uterine rupture and profound difficulty of placental removal. Post-operative postpartum haemorrhage, re-laparotomy and emergency peripartum hysterectomy, second and third re-laparotomy due to intra-peritoneal bleeding, maternal death 19 days after delivery due to Acute Respiratory Distress Syndrome and pneumonia.

Case 4: G2P1, 33 years, sub-Saharan African, with history of sickle cell trait and chronic hepatitis B infection, prolonged labor at term, emergency caesarean section complicated by laceration of left uterine artery. First day postpartum cardiopulmonary resuscitation due to hypovolemic shock, emergency re-laparotomy, bleeding from uterotomy, Acute Respiratory Distress Syndrome, multi-organ failure, maternal death due to obstetric sepsis 22 days post-partum.

Case 5: G1P0, 22 years, sub-Saharan African, previously healthy, induced at 42 weeks, emergency caesarean section due to prolonged labor, complete spinal block, cardiac arrest, maternal death.

Case 6: G1P0, 28 years, previously healthy, induced at 42 weeks, uncomplicated emergency caesarean section due to fetal distress, massive postpartum haemorrhage immediately after surgery, uterotonics, maternal death five days postpartum due to disseminated intravascular coagulation and multi-organ failure.

Case 7: G4P0, 23 years, previously healthy, Surinamese; current pregnancy: HELLP syndrome, breech lie. Emergency caesarean section at 36 weeks, due to fetal distress, post-operative intra-peritoneal bleeding treated with multiple blood transfusion because re-laparotomy was deemed too hazardous, cardiac arrest, Cardiopulmonary resuscitation, re-laparotomy due to abdominal compartment syndrome, maternal death three days postpartum due to multi-organ failure.

Case 8: G2P1, 40 years, obstetric history: eclampsia and caesarean section. Current: pre-eclampsia, preterm labor at 33+5 weeks, emergency caesarean section due to fetal distress, no signs of clotting disorder, complicated by excessive blood loss, postoperative hypovolemic shock, re-laparotomy: emergency peripartum hysterectomy, maternal death one day post-partum due to ischemic complications.

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PART 2

Maternal morbidity

Laparotomy in women with severe acute maternal morbidity: secondary analysis of a nationwide cohort study

T. Witteveen, A.F. Kallianidis, J.J. Zwart, K.W.M. Bloemenkamp, J. van Roosmalen,
T. van den Akker

BMC Pregnancy and Childbirth. 2018;18(1):61.



ABSTRACT

Background: Although pregnancy-related laparotomy is a major intervention, literature is limited to small case control or single center studies. We aimed to identify national incidence rates for postpartum laparotomy related to severe acute maternal morbidity (SAMM) in a high-income country and test the hypothesis that risk of postpartum laparotomy differs by mode of birth.

Methods: In a population-based cohort study in all 98 hospitals with a maternity unit in the Netherlands, pregnant women with SAMM according to specified disease and management criteria were included from 01/08/2004 to 01/08/2006. We calculated the incidence of postpartum laparotomy after vaginal and caesarean births. Laparotomies were analyzed in relation to mode of birth using all births in the country as reference. Relative risks (RR) were calculated for laparotomy following emergency and planned caesarean section compared to vaginal birth, excluding laparotomies following births before 24 weeks' gestation and hysterectomies performed during caesarean section.

Results: The incidence of postpartum laparotomy in women with SAMM in the Netherlands was 6.0 per 10,000 births. Incidence was 30.1 and 1.8 per 10,000 following caesarean and vaginal birth respectively. Compared to vaginal birth, RR of laparotomy after caesarean birth was 16.7 (95% confidence interval [95% CI] 12.2-22.6). RR was 21.8 (95% CI 15.8-30.2) for emergency and 10.5 (95% CI 7.1-15.6) for planned caesarean section.

Conclusions: Risk of laparotomy, although small, was considerably elevated in women who gave birth by caesarean section. This should be considered in counseling and clinical decision making.

BACKGROUND

According to the World Health Organization (WHO), laparotomy is a critical intervention required in the management of life-threatening and potentially life-threatening conditions.¹ In this study, laparotomy is defined as a surgical procedure involving an incision through the abdominal wall to gain access into the abdominal cavity other than caesarean section. Its use is indicative of severe maternal outcome and may be applied as a quality marker for obstetric care.¹ Although it is clear that laparotomy during pregnancy and after childbirth is a major intervention, literature is sparse and limited to case-control or single center studies with limited numbers of cases.

Previous studies only address 're-laparotomy' after caesarean section. Reported incidence rates of 're-laparotomy' are low, varying between 0.2 and 0.9%.²⁻¹¹ Although data on laparotomy after vaginal birth are not reported, it has been suggested that the incidence of laparotomy may be higher after caesarean section, since operative birth is associated with a higher risk of maternal morbidity and mortality.^{12, 13}

In this paper, we report national incidence rates of postpartum laparotomy, using a nationwide cohort of women with severe acute maternal morbidity (SAMM), and test the hypothesis that the risk of pregnancy related laparotomy in the postpartum period differs by mode of birth.

METHODS

This study is part of a well-known two-year nationwide cohort study to assess SAMM during pregnancy, labour and puerperium in the Netherlands, called the 'LEMMoN-study' (*Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland*). Pregnant women sustaining SAMM were included from all 98 hospitals with a maternity unit, in the period 1st August 2004 until 1st August 2006. These were eight tertiary care hospitals, 35 non-academic teaching hospitals and 55 general hospitals. Detailed information regarding data collection was described previously.¹⁴

Inclusion criteria for SAMM were categorised in five groups: admission into an intensive care unit, uterine rupture, eclampsia, major obstetric haemorrhage (defined as four or more units of pack red blood cells or hysterectomy or arterial embolization) and a miscellaneous group with SAMM in the opinion of the treating clinician, which could not be classified in any of the other four groups. Women could be included into more than one group, therefore: one woman could have more than one indication for laparotomy, and more than one comorbidity. For all calculations of risk and incidence, we used the number of women as the denominator. Laparotomy was not a specific inclusion criterion in the LEMMoN-study.

All women in the nationwide SAMM cohort who had a laparotomy after vaginal or caesarean birth were included in this specific study. Incidence of postpartum laparotomy and relative risks with regard to mode of birth were calculated. Only women with a birth after 24 weeks' gestational age were included, and only those who had a laparotomy within six weeks after birth. Women who had hysterectomy or other surgery during caesarean birth were excluded.

The main outcome measure was relative risk (RR) related to caesarean birth (with vaginal birth as reference) and associated risk factors. The Dutch Perinatal Register was used as the source for background denominator data. Clinical characteristics and birth data were analyzed in search of predisposing factors. Maternal characteristics included age, body mass index, parity, gestational age, and previous caesarean section. Data concerning birth included: mode of birth, blood loss, number of units of blood transfused, indication for laparotomy, timing of laparotomy after birth (< 24 h, 2-7 days or > 7 days), number of laparotomies and duration of hospital admission. Indications for laparotomy were clustered into six groups: severe postpartum haemorrhage, intra-abdominal bleeding, (suspected) uterine rupture, sepsis, hematoma and miscellaneous (i.e. removal of purposely-left sterile gauze, bladder damage, rectovaginal fistula). Therapeutic interventions were clustered into: bleeding control, which was then subdivided by location (abdominal wall, intra-abdominal and uterine scar-related), compression sutures such as the B-lynch procedure, ligation of large vessels, hysterectomy, hematoma/abscess drainage, negative laparotomy (exploration without therapeutic intervention) and miscellaneous. More than one indication or intervention could be assigned.

R Rs with 95% confidence intervals (CI) were calculated where appropriate. Differences in characteristics between modes of birth were tested with a chi-square test or Fisher's exact test for categorical data and independent t-test or Mann-Whitney U test for numerical data where appropriate. Statistical analysis was performed using SPSS statistics, version 20.0 (SPSS, Chicago, IL).

RESULTS

During the two years, 355,841 births were registered in the Netherlands Perinatal Register: 302,689 (85.1%) vaginal births and 53,152 (14.9%) caesarean sections, of which 24,580 (46.2%) planned and 28,572 (53.8%) emergency sections. Among 2552 women with SAMM in the cohort, 325 laparotomies were reported in 276 women. This gives a total incidence of laparotomy in women with SAMM in the Netherlands of 7.8 per 10,000 births. Sixty-one women were excluded from analysis of risk as they did not fit the inclusion criteria: 37 had the (initial) laparotomy before birth, 15 had a caesarean section with additional procedures including 11 hysterectomies, 6 had delivered before 24 weeks' gestational age and 3 were more than 42 days postpartum at the time of laparotomy.

The 215 remaining women were included for risk analysis, of whom 160 (74.4%) had laparotomies following caesarean section (10 out of these 160 were failed vacuum extractions) and 55 (25.6%) following vaginal birth (14 out of these 55 were instrumental births -all vacuum extractions, forceps are rarely used in the Netherlands).

One hundred and forty-five women (67.4%) were admitted into an intensive care unit. Comorbidity included major obstetric haemorrhage in 192 (89.3%), uterine rupture in 22 (10.2%), eclampsia in 8 (3.7%) and miscellaneous morbidity in six (2.8%) out of the 215 women. These 'miscellaneous comorbidities' were (A) postoperative adhesion ileus (twice), (B) large abdominal wall hematoma after caesarean section, (C) incarcerated hernia one day postpartum requiring iliocaecal resection, (D) rectovaginal fistula nine days after anal sphincter rupture requiring colostomy, (E) a large wound defect with multiple abscesses.

One hundred thirty-eight women had more than one comorbidity (118 had two, 19 had three and one woman had four co-morbidities). The incidence of laparotomy after childbirth in women with SAMM in the Netherlands, who fitted our inclusion criteria for risk analysis in relation to mode of birth, was 6.0 per 10,000. Incidence was 30.1 per 10,000 caesarean births and 1.8 per 10,000 vaginal births (Table 1). This gives a RR of 16.7 (95% CI 12.2-22.6). The absolute risk of laparotomy was 39.5 per 10,000 births for emergency caesarean section and 19.1 per 10,000 for planned section. Compared to vaginal birth, RRs for emergency and planned caesarean section were 21.8 (95% CI 15.8-30.2) and 10.5 (95% CI 7.1-15.6) respectively (Table 1).

Table 1. Incidence of laparotomy after childbirth, related to mode of birth

	Deliveries (n)	Laparotomy (n)	Incidence*	RR (95% CI)
Total	355,841	215	6.0	
CS	53,152	160	30.1	16.7 (12.2-22.6)
Planned	24,580	47	19.1	10.5 (7.1-15.6)
Emergency	28,572	113	39.5	21.8 (15.8-30.2)
VD	302,689	55	1.8	Reference

RR, relative risk; CI, confidence interval; CS, caesarean section; VD, vaginal delivery. *per 10 000 deliveries.

Women who had laparotomy after caesarean section, were more often nulliparous, had pregnancies of lower gestational age and longer hospital admissions compared to those who gave birth vaginally (Table 2). Large proportions in both groups were found to have scarred uteri: 32.7% of women who delivered by caesarean section and 34.0% of women who delivered vaginally. Among women who had laparotomy after caesarean section the proportion of women with a

scarred uterus secondary to previous caesarean section was larger in the planned caesarean section group (emergency 20.4%, planned 61.7%; $p < 0.01$). There were 103 women (48%) who needed to be transfused nine or more units of red blood cell concentrates: 30 following vaginal and 73 following caesarean birth.

SAMM occurred before childbirth in 14 (6.5%) and after childbirth in 198 (92.1%) women; in three women this information was unknown (Table 2). In 99 women (46.0%), the indication for laparotomy after birth was intra-abdominal bleeding, followed by severe postpartum haemorrhage (83 women, 38.6%) (Table 3). For caesarean section, the main indication was intra-abdominal bleeding (93 women, 58.1%). For vaginal birth, main indications were severe postpartum haemorrhage (34 women, 61.8%) or suspected uterine rupture (12 women, 21.8%).

Table 2. Maternal characteristics and birth information

	VD N=55	CS N=160	P	Emergency CS N=113	Elective CS N=47	P
Age (y)	34.1 (3.4)	33.0 (5.3)	0.08	32.8 (5.5)	33.6 (4.8)	0.35
BMI (kg/m ²)	24.6 (6.7)	24.7 (5.5)	0.55	24.1 (4.7)	25.8 (6.8)	0.37
Nulliparity	13 (24.1%)	72 (45.3%)	<0.001	61 (54.0%)	11 (23.4%)	<0.001
Gestational age (w)	39.4 (2.6)	38.2 (3.4)	<0.05	38.5 (3.7)	37.5 (2.5)	<0.001
Previous CS	18 (34.0%)	52 (32.7%)	0.87	23 (20.4%)	29 (61.7%)	<0.001
Hospital admission (d)	11.7 (13.1)	14.4 (10.9)	<0.05	14.6 (10.5)	13.8 (11.9)	0.18
Blood loss (mL)	5556 (4532)	4262 (3432)	0.053	4166 (3342)	4 3 0 3 (3486)	0.81
Units of RBC (n)	12.4 (9.4)	10.8 (9.0)	0.19	11.6 (9.6)	9.1 (7.1)	0.18
SAMM before birth (n)	3 (5.5%)	11 (6.9%)	0.52	10 (8.9%)	1 (2.1%)	0.275

CS, caesarean section; VD, vaginal birth, RBC, red blood cells. Data is presented as mean (SD) or number (%)

A total of 147 (68.4%) laparotomies were performed within 24 h after birth (caesarean section 63.1% vs. vaginal birth 83.6%; $p < 0.05$). Late laparotomies (within 2-7 days) were more likely to happen following caesarean section (26.9% vs. vaginal birth 9.1%; $p < 0.05$).

During the first laparotomy, hysterectomy was the most frequently performed intervention (63 women, 29.3%), followed by control of intra-abdominal (53 women, 24.7%) and caesarean scar-related bleeding (34 women, 15.8%). In 21 (9.8%) women, no therapeutic intervention was done during laparotomy.

Forty out of the 215 women included in the risk analysis (18.6%) had more than one laparotomy: 32 out of these 40 (80.0%) had two, seven (17.5%) had three and one

(2.5%) had four laparotomies. In 21 (52.5%) of these 40 women, the operation was due to intra-abdominal bleeding and in 5 (12.5%) re-laparotomy resulted in hysterectomy.

Three out of the 215 women died shortly after or during laparotomy (case fatality rate 1.4%): one woman died in the intensive care unit after hysterectomy for severe haemorrhage following vaginal birth. Another woman, who had a history of cardiac disease, died due to massive intra-peritoneal haemorrhage from iatrogenic perforation of the iliac artery during uterine embolization following vaginal birth. Laparotomy was performed as a last resort, but she died shortly afterwards in the intensive care unit. The third maternal death was due to puerperal sepsis with group-A streptococcus. The woman had delivered a stillbirth vaginally and suffered persistent postpartum haemorrhage despite embolization. She died during hysterectomy.

Table 3. Detailed information of laparotomies after childbirth

Total		VD N=55	CS N=160	P	Emergency N=113	Elective N=47	P
Indication*	Intra-abd. bleeding	6 (10.9)	93 (58.1)	<0.001	65 (57.5)	28 (59.6)	0.777
	sPPH	34 (61.8)	49 (30.6)		36 (31.9)	13 (27.7)	
	Suspected rupture	12 (21.8)	1 (0.6)		1 (0.9)	0 (0.0)	
	Sepsis	4 (7.2)	7 (4.4)		6 (5.3)	1 (2.1)	
	Hematoma	0 (0.0)	4 (2.5)		3 (2.7)	1 (2.1)	
	Miscellaneous	9 (16.4)	11 (7.5)		6 (5.3)	5 (10.6)	
	Unknown	0 (0.0)	1 (0.6)		1 (0.9)	0 (0.0)	
	<24h	46 (83.6)	101 (63.1)		71 (62.8)	30 (63.8)	
	2-7d	5 (9.1)	43 (26.9)		30 (26.5)	13 (27.7)	
	>7d	4 (7.3)	12 (7.5)		11 (9.7)	1 (2.1)	
Intervention*	Unknown	0 (0.0)	4 (2.9)	<0.05	1 (0.9)	3 (6.4)	<0.05
	Arrest of bleeding:						
	- Abdominal wall	0 (0.0)	13 (8.1)		10 (8.9)	3 (6.4)	
	- Intra-abdominal	13 (23.6)	40 (25.0)		28 (24.8)	12 (25.5)	
	- CS scar	2 (3.6)	32 (20.0)		22 (19.5)	10 (21.3)	
	B-lymph procedure	1 (1.8)	8 (5.0)		7 (6.2)	1 (2.1)	
	Ligation	6 (10.9)	11 (6.9)		8 (7.1)	3 (6.4)	
	Hysterectomy	31 (56.4)	32 (20.0)		21 (18.6)	11 (23.4)	
	Drainage	3 (5.5)	9 (5.6)		7 (6.2)	2 (4.3)	
	Negative	2 (3.6)	19 (11.9)		16 (14.2)	3 (6.4)	
Number	Miscellaneous	10 (18.2)	24 (15.0)	0.26	18 (15.9)	6 (12.8)	0.44
	Unknown	0 (0.0)	6 (3.8)		3 (2.7)	3 (6.4)	
	1	43 (78.2)	129 (80.6)		88 (77.9)	41 (87.2)	
	≥2	10 (18.2)	30 (18.8)		24 (21.2)	6 (12.8)	
	Unknown	2 (3.6)	1 (0.6)		1 (0.9)	0 (0.0)	

CS, caesarean section; VD, vaginal delivery; sPPH, severe postpartum haemorrhage. Data is presented as number (%). *for 1st laparotomy.

DISCUSSION

This study, using a nationwide cohort of women who suffered SAMM, is the first to report national incidence rates of laparotomy after vaginal and caesarean birth. The risk of postpartum laparotomy was more than 16 times higher in women who gave birth by caesarean section compared to those who gave birth vaginally. The risk for laparotomy is lower when caesarean section is planned, but nevertheless still 10 times higher compared to vaginal birth.

Our results also indicate that laparotomy after childbirth may be an appropriate indicator of severe maternal outcome and quality marker for obstetric care. For example, 183 of 215 women (85.1%), fulfill the WHO Maternal Near Miss criterion of having had five or more units of blood transfused.¹ Based on a previously performed hypothetical experiment based study, 113 out of the 215 women (52.6%) would have died if massive blood transfusion had not been available, as is the case in many low-income countries.¹⁵

The rate of laparotomy after caesarean section in women with SAMM in the Netherlands (0.3%) appears relatively low compared to the literature (0.2-0.9%).²⁻¹¹ Since laparotomy after vaginal birth has not been studied before, the incidence we found for laparotomy following vaginal birth cannot be compared to other studies. The largest study of laparotomy following caesarean section was conducted in a single university medical center in Israel and included 80 women over a period of 20 years. Our study is unique because of its large sample size ($n = 215$), included in a relatively short time frame, and its prospective nationwide design.

Postpartum haemorrhage, placental abruption, uterine rupture and previous caesarean section were previously found to be associated with increased risk of relaparotomy.^{2, 4, 5, 10} We confirmed that the main proportion (68.4%) of all laparotomies was performed within 24 h after birth due to either intra-abdominal bleeding (46.0%) or postpartum haemorrhage (38.6%). One third of women (32.6%) had a previous caesarean section. Although placental abruption was not an endpoint, the majority of these cases are likely represented in the group of major obstetric haemorrhage since women would generally receive at least four units of blood. Thirteen women underwent laparotomy due to (suspected) uterine rupture. Infection or sepsis were not reported as outcomes of interest in previous studies. In our study, sepsis was the indication for laparotomy in 11 cases.

Our results need to be interpreted with caution since our study has several important limitations. First, the data from the LEMMoN-study are rather old and changes in incidence and risk may have occurred since data collection took place. However, we are not aware of any currently ongoing studies of postpartum laparotomy and think that our data are therefore still of considerable importance, since more up-to-date information is unlikely to become available for some time. A second limitation is that laparotomy was not a separate inclusion criterion as having severe acute maternal morbidity. This may introduce selection bias, since

women who were transfused less than five units of blood, those who did not have hysterectomy, embolization, or uterine rupture and those who were not admitted into intensive care may have been missed. These women would only have been included if the treating obstetrician still decided to include her as severe acute maternal morbidity. Nevertheless, the fact that laparotomies in women with SAMM will have been included validates our conclusions for this group. The fact that the overwhelming majority (149, 93.1%) of SAMM in our cohort occurred after birth provides an additional argument for the hypothesis that SAMM may often be related to the mode of birth. Some of these SAMM conditions may be more common after (difficult) caesarean versus vaginal birth and this is precisely what should be included in any clinical counseling about risks of caesarean section. We analyzed all vaginal births as one group and did not subdivide between instrumental and spontaneous births, postulating that the risk of laparotomy following a successful instrumental birth would not be elevated.

With regard to mode of birth (vaginal birth, emergency and planned caesarean section) there are some noteworthy results. In contrast with what is commonly assumed, the proportion of re-laparotomy due to intraabdominal bleeding was comparable for planned and emergency caesarean section. The timing to perform laparotomy is more often between two and seven days after caesarean section than after vaginal birth, where laparotomy is performed earlier. In total, 140 out of 160 (88%) laparotomies after caesarean birth were performed within four days. This means that clinicians should be particularly cautious of the occurrence of complications that may lead to laparotomy in the first four days after caesarean section. It should also be underlined that almost 20% of women had more than one laparotomy after birth and that in 10% of all laparotomies exploration was performed without any therapeutic intervention.

Caesarean birth rates have been increasing for the past decades up to 47.6% in China and 50% in Brazil.^{16, 17} In the Netherlands, although rates are relatively low, the proportion of caesarean section has risen from 11% to 16% between 1999 and 2012.¹⁸ A recent study in China showed that 40% of caesarean sections were performed without medical indication.¹⁹ Considering the elevated risk of laparotomy after caesarean section, such developments will inevitably lead to a rise in unfavorable outcomes. This adds to the results of previous studies in which caesarean birth was also found to be associated with a clearly elevated risk of maternal morbidity and mortality compared to vaginal birth, regardless of the indication.^{12, 13, 20} Our study addresses both short and long-term adverse effects of caesarean section: the complications as a result of initial surgery requiring laparotomy, and the complications in subsequent pregnancies, such as abnormally invasive placentation and the risks of birth in presence of a uterine scar.^{21–23} Women with vaginal birth after previous caesarean section are over-represented (18/55 women, 34.0%) compared to the general Dutch pregnant population (6.0%).¹⁴

WHO has recently stated again that national caesarean birth rates above 10% are not associated with a further decrease in maternal or neonatal mortality.²⁴ It is alarming that caesarean rates are still on the rise in most countries.¹⁶ These rates may be difficult to curb, but it is important to realise that every cut may have its cost. Adverse maternal outcome, including laparotomy, should be kept in mind when caesarean section is considered and women are counselled for mode of birth, particularly when maternal request is the only indication.

CONCLUSION

Main finding of this nationwide cohort study is that the risk of postpartum laparotomy in women with severe acute maternal morbidity in the Netherlands was much higher after caesarean section compared to vaginal birth. This information must be taken into account by clinicians when considering mode of birth and can be interpreted as yet another reason to reduce unnecessary caesarean sections.

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Incidence, Indications, Risk Factors and Outcomes of Emergency Peripartum Hysterectomy Worldwide. A Systematic Review and Meta-analysis

A.F. Kallianidis, D. Rijntjes, C. Brobbel, O.M. Dekkers, K.W.M. Bloemenkamp,
T. van den Akker

Obstetrics & Gynecology 2023;141(1):35-48

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ABSTRACT

Objective: To describe the incidence, indications, risk factors, outcomes, and management of emergency peripartum hysterectomy globally and to compare outcomes among different income settings.

Data sources: PubMed, MEDLINE, EMBASE, Clinical-Trials.gov, Cochrane Library, Web of Science, and Emcare databases up to December 10, 2021. **METHODS OF STUDY SELECTION:** Update of a systematic review and meta-analysis (2016). Studies were eligible if they reported the incidence of emergency peripartum hysterectomy, defined as surgical removal of the uterus for severe obstetric complications up to 6 weeks postpartum. Title and abstract screening and full text review were performed using Endnote data management software. Of 8,775 articles screened, 26 were included that were published after 2015, making the total number of included studies 154. A subanalysis was performed for the outcomes of interest per income setting.

Tabulation, integration, and results: The meta-analysis included 154 studies: 14,409 emergency peripartum hysterectomies were performed in 17,127,499 births in 42 countries. Overall pooled incidence of hysterectomy was 1.1 per 1,000 births (95% CI 1.0–1.3). The highest incidence was observed in lower middle-income settings (3/1,000 births, 95% CI 2.5–3.5), and the lowest incidence was observed in high-income settings (0.7/1,000 births, 95% CI 0.5–0.8). The most common indications were placental pathology (38.0%, 95% CI 33.9–42.4), uterine atony (27.0%, 95% CI 24.6–29.5), and uterine rupture (21.2%, 95% CI 17.8–25.0). In lower middle-income countries, uterine rupture (44.5%, 95% CI 36.6–52.7) was the most common indication; placental pathology (48.4%, 95% CI 43.5–53.4) was most frequent in high-income settings. To prevent hysterectomy, uterotonic medication was used in 2,706 women (17%): 53.2% received oxytocin, 44.6% prostaglandins, and 17.3% ergometrine. Surgical measures to prevent hysterectomy were taken in 80.5% of women, the most common being compressive techniques performed in 62.6% (95% CI 38.3–81.9). The most common complications were febrile (29.7%, 95% CI 25.4–34.3) and hematologic (27.5%, 95% CI 20.4–35.9). The overall maternal case fatality rate was 3.2 per 100 emergency peripartum hysterectomies (95% CI 2.5–4.2) and was higher in lower middle-income settings (11.2/100 emergency peripartum hysterectomies 95% CI 8.9–14.1) and lower in high-income settings (1.0/100 emergency peripartum hysterectomies 95% CI 0.6–1.6).

Conclusion: Substantial differences across income settings exist in the incidence of emergency peripartum hysterectomy. Women in lower-income settings have a higher risk of undergoing emergency peripartum hysterectomy and suffer more procedure-related morbidity

INTRODUCTION

Emergency peripartum hysterectomy (EPH), is the surgical procedure of removing the uterus due to severe complications during pregnancy, birth or postpartum. When all conservative measures have failed to control massive obstetric haemorrhage or life-threatening sepsis, EPH is used as a last-resort intervention. Although EPH can be a life-saving operation, it is uncommon in modern obstetrics.¹ However, since rates of caesarean section and, consequently, placenta accreta spectrum in pregnancies after a previous caesarean section are increasing, the global incidence of EPH is likely to rise as a result.¹⁻³ Resorting to this intervention must follow considerations of risks and benefits of the procedure, but undue delays in performing it may contribute to a woman's death.

We previously identified extreme differences in incidence, indications, risk indicators and outcomes of EPH between high- and low-income countries.¹ Prevalence of EPH tends to be higher in low- and lower middle-income countries. Main indications for EPH are massive obstetric haemorrhage due to placental pathology, uterine atony or uterine rupture, followed by puerperal sepsis.^{4,5}

Since the previous version of this review, new studies about EPH have been published, including several population-based studies, which were very rare at the time of the previous review. Therefore, we performed an update of our previous systematic review and meta-analysis. The aim of this study was firstly, to estimate overall prevalence of EPH and compare prevalence across different income settings and secondly, to describe indications, risk indicators, outcomes and management of EPH and compare these between income settings.

SOURCES

This is an update of the systematic review and meta-analysis previously published by van den Akker *et al.*¹ A systematic search of PubMed, MEDLINE, Embase, Clinicaltrials.gov, Cochrane Library, Web of Science and Emcare was performed up to December 10, 2021. (For search strategy see Appendix 1, available online at <http://links.lww.com/AOG/C968>).

Study selection

Study selection was performed independently by two of the authors (D.R. and A.F.K.). Studies published before 2015 were previously selected and included.¹ First, articles were assessed based on title and abstract. Selected studies were further assessed for eligibility based on the full text.

We used the same inclusion criteria as before; in brief, studies were included if they reported the incidence, management, or outcomes of emergency peripartum hysterectomy up to 6 weeks postpartum in a hospital, region, or country. Emergency

peripartum hysterectomy was defined as partial or total surgical removal of the uterus for severe obstetric complications. Case-control, cohort, and cross-sectional study designs were eligible.

Excluded study designs were case reports, case series (sample size less than 10), comments, and personal communications. Other exclusion criteria were studies not reported in English and those published in journals with an impact factor less than 1. Studies were also excluded if they did not indicate the absolute number of births and emergency peripartum hysterectomies. Where possible, hysterectomies for malignancies or other non-obstetric indications were excluded from the calculation of incidence, indications, and outcomes. So-called “elective” or “planned” hysterectomies were not excluded, because most often these were performed for placenta accreta spectrum pathology.

Data extraction was performed by two authors (D.R. and A.F.K.). Data on incidence, indications, complications, maternal characteristics, and preventive measures were extracted and combined with data from the previous systematic review.¹ If studies reported on the same study population, only the most recent study was included.

The main outcome was overall pooled incidence. Incidence was calculated per income setting as well as for all countries separately. The income setting of a country was based on the gross national income per capita. Countries were classified as low-income (\$1,045 or less), lower middle-income (\$1,046–4,095), upper middle-income (\$4,096–12,695), or high-income (\$12,696 or more).⁶

Secondary outcomes were indications, risk factors, outcomes, and management characteristics of emergency peripartum hysterectomy. Indications for emergency peripartum hysterectomy were subdivided into placental pathology (placenta accreta spectrum, placenta previa, combined placental pathology, or placental abruption), uterine atony, uterine rupture, unspecified haemorrhage, infection, cervical tear or laceration, leiomyomas with major obstetric haemorrhage, disseminated intravascular coagulation, hematoma, abnormal location of pregnancy, other, and unknown. Outcomes included transfusion of any type, intensive care unit admission, complications, and maternal morbidity and mortality. Characteristics of emergency peripartum hysterectomy described were hysterectomy type (total or subtotal), preventive measures used before emergency peripartum hysterectomy (medical or surgical), duration of surgery, blood loss, and additional procedures performed. Indications, outcomes, and management characteristics were stratified based on income setting, and the highest and lowest proportions were described. Maternal characteristics were antenatal care registration, age, and parity.

Risk-of-bias assessment was performed for all included articles. The COSMOS-E (Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology) methodology was followed to create study-specific guidelines for describing the risk of bias of included articles.⁷ These guidelines assisted in

describing selection, information, and confounding biases (Appendix 2, available online at <http://links.lww.com/AOG/C968>).

Sources of selection bias considered were extent of the catchment area, length of postpartum inclusion period, definition of emergency peripartum hysterectomy, definition of study time period, and gestational age limits. For case–control studies, the selection process and comparability by design were also taken into account. Potential causes of information bias were duration of the follow-up period and the source of data extraction. Possible confounders included age and parity, because they are commonly accepted to influence a woman’s risk of emergency peripartum hysterectomy.

Overall weighted pooled incidence was calculated using a random-effects analysis with 95%CI. Proportions of indications, outcomes, maternal, and procedure characteristics were pooled using a random effects analysis. Continuous variables were examined

with pooled mean difference and 95% CI (inverse variance weighting). We used R software for statistical computing.

RESULTS

In total, 154 studies were included (Fig. 1); 128 had been included in the previous meta-analysis.¹ This update includes 26 additional studies and presents data for an additional 7,741 women in 22 nations^{8–33} (Appendix 3, available online at <http://links.lww.com/AOG/C968>). Eight of the new studies were from countries from which we previously did not have data: Belgium, France, Germany, Romania, Slovakia, Sweden, Iceland, and Papua New Guinea. All studies combined included a total of 15,599 women who underwent emergency peripartum hysterectomy—193 (1.2%) from low-income settings, 2,403 (15.4%) from lower middle–income settings, 1,975 (12.7%) from upper middle–income settings, and 11,028 (70.7%) from high-income settings.

Overall, risk of bias was considered low in 25 studies (16.2%), moderate in 66 studies (42.8%), and high in 63 studies (40.5%) (Appendix 2, <http://links.lww.com/AOG/C968>). Risk of selection bias was considered high in 55 of the studies (35.7%). Risk of information bias was low in 106 studies (68.8%), moderate in 35 studies (22.7%), and high in 13 studies (8.4%). Fifteen of 24 case–control studies did not account for confounding by age or parity. Risk of confounding bias was thus assessed as high in these 15 studies, moderate in two studies, and low in seven studies.

Seventeen of the included studies were population- based.^{17–19,22,23,27,34–45} The other 137 were hospital-based, of which six were multicenter studies. Two population-based studies reported data from more than one country.^{18,19} Information on these countries was subdivided and analyzed separately.

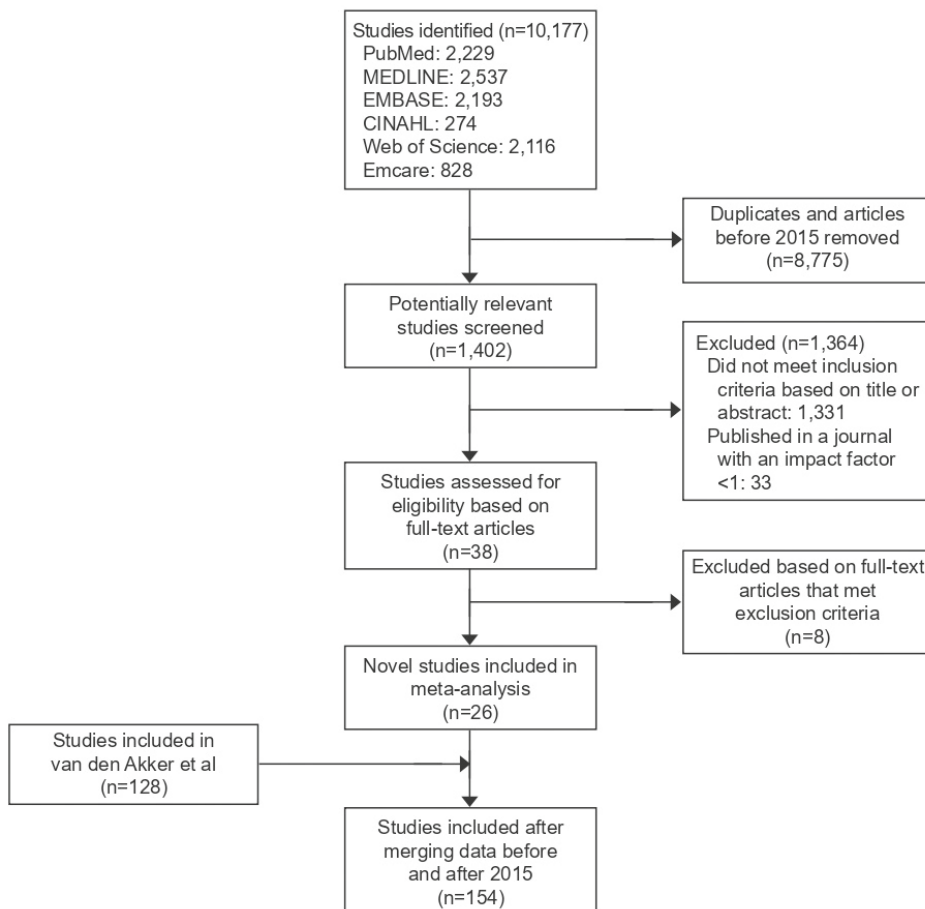


Figure 1. Flowchart showing selection of studies included in the meta-analysis.

In 89 studies, case definitions of emergency peripartum hysterectomy were described. Definitions varied widely among studies. In 13 studies, women undergoing hysterectomy up to 6 weeks postpartum were included,^{11,17,30,31,41,44–51} 54 studies included women up to 24 hours postpartum,^{9,12,14–16,25,28,29,33,34,38,39,52–94} and 22 studies included women within another time range (but within 6 weeks).^{18,19,21,27,32,35,36,40,42,89,95–106} In 31 studies, only emergency peripartum hysterectomies beyond 24 weeks of gestation were included.^{11,12,31–33,40,47,50,53,58,71–73,76–78,83,86,90,97,98,100,107–117} Another 20 studies excluded women based on limits other than 24 weeks of gestation.^{9,18,19,23,24,27,34,41,46,48,51,57,59,64,67,69,85,87,118,119} Nine studies included peripartum hysterectomies regardless of gestational age.^{37,44,45,91,102,117,120–123} All other studies (n=91) lacked specific exclusion criteria for gestational age. There were no new case–control studies since 2015. Information on indications, complications, and

preventive measures for hysterectomy was extracted from medical records in 130 studies.

The incidence of emergency peripartum hysterectomy was reported in 147 studies; seven studies were not included because they reported only caesarean^{64,70,106} or postpartum hysterectomies⁸⁷ or did not report an incidence at all.^{42,89,124} Altogether, 14,409 emergency peripartum hysterectomies were performed over 17,127,499 births in 42 countries. The overall weighted incidence was 1.1 cases per 1,000 births (95% CI 1.0–1.3).

The reported incidence differed considerably across income settings (Table 1). The highest incidence was observed in lower middle-income settings (3.0, 95% CI 2.5–3.5), and the lowest incidence was observed in high-income settings (0.7, 95% CI 0.5–0.8). Incidence varied from 0.2 per 1,000 births in Denmark,³⁵ Ireland,¹⁰³ Norway,⁷⁸ and Turkey⁶⁷ to 10.1 per 1,000 births in India.¹²³ Figures 2 and 3 show incidence of emergency peripartum hysterectomy worldwide and in Europe, respectively.

Table 1. Prevalence per Income Setting*

Income Setting	No. of Studies	No. of Emergency Peripartum Hysterectomies	No. of Women	Incidence (95% CI)
Low	2	193	93,355	1.5 (0.6 - 4.0)
Lower middle	43	2,257	849,772	3.0 (2.5 - 3.5)
Upper middle	34	1,924	2,573,707	0.9 (0.7 - 1.1)
High	75	10,035	13,610,665	0.7 (0.5 - 0.8)
Total	154	14,409	17,127,499	1.1 (1.0 - 1.3)

* Weighted incidence per 1,000 births using random-effects model.

Maternal age ranged from 11⁶ to 54^{22,47} years, with an overall mean age of 32.1 years (95% CI 31.9–32.8). The overall mean gestational age was 36^{5/7} weeks (95% CI 35 3/7–37 1/7 weeks). Parity was reported in 105 studies, representing 7,555 women: 6,324 (83.7%) women were multiparous.

Prior uterine surgery was described in 101 studies, representing 6,841 women. A total of 3,319 (49.8%, 95% CI 45.1–54.6) women had previously undergone caesarean delivery. The total number of caesarean deliveries was provided for 1,362 women; 671 (51.0%, 95% CI 44.4–57.7) of these women had had two or more caesarean deliveries. Other uterine surgery (eg, myomectomy, curettage, hysteroscopic septum resection, cornual resection) had previously been performed in 556 women (0.4%, 95% CI 0.1–1.2). In 44 studies, registration status was mentioned: 877 of 2,251 women (37.4%, 95% CI 28.5–47.4) had been registered for antenatal care. The lowest proportion of women registered in the first trimester was in lower middle-income

settings (490/1,461, 29.4%, 95% CI 22.31–37.6), followed by 76 of 165 (46.1%) women in low-income settings, based on one study only.

Indications for emergency peripartum hysterectomy were described in 157 studies for 9,258 women (Table 2). The most common indications were placental pathology (38.0%, 95% CI 33.9–42.4), uterine atony (27.0%, 95% CI 24.6–29.5), and uterine rupture (21.2%, 95% CI 17.8–25.0). The distribution of these indications varied considerably across income settings. The most common indication in lower middle-income settings was uterine rupture (44.5%, 95% CI 36.5–52.7); in high-income countries it was placental pathology (48.4%, 95% CI 43.5–53.4) (Table 3).

Measures that were taken to prevent hysterectomy were described for 3,401 women in 46 studies (including one multinational study¹⁸). Uterotonic medication was given to 2,706 women: oxytocin in 1,439 (53.2%), prostaglandins in 1,207 (44.6%), and ergometrine in 467 (17.3%). Five hundred seventy-five women (21.2%) received uterotonics without further specification. Surgical measures to prevent emergency peripartum hysterectomy were described in 2,740 women (80.5%) (Table 4). Compressive surgical measures were the most commonly performed interventions before emergency peripartum hysterectomy (62.6%, 95% CI 38.3–81.9) and included bimanual compression in 235 women (98.9%, 95% CI 6.6–100.0), vaginal or uterine packing in 266 (20.5%, 95% CI 14.3–28.5), uterine balloon tamponade in 382 (16.3%, 95% CI 11.9–22.0), and uterine compression sutures in 383 (14.3%, 95% CI 9.3–21.4).

The type of hysterectomy was known for 6,240 women; total abdominal hysterectomy was performed in 3,128 (50.1%) and subtotal hysterectomy in 3,112 (49.8%). Type of hysterectomy varied among income settings; total abdominal hysterectomy was performed in 175 of 193 (90.6%) of the surgeries in low-income countries, 783 of 2,154 (36.3%) in lower middle-income countries, 752 of 1,463 (51.4%) in upper middle-income countries, and 1,418 of 2,492 (56.9%) in high-income countries.

Additional surgery performed during or after hysterectomy was detailed for 5,248 women. Repeat laparotomy was required in 434 patients (8.9%, 95% CI 6.9–11.6) (Table 5). Relaparotomy was performed most often in high-income countries (265/2,813, 10.9%, 95% CI 8.2–14.9), followed by upper middle-income (139/1,492, 9.7%, 95% CI 6.2–16.1), lower middle-income (28/750, 7.4%, 95% CI 3.5–11.1), and low-income (2/193, 1.0%, 95% CI 0.2–4.2).

Weighted mean operating time was 137 minutes (95% CI 132–153). The weighted mean volume of blood loss during surgery was 3.9 L (95% CI 3.3–4.2).

Table 2. Indications for Emergency Peripartum Hysterectomy

Indication	Studies (n)	Women (n/N)	Proportion (95% CI)
Placental pathology	157	3,791/9,213	38.0 (33.9–42.4)
Placenta accreta spectrum	130	2,293/8,115	23.9 (20.5–27.7)
Placenta previa	71	809/4,822	13.9 (11.8–17.1)
Combined or unspecified placental pathology	32	416/1,606	26.1 (20.5–32.5)
Placental abruption	42	147/2,913	5.2 (4.0–6.9)
Uterine atony	143	2,638/8,157	27.0 (24.6–29.5)
Uterine rupture ^a	140	2,019/8,421	21.2 (17.8–25.0)
Unspecified haemorrhage	48	397/2,549	13.3 (9.8–17.9)
Infection ^b	41	170/3,083	4.4 (3.9–6.0)
Cervical tear or laceration	25	99/2,250	4.0 (2.7–5.9)
Disseminated intravascular coagulation	15	104/1,551	4.0 (1.8–8.8)
Hematoma ^c	18	41/1,117	4.3 (3.2–5.8)
Abnormal location of pregnancy ^d	8	14/465	3.0 (1.8–5.0)
Leiomyomas with major obstetric haemorrhage	30	65/2,970	2.3 (1.6–3.1)
Other ^e	22	55/1,590	3.8 (2.7–5.4)
Unknown	14	149/2,313	3.7 (2.0–6.8)

Proportions calculated using random-effects model and exceed 100% because more than one indication was possible.

a Includes both uterine rupture and extension of uterine incision.

b Includes endometritis, pelviperitonitis, chorioamnionitis, gangrenous uterus, puerperal sepsis, pelvic abscess and haemorrhage due to these infections.

c Includes broad ligament, retroperitoneal and unspecified hematoma.

d Includes abdominal, cervical, molar and ruptured cornual pregnancy.

e Includes avulsion of uterine artery, uterine inversion, septic abortion, MTP perforation, malignancy with haemorrhage, sterilization, arteriovenous malformation, uterine anomaly, retained tissue.

Table 3. Indications per Income Setting

Income Setting	Placental Pathology		Uterine Atony		Uterine Rupture	
	Proportion (95% CI)	Studies (n)	Proportion (95% CI)	Studies (n)	Proportion (95% CI)	Studies (n)
Low	25 (-)	1	36 (-)	1	25 (-)	1
Lower-middle	20.7 (15.8–26.8)	44	20.9 (17.6–24.7)	38	44.5 (36.6–52.7)	44
Upper-middle	41.8 (33.3–50.9)	35	31.0 (25.0–37.6)	33	13.8 (9.8–19.2)	34
High	48.4 (43.4–53.4)	77	28.9 (25.7–32.3)	71	9.3 (7.0–12.1)	77

Proportion of indications per 100 emergency peripartum hysterectomies, calculated using random-effects model.

Table 4. Mechanical Measures to Prevent Emergency Peripartum Hysterectomy

Measure	No. of Studies	No. of Patients (n/N)	Proportion (95% CI)*
Fundal massage	6	210/319	83.8 (33.7–98.1)
Compression ^a	36	1,274/2,700	62.6 (38.3–81.9)
<i>Bimanual compression</i>	7	235/686	98.9 (6.6–100)
<i>Vaginal/uterine packing</i>	21	266/1,195	20.5 (14.3–28.5)
<i>Uterine balloon tamponade</i>	20	382/1,870	16.3 (11.9–22.0)
<i>Uterine compression sutures^b</i>	26	383/2,367	14.3 (9.3–21.4)
Artery ligation ^c	38	603/2,407	22.4 (16.4–29.8)
Oversewing of placental bed ^d	17	190/985	19.1 (13.4–26.5)
Manual removal of placenta ^e	8	68/493	10.8 (6.1–18.4)
Uterine artery embolization	14	136/1,569	7.9 (5.5–11.2)
Curettage	10	116/583	2.2 (8.0–48.1)
Other ^f	9	143/787	15.9 (10.7–23.0)

* Weighted proportions per 100 emergency peripartum hysterectomies using random-effects model.

a Including eight cases in whom compression was unspecified.

b Includes B-Lynch procedure and other or unspecified procedures.

c Includes ligation of the uterine, ovarian, internal iliac and hypogastric arteries.

d Includes suturing of bleeding points and cervical lacerations.

e Includes examination under anaesthesia.

f Includes placenta left in-utero, intraabdominal packing, internal iliac artery balloon placement, hot saline packs, lower segment belt, securing of uterine angles and unspecified measures.

Table 5. Procedures in Addition to Hysterectomy

Procedure	No. of Studies	No. of Patients (n/N)	Proportion (95% CI)*
Salpingo-oophorectomy	33	234/2,244	10.1 (8.2–12.5)
Relaparotomy	63	434/4,014	9.0 (6.9–11.6)
Bladder or ureteral repair	23	115/1,156	8.6 (6.1–12.0)
Artery ligation or embolisation	7	35/406	8.2 (3.9–16.5)
Other ^a	5	20/308	6.8 (2.8–15.4)

* Weighted proportions per 100 emergency peripartum hysterectomies using random-effects model. a Includes abdominal packing, bowel repair, appendectomy, uterine curettage and unspecified procedures.

Most women undergoing hysterectomy (4,930/5,420, 91.4%) received transfusion of red blood cells, with a weighted mean of 8 units per person (95% CI 7.1–8.9). Two studies mentioned salvage of blood cells, accounting for 12 of 143 women included (8.4%).^{23,38} Fresh frozen plasma was administered to 847 of 1,431 women (59.1%). Other transfusions given to treat coagulopathy were platelets in 213 of 407 women (52.3%), tranexamic acid in 154 of 486 (31.7%), fibrinogen in 135 of 707 (19.1%), cryoprecipitate in 30 of 204 (14.7%), recombinant factor VIIa in 90 of 1,125 (8.0%), and prothrombin complex in 3 of 126 (2.4%).

The proportion of women receiving transfusion of packed red blood cells differed among income settings: 79 of 165 in low-income settings (47.8%), 1,248 of 1,285 (97.1%) in lower middle-income settings, 783 of 816 (95.6%) in upper middle-income settings, and 2,816 of 3,154 (89.2%) in high-income settings. The mean number of units of red blood cells given per person increased with income setting; 2.4 in low-income settings, 4.4 in lower middle-income settings, 7.3 in upper middle-income settings, and 9.7 in high-income settings.

The duration of hospital stay ranged from 6 hours¹¹ to 240 days¹²⁵; the pooled average time of admission was 9.2 days (95% CI 8.4–10.1). A total of 1,588 of 3,438 (46.2%) women were admitted into the intensive care unit, with a mean stay of 2.4 days (95% CI 2.0–3.2).

Information on complications was given in all but 24 studies,^{19,21,22,25,26,28,34,41,42,57} representing ^{63,66,68,69,82,89,93,104,111, 126–129} a total of 7,469 women (Table 6). The most common complications described were febrile morbidity in 1,175 women (29.7%, 95% CI 25.4–34.3), hematologic in 1,787 women (27.5%, 95% CI 20.4–35.9), and infection in 713 women (12.7%, 95% CI 10.0–15.9).

Maternal case fatality rates were given in all but seven studies.^{19,22,46,79,96,113,128} Overall, maternal death occurred in 453 of 9,814 hysterectomies, resulting in a case fatality rate of 3.2% (95% CI 2.5–4.2). Maternal case fatality rates differed among income settings; low- and lower middle-income countries had mean case fatality rates of 9.3% (95% CI 5.9–14.3) and 11.2% (95% CI 9.0–14.0), respectively, whereas, in upper middle- and high-income countries, case fatality rates were 3.9% (95% CI 2.8–5.7) and 1.0% (95% CI 0.5–1.6), respectively. The highest maternal case fatality rate was reported in Nigeria: 13 of 22 women (59.1%) undergoing hysterectomy died.

Data on perinatal death were provided in 94 studies. The overall perinatal case fatality rate was 19% (14.4–24.9). The perinatal case fatality rate was 14.3% (95% CI 4–32.7) in low-income settings, 54.7% (95% CI 46.7–62.6) in lower middle-income settings, 18% (95% CI 13.9–24.8) in upper middle-income settings, and 5.6% (95% CI 4.1–7.5) in high-income settings.

No new case-control studies were included. Appendix 4 (available online at <http://links.lww.com/AOG/C968>) describes risk factors.

Table 6. Complications After Emergency Peripartum Hysterectomy

Complication	No. of Studies	No. of Patients (n/N)	Proportion (95% CI)*
Febrile morbidity	81	1,175/4,252	29.7 (25.4–34.3)
Hematologic ^a	115	1,787/4,058	27.5 (20.4–35.9)
Infection ^b	77	647/4,372	12.7 (10.0–15.9)
Wound ^c	88	643/4,643	11.8 (9.8–14.3)
Genitourinary ^d	109	713/6,531	9.9 (8.5–11.5)
Pulmonary ^e	38	179/2,229	6.1 (4.1–8.9)
Psychological disturbance	16	60/990	5.9 (3.7–9.3)
Gastrointestinal ^f	55	170/2,827	5.5 (4.2–7.2)
Renal ^g	45	181/3,428	4.2 (3.0–6.4)
Cardiovascular ^h	31	69/2,504	3.2 (2.4–4.4)
Thromboembolic ⁱ	35	67/2,137	3.2 (2.5–4.3)
Neurologic ^j	6	8/295	3.0 (1.5–5.9)
Endocrinologic ^k	5	8/243	3.3 (1.7–6.4)
Other ^l	19	93/1728	4.6 (2.6–7.9)

Proportions per 100 EPH.

a Includes bleeding, anemia, hypovolemic shock, hematomas and coagulopathy.

b Includes septicemia, (pelvic, subphrenic, vaginal cuff) abscess, thrombophlebitis, respiratory infection, urinary infection, UTI and peritonitis.

c Includes dehiscence, hematoma, infection or sepsis and incisional hernia.

d Includes bladder or ureteric injury, fistula, incontinence and urine retention.

e Includes atelectasis, pneumothorax, pulmonary edema, pleural effusion, acute respiratory distress syndrome and ventilation requirement.

f Includes paralytic ileus, jaundice, liver dysfunction, ascites, bowel injury and intestinal obstruction.

g Includes acute renal failure, hydronephrosis and oliguria.

h Includes cardiac arrest, myocardial infarction, heart failure and cardiomyopathy.

i Includes deep vein thrombosis, pulmonary embolism, air embolism and amniotic fluid embolism.

j Includes stroke, seizure and coma.

k Includes Sheehan's syndrome and premature ovarian failure.

l Includes prolonged pain, reactive splenomegaly, multiorgan failure, compartment syndrome, bed sores, anaphylactic shock and cortical blindness.

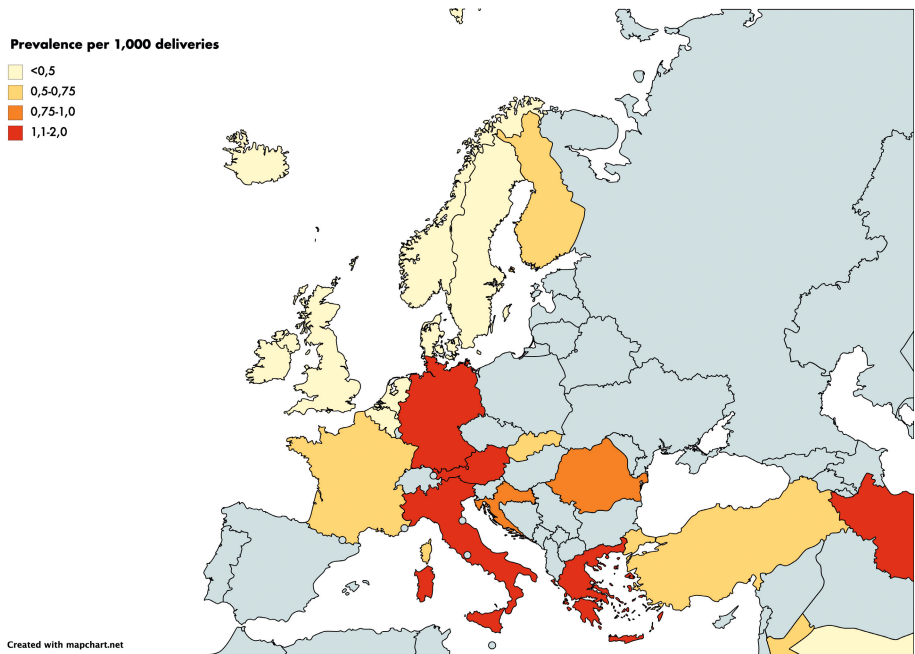


Figure 2. Map of Europe showing the incidence of emergency peripartum hysterectomy per country. Image created with ©mapchart.net

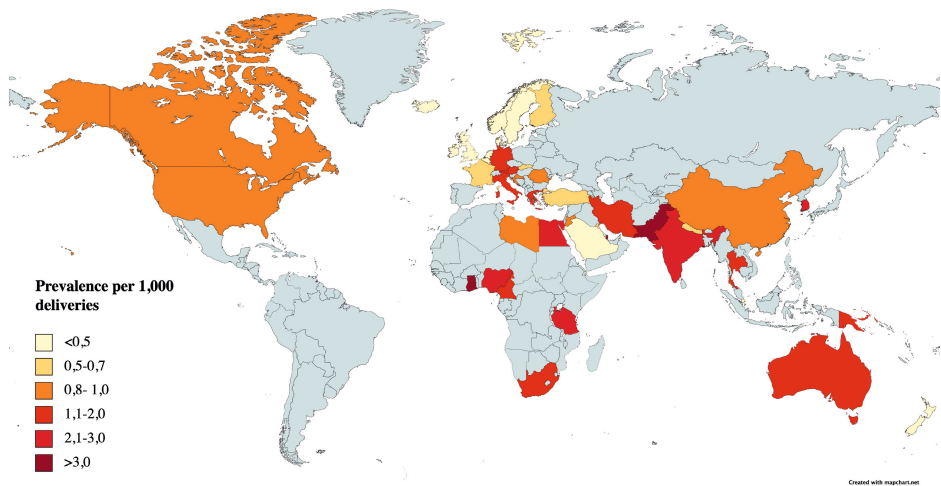


Figure 3. World map showing the incidence of emergency peripartum hysterectomy per country. Image created with ©mapchart.net

DISCUSSION

Marked differences in incidence, indications, management, and outcomes of emergency peripartum hysterectomy that were previously identified remain among countries with different income levels. Of the 26 newly included studies, a substantial proportion were population-based studies, which contributed to the validity of the present review. Overall, the incidence of emergent peripartum hysterectomy was 1.1 per 1,000 births, with the highest incidence observed in lower middle-income settings (3.0/1,000 births). The most common indication in low-income settings was uterine rupture; in high-income settings, it was placental pathology. Half of all women undergoing emergency peripartum hysterectomy previously underwent caesarean delivery.

There was a considerable difference in incidence of emergency peripartum hysterectomy among income settings. International differences in the incidence of emergency peripartum hysterectomy may be caused by variations in maternal age and health status, caesarean delivery rates, clinical management of major obstetric haemorrhage, study setting, and definition and availability of other surgical or radiologic interventions.^{1,130,131} Data suggest that the incidence also varies among high-income countries. This may be attributed to large geographic distances within countries; countries with spread out populations (eg, Canada, Australia) seem to have a higher incidence of emergency peripartum hysterectomy. Transport to health care facilities may result in longer delay, with women presenting already in shock in case of haemorrhage necessitating prompt intervention, or transport to a referral hospital with options for uterus-sparing interventions being logistically impossible.

For low-income countries, the incidence of emergency peripartum hysterectomy should be interpreted with caution because it was based on only two hospital-based studies from Tanzania (low-income during the study period) and Nepal. Low-income countries face multiple challenges, including difficulties for women to access health care facilities, limited availability of conservative management options, and low numbers of skilled birth attendants. Moreover, research output is limited compared with higher income countries and might be published in lower impact journals, thereby making it harder to identify. This makes the representativity of our findings for these countries limited.

Worldwide, placental pathology was the most common indication for emergency peripartum hysterectomy. This is likely a result of the increasing rates of caesarean delivery.¹³² Indications varied among income settings. Uterine rupture was most common indication in lower middle-income settings, and placental pathology was most frequently observed in high-income settings. This difference may be attributable to higher rates of obstructed labor, lack of monitoring of labor progress, and reduced accessibility and availability of maternity care in lower-income settings.¹³³

Previous studies have demonstrated that registration for antenatal care is a protective factor for emergency peripartum hysterectomy.¹³⁴ Although many women were registered as not having received antenatal care, the association between antenatal care and emergency peripartum hysterectomy remains unclear because of possible lack of documentation. First, it was not possible to distinguish truly unregistered women from women referred who received antenatal care outside the facility where emergency peripartum hysterectomy was performed. Also, antenatal care registration was mentioned almost exclusively for low- and lower middle-income countries, where women may have a higher chance of not accessing antenatal care.

Postoperative maternal morbidity and mortality rates were considerable. A quarter of the women had infectious or bleeding complications. This is likely due to the high volume of blood loss associated with emergency peripartum hysterectomy (average volume of blood loss 3.9 L).¹³⁵ The highest rates of blood transfusion were found in lower middle-income settings. The highest quantities of red blood cells, however, were transfused in high-income settings. This inverse relationship may be explained by fewer alternative preventive measures and a limited availability of blood transfusion in lower-income settings.¹³⁶ The ability to transfuse a woman will undoubtedly influence the decision to perform emergency peripartum hysterectomy, which may happen earlier in the course of haemorrhage in some settings as a result. The same may happen when few other conservative management options are available. Access to safe blood transfusion is likely to be an efficient and cost-effective intervention to reduce maternal mortality associated with emergency peripartum hysterectomy in lower income settings.

There was also a remarkable difference in perinatal mortality among income settings; rates in lower income settings were disproportionately higher compared with high-income settings. Risk of perinatal death was up to nine times higher in lower middle-income compared with high-income settings. These impressive inequities can be explained by resource limitations and delays in accessing maternity care, as well as by inadequate management compounded by a lack of skilled birth attendants.^{133,137,138}

To our knowledge, this is the largest and most comprehensive review to date on incidence, indications, and outcomes of emergency peripartum hysterectomy. It provides a robust global overview of emergency peripartum hysterectomy through reporting on data from 42 countries. Our study includes a thorough assessment of the quality of included studies. Whereas the previous article used an adaptation of the Newcastle-Ottawa scale, we assessed all 154 studies again, this time using the COSMOS-E criteria.

Nevertheless, this study has several limitations. First, women from low-income settings were underrepresented in this meta-analysis. Second, this meta-analysis includes few population-based studies. However, population-based studies have their own limitations, such as unknown data quality, data collection not usually

done by the researchers, and possibly missing confounder information. Third, in the absence of individual data, multivariable analysis was not possible and multiple or sequential measures could not be described, as often occurs in practice. Fourth, risk of bias was assessed as high in 35.7% of the studies. We did not exclude studies after quality assessment, to calculate a more accurate estimate of mean values. Also, by excluding such a high number of studies, we deemed that estimations of incidence would become problematic.

These data suggest a number of considerations. First, there is a need for a universal definition for emergency peripartum hysterectomy. We suggest that future studies on emergency peripartum hysterectomy include all hysterectomies up to 6 weeks postpartum, because most infectious complications will arise later than 24 or 48 hours postpartum.¹⁷ Also, almost none of the studies included hysterectomies in the first trimester due to abortive complications, which would also be of importance. Second, literature on emergency peripartum hysterectomy in low-income countries and in South America, Asia, and Africa is scarce. Clearly more data are needed from these regions. Third, we observed an increase in the number of population-based studies that were included compared with 7 years ago. Although population-based studies provide the most accurate representation of a country's incidence, use of routinely collected data may have some degree of inaccuracy. Forth, this review underlines the importance of reducing caesarean delivery rates, which remain the most important risk factor for placenta accreta spectrum, uterine rupture, and massive obstetric haemorrhage. Fifth, because placental pathology is the most frequent indication for emergency peripartum hysterectomy in high-income settings, we recommend that increased efforts should be undertaken to care for these complex patients.

To conclude, considerable inequity exists in incidence and associated morbidity and mortality of emergency peripartum hysterectomy across the world. This inequity can be reduced only by improving accessibility, availability, and quality of care for the vulnerable group of pregnant women globally.

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Epidemiological analysis of peripartum hysterectomy across nine European countries

A.F. Kallianidis, A. Maraschini, J. Danis, L.B. Colmorn, C. Deneux-Tharaux, S. Donati, M. Gissler, M. Jakobsson, M. Knight, A. Kristufkova, P.G. Lindqvist, G. Vandenberghe, T. van den Akker

On behalf of the International Network of Obstetric Survey Systems

Acta Obstetricia et Gynecologica Scandinavica. 2020;99(10):1364-1373.



ABSTRACT

Introduction: Peripartum hysterectomy is a surgical procedure performed for severe obstetric complications such as major obstetric haemorrhage. The prevalence of peripartum hysterectomy in high-resource settings is relatively low. Hence, international comparisons and studying indications and associations with mode of birth rely on the use of national obstetric survey data. Objectives were to calculate the prevalence and indications of peripartum hysterectomy and its association with national caesarean section rates and mode of birth in nine European countries.

Material and methods: We performed a descriptive, multinational, population-based study among women who underwent peripartum hysterectomy. Data were collected from national or multiregional databases from nine countries participating in the International Network of Obstetric Survey Systems. We included hysterectomies performed from 22 gestational weeks up to 48 hours postpartum for obstetric haemorrhage, as this was the most restrictive, overlapping case definition between all countries. Main outcomes were prevalence and indications of peripartum hysterectomy. Additionally, we compared prevalence of peripartum hysterectomy between women giving birth vaginally and by caesarean section, and between women giving birth with and without previous caesarean section. Finally, we calculated correlation between prevalence of peripartum hysterectomy and national caesarean section rates, as well as national rates of women giving birth after a previous caesarean section.

Results: A total of 1,302 peripartum hysterectomies were performed in 2,498,013 births, leading to a prevalence of 5.2 per 10,000 births ranging from 2.6 in Denmark to 10.7 in Italy. Main indications were uterine atony (35.3%) and abnormally invasive placenta (34.8%). Relative risk of hysterectomy after caesarean section compared with vaginal birth was 9.1 (95% CI 8.0-10.4). Relative risk for hysterectomy for birth after previous caesarean section compared with birth without previous caesarean section was 10.6 (95% CI 9.4-12.1). A strong correlation was observed between national caesarean section rate and prevalence of peripartum hysterectomy ($\rho = 0.67$, $P < 0.05$).

Conclusions: Prevalence of peripartum hysterectomy may vary considerably between high-income countries. Uterine atony and abnormally invasive placenta are the commonest indications for hysterectomy. Birth by caesarean section and birth after previous caesarean section are associated with nine-fold increased risk of peripartum hysterectomy.

INTRODUCTION

Peripartum hysterectomy refers to surgical removal of the uterus during pregnancy or postpartum.¹ It is usually performed for severe obstetric complications such as major obstetric haemorrhage, abnormally invasive placenta, uterine rupture, or sepsis. Peripartum hysterectomy is defined by the World Health Organization as a maternal near-miss criterion and used as a proxy for severe postpartum haemorrhage and therefore frequently used as an outcome of interest in obstetric surveillance.²

The association between peripartum hysterectomy and caesarean section has previously been described, with relative risk for women giving birth by caesarean section ranging from 8.5 to 18.3.³⁻⁸ In addition, pregnancy in a woman who gave birth by caesarean section previously is a risk factor for abnormally invasive placentation, which may in turn lead to hysterectomy. This risk is known to increase for every additional previous caesarean section.⁹ Such associations are of particular interest in light of the rising caesarean section rates worldwide because these could potentially lead to increasing rates of peripartum hysterectomies as well.

Prevalence of peripartum hysterectomy in high-resource settings is relatively low.¹⁰ Hence, indications and outcomes are often studied retrospectively, or through national obstetric survey systems.¹¹⁻¹⁵ Multinational comparisons of prevalence and outcomes to optimise management strategies may be facilitated by international collaborations combining national data.^{1,16}

The main aim of this study was to compare the prevalence of peripartum hysterectomy between high-income countries, as part of the International Network of Obstetric Survey Systems (INOSS). Secondary aims were to describe the indications for hysterectomy, and perform analyses of prevalence of peripartum hysterectomy stratified by mode of birth and previous caesarean section. In addition, we examined the correlation between national rates of peripartum hysterectomy and national caesarean section rates, and the rate of women giving birth after previous caesarean section.

MATERIAL AND METHODS

This was a descriptive, multinational, population-based study. We used data from nine countries participating in INOSS that had previously conducted studies on peripartum hysterectomy. Most of these countries, except France and Slovakia, have previously published outcomes of peripartum hysterectomy surveillance.^{11-15,17-20} INOSS is an international collaboration of national obstetric survey systems, aiming to increase knowledge of management of uncommon obstetric complications.¹⁶ Participating in this study were: Slovak Obstetric Survey System (SOSS) in Slovakia, Italian Obstetric Surveillance System (ItOSS) in Italy, Belgian Obstetric Surveillance

System (B.OSS) in Belgium, Épidémiologie de la Morbidité Maternelle Sévère (EPIMOMS) in France, Nordic Obstetric Surveillance System (NOSS) with data from Denmark, Finland and Sweden, Landelijke studie naar Etnische determinanten van Maternale Morbiditeit (LEMMoN) in the Netherlands, and United Kingdom Obstetric Surveillance System (UKOSS) in the UK. All were nationwide studies except for EPIMOMS in France, which included six regions (Alsace, Auvergne, Basse-Normandie, Île-de-France, Lorraine, and Rhône-Alpes) covering 20% of national births and ItOSS, which encompassed six regions (Piedmont, Emilia-Romagna, Tuscany, Lazio, Campania, and Sicily) representing 49% of births in Italy.

Methods of data collection were described previously.²⁰⁻²⁵ In brief, all countries performed national or multiregional survey studies in which women who underwent peripartum hysterectomy were identified. Identification of cases was performed in most countries by monthly communication (electronic database, mailing or paper) to appointed clinicians in each maternity unit. When a case was reported, further details were requested through a data collection form. To ensure completeness of data, regular reminders were sent and a 'nothing to report' response was requested. All data were collected prospectively, except for the data from Slovakia, which were collected retrospectively. Studies were performed during different periods, from August 2004 to August 2016. Validation and identification of additional cases were performed after cross-checking health registers and hospital databases for the Nordic countries (Hospital Discharge Register, Medical Birth Register and delivery logbooks). Each country managed and cleaned their own database after which all anonymised databases were merged in Leiden, The Netherlands (see Supplementary material, Table S1).

In order to overcome differences in case selection between studies we applied a uniform case definition. Definitions used in the different survey studies were specified for inclusion criteria such as minimum gestational age, postpartum follow up, inclusion of non-obstetric indications (such as malignancy), or other specific inclusion or exclusion criteria if present (such as including only cases of obstetric haemorrhage in Italy). To arrive at a uniform definition, the most restrictive definition was chosen to account for differences. We opted not to exclude hysterectomies in case of missing information regarding indication or gestational age, as it was postulated that the very few women who would have had an indication other than obstetric haemorrhage or a peripartum hysterectomy before 22 weeks of gestation would be greatly outnumbered by those with haemorrhage or hysterectomy ≥ 22 weeks. The most restrictive definition was defined as hysterectomies performed from the 22nd week of gestation up to 48 hours postpartum performed for obstetric haemorrhage (see Supplementary material, Table S2).

All countries provided background data on number of births during the study period. Background data differed between countries on the lower limit of gestational age, ranging from ≥ 22 weeks to 25+6 weeks (see Supplementary material, Table S1). For countries registering births ≥ 24 weeks, calculation of births

≥22 weeks was not possible. In a previous INOSS study, correction of background data resulted in minimal non-significant differences because the proportion of births at those gestational ages was very low in all countries, so we decided not to perform such a correction.²⁶ Additionally, all countries provided aggregate data on national caesarean section rates, and numbers of caesarean sections and vaginal births. When actual numbers of caesarean section and vaginal births were unknown, these were estimated by multiplying the total number of births by the caesarean section rate. Numbers of women giving birth with and without previous caesarean section were calculated accordingly.

There were differences between studies in coding indications of hysterectomy. Some countries reported only one indication per hysterectomy whereas others coded all indications that arose during the process leading to hysterectomy. Therefore, we included the most important indication of those registered by applying a hierarchical system. From the indications listed, the one highest in rank was used. The hierarchy of indications, which was determined after reaching consensus among researchers of participating countries, in order of importance, was as follows: abnormally invasive placenta, placenta previa, uterine rupture, placental abruption, uterine atony, infection, cervical laceration, fibroids, unspecified haemorrhage, diffuse intravascular coagulation, and other.

Main outcomes were overall prevalence and indications of peripartum hysterectomy. Secondary outcomes were prevalence of peripartum hysterectomy for women giving birth vaginally and women who underwent cesarean section, and for women giving birth with and without previous cesarean section, with calculations of relative risk. Additionally, correlations between prevalence of peripartum hysterectomy and national cesarean section rates and national proportion of women giving birth after previous caesarean section were recorded.

Statistical analyses

Prevalence was calculated per 10,000 births with 95% CI or per 10,000 caesarean sections or vaginal births where appropriate. For calculation of relative risk, individual data were used from women with hysterectomy, but only aggregate data were available for women without hysterectomy. To adjust for weighting and clustering, calculation of total proportions and relative risks was done using a fixed-effects model. Descriptive data are presented with mean (95% CI) or median (interquartile range) whenever appropriate. Proportions were calculated after subtracting the missing data from the totals, as they cannot be classified in either category of binary variables. Correlation between prevalence of peripartum hysterectomy and mode of birth and previous caesarean section rates per country were calculated using nonparametric Spearman rank order correlations (ρ). Results were considered statistically significant when $P < .05$. All analyses were performed using IBM SPSS Statistics version 18.0 (IBM Corp.), R version 6.3.6 (cran.r-project.org) and Office Excel 2019 (Microsoft Corp.).

Ethical approval

Due to the nature of this study, ethical approval was not required. Each study, from which data were used, was approved by their national or local ethics committee.

RESULTS

A total of 1393 peripartum hysterectomies were reported in the nine participating countries. During the study period, 2 498 013 births were registered. A total of 91 hysterectomies were excluded: 17 because the hysterectomy was performed at gestational age <22 weeks, 72 because of postpartum interval >48 hours, two hysterectomies because of indication other than obstetric haemorrhage (one gynecological malignancy and one necrotic uterus after uterine artery embolization). Using the uniform definition for all data sets, 1302 hysterectomies were included leading to a prevalence of 5.2 (95% CI 4.9-5.5) per 10,000 births. Prevalence was highest in Italy with 10.7 (95% CI 9.8-11.6) hysterectomies per 10,000 births and lowest in Denmark with 2.6 (CI 2.0-3.5) hysterectomies per 10,000 births (Table 1, Figure 1). As the result of differences in the time period in which studies were performed, we compared countries that included cases before 2012 (The Netherlands, Denmark, the UK, Finland, Sweden) with countries that included cases starting in 2012 (Italy, France, Belgium, Slovakia). The prevalence was 3.7 (3.4-4.0) versus 7.3 (6.8-7.9) per 10,000 births, respectively.

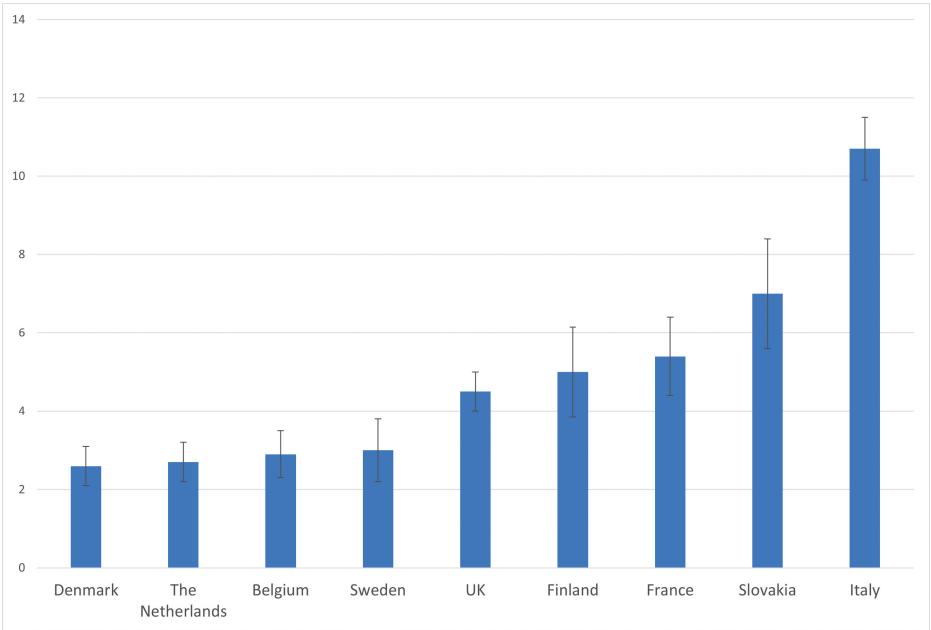


Figure 1. Prevalence of peripartum hysterectomy

Overall, background characteristics such as maternal age, parity, and body mass index were comparable between countries (Table 2). A total of 996/1292 (77.1%) women gave birth by caesarean section and 452/770 (58.7%) were planned. Moreover, 586/1177 (49.8%) women had given birth by caesarean section in a previous pregnancy.

In 670 women multiple indications were coded before use of the hierarchical system. Commonest indication was uterine atony for 459 women (35.3%) followed by abnormally invasive placenta for 453 women (34.8%), and uterine rupture in 98 women (7.5%). Observed frequencies for abnormally invasive placenta indication varied from 14/73 (19.2%) in Belgium up to 26/52 (50%) in Sweden. Hysterectomy in case of placenta previa only was not performed at all in Belgium and Denmark whereas this was the indication in 41/276 (14.9%) of women in the UK. Haemorrhage due to cervical lacerations was notably higher in Denmark (6/44) compared with other countries (Table 3).

Prevalence of peripartum hysterectomy after caesarean section was highest in Italy with 23.2 per 10,000 caesarean sections (95% CI 21.1-25.6) and lowest in Belgium with 9.0 per 10,000 caesarean sections (95% CI 6.8-11.9). Following vaginal birth, prevalence was highest in Slovakia with 4.6 per 10,000 births (95% CI 3.5-6.1) and lowest in Sweden with 0.4 per 10,000 births (95% CI 0.2-0.9). Overall relative risk for hysterectomy after caesarean section compared with vaginal birth was 9.1 (95% CI 8.0-10.4) (Table 4). Relative risk ranged from 2.5 (95% CI 1.7-3.7) in Slovakia to 38.2 (95% CI 16.3-89.5) in Sweden, in the latter country this being due to a very low incidence after vaginal birth. Because of the unknown number of planned caesarean hysterectomies in case of suspected abnormally invasive placenta, calculations were repeated after excluding women with hysterectomy for abnormally invasive placenta. Relative risk of peripartum hysterectomy in women who gave birth by caesarean section versus those who gave birth vaginally was 6.8 (95% CI 5.9-8.0) per 10,000 births (see Supplementary material, Table S3). There was a strong, positive correlation between national caesarean section rate and prevalence of peripartum hysterectomy ($\rho = 0.67$, $n = 9$, $P < 0.05$) (Figure 2).

Prevalence of peripartum hysterectomy in women with previous caesarean section varied from 10.7 per 10,000 births (95% CI 7.9-14.6) in the Netherlands to 36.7 (95% CI 31.3-43.1) in the UK. In women without previous caesarean section, prevalence varied considerably less, ranging from 1.3 per 10,000 births (95% CI 0.8-2.0) in Denmark to 3.7 per 10,000 births in Finland and France. Overall relative risk for peripartum hysterectomy in women who had given birth by caesarean section in a previous pregnancy compared with women without a previous caesarean section this was 10.6 (95% CI 9.4-12.1) (Table 5). After excluding women with hysterectomy for abnormally invasive placenta this relative risk was still 6.4 (95% CI 5.5-7.6) per 10,000 births (see Supplementary material, Table S4). A statistically non-significant weak correlation was observed between national proportions of women giving birth with a previous caesarean section and national prevalence of pregnancy-related hysterectomy ($\rho = 0.26$, $n = 8$, $P = 0.5$) (Figure 3).

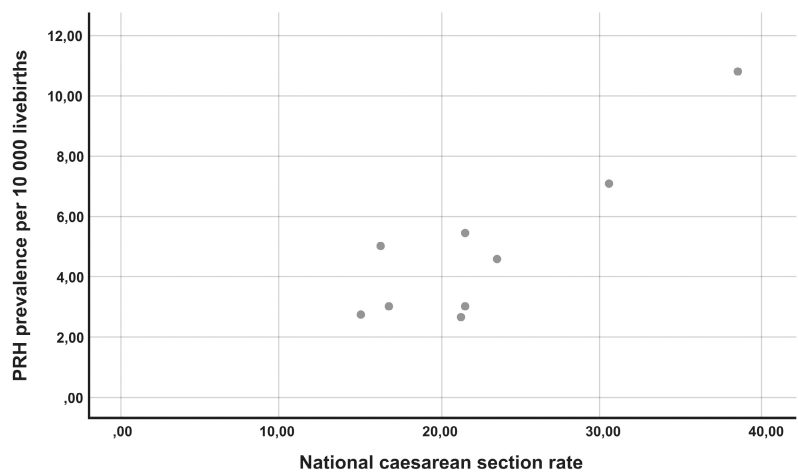


Figure 2. Correlation of peripartum hysterectomy with national caesarean section rates.

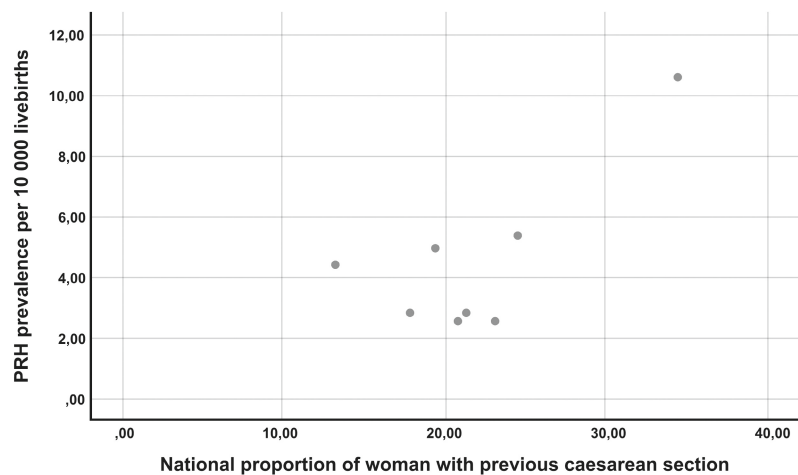


Figure 3. Correlation of prevalence of peripartum hysterectomy with national rates of women with previous caesarean section. *PRH, peripartum hysterectomy

Table 1. Prevalence of peripartum hysterectomy using national definitions and after use of uniform definition

Countries (study)	PRH ^a (n)	Births (n)	Prevalence per 10 000 births (95% CI)	PRH ^a uniform definition (n)	Prevalence -uniform definition per 10 000 births (95% CI) ^b
Denmark (NOSS) Apr 2009-Dec 2011	50	168 170	3.0 (2.3 – 3.9)	44	2.6 (2.0 – 3.5)
Netherlands (LEMMoN) Aug 2004-Aug 2006	110	358 874	3.1 (2.5 – 3.7)	95	2.7 (2.2 – 3.2)
Belgium (BOSS) Jan 2012- Dec 2013	84	252 272	3.3 (2.7 – 4.1)	73	2.9 (2.3 – 3.6)
Sweden (NOSS) Sep 2009-Aug 2011	52	175 575	3.0 (2.3 – 3.9)	52	3.0 (2.3 – 3.9)
UK (UKOSS) Feb 2005-Feb 2006	315	609 300	5.2 (4.6 – 5.8)	276	4.5 (4.0 – 5.0)
Finland (NOSS) Apr 2009-Aug 2011	74	145 546	5.1 (4.1 – 6.4)	72	5.0 (3.9 – 6.2)
France (EPIMOMS) May 2012-Nov 2013	104	182 309	5.7 (4.7 – 6.9)	98	5.4 (4.4 – 6.6)
Slovakia (SOSS) Jan 2012-Dec 2014	104	146 972	7.1 (5.8 – 8.6)	103	7.0 (5.8 – 8.5)
Italy (ITOSS) Sep 2014-Aug 016	500	458 995	10.9 (10.0 – 11.9)	489	10.7 (9.8 – 11.6)
Total	1 393	2 498 013		1 302	5.2 (4.9 – 5.5)

^aPRH, peripartum hysterectomy; ^bCI, confidence interval

Table 2. Maternal and pregnancy characteristics at time of peripartum hysterectomy

Women's characteristics	Belgium (n=73)	Denmark (n=44)	Finland (n=72)	France (n=98)	UK (n=276)	Italy (n=489)	Netherlands (n=95)	Slovakia (n=103)	Sweden (n=52)	TOTAL (n=1032)
Maternal age, years	34.6 ± 4.4	33.7 ± 5.2	34.2 ± 5.1	34.4 ± 6.0	34.0 ± 5.4	35.6 ± 5.7	34.3 ± 4.3	31.7 ± 5.5	34.2 ± 4.9	34.5 ± 5.5
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.0)	0 (0.0)	3 (2.9)	0 (0.0)	8 (0.6)
BMI kg/m²	24.6 ± 4.5	26.1 ± 5.5	24.9 ± 5.5	24.9 ± 5.4	26.7 ± 5.7	24.9 ± 4.5	24.9 ± 6.1	27.1 ± 3.8	28.0 ± 5.9	25.6 ± 5.2
Missing n(%)	14 (19.2)	2 (4.5)	2 (2.8)	8 (8.2)	36 (13.0)	71 (14.7)	31 (32.6)	8 (7.8)	7 (13.5)	180 (13.8)
Parity n(%)										
Primiparous	10 (13.7)	12 (27.3)	19 (26.4)	25 (26.0)	33 (12.0)	145 (31.5)	16 (16.8)	18 (18.0)	10 (19.2)	288/1269 (22.7)
Multiparous	63 (86.3)	32 (72.7)	53 (73.6)	71 (74.0)	243 (88.0)	316 (68.5)	79 (83.2)	82 (82.0)	42 (80.8)	981/1269 (77.3)
Missing n(%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	28 (5.7)	0 (0.0)	3 (2.9)	0 (0.0)	33 (2.5)
Mode of birth n(%)										
Caesarean section	49 (68.1)	36 (81.8)	52 (72.2)	67 (68.4)	226 (81.9)	410 (84.5)	59 (62.1)	51 (52.0)	46 (88.5)	996/1202 (77.1)
Vaginal birth	23 (31.9)	8 (18.2)	20 (27.8)	31 (31.6)	50 (18.1)	75 (15.5)	36 (37.9)	47 (48)	6 (11.5)	296/1202 (22.9)
Missing n(%)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	5 (4.9)	0 (0.0)	10 (0.8)
Planned caesarean section n(%)^a	13 (26.5)	15 (34.1)	28 (38.9)	43 (43.9)	N/A	285 (69.5)	11 (11.6)	26 (25.2)	31 (59.6)	452/907 (58.7)
Missing n(%)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	N/A	88 (18.0)	0 (0.0)	0 (0.0)	0 (0.0)	89 (6.8)
Gestational Age										
22 ⁺⁰ – 23 ⁺⁶	1 (1.4)	0 (0.0)	0 (0)	1 (1.0)	0 (0.0)	2 (0.4)	1 (1.1)	0 (0.0)	0 (0.0)	5/992(0.4)
24 ⁺⁰ – 31 ⁺⁶	9 (12.3)	2 (4.5)	4 (5.6)	6 (6.1)	24 (8.9)	31 (6.8)	5 (5.3)	11 (11.1)	3 (5.8)	95/992 (7.5)
32 ⁺⁰ – 36 ⁺⁶	23 (31.5)	13 (29.5)	20 (27.8)	22 (22.4)	80 (29.5)	166 (36.2)	16 (16.8)	26 (25.7)	21 (40.4)	387/992 (30.7)
≥37 ⁺⁰	40 (54.8)	29 (65.9)	48 (66.7)	69 (70.4)	167 (61.6)	259 (56.6)	73 (76.8)	62 (61.4)	28 (53.8)	775/992 (61.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	31 (6.3)	0 (0.0)	4 (3.9)	0 (0.0)	40 (3.1)
Previous caesarean section	36 (50.0)	25 (56.8)	24 (33.3)	36 (37.9)	149 (54.0)	228 (51.0)	40 (42.1)	20 (83.3)	28 (53.8)	586/1177 (49.8)
Missing n(%)	1 (1.4)	0 (0.0)	0 (0.0)	3 (3.1)	0 (0.0)	42 (8.6)	0 (0.0)	79 (76.7)	0 (0.0)	125 (9.6)

All data are presented as n (%) or mean ± standard deviation unless otherwise specified. Percentages are calculated after subtracting missing data.

^aPresented as percentage of number of caesarean sections.

Table 3. Most important indication for peripartum hysterectomy presented as n (%).

Indications of hysterectomy	Belgium (n=73)	Denmark (n=44)	Finland (n=72)	France (n=98)	UK (n=276)	Italy (n=489)	Netherlands (n=95)	Slovakia (n=103)	Sweden (n=52)	Total (n=1302)
Uterine atony	29 (39.7)	12 (27.3)	17 (23.6)	42 (42.9)	98 (35.5)	199 (40.7)	34 (35.8)	18 (17.5)	10 (19.2)	459 (35.3)
Abnormally invasive placenta	14 (19.2)	17 (38.6)	16 (22.2)	23 (23.5)	103 (37.3)	188 (38.4)	36 (37.9)	30 (29.1)	26 (50)	453 (34.8)
Uterine rupture	10 (13.7)	2 (4.5)	17 (23.6)	9 (9.2)	17 (6.2)	14 (2.9)	10 (10.5)	16 (15.5)	3 (5.8)	98 (7.5)
Unspecified Haemorrhage	5 (6.8)	0	11 (15.3)	2 (2)	0	44 (9)	8 (8.4)	16 (15.5)	7 (13.5)	93 (7.1)
Placenta previa	0	0	9 (12.5)	2 (2)	41 (14.9)	15 (3.1)	4 (4.2)	11 (10.7)	2 (3.8)	84 (6.5)
Placental abruption	0	2 (4.5)	0	6 (6.1)	2 (0.7)	20 (4.1)	0	2 (1.9)	2 (3.8)	34 (2.6)
Cervical laceration	0	6 (13.6)	2 (2.8)	0	2 (0.7)	4 (0.8)	1 (1.1)	0	0	15 (1.2)
Fibroids	0	2 (4.5)	0	0	1 (0.4)	2 (0.4)	1 (1.1)	0	2 (3.8)	8 (0.6)
DIC ^a	0	0	0	6 (6.1)	1 (0.4)	1 (0.2)	0	0	0	8 (0.6)
Infection	0	0	0	1 (1)	0	0	1 (1.1)	0	0	2 (0.2)
Other	2 (2.7)	3 (6.8)	0	7 (7.1)	8 (2.9)	2 (0.4)	0	3 (2.9)	0	25 (1.9)
Missing	13 (17.8)	0	0	0	3 (1.1)	0	0	7 (6.8)	0	23 (1.8)

DIC, disseminated intravascular coagulopathy

Table 4. Relative risk of peripartum hysterectomy for caesarean section compared to vaginal birth

Country	Caesarean section rate (%)	Caesarean section			Vaginal birth			Relative risk
		Number of PRH ^a	Number of CS ^b	Prevalence* (95% CI) ^c	Number of PRH	Number of vaginal births	Prevalence* (95% CI)	
Belgium	21.5	49	54 369	9.0 (6.8 - 11.9)	23	197 903	1.2 (0.7 - 1.7)	7.8 (4.7 - 12.7)
Denmark	21.3	36	35 821	10.1 (7.3 - 13.9)	8	132 349	0.6 (0.3 - 1.2)	16.6 (7.7 - 35.8)
Finland	16.2	52	23 542	22.1 (16.9 - 29.0)	20	122 004	1.6 (1.1 - 2.6)	13.5 (8.0 - 22.6)
France	21.5	67	39 194	17.1 (13.5 - 21.7)	31	143 115	2.2 (1.5 - 3.1)	7.9 (5.2 - 12.1)
Italy	38.5	410	176 713	23.2 (21.1 - 25.6)	75	282 282	2.6 (2.1 - 3.3)	8.8 (6.8 - 11.2)
The Netherlands	15.0	59	53 762	11.0 (8.5 - 14.2)	36	305 112	1.2 (0.9 - 1.6)	9.3 (6.1 - 14.1)
Slovakia	30.5	51	44 826	11.4 (8.7 - 15.0)	47	102 146	4.6 (3.5 - 6.1)	2.5 (1.7 - 3.7)
Sweden	16.7	46	29 327	15.7 (11.8 - 20.9)	6	146 248	0.4 (0.2 - 0.9)	38.2 (16.3 - 89.5)
United Kingdom	23.5	226	143 185	15.8 (13.9 - 18.0)	50	466 115	1.1 (0.8 - 1.4)	14.7 (10.8 - 20.0)
Total	24.0	996	600 739		296	1 897 274		9.1 (8.0-10.4)

^a PRH: peripartum hysterectomy, ^b CS: Caesarean sections, ^c CI: Confidence Interval, *Prevalence per 10 000 births or caesarean sections.

Table 5. Relative Risk of peripartum hysterectomy for women with versus without previous caesarean section.

Country	% of women with previous CS	With previous caesarean section		Without previous caesarean section			Relative risk
		PRH ^a (n)	Births (n)	Prevalence (95% CI) *	PRH ^a (n)	Births (n)	Prevalence (95% CI) ^b *
Belgium	10.7	36	27 007	13.3 (9.6 - 18.5)	36	225 265	1.6 (1.2 - 2.2)
Denmark	11.6	25	19 626	12.7 (8.6 - 18.8)	19	148 544	1.3 (0.8 - 2.0)
Finland	9.7	24	14 167	16.9 (11.4 - 25.2)	48	131 379	3.7 (2.8 - 4.8)
France	12.3	36	22 424	16.1 (11.6 - 22.2)	59	159 885	3.7 (2.9 - 4.8)
Italy	16.8	228	77 111	29.6 (25.9 - 33.7)	74	381 884	1.9 (1.5 - 2.4)
Netherlands	10.4	40	37 343	10.7 (7.9 - 14.6)	55	321 531	1.7 (1.3 - 2.2)
Slovakia				Data not available			
Sweden	8.9	28	15 698	17.8 (12.3 - 25.8)	24	159 877	1.5 (1.0 - 2.2)
United Kingdom	6.6	149	40 600	36.7 (31.3 - 43.1)	127	568 700	2.2 (1.9 - 2.7)
Total	10.9	566	253 976		442	2 097 065	10.6 (9.3 - 12.0)

^a PRH: peripartum hysterectomy, ^b CI: Confidence Interval, *Prevalence per 10 000 births or caesarean sections.

DISCUSSION

The prevalence of peripartum hysterectomy varied significantly in nine European countries. Prevalence was considerably higher in women giving birth by caesarean section and in women who had given birth by caesarean section in a previous pregnancy. Additionally, indications for hysterectomy also varied notably between countries and considerable variance was observed for all reported indications. Such differences may result from differences in women's characteristics, national caesarean section rates, and national rates of pregnant women with scarred uteri. Such differences may also reflect differences in clinical management of major obstetric haemorrhage between participating countries.

Compared with a systematic review and meta-analysis where weighted prevalence for upper- and high-income countries was calculated at 7 per 10,000 births, our study demonstrated lower prevalence for all countries except Italy.¹⁰ Another study on emergency peripartum hysterectomy in high-income countries, reported prevalence for most European countries <10 per 10,000 births, in line with our results.⁸

We found a nine-fold higher risk of hysterectomy after caesarean section. However, 77% of women undergoing hysterectomy were delivered by caesarean section and more than half of these were planned. Reason for this may be antenatal diagnosis of placenta previa with or without abnormally invasive placenta, in which case vaginal birth is not an option and risk of hysterectomy is very high.²⁷ The number of planned caesarean hysterectomies was not known. Therefore, we repeated calculations after excluding women who had hysterectomy for abnormally invasive placenta, which was the second most frequent indication among all hysterectomies. In these women, it is the indication for the caesarean section that places them at increased risk of hysterectomy rather than the indication itself. Some of these hysterectomies might in fact have been planned before birth. However, even following exclusion of women with abnormally invasive placenta, the prevalence of hysterectomy after caesarean section and in birth following a previous caesarean section both remained significantly higher. Our results are in line with literature, where caesarean section is a strong risk factor for emergency peripartum hysterectomy.⁸ Increased risk of hysterectomy after previous caesarean section has been shown before and was demonstrated to be independent of the intended mode of birth.^{8,28} As such, the variance of prevalence between countries might, to a considerable extent, be explained by the difference in national caesarean section rates.

The strength of this study is its unique multinational character including data from nine nationwide or multiregional studies. Collaboration between national and multiregional obstetric survey systems previously led to insights into prevalence and management of uterine rupture.²⁶ The INOSS collaboration enables the collection of considerably robust data regarding rare obstetric diseases.

Main limitations arise from the fact that included studies were performed in different time intervals, over 2 or 3 consecutive years with little or no overlap. Obstetric practice and risk factors such as caesarean section rates might have changed over time.^{8,13,29} Data stratified by year would reflect differences between studies rather than being indicative of changes in practice over time. However, pooling data from recent and older studies showed a marked difference in prevalence of hysterectomy which, in light of other evidence, may be the result of rising caesarean section rates. Furthermore, there were 40 registered hysterectomies with missing information on gestational age. Given the fact that only 1% of all hysterectomies in the database were excluded because of a gestational age <22 weeks, we opted that excluding these cases would lead to exclusion of actually valid cases, which would lead to underestimation of prevalence. Also, a previous caesarean section is strongly associated with birth by caesarean in the index pregnancy. In the calculation of the correlation between prevalence of hysterectomy and mode of birth, previous caesarean section should be taken into consideration. As such, calculation of adjusted relative risks for each exposure would have led to better estimation of the independent role of each of them. However, for the background data we only had aggregate numbers for mode of birth and for previous caesarean section and could not perform such analysis. Accordingly, in the correlation of prevalence of peripartum hysterectomy with previous caesarean section, taking parity into account would lead to more valid results. Also, the number of previous caesarean sections adds up to the risk of hysterectomy and other serious morbidity with every additional operation, as previously described.⁹ Unfortunately, in our database we only had access to binary information on presence of a previous caesarean section. Therefore, the effect of number of previous caesareans was not measured. Another limitation is the fact that case identification and study objectives differed between countries. Seven of nine studies were designed specifically to report peripartum hysterectomy whereas the studies from the Netherlands and France included women with severe maternal morbidity. In Slovakia, data were collected retrospectively, which may have led to some underreporting. Nonetheless, their numbers still gave them the second highest prevalence; actual prevalence may have been even higher.

For enhanced comparability of national survey studies, collectively designed surveillance studies using uniform criteria are required and INOSS may provide an important platform to perform such studies. In addition, use of a uniform definition for upcoming studies is important. Therefore, INOSS proposed a definition of 'pregnancy-related hysterectomy' using a Delphi process:¹ "Surgical removal of the uterus during pregnancy or up to 42 days postpartum". This definition is wide enough to include all indications and pregnancy intervals. As our specific study includes only a subset of women who had a hysterectomy around the time of birth, we decided to apply the common terminology "peripartum hysterectomy" in this

paper. Streamlining multiple national surveys is necessary to overcome problems related to different study intervals.

CONCLUSION

Prevalence of peripartum hysterectomy varied widely between countries and was higher in countries with higher caesarean section rates. Commonest indications were uterine atony and abnormally invasive placenta. Rate of peripartum hysterectomy was considerably higher in women who gave birth by caesarean section as well as in women with a previous caesarean section. Further investigation is necessary to fully understand the underlying factors that contribute to these differences. Further work is needed to determine optimal management strategies and comparison of those strategies between countries.

ACKNOWLEDGMENTS

We thank Ms Bente Elgersma for her contribution to building the database. The Netherlands: NethOSS board Kitty Bloemenkamp (also INOSS chair), Jos van Roosmalen, Timme Schaap, Thomas van den Akker, Joost Zwart. We would like to acknowledge all clinicians reporting data to the LEMMoN study between 2004 and 2006. Italy: We would like to acknowledge all clinicians reporting data to the ItOSS study. Finland: Kati Ojala (Oulu University Hospital); Maija-Riitta Ordén (Kuopio University Hospital), Nanneli Pallasmaa (Turku University Hospital) and Outi Palomäki (Tampere University Hospital), Anna-Maija Tapper (HUCH Hyvinkää Hospital), Outi Äyräs (Helsinki University Hospital). Sweden: Karin Källén, Karin Gottvall and all clinicians reporting to the NOSS study between 2009 and 2011. France: Epimoms study, all clinicians and research staff who contributed to case identification and data collection. We also want to thank all clinicians who contributed to case identification and data collection in the UK, Denmark, Slovakia and Belgium. Permission has been obtained from all named persons.

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SUPPORTING INFORMATION

Table S1. Methodology of case collection for each participating country and summary of background data of total number of births.

Country	Methodology	Background data
Denmark (NOSS) Apr '09-Dec '11	Clinicians in each maternity unit reported peripartum hysterectomies spontaneously through electronic or paper data collection forms.	Births ≥ 22 weeks of gestational age
Finland (NOSS) Apr '09-Aug '11	Clinicians in each maternity unit reported peripartum hysterectomies spontaneously through electronic or paper data collection forms.	Births ≥ 22 weeks of gestational age
Sweden (NOSS) Sep '09-Aug '11	Monthly mailing to appointed clinician in each maternity unit. When a case was reported, further details were requested through a data collection form. 'Nothing to report' response requested.	Births ≥ 22 weeks of gestational age
Italy (ITOSS) Sep '14-Aug '16	Maternity units reported cases through electronic collection forms followed by a monthly reminder by e-mail to promote complete reporting.	Births from 25+6 weeks of gestational age
France (EPIMOMS) May '12-Nov '13	Maternity units reported cases through electronic collection forms followed by a monthly reminder by e-mail to promote complete reporting.	Births ≥ 22 weeks of gestational age
Belgium (B.OSS) Jan '12- Dec '13	Monthly mailing to appointed clinician in each maternity unit. When a case was reported, further details were requested through a data collection form. 'Nothing to report' response requested.	Births ≥ 22 weeks of gestational age
The Netherlands (LEMMoN) Aug '04-Aug '06	Monthly mailing to maternity units to report women with severe maternal morbidity. All women with hysterectomy because of obstetric haemorrhage during pregnancy, delivery, and puerperium (limited to 6 weeks after delivery) were included. 'Nothing to report' response requested.	Births ≥ 24 weeks of gestational age
UK (UKOSS) Feb '05-Feb '06	Monthly mailing to appointed clinician in each maternity unit. When a case was reported, further details were requested through a data collection form. 'Nothing to report' response requested.	Births of any gestational age, including stillbirths ≥ 24 weeks
Slovakia (SOSS) Jan '12-Dec '14	Women who underwent peripartum hysterectomy in the year before were identified after correspondence with all maternity units. Questionnaire with additional information was filled for every case.	Births ≥ 24 weeks of gestational age

Table S2. National definitions of peripartum hysterectomy.

Country	Definition	Minimum gestational age	Postpartum period (days)
Denmark (NOSS) Apr '09-Dec '11	Delivery at or after 22 +0 gestational weeks and subsequent hysterectomy performed within 1 week of delivery	22+0	7
Finland (NOSS) Apr '09-Aug '11	Delivery at or after 22 +0 gestational weeks and subsequent hysterectomy performed within 1 week of delivery	22+0	7
Sweden (NOSS) Sep '09-Aug '11	Delivery at or after 22 +0 gestational weeks and subsequent hysterectomy performed within 1 week of delivery	22+0	7
Italy (ITOSS) Sep '14-Aug '16	Delivery at or after 22 +0 gestational weeks and subsequent hysterectomy performed within 1 week of delivery due to obstetric haemorrhage	22+0	7
France (EPIMOMS) May '12-Nov '13	Hysterectomy performed during pregnancy or in the 42 days postpartum, in a woman having Severe Acute Maternal Morbidity according to a multicriteria definition	22+0	42
Belgium (B.OSS) Jan '12- Dec '13	Any woman giving birth to a fetus or infant and undergoing a hysterectomy in the same clinical episode	none	42
The Netherlands (LEMMoN) Aug '04-Aug '06	Hysterectomy performed during pregnancy or in the 42 days postpartum, in a woman with Severe Acute Maternal Morbidity	none	42
UK (UKOSS) Feb '05-Feb '06	Any woman giving birth to a fetus or infant and undergoing a hysterectomy in the same clinical episode	none	42
Slovakia (SOSS) Jan '12-Dec '14	Acute hysterectomy within 48 hours from labor	none	2

Table S3. Relative risk of peripartum hysterectomy for caesarean section compared to vaginal birth after excluding hysterectomies due to abnormally invasive placenta.

Country	Caesarean section			Vaginal birth			Relative risk
	Number of PRH ^a	Number of CS ^b	Prevalence* (95% CI) ^c	Number of PRH	Number of vaginal births	Prevalence* (95% CI)	
Belgium	38	54 369	7.0 (5.1 - 9.6)	20	197 903	1.0 (0.6 - 1.6)	6.9 (4.0 - 11.9)
Denmark	20	35 821	5.6 (3.6 - 8.6)	7	132 349	0.5 (0.3 - 1.1)	10.6 (4.5 - 25.0)
Finland	37	23 542	15.7 (11.4 - 21.7)	19	122 004	1.6 (1.0 - 2.4)	13.1 (7.7 - 22.3)
France	48	39 194	12.2 (9.2 - 16.2)	27	143 115	1.9 (1.3 - 2.7)	6.5 (4.1 - 11.4)
Italy	234	176 713	13.2 (11.7 - 15.0)	63	282 282	2.2 (1.7 - 2.9)	5.9 (4.5 - 7.8)
The Netherlands	35	53 762	6.5 (4.7 - 9.1)	24	305 112	0.8 (0.5 - 1.2)	8.3 (4.9 - 13.9)
Slovakia	33	44 826	7.4 (5.2 - 10.3)	35	102 146	3.4 (2.5 - 4.8)	2.1 (1.3 - 3.5)
Sweden	21	29 327	7.2 (4.6 - 10.9)	5	146 248	0.3 (0.1 - 0.8)	21.0 (7.9 - 55.6)
United Kingdom	135	143 185	9.4 (8.0 - 11.2)	38	466 115	0.8 (0.6 - 1.1)	11.6 (8.1 - 16.6)
Total	601	600 739		211	1 897 274		9.0 (7.7 - 10.5)

^a PRH: peripartum hysterectomy, ^b CI: Confidence Interval, ^cPrevalence per 10 000 births or caesarean sections.

Table S4. Relative risk of peripartum hysterectomy for women with a history of previous caesarean section compared women without previous caesarean section after excluding hysterectomies due to abnormally invasive placenta.

Country	% of women with previous CS	With previous caesarean section			Without previous caesarean section			Relative risk
		PRH ^a (n)	Births (n)	Prevalence (95% CI) ^b *	PRH (n)	Births (n)	Prevalence (95% CI) *	
Belgium	10.7	27	27 007	10.0 (6.9 - 14.5)	31	225 265	1.4 (1.0 - 2.0)	7.3 (4.3 - 12.2)
Denmark	11.6	12	19 626	6.1 (3.5 - 10.7)	15	148 544	1.0 (0.6 - 1.7)	6.1 (2.8 - 12.9)
Finland	9.7	14	14 167	9.8 (5.9 - 16.6)	42	131 379	3.2 (2.4 - 4.3)	3.1 (1.7 - 5.7)
France	12.3	20	22 424	8.9 (5.8 - 13.8)	52	159 885	3.3 (2.5 - 4.3)	2.7 (1.6 - 4.6)
Italy	16.8	82	77 111	10.6 (8.6 - 13.2)	39	381 884	1.0 (0.7 - 1.4)	10.4 (7.1 - 15.3)
Netherlands	10.4	17	37 343	4.6 (2.8 - 7.3)	42	321 531	1.3 (0.9 - 1.8)	3.5 (2.0 - 6.1)
Slovakia				Data not available				
Sweden	8.9	11	15 698	7.0 (3.9 - 12.5)	15	159 877	0.9 (0.6 - 1.5)	7.5 (3.4 - 16.3)
United Kingdom	6.6	69	40 600	17.0 (13.4 - 21.5)	102	568 700	1.7 (1.5 - 2.2)	9.5 (7.0 - 12.9)
Total	10.9	254	253 976		338	2 097 065		6.2 (5.3 - 7.3)

^a PRH: peripartum hysterectomy, ^bCI: Confidence Interval, * Prevalence per 10 000 births.

Management of major obstetric haemorrhage prior to peripartum hysterectomy and outcomes across nine European countries

A.F. Kallianidis, A. Maraschini, J. Danis, L.B. Colmorn, C. Deneux-Tharaux, Serena Donati, M. Gissler, M. Jakobsson, M. Knight, A. Kristufkova, P.G. Lindqvist, G. Vandenberghe, T. van den Akker

On behalf of the International Network of Obstetric Survey Systems

Acta Obstetricia et Gynecologica Scandinavica. 2021;100(7):1345-1354.



ABSTRACT

Introduction: Peripartum hysterectomy is applied as a surgical intervention of last resort in case of major obstetric haemorrhage. It is performed in an emergency setting except for women with a strong suspicion of placenta accreta spectrum (PAS) where it may be anticipated before caesarean section. The aim of this study was to compare management strategies in case of obstetric haemorrhage leading to hysterectomy between nine European countries participating in the International Network of Obstetric Survey Systems (INOSS), and to describe pooled maternal and neonatal outcomes following peripartum hysterectomy.

Material and methods: We merged data from nine nationwide or multi-regional obstetric surveillance studies performed in Belgium, Denmark, Finland, France, Italy, the Netherlands, Slovakia, Sweden and the United Kingdom collected between 2004 and 2016. Hysterectomies performed from 22 gestational weeks up to 48 hours postpartum due to obstetric haemorrhage were included. Stratifying women with and without PAS, procedures performed in the management of obstetric haemorrhage prior to hysterectomy between countries were counted and compared. Prevalence of maternal mortality, complications after hysterectomy and neonatal adverse events (stillbirth or neonatal mortality) were calculated.

Results: A total of 1,302 women with peripartum hysterectomy were included. In women without PAS who had major obstetric haemorrhage leading to hysterectomy, uterotonics administration was lowest in Slovakia (48/73, 66%) and highest in Denmark (25/27, 93%), intrauterine balloon use was lowest in Slovakia (1/72, 1%) and highest in Denmark (11/27, 41%) and interventional radiology varied between none in Denmark and Slovakia to 11/59 (79%) in Belgium. In women with PAS, uterotonics administration was lowest in Finland (5/16, 31%) and highest in the UK (84/103, 82%), intrauterine balloon use varied between none in Belgium and Slovakia to 29/103 (28%) in the UK. Interventional radiology was lowest in Denmark (0/16) and highest in Finland (9/15, 60%). Maternal mortality occurred in 14/1,226 (1%), commonest complications were hematologic (95/1,202, 8%) and respiratory (81/1,101, 7%). Adverse neonatal events were observed in 79/1259 (6%) births.

Conclusions: Management of obstetric haemorrhage in women who eventually underwent peripartum hysterectomy varied greatly between these nine European countries. This potentially life-saving procedure is associated with substantial adverse maternal and neonatal outcome.

INTRODUCTION

Being the most invasive surgical procedure peripartum and non-reversible in terms of fertility, peripartum hysterectomy is applied as an intervention of last resort in the course of major obstetric haemorrhage. When all other management interventions such as uterotonics, surgical or interventional radiology procedures have failed, peripartum hysterectomy can be a live-saving procedure. It has therefore been included as a maternal near miss event by the World Health Organization (WHO).¹ However, the optimal timing of peripartum hysterectomy in the course of haemorrhage and its order in the chain of interventions, remain subject of discussion.

Prevalence of peripartum hysterectomy differs considerably between countries, but little is known as to whether similar differences are present in terms of management strategies applied during major obstetric haemorrhage prior to resorting to hysterectomy.^{2,3} After unsuccessful medical management, proceeding to surgical interventions starting with the least invasive and most readily accessible intervention is a common strategy. However, data comparing effectiveness of different medical and surgical interventions are scarce and hampered by differences in timing and clinical setting resulting in low quality evidence.^{4,5} Relating management strategies in major obstetric haemorrhage to prevalence of hysterectomy and maternal outcomes may provide new insights into which strategies are most successful in preventing both maternal mortality and potentially preventable hysterectomies. We postulated that management of major obstetric haemorrhage would vary considerably between countries, given the lack of international clinical guidance and controlled trials comparing management interventions.

Peripartum hysterectomy, in most women, will be unplanned, taking place in an emergency setting of severe obstetric haemorrhage. However, in women with antenatally suspected placenta accreta spectrum (PAS), planned caesarean hysterectomy can be anticipated management.^{6,7} PAS was found to be the second most common indication for peripartum hysterectomy in European countries, occurring in 34.8% women who underwent hysterectomy.³ The diagnosis of PAS, however, is notoriously difficult with up to 70% of PAS remaining undiagnosed antenatally.⁸

Primary aim of this study was to compare management interventions performed in the course of major obstetric haemorrhage ultimately leading to peripartum hysterectomy between nine European countries. Additionally, we aimed to pool together a large dataset of peripartum hysterectomies to obtain more robust calculations of prevalence of maternal mortality and complications, as well as neonatal adverse events.

MATERIAL AND METHODS

We performed a multi-country, population-based study combining data from nine countries of the International Network of Obstetric Survey Systems (INOSS).⁹⁻¹⁶ INOSS is an international collaboration of national survey systems, aiming to improve management of uncommon obstetric complications.¹⁷ Data from obstetric surveillance studies on peripartum hysterectomy were collected from: the Belgian Obstetric Surveillance System (B.OSS), *Epidemiologie de la Morbidite Maternelle Severe* (EPIMOMS) in France, the Italian Obstetric Surveillance System (ItOSS), *Landelijke studie naar Etnische determinanten van Maternale Morbiditeit* (LEMMoN) in The Netherlands, the Nordic Obstetric Surveillance System (NOSS) from Denmark, Finland and Sweden, the Slovak Obstetric Survey System (SOSS) and the UK Obstetric Surveillance System (UKOSS). All studies were nationwide except for EPIMOMS which included six regions of France (Alsace, Auvergne, Basse-Normandie, Île-de-France, Lorraine and Rhône-Alpes) covering 20% of national births and ItOSS, which encompassed six regions in Italy (Campania, Emilia-Romagna, Lazio, Piedmont, Sicily and Tuscany) representing 49% of national births.

Methods of data collection for all individual survey studies have previously been described more extensively.¹⁸⁻²³ In short, all countries performed prospective national or multi-regional obstetric survey studies on peripartum hysterectomy, except for Slovakia, where data were collected retrospectively. Duration of studies varied between 12 and 36 months over different periods between 2004 and 2016. In Belgium, Sweden, Italy and the UK, monthly mailing to an appointed clinician was used to identify women who underwent peripartum hysterectomy. Further details were requested through a case report form and a 'nothing to report' response was requested when there was no reported case. In Denmark and Finland appointed clinicians in each maternity unit reported peripartum hysterectomies by means of electronic or paper data collection forms. In Sweden, Denmark and Finland, who jointly performed a previous NOSS hysterectomy study, validation and identification of additional cases was performed after cross-checking health registers and hospital databases (Hospital Discharge Register, Medical Birth Register and delivery logbooks). In The Netherlands and France, registration studies identified women with severe maternal morbidity in a similar manner and within those, women who had a peripartum hysterectomy. In Slovakia, women who underwent peripartum hysterectomy in the year before were identified after correspondence with all maternity units. Except for France and Slovakia, all countries have previously published national data on peripartum hysterectomies.^{9, 10, 14-16, 19}

To overcome differences in case selection between studies, we included women who underwent hysterectomy performed from the 22nd week of gestation up to 48 hours postpartum performed due to obstetric haemorrhage. This was the broadest overlapping definition between all studies. A more detailed description

of methods used for case selection and background characteristics of women have been described previously.³

The main outcome of this study was to describe the frequency of management interventions performed in the train of events leading to peripartum hysterectomy in the nine countries. These were: administration of uterotonics, performance of arterial ligation, manual removal of the placenta, vaginal or uterine packing, balloon tamponade, uterine compression sutures, curettage, suturing the placental bed, leaving the placenta in situ in women with PAS and interventional radiology. Interventional radiology was not always available in hospitals where hysterectomies were performed. In addition, transfusion of blood products and counts were described. For women with PAS, information was not available as to whether the hysterectomy was anticipated prior to caesarean section or took place in an emergency setting. Therefore, we decided to stratify outcomes according to the indication of hysterectomy into women with and without PAS.

Secondary outcomes were maternal mortality and complication rates after hysterectomy, and adverse neonatal outcome. Complications were coded by the lead investigators of each study according to the following options: hematologic, febrile/infection, genitourinary, wound, respiratory, renal, gastrointestinal, thromboembolic, cardiovascular, psychological, neurologic, endocrinologic. Adverse neonatal outcome was defined as stillbirth or neonatal mortality including deaths up to 28 days postpartum.

After receiving all nine de-identified national datasets, these were merged and analyzed at Leiden University Medical Centre, The Netherlands. If data for a specific variable were not available for a country or had more than 50% missing values, data were presented as "not reported", since quality of the data for that variable was then considered unreliable. Variables are presented descriptively as numbers with corresponding percentages. In the calculation of percentages missing values are subtracted from the denominator, since it was impossible to identify them as positive or negative, which would have led to considerable under- or overestimation. Cumulative percentages were calculated using a fixed-effects model in order to take into account differences in study sample size. Analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, USA) and R for Statistics (<https://www.r-project.org/>).

Ethical approval

All national and multiregional studies were previously approved by their national or local Ethics Committees. (Supplementary material, Table S1)

RESULTS

A total of 1,302 peripartum hysterectomies were identified amongst 2,498,013 births (5.2/10,000 births).

Variation in management of women without PAS between countries

Of 849 women who underwent peripartum hysterectomy for an indication other than PAS, 671/849 (79%) received uterotonics. In Belgium, Italy and Slovakia fewer than 80% received uterotonics. In Slovakia, use of oxytocin and prostaglandins was lower than in other countries, whilst the proportion of women receiving ergometrin was highest (42/73, 59%). The most frequently performed surgical procedure was suturing the placental bed in case of placenta previa (44/157, 28%), varying from 0/59 (0%) in the Netherlands to 22/27 (82%) in Denmark. Vaginal and/or uterine packing was performed in 102/301 (34%) women in Italy to 5/40 (13%) women in Belgium. Intrauterine balloon tamponade varied considerably, ranging between 1/71 (1%) in Slovakia and 11/27 (41%) in Denmark, with a proportion of 116/528 (22%) overall. Arterial ligation was applied much more frequently in France 35/75 (47%) compared to all other countries. Use of uterine compression sutures was highest in Denmark 10/27 (37%) and lowest in Slovakia 0/71 (0%). Interventional radiology procedures were not performed in Denmark and Slovakia while in the Netherlands and Belgium these were performed in 7/59 (12%) and 11/59 (19%) respectively. Curettage was performed in 89/301 (30%) women in Italy while in only one other woman in the Netherlands. (Table 1) The number of women in whom no surgical interventions were performed before peripartum hysterectomy varied between 70/73 (96%) in Slovakia to 2/27 (7%) in Denmark. (Table 2)

Erythrocytes were administered to 752/837 (90%) women, ranging from 38/55 (69%) in Belgium to 100% in Finland and Sweden. Number of erythrocyte units transfused varied greatly with women in the Netherlands receiving a median of 16 units (IQR 11-24) vs. four in both Belgium (IQR 0-8) and Italy (IQR 2-6). (Table 3)

Variation in management of women with PAS between countries

In 453 women indication for hysterectomy was PAS, diagnosed either before or during surgery; 58/453 (13%) women had a vaginal birth. Uterotonics were administered to 265/453 (59%) women. Proportions of women in Italy and Finland receiving uterotonics were 71/188 (38%) and 5/16 (31%) respectively, much lower than in other countries. Interventional radiology procedures were performed in 79/451 (17.5%) women overall and not performed at all in Denmark, vs. in 9/15 (60%) in Finland. Intrauterine balloon tamponade was applied in 39/446 (9%) women overall, again with great variance between countries: none in Belgium and Slovakia vs. 29/103 (28%) in the UK. Leaving the placenta in situ was commonly performed in France (10/23, 44%) unlike other countries (only performed in one other woman, in Belgium). Manual removal of the placenta occurred in 10/13 (77%) women in

Belgium and 6/16 (38%) women in Denmark, vs. none in Finland and Sweden. (Table 4) The number of women in whom no surgical interventions were performed before hysterectomy varied between 25/30 (83%) in Slovakia and 21/26 (81%) in Sweden to 1/14 (7%) in Belgium. (Table 2)

A total of 399/451 (89%) women received transfusion of erythrocytes, 264/445 (59%) fresh frozen plasma and 136/448 (30%) thrombocytes. Women in Denmark and Finland received relatively high numbers of erythrocyte units: 13 (IQR 5-22) and 12 (IQR 6-12) respectively. (Table 3)

Outcomes and complications

Maternal mortality occurred in 14/1,272 women, giving a case fatality rate of 1%. The commonest complications following peripartum hysterectomy were hematologic (95/1,202, 8%) or respiratory (81/1,101, 7%). (Table 5) Admission into the Intensive Care Unit (ICU) occurred for 760/1,272 (60%) women. In Slovakia only 20/103 (20%) were admitted into an ICU. The total duration of admission into ICU and the total duration of hospital stay were comparable between countries that had such data available. Neonatal adverse outcome occurred in 79/1259 (6%) births, likely associated with the considerable proportion of preterm births (487/1302, 37%).³ (Table 6)

Table 1. Management of women with obstetric haemorrhage for indications other than placenta accreta spectrum.

Country	BE n = 59	DK n = 27	FI n = 56	FR n = 75	UK n = 173	IT n = 301	NL n = 59	SK n = 73	SE n = 26	Total n = 849
Uterotonics										
Oxytocin	42 (71)	25 (93)	49 (88)	63 (84)	156 (90)	219 (73)	48 (81)	48 (66)	21 (81)	671 (79)
missing	38 (78)	25 (96)	49 (88)	40 (53)	151 (89)	207 (69)	43 (73)	46 (65)	21 (81)	620 (74)
Prostaglandins	10 (17)	1 (4)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	16 (2)
missing	31 (65)	22 (85)	36 (67)	58 (77)	110 (65)	153 (51)	45 (76)	14 (20)	11 (42)	480 (58)
Ergometrin	11 (19)	1 (4)	2 (4)	0 (0)	3 (2)	0 (0)	0 (0)	2 (3)	0 (0)	19 (2)
missing	16 (35)	N/R*	N/R	N/R	91 (54)	N/R	9 (15)	42 (59)	5 (19)	163 (44)
	13 (22.0)				3 (2)		0 (0)	0 (0)	0 (0)	16 (4)
Surgical Intervention										
Suturing placental bed	14 (31)	22 (82)	N/R	N/R	N/R	N/R	0 (0)	N/R	8 (31)	44 (28)
missing	14 (23.7)	0 (0)					0 (0)		0 (0)	14 (8)
Vaginal/Uterine Packing	5 (13)	N/R	18 (32)	11 (15)	22 (13)	102 (34)	8 (14)	N/R	6 (23)	172 (24)
missing	19 (32)		0 (0)	0 (0)	3 (2)	0 (0)	0 (0)		0 (0)	22 (3)
Balloon Tamponade	8 (18)	11 (41)	17 (30)	18 (24)	44 (26)	N/R*	13 (22)	1 (1)	4 (15)	116 (22)
missing	15 (25)	0 (0)	0 (0)	0 (0)	3 (2)		0 (0)	2 (3)	0 (0)	20 (4)
Curettage	N/R	N/R	N/R	N/R	0 (0)	89 (30)	1 (2)	N/R	0 (0)	90 (17)
missing					3 (2)	0 (0)	0 (0)		0 (0)	3 (0.1)
Manual Removal of Placenta	20 (47)	3 (11)	4 (7)	N/R	N/R	N/R	4 (7)	N/R	0 (0)	31 (15)
missing	16 (27)	0 (0)	0 (0)				0 (0)		0 (0)	16 (7)
Arterial Ligation	3 (6)	0 (0)	5 (9)	35 (47)	21 (12)	N/R	8 (14)	2 (3)	1 (4)	75 (14)
missing	12 (20)	0 (0)	0 (0)	0 (0)	3 (2)		0 (0)	2 (3)	0 (0)	17 (3)
Uterine Compression Sutures	3 (8)	10 (37)	8 (14)	13 (17)	38 (22)	29 (10)	3 (5)	0 (0)	4 (15)	108 (13)
missing	19 (32)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	2 (3)	0 (0)	24 (3)
Interventional radiology	11 (19)	0 (0)	3 (5)	7 (9)	6 (4)	2 (1)	7 (12)	0 (0)	1 (4)	37 (4)
missing	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	2 (3)	0 (0)	5 (0.6)

Presented as n (%). Percentages calculated after excluding missings.

BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden. N/R= Not Reported. *Not reported due to ≥50% missing values.

Table 2. Number of surgical interventions, including radiological intervention, performed during the management before peripartum hysterectomy.

Country	BE <i>n</i> = 59	DK <i>n</i> = 27	FI <i>n</i> = 56	FR <i>n</i> = 75	UK <i>n</i> = 173	IT <i>n</i> = 301	NL <i>n</i> = 59	SK <i>n</i> = 73	SE <i>n</i> = 26	Total <i>n</i> = 849
<i>Women without PAS</i>										
0	18 (31)	2 (7)	28 (50)	20 (27)	80 (46)	140 (47)	30 (51)	70 (96)	13 (50)	401 (47)
1	19 (32)	9 (33)	8 (14)	30 (40)	54 (31)	36 (12)	14 (24)	3 (4)	6 (23)	179 (31)
2	12 (20)	6 (22)	14 (25)	21 (28)	31 (18)	36 (12)	10 (17)	0 (0)	4 (15)	134 (16)
3	2 (3)	6 (22)	5 (9)	4 (5)	7 (4)	33 (11)	4 (7)	0 (0)	3 (12)	64 (8)
≥4	8 (14)	4 (15)	1 (2)	0 (0)	1 (1)	56 (19)	1 (2)	0 (0)	0 (0)	71 (8)
Country	BE <i>n</i> = 14	DK <i>n</i> = 17	FI <i>n</i> = 16	FR <i>n</i> = 23	UK <i>n</i> = 103	IT <i>n</i> = 188	NL <i>n</i> = 36	SK <i>n</i> = 30	SE <i>n</i> = 26	Total <i>n</i> = 453
<i>Women with PAS</i>										
0	1 (7)	2 (12)	7 (44)	4 (17)	56 (54)	90 (48)	24 (67)	25 (84)	21 (81)	230 (51)
1	8 (57)	5 (29)	7 (44)	7 (30)	29 (28)	76 (40)	7 (19)	4 (13)	4 (15)	147 (33)
2	4 (29)	5 (29)	1 (6)	10 (44)	16 (16)	19 (10)	4 (11)	1 (3)	1 (4)	61 (14)
3	0 (0)	3 (18)	1 (6)	2 (9)	2 (2)	3 (2)	1 (3)	0 (0)	0 (0)	12 (3)
≥4	1 (7)	2 (12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)

Presented as n (%). BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden, PAS= Placenta accreta spectrum.

Table 3. Proportions and numbers of transfusion of blood products.

Country	BE n = 59	DK n = 27	FI n = 56	FR n = 75	UK n = 173	IT n = 301	NL n = 59	SK n = 73	SE n = 26	Total n = 849
Women without PAS										
Erythrocytes	38 (69)	25 (93)	54 (100)	69 (96)	166 (98)	251 (83)	58 (98)	65 (89)	26 (100)	752 (90)
Median n (IQR)	4 (0-8)	15 (9-22)	12 (8.75-18)	8 (5.25-10.75)	11 (7-18)	4 (2-6)	16 (11-24)	N/R	11.5 (9-18.25)	7 (4-12)
missing	4 (7)	0 (0)	2 (4)	3 (4)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	12 (1)
Fresh Frozen Plasma	40 (74)	24 (89)	48 (100)	62 (87)	137 (81)	157 (52)	45 (85)	41 (56)	21 (91)	575 (70)
Median n (IQR)	2 (0-5.25)	8 (4-14)	8 (4.25-13.5)	6 (4-9)	4 (2-6)	1 (0-3)	6 (3-10)	N/R	6 (2-15)	4 (0-6)
missing	5 (9)	0 (0)	8 (14)	4 (5)	3 (2)	0 (0)	6 (10)	0 (0)	3 (12)	29 (3)
Thrombocytes	25 (50)	24 (89)	38 (75)	27 (39)	76 (45)	39 (13)	38 (68)	41 (57)	16 (67)	324 (39)
Median n (IQR)	0 (0-2)	3 (2-5)	16 (0-24)	0 (0-1)	0 (0-2)	0 (0-0)	2 (0-2)	N/R	1 (0-2)	0 (0-2)
missing	9 (15)	0 (0)	5 (9)	5 (7)	3 (2)	0 (0)	3 (5)	0 (0)	2 (8)	27 (3)
Country	BE n = 14	DK n = 17	FI n = 16	FR n = 23	UK n = 103	IT n = 188	NL n = 36	SK n = 30	SE n = 26	Total n = 453
Women with PAS										
Erythrocytes	8 (62)	14 (82)	15 (100)	22 (96)	100 (97)	157 (84)	35 (97)	25 (83)	23 (89)	399 (89)
Median No (IQR)	4 (0-13.5)	13 (4.5-21.5)	12 (6-19)	8 (5-10)	10 (6-16)	3 (2-4)	11 (5.25-16)	N/R	7 (2-17)	5 (2-10)
missing	1 (7)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.4)
Fresh Frozen Plasma	10 (77)	13 (77)	11 (100)	22 (96)	73 (71)	69 (37)	27 (79)	22 (73)	17 (65)	264 (59)
Median No (IQR)	3.5 (0.75-10)	8 (0.5-15)	8 (6-11)	4 (3-7)	4 (0-6)	0 (0-2)	3.5 (2-6.25)	N/R	4 (0-9)	2 (0-9.25)
missing	1 (7)	0 (0)	5 (31)	0 (0)	0 (0)	0 (0)	2 (5.6)	0 (0)	0 (0)	8 (2)
Thrombocytes	6 (46)	13 (77)	8 (53)	10 (44)	43 (42)	10 (5)	13 (38)	22 (73)	11 (44)	136 (30)
Median No (IQR)	1 (0-5.5)	2 (1-5.5)	8 (0-24)	0 (0-2)	0 (0-2)	0 (0-0)	0 (0-1)	N/R	0 (0-2)	0 (0-1.5)
missing	1 (7)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	1 (4)	5 (1)

Presented as n (%). BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden, IQR= Interquartile range, PAS= Placenta accreta spectrum.

Table 4. Management of women with obstetric haemorrhage due to placenta accreta spectrum.

Country	BE n = 14	DK n = 17	FI n = 16	FR n = 23	UK n = 103	IT n = 188	NL n = 36	SK n = 30	SE n = 26	Total n = 453
Uterotonics	9 (64)	13 (77)	5 (31)	17 (74)	84 (82)	71 (38)	29 (81)	18 (60)	19 (73)	265 (59)
Oxytocin	7 (54)	13 (81)	5 (33)	12 (52)	84 (82)	68 (36)	26 (72)	17 (57)	18 (69)	250 (56)
missing	1 (7)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.7)
Prostaglandins	7 (58)	9 (60)	2 (13)	13 (57)	47 (46)	27 (14)	20 (56)	9 (30)	2 (8)	136 (30)
missing	2 (21)	2 (12)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)
Ergometrin	1 (10)	N/R	N/R	N/R	38 (37)	N/R	7 (19)	15 (50)	1 (4)	62 (30)
missing	4 (29)				0 (0)		0 (0)	0 (0)	0 (0)	4 (2)
Surgical Interventions										
Suturing Placental Bed	2 (20)	13 (77)	N/R	N/R	N/R	N/R	0 (0)	N/R	3 (12)	18 (20)
missing	4 (28.6)	0 (0)					0 (0)		0 (0)	4 (4)
Interventional Radiology	4 (29)	0 (0)	9 (60)	3 (13)	3 (3)	50 (27)	4 (11)	1 (3)	5 (19.6)	79 (17.5)
missing	0 (0)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.4)
Arterial Ligation	1 (10)	5 (6)	0 (0)	12 (52)	12 (12)	N/R	1 (3)	4 (13)	0 (0)	35 (14)
missing	4 (29)	0 (0)	1 (6)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	5 (2)
Manual Removal of Placenta	10 (77)	6 (38)	0 (0)	N/R	N/R	N/R	8 (22)	N/R	0 (0)	24 (12)
missing	1 (7)	1 (6)	1 (6)				0 (0)		0 (0)	3 (3)
Placenta Left in Situ	1 (8)	N/R	N/R	10 (44)	N/R	N/R*	0 (0)	N/R	0 (0)	11 (12)
missing	1 (7)			0 (0)			0 (0)		0 (0)	1 (1)
Vaginal/Uterine Packing	2 (22)	N/R	1 (7)	1 (4)	15 (15)	22 (12)	2 (6)	N/R	1 (4)	44 (11)
missing	5 (36)		1 (6)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	6 (2)
Uterine Compression Sutures	2 (20)	1 (7)	1 (7)	6 (26)	8 (8)	22 (12)	0	1 (3)	0 (0)	41 (9)
missing	4 (29)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)
Balloon Tamponade	0 (0)	1 (6.7)	3 (21)	1 (4)	29 (28)	N/R*	3 (8)	0 (0)	2 (8)	39 (9)
missing	5 (35.7)	1 (6.3)	1 (6.3)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	7 (3)
Curettage	N/R	N/R	N/R	N/R	0 (0)	8 (4)	0 (0)	N/R	0 (0)	8 (2)
missing					0 (0)	0 (0)	0 (0)		0 (0)	0 (0)

Presented as n (%). Percentages calculated after excluding missings. BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden. N/R= Not Reported. *Not reported due to ≥50% missing values

Table 5. Complications of peripartum hysterectomy.

Country	BE n=73	DK n=44	FI n=72	FR n=98	UK n=276	IT n=489	NL n=95	SK n=103	SE n=52	Total n=1302
Hematologic	12 (16)	2 (5)	0 (0)	N/R	16 (6)	46 (9)	2 (2)	17 (17)	0 (0)	95/1,202 (8)
Respiratory	3 (4)	5 (11)	0 (0)	N/R	26 (9)	35 (7)	5 (5)	N/R	7 (14)	81/1,101 (7)
Genito-Urinary	3 (4)	0 (0)	3 (4)	N/R	0 (0)	N/R	13 (14)	5 (6)	4 (8)	29/713 (4)
Cardiovascular	0 (0)	4 (9)	2 (3)	9 (9)	7 (3)	15 (3)	5 (5)	N/R	1 (2)	43/1,195 (4)
Gastro-Intestinal	2 (3)	1 (2)	2 (3)	N/R	N/R	N/R	4 (4)	1 (1)	0 (0)	10/437 (2)
Endocrinological	0 (0)	1 (2)	0 (0)	N/R	N/R	N/R	6 (6)	N/R	0 (0)	7/336 (2)
Wound-related	0 (0)	0 (0)	0 (0)	5 (5)	0 (0)	N/R	4 (4)	4 (4)	0 (0)	13/808 (2)
Thromboembolic	0 (0)	1 (2)	1 (1)	3 (3)	4 (1)	1 (0.2)	1 (1)	N/R	2 (4)	13/1,196 (1)
Infection	1 (1)	0 (0)	0 (0)	5 (5)	0 (0)	1 (0.2)	9 (10)	N/R	1 (2)	17/1,196 (1)
Renal	1 (1)	0 (0)	1 (1)	N/R	3 (1)	7 (1)	2 (1)	N/R	0 (0)	14/1,101 (1)
Psychological	1 (1)	0 (0)	0 (0)	N/R	N/R	N/R	2 (2)	N/R	0 (0)	3/336 (0.9)
Neurological	2 (1)	2 (5)	0 (0)	0 (0)	0 (0)	5 (1)	0 (0)	N/R	0 (0)	8/1,196 (0.7)

Presented as n (%). Denominator in totals calculated after subtracting missing or not reported values. BE= Belgium, DK= Denmark, FI=Finland, FR=France, UK= United Kingdom, IT=Italy, NL=The Netherlands, SK=Slovakia, SE=Sweden.

Table 6 . Maternal and neonatal outcome after peripartum hysterectomy.

Country	BE n = 73	DK n = 44	FI n = 72	FR n = 98	UK n = 276	IT n = 489	NL n = 95	SK n = 103	SE n = 52	Total n = 1302
Maternal mortality	1 (1)	1 (2)	0 (0)	3 (3)	2 (0.7)	5 (1)	2 (2)	0 (0)	0 (0)	14 (1)
missing	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	28 (6)	0 (0)	0 (0)	0 (0)	30 (2)
Mother admitted into ICU	48 (67)	26 (59)	34 (48)	49 (50)	231 (84)	230 (50)	81 (85)	20 (20)	41 (79)	760 (60)
missing	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	27 (6)	0 (0)	1 (1)	0 (0)	30 (2)
ICU (days)*	3 (2-4)	N/R	N/R	3 (1-4)	2 (1-3)	2 (1-3)	2 (1-3)	2 (2-3)	N/R	2 (1-3)
Hospital stay (days)*	9 (7-12)	N/R	N/R	8 (7-13)	N/R	N/R	8 (6-13)	7 (5-8)	N/R	8 (6-11)
Neonatal adverse events	7 (10)	5 (11)	5 (7)	6 (6)	8 (3)	31 (7)	6 (6)	7 (7)	4 (8)	79 (6)
missing	1 (1)	0 (0)	0 (0)	0 (0)	4 (1)	36 (7)	1 (1)	1 (1)	0 (0)	43 (3)

Presented as n (%). * Presented as median (interquartile range). BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT=Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden, ICU= Intensive Care Unit.

DISCUSSION

The main finding of our study was the considerable inter-country variation in the management of major obstetric haemorrhage ultimately leading to hysterectomy for women with as well as without PAS. Use of uterotonics, surgical procedures and transfusion rates all varied considerably between nine European countries. In women who underwent peripartum hysterectomy substantial rates of maternal mortality, complications and neonatal adverse outcomes were observed.

Many differences in management were found. In Slovakia, intrauterine balloon tamponade, uterine compression sutures and interventional radiology procedures were almost never performed. Low rates of interventional radiology are in line with low availability, with only two hospitals in the country performing interventional radiology for obstetric indications. At the same time Slovakia had the second highest prevalence of peripartum hysterectomy of included countries (7 per 10,000 births), which may reflect a practice of performing hysterectomy in a relatively early stage in the course of haemorrhage.³ In the Nordic countries, interventional radiology is also not available in every hospital and use varies with the highest rate in Finland.⁹ In Denmark, combining intrauterine balloon tamponade with uterine compression sutures ('the sandwich model') appears to be frequently used.²⁴ Conservative management, such as leaving the placenta in situ in women with PAS, appears to be common practice in France. In women with PAS, clinicians in Sweden, the Netherlands and Slovakia performed almost no other surgical intervention before performing hysterectomy. This contrasts starkly with clinical practice in the UK, Finland and Belgium where multiple other interventions are attempted to stop bleeding and preserve the uterus. Use of surgical procedures other than interventional radiology and administration of blood products will be less susceptible to availability and accessibility but rather reflect differences in preference between countries. These differences underline the results of a previous international review of hysterectomy, where in-depth audit revealed possible differences in management between countries.²⁵

In a previous systematic review and meta-analysis, maternal mortality within women undergoing peripartum hysterectomy was 1.4% in high-income settings, comparable to our results.² The same meta-analysis demonstrated different rates of complications, the most prominent being hematologic (26%) and infectious (19%) complications versus hematologic (8%) and respiratory (7%) in our study. That study included hysterectomies up to six weeks postpartum, thereby also including indications such as infection, which are more likely to occur beyond the 48-hour time limit.

A major strength of our study is that we pooled data from seven nationwide and two multi-regional obstetric surveillance studies, which led to the largest cohort of women who had peripartum hysterectomy described in the literature, as far as we are aware. The vast majority of previous studies are from single institutions.

Management interventions in such studies are biased by availability of surgical interventions such as interventional radiology, operator preference and local protocols. By using nationwide data such local differences are diminished and national trends become noticeable. Furthermore, quality of data is high with low rates of missings, even though not all countries were able to report all variables.

Main limitation of this study remains the fact that it encompasses data from 9 studies performed during different time periods, the first starting in August 2004 and the last ending in August 2016.³ Inevitably, obstetric practice might have changed over time such as preferences and management protocols within countries. However, recent literature has not added significant new insight into management of postpartum haemorrhage other than administration of tranexamic acid.²⁶ Novel surgical interventions such as local uterine segment resection known as "one-step" surgery or modified uterine compression suturing techniques were not described in our cohort. We had no information as to whether the hysterectomy was anticipated or took place in an emergency setting. Some hysterectomies will have been planned, especially in women with suspicion of PAS. However, the finding that one in eight women with PAS gave birth vaginally illustrates that a sizable proportion would have been unplanned hysterectomies. As such, women with PAS might have undergone fewer additional interventions, with lower transfusion rates and possibly fewer complications because surgery took place in a planned setting. Some women with PAS performed in planned settings, will not have experienced haemorrhage ($\geq 1L$). Given that our dataset did not include total amount of blood loss, these women will have been included in our study. This might partly explain the relatively low rates of uterotonic use and transfusion rates in some countries. Variation in use of uterotonics in women without PAS may be explained by the contribution of non-atonic bleeding, such as surgery-related bleeds around hysterectomy, and -to a limited extent- coding problems. It is clear that in case of atony, uterotonics should be first-line management. Additionally, it was impossible to identify in how many women hysterectomy initiated the haemorrhage rather than being the ultimate measure taken to stop bleeding. Also, variation in available resources, particularly with regard to interventional radiology, hampers comparisons. Finally, complications were coded by the principal investigator of each study, possibly leading to differences in definitions used. Complication rates should be interpreted with caution as these may, in some women, result from the major bleeding rather than the surgery itself. For example, thromboembolism can result from major bleeding with subsequent disseminated intravascular coagulation.

One might argue that in the management of obstetric haemorrhage in these women, all interventions performed up to the hysterectomy were unsuccessful and led to a delay that sometimes even contributed to the deaths of women whose hysterectomies were delayed too much. On the other hand, in other women hysterectomy was probably performed in an early stage of the course of bleeding. A decision to perform hysterectomy may be taken more readily in older and parous

women and by a surgically skilled obstetrician. However, we believe that the greatest contributor to the variance is the lack of international guidance on optimal management of life threatening major obstetric haemorrhage. There is no conclusive evidence about the superiority of one management intervention over another.^{5, 27} Moreover, any management strategy should take into account the underlying cause of haemorrhage, and local availability and accessibility of management interventions. Implementation of standardised step-down management strategies previously has shown to reduce rates of hysterectomy and maternal mortality.²⁸ Finally, for women with PAS, guidelines propose a multidisciplinary approach and, although evidence for interventional radiology is limited, accessibility is recommended.²⁹

To identify the optimal management strategy for every woman with major obstetric haemorrhage, further research is necessary. Ideally, a case-control design could help establish associations between different surgical interventions and maternal outcomes or clinical parameters related to the bleeding, taking into account known risk factors.. Larger cohorts could potentially enable propensity-matched comparisons between management strategies. To gather adequate numbers of participant INOSS provides an ideal platform. A prospectively designed cohort study conducted simultaneously in multiple nationwide surveys could be a next step.

CONCLUSION

Obstetric haemorrhage remains a leading cause of maternal morbidity and mortality. Management strategies differed markedly between the nine European countries studied. The optimal management strategy remains subject of discussion.⁵ Practice variation related to the use of oxytocin, balloon tamponade and interventional radiology may contribute to increased hysterectomy rates in some countries. Risk factors for haemorrhage, such as caesarean sections, are rising, translating into increased rates of peripartum hysterectomy. This illustrates the importance of optimizing management strategies in major obstetric haemorrhage.²⁷ This includes the timing of hysterectomy, avoiding early and preventable removal of the uterus, as well as late hysterectomies associated with severe morbidity and death.

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PART 3

Discussion and summary

General discussion



MAIN RESULTS

In this thesis, I present the latest trends in maternal mortality in the Netherlands, the association of caesarean section with maternal morbidity and mortality and an analysis of postpartum laparotomy and peripartum hysterectomy as a specific indicator of severe morbidity at national, continental and global levels.

With the results from thirteen years of confidential enquiry into maternal deaths in the Netherlands, performed by the Dutch Audit Committee on Maternal Morbidity and Mortality (*Auditcommissie Maternale Sterfte en Morbiditeit, AMSM*), this thesis gives an update on the maternal mortality ratio (MMR), causes of death and lessons learned from maternal death audit. In 2006-2018, the MMR in the Netherlands dropped to half that of 1993-2005, and we have now entered a 'new era' for the further reduction of maternal mortality in the Netherlands, where for the first time pre-eclampsia is not the leading cause of death anymore, having been overtaken by cardiac disease. The inner circle of mortality has become smaller than ever before, however the outer circles of morbidity remain substantial in size and importance. (Figure 1)

Caesarean section rates are rising worldwide.¹ Given its surgical character, complications are inherent, leading to the procedure contributing to or even initiating the chain of events leading to morbidity or death in some women. When complications of childbirth arise, ultimately surgical intervention may be necessary to prevent further deterioration and avoid mortality. Therefore, though caesarean section, if performed for a clear evidence-based indication and under safe circumstances can save lives of women and neonates, possible maternal complications -however rare- should not be neglected or underestimated. Continuing along the line of surgical interventions during childbirth, we demonstrate that laparotomy postpartum is performed more frequently among women who underwent caesarean section compared to vaginal birth, with postpartum hysterectomy being performed as the main intervention during such surgery.

Thanks to the International Network of Obstetric Survey Systems (INOSS) the prevalence, indications and outcomes of peripartum hysterectomy could be compared between nine European countries on a nation-wide scale. In this multi-country study, it becomes clear that countries with higher rates of caesarean section and rates of women with previous caesarean section, have higher national prevalence figures of peripartum hysterectomy. Additionally, management of severe postpartum haemorrhage, in terms of surgical interventions and transfusion rates, differs greatly, with some countries performing hysterectomy relatively early in the course of morbid events, while others attempt multiple alternative uterus-sparing options before eventually removing the uterus. This might, to some extent, be explanatory for the observed differences in prevalence. Finally, peripartum hysterectomy is associated with substantial rates of maternal morbidity, not

only in high-income countries, but also in low- and middle-income countries as demonstrated in our worldwide meta-analysis.

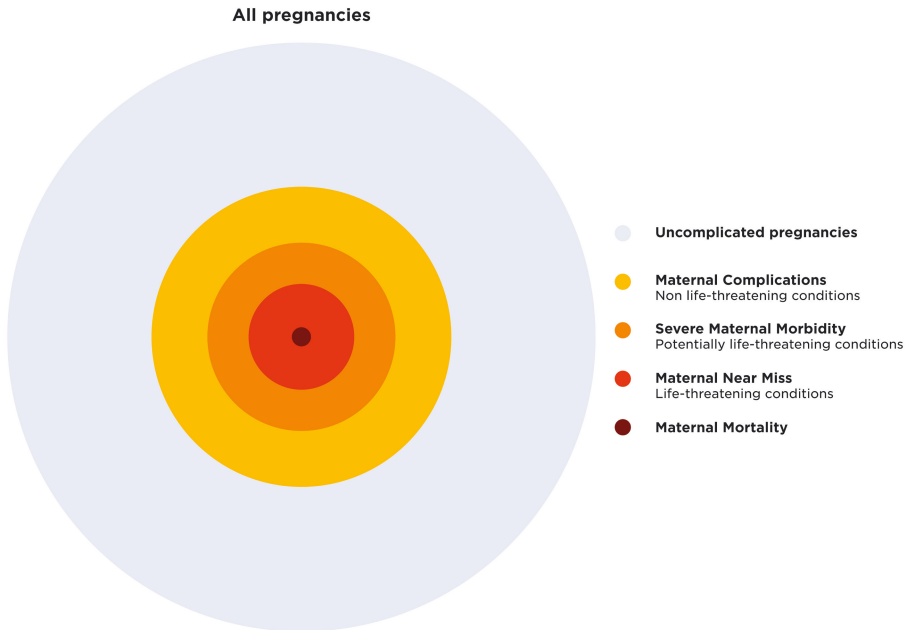


Figure 1. The circle of disease. From uncomplicated pregnancy to maternal mortality. Adapted from the Pyramid of Disease.

MATERNAL MORTALITY– A STEEP DECLINE

With global trends of maternal mortality dropping, the Netherlands now also follows this trend with the MMR dropping to 6.2 per 100,000 livebirths, the lowest ever described in our country.² This means that a decreasing trend has been achieved after the previous increase of the MMR in the Netherlands, when the MMR rose from 9.7 in 1982–1992 to 12.1 per 100,000 livebirths in 1993–2005.³ This finding is comparable to the trend of other high-income countries, where mortality rates seemed to stabilise or even rise in the nineties, followed by a steeper decline afterwards.⁴ The decrease of maternal mortality however, is under pressure and close monitoring remains crucial, also in high-income countries. In the US, a high-income country with generally high standards of care, a considerable increase in maternal mortality was observed, between 2000–2014 with an increase of by 26.6%, from 18.8 to 23.8.⁵ Contributors to this increase are sociodemographic risk factors, such as advanced maternal age or pre-existing non-communicable conditions such as diabetes, obesity and hypertension. There is also considerable inequity, with

women of black (non-Hispanic) ethnicity having a much higher chance to die. This increasing trend in MMR is not only a matter of concern in the US. From a global perspective, the recent COVID-19 pandemic did not only have a major impact on the well-being of the general population, but notably also on maternal health. While the first publications suggested no increased risk of adverse maternal outcomes among pregnant women, a recent systematic review and meta-analysis showed that there is an increased risk on ICU admission especially for women with pre-existing morbidity, advanced maternal age and obesity.^{6,7} This was also confirmed in a Dutch cohort of pregnant women with COVID-19, revealing that infected pregnant women were at increased risk of hospital admission, ICU admission and birth by caesarean section.⁸ Also, on a bigger scale, concerning the total pregnant population, concerns have been raised about the indirect impact on maternal and child health services, such as the effect that lockdowns had on e.g. accessibility of healthcare disruption of health systems and decreased access to food. Prediction models foresee a relative increase of 8.3 – 38.6% in maternal deaths per month in low- and middle-income countries.⁷ More recent publications, from the first year after the pandemic, from Brazil and Mexico, confirmed these concerns, showing substantial increase in the national maternal mortality rates.^{9,10}

Our findings are also in line with data from the EuroPeristat report in 2015, where the MMR was shown to be below 10 per 100,000 livebirths in most European countries.¹¹ Comparisons, however, should take place with caution since the vast majority of countries provide data from routine statistics and only very few are able to provide data from *enhanced systems* (i.e. record linkage usually combined with confidential enquiry). Maternal mortality reporting with information from only routine statistics leads to considerable underestimation.^{12, 13} As such, it may seem like the Netherlands or the UK have high MMRs compared to countries like Belgium, Germany, Greece and Spain which report exceptionally low MMRs (2.9 – 4.6). These differences may well be explained by differences in reporting and incomplete case ascertainment. Our findings underline once more that comparisons are only fair when these take into account the different strategies used to identify maternal deaths.

Best possible comparisons of the Dutch numbers are with Italy, France and the UK, countries within the same European region, of comparable high-income status, and with maternal mortality committees conducting confidential enquiries into maternal deaths. Both Italy (2007-2013) and France (2010 – 2012) reported higher rates of maternal deaths, the MMR being 9.2 and 10.3 per 100,000 livebirths respectively with haemorrhage being the leading cause of death in both countries.^{13,14} In the MMBRACE report from the UK for 2015-2017, the national MMR was 9.2, with indirect causes of death exceeding direct ones, and leading cause of death being cardiac disease.¹⁵ As such, in the Netherlands, the distribution of direct and indirect is comparable to that of Italy and France, with the leading cause of death, cardiac disease, the same as that of the UK.

Neurologic causes are now the third most common along with suicides when including late deaths. This implies that maternal mortality ceases to be a purely 'obstetric' problem. In the general population, there is an increased number of women with pre-existing health conditions who, thanks to improved medical care before conception reach fertile age and are now able to conceive and have 'high-risk' pregnancies. The physiological changes in pregnancy can aggravate pre-existing diseases (such as cardiological and neurological diseases) and make these women vulnerable for complications and adverse outcomes. Effort should be made to achieve early identification and counselling of these women. Pre-conception counselling and family planning must be a conjoined effort from general practitioners, other treating physicians and obstetricians. Women may not discuss family planning during routine follow up of chronic diseases, awareness should be created amongst all specialists (such as cardiologists, neurologists, internal medicine specialists, oncologists and psychiatrists) to bring up the topic. It should be routine practice to advise women proactively on these matters during their reproductive years. Pre-conception counselling is becoming a growing matter of interest, with non-obstetric specialists calling for timely counselling for women with cardiac disease, rheumatic disease and organ transplantation like kidney and pancreas.¹⁶⁻¹⁸ Additional insight into the causes of maternal mortality, and how pre-existing morbidities are influenced by pregnancy and vice versa, will hopefully lead to concrete advice for daily practice and improve future maternal outcome.

PURSUIT OF COMPLETENESS

For epidemiological studies of infrequent events, accuracy of prevalence relies on the quality of identification and collection processes. In the pursuit of completeness, complete case ascertainment will lead to more robust conclusions and validity. In the Netherlands, annual reports on causes of death are published by Statistics Netherlands relying on vital statistics, with information extracted from death certificates. Causes of death are coded according to ICD codes, and those related to maternal and pregnancy related death (ICD10 O00 – O99) represent the estimated number of maternal mortality.¹⁹ Parallel monitoring of maternal deaths is performed by the AMSM which is based on reporting of maternal deaths by clinicians. And while we find it hard to imagine that obstetricians in the Netherlands will omit to report the death of a woman under obstetric care, it is questionable whether the same applies for specialists outside the obstetric field. During early pregnancy or late postpartum, when no obstetric caregiver is involved, a death might not be attributed or related to pregnancy and thus not reported as such in the death report forms or to the AMSM.

These omissions may be compounded by the fact that maternal mortality has become such an infrequent event, not only for obstetricians but even more for other

specialists and general practitioners. In the previous maternal death reports in the Netherlands, cross-checking with Statistics Netherlands resulted in identification of additional cases, not reported to the AMSM, underreporting being 11%.³ And while information about these deaths was limited to age and cause of death, rendering external auditing impossible, addition of these cases makes the actual number of maternal deaths more accurate, enabling more robust MMR calculations and comparisons with other countries.

Even while the MMR is decreasing, caution should be taken first of all to remain vigilant and improve case ascertainment while keeping high quality of data available for enquiry. In other countries, for example Italy and France, case identification is performed after cross linkage of hospital discharge or birth and death registries.¹³ ²⁰ Linkage of electronic databases provides a way to identify underreporting, which is likely when relying only on reporting by clinicians without double-checking, such as is currently the situation in the Netherlands. However, despite this limitation, the Dutch system, with anonymous medical records being fully available rendering confidential enquiry a possibility in almost all reported deaths, still enables a unique insight into the care received during the chain of events leading to death. As such, there seems to be a complementary balance between complete exhaustivity on the one hand, where the actual number of maternal deaths is identified but information is sometimes incomplete and does not allow for full enquiry, and the quality of data on the other hand, accepting some degree of underreporting. The numbers themselves do not suffice in understanding the true reasons that led to the deaths of these women. It is the stories behind them that eventually, when understood in-depth, lead to lessons learned and improvements in care and avoid future maternal deaths by informing changes in clinical practice.

OVERCOMING CLASSIFICATION DIFFERENCES

Traditionally, causes of death are classified into direct, indirect and non-pregnancy related.²¹ The difference between direct and indirect may seem intuitive at first sight, but differences between countries suggest otherwise. By definition, indirect deaths are those from pre-existing disease aggravated during or due to pregnancy. However, pre-existing diseases might not be diagnosed beforehand or be present in a subclinical stage. Clear example are psychiatric disorders, with pre-existing disease often remaining undiagnosed if women never sought psychiatric evaluation before pregnancy. This resulted in different categorisation of suicide-related deaths between countries. Maternal suicides were previously categorised as indirect deaths. Later, in order to conform to the definition of indirect deaths (aggravation of pre-existing disease) these were categorised as direct or indirect depending on the presence of pre-existing psychiatric conditions.²² However, after the recommendation of the new ICD-MM, these are now categorised as direct

maternal deaths. Comparable difficulties are faced when deaths due to malignant conditions are categorised. During pregnancy, diagnostics and treatment are sometimes -often unjustified- adjusted to protect the foetus, leading to potential delays in diagnosis and therapy. Also, growth and malignant potential might be influenced by the hormonal status of pregnancy.

These dilemmas arise also in the attribution of the cause of death. This was previously demonstrated by comparison of differences in designating the cause of deaths between the UK and the Netherlands.^{23, 24} In the Netherlands, cause of death is attributed to the initial event initiating morbidity, while in the UK it is attributed to the most important morbid event.

All of the above lead to differences in categorisation of deaths between countries, not only with regard to direct and indirect but also in terms of the designated cause of death. This hampers comparisons between countries and settings. In light of declining numbers of maternal mortality it is time to shift the focus from the division into arbitrary categories, and work towards uniformity. The goal of maternal morbidity research ultimately is to reduce preventable deaths. We therefore agree with the previously suggested concept of addressing and comparing all pregnancy-related maternal deaths, using cause of death as the main category identifier. For this to succeed, uniformity of attribution of causes of death should be reached. In the absence of guidelines from the WHO, we propose an international comparison of classification strategies, between countries with an enhanced maternal mortality system and use of confidential enquiry, within a collaborative platform such as INOSS.

The latest trend in the Netherlands shows a reduction by fifty percent of the MMR. Efforts of past studies on morbidity and mortality seem to have contributed to shrinking the inner circle of morbidity: mortality. (Figure 1) In the conceptual framework of maternal morbidity, the proportions of these two inner most circles (severe morbidity and mortality) are correlated with each other. The progress from non-life-threatening complications to, eventually, maternal death is a continuum of the same pathophysiological morbidity pathway. The size of the circles is influenced directly by external factors such as demographic changes (older women, increase in migration), rising prevalence of risk factors (e.g. obesity), and changes in obstetric practice (such as increasing caesarean section rates). The results of the LEMMoN study, demonstrated substantial rates of severe maternal morbidity and a concordant increase in mortality in the nineties and early 2000 was also documented by Schutte et al. ^{3, 25} It was time to curb the increase. It is likely that these results created increased awareness for maternal conditions among obstetricians and patients. The NethOSS study on eclampsia revealed, for the first time, that the circle of life-threatening conditions had shrunk, with a decrease in eclampsia rates. With our results now also demonstrating a decrease in mortality, the lowest ever reported during 30 years of maternal morbidity and mortality registration. However, the progress should not always be taken for granted. Particularly in this time of

COVID-19, past gains are not to be taken for granted. Such unanticipated factors, can have serious rebound effects, and contribute to increases in maternal morbidity and mortality. Therefore, ongoing monitoring of the outcomes of maternity care is necessary. Only by timely recognition of increasing morbidity rates can new interventions lead to stable or smaller inner circles.

CAESAREAN SECTION – SHIFTING THE FOCUS FROM RATES TO OUTCOME

Caesarean section can be a lifesaving procedure when performed on strict medical indications such as correctly identified foetal distress, confirmed failure to progress or placenta praevia amongst others. It is the second most common performed surgery in the EU-27, performed more than 1.16 million times in 2018 and comprises almost 1/3 of all surgeries in very low-expenditure WHO member states.^{26, 27} However, this procedure is also associated with short- and long-term complications and, given its frequency, these complications deserve being scrutinized. The global caesarean section rate has risen, from 12.1% in 2000 to 21.1% in 2015.¹ This, contrary to previous advice by the WHO that rates above 9-16% do not lead to improved maternal or neonatal outcome.²⁸ Increase in caesarean section rates will concurrently lead to increases in complications rates. While in the poorest countries, at the population level, underuse and poor accessibility have to be overcome for maternal outcomes to further improve, at facility level in low-income and across the board in middle- and high-income settings increasing attention is rightly attributed to curb the unjustified increase of caesarean section rates. Proposed strategies aim to introduce clinical interventions such as external cephalic version (and in some settings re-introducing vaginal breech birth), promoting trial of labour after caesarean and midwife-led care, as well as approaches to educate women on unfounded beliefs with regard to mode of birth and promoting the dialogue between obstetricians, midwives and women on fear of childbirth.²⁹ In order to come to a change in actual clinical practice, clinicians and women and their communities must be made aware of the impact of surgery on maternal and neonatal outcome.

The most serious complication of caesarean section is maternal death, although this is infrequent in high-income settings. With absolute numbers of maternal mortality in high-income settings being low, the association with or contribution of caesarean section to mortality is difficult to estimate. Estimations are hampered by small numbers, differences in categorisation of elective and emergency caesarean, confounders like pre-existing morbidity or the indications that lead to caesarean section which can, in turn, be the cause of death. The results of our study demonstrate a threefold higher risk of death after caesarean section compared to vaginal birth, in line with previous literature from the US, Brazil, France.³⁰⁻³² With use

of detailed information from medical charts, we were able to distinguish cases in which the surgery was not related to the death, was the direct cause of death or was associated with the death somewhere in the chain of morbid events. By subtracting the first group from our analyses, we are able to calculate the contribution of caesarean section to maternal mortality. While previous studies aimed for a comparison of women with an uncomplicated medical history, undergoing either vaginal birth or caesarean section in a case-control study design, we were interested in maternal outcome of all women undergoing caesarean section from a nationwide perspective. In two other studies from Ireland and Turkey, a decreasing or stable MMR was observed during a period of increasing caesarean section rates.^{33, 34} The Irish study was based on one single hospital and two maternal deaths, making it too thin to generalise conclusions to the country or other facilities. The nationwide study from Turkey demonstrated that in an 11-year period with CS-rates rising above 50%, maternal mortality decreased simultaneously. However, better maternal outcomes were likely attributable to improved health care facilities rather than to the increased caesarean section rate. Our study goes beyond calculating the association of caesarean section with rates of mortality, but gives an estimation of the contribution of surgery to maternal mortality.

As caesarean section influences the size of the inner circle, mortality, it also influences the outer circles of maternal life-threatening events. In a previous nationwide study in the Netherlands, caesarean section (planned or emergency) was associated with five times higher risk of Severe Acute Maternal Morbidity (SAMM) and this was also the case for women with a previous caesarean section.²⁵ Caesarean section in a previous pregnancy increased the risk of SAMM threefold. (35) In the 2007 NICE guideline on caesarean section, reference is made to the potential complications of caesarean section. Referring to nine prospective studies that compared planned vaginal birth to planned caesarean section with the risk of postpartum hysterectomy, caesarean section was found to be six to ten times higher compared to vaginal birth. The studies included healthy women, with no previous caesarean section and uncomplicated pregnancies, and did not include women from low-income settings. Level of evidence of these studies was assessed to be low.

These results are supported by the three studies on laparotomy and hysterectomy in this thesis. Incidence of laparotomy postpartum after caesarean section is fifteen times higher compared to vaginal birth and even twenty-fold after emergency caesarean. This risk increase does not cease to exist at the end of the puerperium, which was demonstrated for long-term complications in a Danish population-based study where risk of re-laparotomy after hysterectomy was shown to be increased later in life among women with a history of caesarean section compared to women who only had vaginal birth(s).³⁶ Additionally, we demonstrate that hysterectomy is more prevalent in countries with higher caesarean section rates, and national rates of women with previous caesarean section. This is in line with

the fact that haemorrhage is one of the major short-term complications during and after caesarean section as well, the risk of abnormally invasive placentation being linearly associated with the number of previous caesarean sections, posing women at higher risk of bleeding complications and hysterectomy.

Although these complications may seem infrequent, it is only a matter of time before clinicians or women are confronted with them. In order to further unravel the extent to which caesarean sections contribute to maternal mortality, more robust studies can be performed by combining data from multiple countries, which should preferably have nationwide coverage. The INOSS has to date provided new insights into gaps of knowledge and has turned out to be a valuable platform to proceed with such research. This platform will help collect robust number of deaths for analysis and also, when studies are performed prospectively and in collaboration, may help eliminate problems arising from retrospectively pooled data, such as different study periods or categorisations.

For the Netherlands, where the latest rate of caesarean sections (17% in 2020³⁷) are generally relatively low compared to most other European countries, our results can contribute to: 1) improved counselling of women on mode of birth, 2) enhanced motivation to curb the increase in caesarean rates, 3) supporting future monitoring of maternal morbidity and its association with caesarean section.

PERIPARTUM HYSTERECTOMY, A SUFFICIENT INDICATOR FOR MAJOR OBSTETRIC HAEMORRHAGE?

Major obstetric haemorrhage is the leading cause of maternal mortality worldwide, accounting for almost one out of three deaths globally.³⁸ In high-income countries, haemorrhage has been pushed back to third place accounting for 16.3% of all deaths, as was shown in a systematic analysis by the WHO. At the same time, in some high-income countries, like Italy and France, haemorrhage has remained the commonest cause of death.^{13, 14} The incidence of postpartum haemorrhage has been shown to increase in many high-income countries, including the Netherlands where it rose from 4.1% in 2000 to 6.4% in 2013.³⁹ As such, although haemorrhage-related mortality rates are dropping in high-income settings, the incidence of postpartum haemorrhage appears to be increasing paradoxically. The burden of disease thus lies in bigger outer circles of morbidity (Figure 1) which, due to earlier recognition and improved management may be prevented from progressing to the inner circle of mortality. In the Netherlands, this rise was also observed in the increase of “mild” postpartum haemorrhage (1000 – 1500ml), and the concomitant decrease in transfusion rates.⁴⁰

During the first stages of bleeding, administration of colloids or crystalloid fluids, uterotonics and also the recent insight of adding tranexamic acid, is somewhat consistently reflected in international haemorrhage protocols. However,

the management of persistent bleeding is still a matter of ongoing debate. A population-based study, between six INOSS members (France, UK, Italy, Australia, the Netherlands and Denmark), on women with massive transfusion post-partum (eight or more units of red blood cells), identified great variation in the incidence of massive transfusion, as well as large differences in transfusion management and obstetric management.⁴¹ Striking was that 74% of women in Italy underwent hysterectomy, compared to approximately half of all women in the UK, France and Australia, versus just under 30% in the Netherlands and Denmark. The same trends are demonstrated in our studies, where prevalence of women who underwent hysterectomy varied considerably between nine countries participating in the INOSS, and also the same variation in surgical and obstetric management was observed. Both studies, with a different manner of identifying women with severe postpartum haemorrhage (massive transfusion vs. hysterectomy) arrive at the same conclusions and demonstrate similar differences in management, strengthening the validity of the conclusions. Studies comparing different interventions have, until now, not provided conclusive evidence on the optimal management sequence, leaving a large gap of knowledge.⁴² Additional research is therefore necessary to unravel and compare the effectiveness of surgical management of postpartum haemorrhage such as arterial embolisation and intrauterine balloon tamponade.

Severe obstetric haemorrhage is an important indicator of severe maternal morbidity. Unlike maternal mortality, which is a binary outcome, tools to measure maternal mortality have always been prone to discussions on matters of definition. The near-miss approach as defined by the WHO is based on organ-dysfunction criteria. As such, the approach enables identification of women with complications of severe postpartum haemorrhage when bleeding leads to organ disfunction such as shock, oliguria, failure to form clots or massive transfusion (≥ 5 units).⁴³ Peripartum hysterectomy performed for indication of infection or haemorrhage is one of the suggested clinical criteria. By identifying women with 'near miss', comparison of quality of health systems and facilities may perhaps be improved. The approach may also enable comparisons of prevalence and maternal outcomes of women with postpartum haemorrhage. Laparotomy postpartum with or without hysterectomy, transfusion with blood products or interventional radiology may all serve as indicators of severe postpartum haemorrhage. Prevalence of peripartum hysterectomy in low- and middle-income settings was found to be higher than in high-income countries, reflecting the different timing at which the procedure is performed, namely earlier in the course of bleeding in absence of conservative alternatives. In high-income countries, uterus-sparing interventions such as blood products, intrauterine balloon tamponade, interventional radiology are increasingly available.

As such, in the train of events during massive haemorrhage, not all women will reach the clinical and laboratory criteria to be identified as a "near-miss", which should not be taken to imply that these women did not have a severe clinical course

after childbirth or potentially-life threatening events. For example, women who underwent timely laparotomy for bleeding complications without hysterectomy, or averted hysterectomy by radiological interventions should be regarded as having sustained severe maternal morbidity. This suggests that the WHO tool may be more valuable for maternal morbidity identification in low- and middle-income settings.⁴⁴ Multiple other sets of indicators have been proposed, including recently by the American College of Obstetrics and Gynaecology and the EuroPeristat group, for maternal morbidity indicators in high-income settings.^{45, 46} The abundance of sets of indicators however make comparability across settings even more difficult. As proposed by prof Marian Knight from the University of Oxford, the next step could be a core indicator set, with core criteria applicable for all income settings with the ability to personalise for individual regions and countries.⁴⁷ An outcome set for conditions of severe maternal morbidity had already been proposed through a Delphi process by the INOSS.⁴⁸

Hysterectomy itself is an outcome of interest, but will not suffice as the optimal evaluation of all critical haemorrhage cases. In order to address all women with severe postpartum haemorrhage, we propose including all advanced clinical interventions used such as laparotomy for bleeding complications (with or without performing hysterectomy), radiological intervention or receiving ≥ 4 units of red cells. These data are relatively easy to collect retrospectively from clinical registries as well as prospectively in a manner comparable to what is already used by many of the INOSS countries. Such a definition does not vary greatly from the core outcome set proposed by the INOSS, except for the addition of radiological interventions, which are increasingly used in many European countries.⁴⁸

RECOMMENDATIONS

1. Raise awareness for reporting maternal deaths among all medical specialists and general practitioners, by involving them into the study of maternal mortality, presenting them outcomes and performing specific enquiries into cardiological, neurological or psychiatric related causes of mortality.
2. The Netherlands appears to be lagging behind in identification of late maternal deaths. Cross-checking with information from Statistics Netherlands should be re-introduced in order to minimise underreporting. Ideally, this is followed by access to medical records from the hospitals of midwifery practices enabling confidential enquiry.
3. Address all important underlying pregnancy-related causes of death and important non-pregnancy related conditions, with clear identification of lessons learned rather than focusing on arbitrary categorisation into direct and indirect.
4. Overcome differences in attribution of cause of death, by collaboration of different maternal mortality committees or through international obstetric collaborations such as the INOSS.
5. Broaden indicators for severe obstetric haemorrhage by incorporating additional clinical interventions other than peripartum hysterectomy only, such as mass transfusion, laparotomy and interventional radiology.
6. Harmonise definitions and outcome sets of obstetric haemorrhage within the INOSS collaboration. Thereby, future studies could create additional insight into the optimal management of major obstetric haemorrhage.
7. Data on obstetric haemorrhage and hysterectomy in the Netherlands are now outdated by almost a decade or longer. New prospective NethOSS studies on major obstetric haemorrhage including pregnancy-related hysterectomy should be set up in combination with the INOSS.

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Summary
Samenvatting



SUMMARY

Maternal morbidity and mortality are severe, unforeseen and sorrowful outcomes of pregnancy. They serve as quality indicators of obstetric care and studies on this subject are essential for improving obstetric care. The two main topics of this thesis are maternal mortality in the Netherlands and peripartum hysterectomy. Peripartum hysterectomy is a last-resort intervention in case of severe pregnancy- or birth-related complications and therefore used as a morbidity indicator. **Part 1** of this thesis focused on maternal mortality in the Netherlands. We presented the incidence, causes of death and lessons learned from the audit of every maternal death by the Dutch Auditcommittee Maternal Mortality and Severe Morbidity (*Auditcommissie Maternale Sterfte en Morbiditeit*, AMSM). In **part 2** we studied the incidence, outcomes and management of peripartum hysterectomy on national, European and global level thanks to the International Network of Obstetric Survey Systems (INOSS).

PART 1: MATERNAL MORTALITY IN THE NETHERLANDS

In **chapter 2** we presented the results of maternal mortality registration and auditing, in the Netherlands, between 2006-2018. We calculated the national maternal mortality ratio (MMR), described main causes of death and presented the *lessons learned* from auditing of maternal deaths by the AMSM. The ultimate goal of confidential enquiries into maternal deaths is to improve obstetric outcomes and prevent avoidable maternal deaths. Main results were the decline of the national MMR, being the lowest ever calculated. Most common underlying cause of death were cardiovascular diseases followed by hypertensive disorders and thromboembolism. We identified risk-factors such as teenage pregnancies, advanced maternal age and severe underlying health disorders. Also, we saw that women with a non-Western ethnic background, especially those from Surinam or the Dutch Antilles had a significantly higher risk of dying during pregnancy compared to white native women. In nearly half of all maternal deaths we observed *improvable factors* in the healthcare process. Our results depict the high standards of maternal and obstetric care in the Netherlands. However, we need to remain vigilant, the decrease in MMR should not be taken for granted for the future.

In **chapter 3** we explore the association between caesarean section and maternal mortality. We included all maternal deaths reported to the AMSM between 1999 and 2013 and compared the risk of death for women after vaginal birth and caesarean section. After in-depth assessment of all maternal deaths, we were able to exclude cases where the caesarean section was not associated with the death of the woman. Also we discriminated between cases in which the death was associated with the caesarean section, and those in which the surgery directly led to death. Our

results showed that women after caesarean section had a three times higher risk of death compared to vaginal birth. In one out of ten deaths the caesarean in fact initiated the train of events that led to death. These results underline that the short term risks and complications of caesarean section should not be underestimated, especially in light of the rapidly increasing caesarean section rates worldwide.

PART 2: MATERNAL MORBIDITY

Chapter 4 is a secondary analysis of data from the LEMMoN-study (*Landelijke studie naar Ethnische determinanten van Maternale Morbiditeit in Nederland*). This was a prospective, population-based cohort study between 2004-2006, which included women with severe acute maternal morbidity. We analysed women who underwent a (re-)laparotomy after vaginal birth or caesarean section. We found a 16-times higher risk for laparotomy following caesarean section compared to vaginal birth. This risk was highest for women following emergency caesarean section and women with a previous caesarean scar. During the re-intervention, peripartum hysterectomy was the most commonly performed procedure. This finding formed the basis for the following chapters where peripartum hysterectomy was used as a proxy for severe maternal morbidity.

Chapter 5 is an update of a previous systematic review and meta-analysis on the incidence, indications and outcomes of emergency peripartum hysterectomy worldwide. We included studies reporting on the emergency peripartum hysterectomy and compared these outcomes between different income settings. The results showed that countries from low- and middle-income settings had the highest incidence of peripartum hysterectomy, which was most commonly performed due to uterine rupture. Globally, the commonest indication was *placenta accreta spectrum disorder* and we saw that compression techniques were the most commonly applied type of management to prevent peripartum hysterectomy. This update was improved by the inclusion of several population-based studies, which present the most accurate national estimates. We recommend using a broader definition of emergency peripartum hysterectomy, including hysterectomies up to six weeks postpartum, in order to include indications such as severe postpartum infections. Finally, the results point out the considerable differences that persist between different income settings.

Chapters 6 and 7 are paired publications made possible by the collaboration of national obstetric surveillance systems within the INOSS. We compared data on peripartum hysterectomy between nine nationwide studies from Belgium, Denmark, England, France, Italy, the Netherlands, Norway, Slovakia and Sweden. In **chapter 6** we focused on the differences in definitions and indications. After overcoming the differences in applied definitions, we found marked variation in the incidence between countries. Countries with higher caesarean section rates and

larger proportions of women with a previous caesarean section had higher national rates of peripartum hysterectomy. Most common indications were uterine atony and *placenta accreta spectrum* disorder. In continuation of these results, in **chapter 7**, we compared the management of severe postpartum haemorrhage that eventually led to peripartum hysterectomy between countries. We separated women who underwent hysterectomy due to *placenta accreta spectrum* as a separate category and described all surgical and non-surgical management options, again pointing out marked variation in management. These two publications underline the importance of collaboration between nationwide studies of (rare) obstetric interventions. This will enable pooling sufficient numbers, more powerful conclusions and identification of best clinical practice.

SAMENVATTING

Maternale morbiditeit en mortaliteit zijn ernstige, onvoorziene en verdrietige uitkomsten van een zwangerschap. Onderzoek naar de verschillende oorzaken en vormen van sterfte en ziekte heeft enerzijds als doel om inzicht te krijgen in de frequentie, welke dient als een kwaliteitsindicator van de geleverde zorg, en anderzijds om de kwaliteit van de geleverde obstetrische zorg te verbeteren.

In dit proefschrift ligt de nadruk op twee belangrijke uitkomsten: moedersterfte in Nederland en de baarmoederverwijdering rond de bevalling, een indicator van zeer ernstige maternale morbiditeit. Een dergelijke ‘peripartum hysterectomie’ is een laatste redmiddel bij zeer ernstig bloedverlies of ernstige infectie in het kraambed. **Deel 1** van dit proefschrift omvat ons onderzoek naar moedersterfte in Nederland met behulp van gegevens van de Auditcommissie Maternale Sterfte en Morbiditeit. **Deel 2** van dit proefschrift is gericht op de peripartum hysterectomie in Nederland, en daarbuiten.

DEEL 1: MATERNALE MORTALITEIT IN NEDERLAND

In **hoofdstuk 2** onderzochten we het optreden van moedersterfte in Nederland in de periode 2006-2018. We berekenden de maternale mortaliteitsratio (MMR) en beschreven de oorzaken. Daarnaast, presenteerden we de *lessons learned* die de Auditcommissie Maternale Sterfte en Morbiditeit (AMSM) formuleert na de inhoudelijke beoordeling van elk sterftegeval. Doel van dit onderzoek naar moedersterfte is om, naast het monitoren van de aantallen, vermijdbare sterfte in de toekomst te voorkomen. We zagen dat de MMR van Nederland sterk gedaald is. De meest voorkomende doodsoorzaak waren aandoeningen van het hart- en vaatstelsel, gevolgd door hypertensieve aandoeningen en trombo-embolieën. We identificeerden risicofactoren zoals tienerzwangerschappen, gevorderde maternale leeftijd, ernstige pre-existente aandoeningen, maar ook de etnische achtergrond van de zwangere. Vrouwen met een niet-Westerse migratie achtergrond, in het bijzonder vrouwen uit Suriname en de Nederlandse Antillen, hadden een driemaal hogere kans te overlijden in vergelijking met Nederlandse vrouwen zonder migratieachtergrond. In de helft van alle overleden vrouwen was sprake van *verbeterbare factoren* in de geleverde zorg. Het relatief lage aantal ‘late’ moedersterfte (sterfte later dan 6 weken na de bevalling) en indirecte doodsoorzaken, in vergelijking met andere Europese landen met een moedersterfte commissie zoals bijvoorbeeld Engeland, zijn suggestief voor enige mate van onderrapportage en pleiten voor de noodzaak van betrouwbaardere registratiemethodes in de toekomst.

In **hoofdstuk 3** onderzochten we de mate waarin een keizersnede een rol speelt in het overlijden van een vrouw. We onderzochten alle gevallen van moedersterfte die gemeld waren bij de AMSM tussen 1999 en 2013 en vergeleken

het aantal vrouwen dat overleed na een keizersnede met vrouwen die overleden na een vaginale baring. Middels een inhoudelijke beoordeling van elk afzonderlijk overlijden, excludeerden wij sterfgevallen waarin de keizersnede geen rol speelde. We concludeerden dat drie keer meer vrouwen waren overleden na een keizersnede dan na een vaginale bevalling. Verder vonden we dat in een op de tien vrouwen die waren overleden na een keizersnede, de dood het directe gevolg was van de keizersnede. De resultaten benadrukken dat de korte termijn risico's en complicaties van een keizersnede niet moeten worden onderschat, vooral met de kennis dat wereldwijd het aantal keizersneden al jaren rap stijgt.

DEEL 2: MATERNALE MORBIDITEIT

Hoofdstuk 4 is een secundaire analyse van data van de LEMMoN-studie (*Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland*). Deze landelijke studie tussen 2004 en 2006 includeerde vrouwen met vooraf gedefinieerde zeer ernstige zwangerschapscomplicaties. Binnen deze groep analyseerden wij vrouwen die een (re-)laparotomie ondergingen na hun bevalling. Hieruit kwam naar voren dat vrouwen na een keizersnede een 16 keer hoger risico hadden een re-laparotomie te ondergaan, ten opzichten van vrouwen die vaginaal waren bevallen. Het risico op een reïnterventie was hoger na een spoed-keizersnede, en voor vrouwen die een keizersnede in de voorgeschiedenis hadden. Een peripartum hysterectomie was de meest uitgevoerde ingreep tijdens de chirurgische reïnterventie. Deze uitkomsten vormden de basis om peripartum hysterectomie, als indicator van ernstige maternale morbiditeit, nader te onderzoeken in de volgende hoofdstukken.

Hoofdstuk 5 is een *systematic review* en meta-analyse over peripartum hysterectomie. We onderzochten de wereldwijde incidentie, indicaties en uitkomsten van peripartum hysterectomie en vergeleken deze tussen laag-middel- en hoge-inkomenslanden. We zagen dat lage- en middeninkomenslanden de hoogste incidentie hadden van peripartum hysterectomie. De belangrijkste indicatie wereldwijd was een abnormaal ingegroeide placenta in de baarmoeder (*placenta accreta spectrum*). Verder laten de resultaten het belang zien van populatie-brede studies naar zeldzame oorzaken van maternale morbiditeit. Ook is het belangrijk een uniforme definitie te hanteren die reikt tot zes weken postpartum, om hysterectomieën in verband met ernstige infecties tijdens het kraambed te kunnen bestuderen naast die in verband met ernstig bloedverlies. Tenslotte lijkt er nog altijd een groot verschil te bestaan in de incidentie maar ook in de uitkomsten van moeders die deze zeldzame maar ingrijpende operatie ondergaan.

Hoofdstuk 6 en 7 vormt een tweeluik over peripartum hysterectomie, dat te danken is aan de internationale samenwerking van verschillende landelijke obstetrische registratiestudies binnen de *International Network of Obstetric Survey*

Systems (INOSS). We vergeleken de gegevens van negen landelijke studies naar peripartum hysterectomie uitgevoerd in België, Denemarken, Engeland, Frankrijk, Italië, Nederland, Noorwegen, Slowakije en Zweden. Het eerste deel, **hoofdstuk 6** gaat over de gehanteerde definities en indicaties. We zagen dat meerdere definities gebruikt werden, al naar gelang het te onderzoeken doel. Na het uniformeren van de definitie vonden we grote verschillen in de frequentie van uitvoeren van peripartum hysterectomie tussen de negen landen. We zagen dat de incidentie hoger was in landen met een hoger percentage keizersneden, onder vrouwen die bevielen middels een keizersnede of met een keizersnede in de voorgeschiedenis hadden. De belangrijkste oorzaken waren een niet goed contraherende baarmoeder na de bevalling (uterus atonie) en *placenta accreta spectrum*. Vervolgens, in **hoofdstuk 7**, onderzochten we het klinisch beloop dat leidde tot de baarmoederverwijdering. Hierin maakte we onderscheid tussen vrouwen met en zonder en *placenta accreta spectrum* en beschreven de belangrijkste toegepaste chirurgische en niet-chirurgische obstetrische interventies die vrouwen ondergingen. We zagen dat er grote verschillen waren in de toegepaste interventies tussen de 9 landen. Deze twee studies onderstrepen het belang van internationale samenwerking. Op deze manier is het mogelijk om zeldzame obstetrische aandoeningen beter te bestuderen, door voldoende grote aantallen te verzamelen en inzicht te verkrijgen in de verschillen tussen landen en, op die manier, te komen tot aanbevelingen voor betere zorg voor zwangere vrouwen.

APPENDICES

List of Publications

Curriculum Vitae

Dankwoord

Safe Motherhood Series



LIST OF PUBLICATIONS

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* Contributed equally. Confidential enquiry into maternal deaths in the Netherlands, 2006-2018.

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CURRICULUM VITAE

Athanasios Kallianidis was born on march 7th, 1990 in Thessaloniki, Greece and lived together with his parents (Vasilis and Sandra) and sister (Christina). He graduated from the secondary school *Geniko Lykeio* in Panorama, Thessaloniki in 2007. He moved to the Netherlands, to study Mechanical Engineering at the Technical University of Delft for one year, after which he decided to study Medicine in Leiden. During the beginning of his Master of Science he met prof. Jos van Roosmalen, and together with Marrit Smit he wrote his first scientific article in the field of Obstetrics. This formed the basis of his interest in Obstetrics and Gynaecology. In 2015 he obtained his medical degree, after which he worked as a physician (ANIOS) at the *Westeinde* Hospital in the Hague and *HAGA* Hospital. During this period he met dr. Thomas van den Akker (later prof.), with who he continued his research into the field of maternal morbidity and mortality, which later proved to be the start of a successful PhD under the supervision of prof. van Lith. In 2017 he started his residency in Obstetrics and Gynaecology at Reinier de Graaf Gasthuis, Delft and at Leiden University Medical Centre. Now Athanasios lives together with Rinske Krul in Wassenaar.

DANKWOORD

Thomas, Parijs voelde zo ver weg, met talloze cols van de buitencategorie die we moesten trotseren, maar deze teamprestatie is volbracht dankzij een ongekende ploegleider zoals jij. Bedankt voor je steun, hulp, mentorschap en vertrouwen in mij; samen zullen we blijven koersen om de obstetrische zorg tot een hoger niveau te brengen.

Jos, bedankt voor jou begeleiding vanaf het prille begin van mijn carrière; jij was voor mij een mentor, begeleider en vriend. Je inspireerde mij om een gynaecoloog te worden met hart voor de kliniek, de vrouw en de wetenschap.

Jan, bedankt voor je hulp tijdens dit hele traject. Jouw helicopterview heeft het mogelijk gemaakt om dit traject te kunnen afronden tijdens mijn opleiding.

Kitty, jouw rol als voorzitter van de AMSM en de INOSS was van onschatbare waarde in het voltooien van dit proefschrift. Bedankt voor de mogelijkheden die jij mij gaf en je kritische en scherpe blik in al onze gezamenlijke publicaties.

Leden van de Auditcommissie Maternale Sterfte en Morbiditeit van nu en van vroeger, dit proefschrift was nooit mogelijk geweest zonder jullie onvoorwaardelijke inzet voor het verzamelen en auditen van moedersterfte in Nederland. Het is een ontzettende eer om lid te zijn van deze commissie en samen een steentje bij te dragen aan de obstetrische zorg in Nederland.

Dear Marian, Serena, Catherine and all INOSS members, thank you for giving me the opportunity to contribute to your mission in improving knowledge and contributing to evidence in obstetrics. It is an honor to be part of such an incredible ambitious club of people.

Beste Bente, Loutje en Douwe, zonder jullie was het een stuk minder leuk geweest om onderzoek te doen, bedankt voor jullie hulp, enthousiasme en inzet in onze gezamenlijke artikelen.

Ivanka, jou hulp was zo ontzettend belangrijk en heeft onderzoek doen en in opleiding zijn zo veel makkelijker gemaakt. Jou ondersteuning in alle praktische zaken rondom de PhD was van onschatbare waarde.

Kitty, Marieke en Claudia, ik kon mezelf geen betere opleiders wensen dan jullie. Jullie hebben mij gevormd tot de gynaecoloog die ik (bijna) ben, mij altijd ondersteund en ruimte gegund om onderzoek te doen.

Nadia, Angelos, Jeroen, Kim, Fokkeden, Merlijn een echte K6'er ben ik nooit geweest, maar jullie hebben mijn flitsbezoek aan fulltime onderzoek een stuk leuker gemaakt.

Collega's van het LUMC, Reinier de Graaf, Groene Hart, HMC Westeinde en HagaZiekenhuis wat heb ik genoten van samenwerken met jullie. Samen dragen we ons steentje bij in goeie zorg voor zwangeren, waar dit proefschrift in zijn kern over gaat.

Mannen van A.H.C. Sap: Ties, Jesse, Daniël, Daan, Pieter, Rik, Lennart, Wim, Barry en Stefan, we hebben een stevige band gevormd met zijn allen in Leiden en

sindsdien zijn wij een onafscheidelijke groep vrienden. Ik hoop samen met jullie nog talloze prachtige momenten te mogen beleven.

Hanna, Hester, Mink en Daniël, studeren met jullie was een feestje en ik ben zo blij dat we tot op de dag van vandaag zo een goede band met zijn allen onderhouden. Dank voor alle prachtige herinneringen in Leiden en al onze city-trips.

Max, Emiel, Ard, Patrick, Arie en Martijn, ik was diegene die geen ingenieur zou worden. Dankzij jullie ben ik zo goed geland in Nederland in 2007 en onze Delftse vriendschap is mij ontzettend dierbaar.

Lieve mam, pap en Stien dank voor jullie onvoorwaardelijke liefde en steun de afgelopen jaren. Ik ben enorm trots om dit moment met jullie te kunnen delen.

Wim, Marijke, Ellen en Claudia jullie liefde en hulp is altijd van onschatbare waarde geweest. Een goed begin is het halve werk, dank jullie wel dat jullie er altijd voor mij waren.

Freek en Ferry, het leven is zo veel meer dan alleen maar wetenschap en dienst doen, en dankzij jullie bleef ik gemotiveerd en opgeladen. We hebben samen zo een mooie tijd gehad tijdens de opleiding en daarbuiten, ik reken me zelf rijk met vrienden zoals jullie.

Daan, vanaf dag één in Leiden trokken we veel op samen en hebben we ontzettend veel mooie momenten beleefd dankzij jou sportieve, reislustige, openhartige en eerlijke karakter. Ik vind het een ongelofelijke eer dat jij mij wil bij staan bij deze promotie.

Allerliefste Rinske, jij bent zo ontzettend belangrijk voor mij geweest afgelopen jaren, samen hebben de grootste lol tijdens reizen, klimmen, fietsen, hardlopen en zo veel meer. Ik beloof je dat we alle *quality-time* dubbel in gaan halen die ik afgelopen jaren van ons geleend heb.

SAFE MOTHERHOOD SERIES

International Safe Motherhood & Reproductive Health



The Dutch Working Party 'International Safe Motherhood and Reproductive Health' aims to contribute to improvement of the reproductive health status of women around the globe, in particular by collaborating with local health workers (<http://www.safemotherhood.nl>). The Working Party is part of both the Dutch Society of Obstetrics and Gynaecology (NVOG) and the Dutch Society for International Health and Tropical Medicine (NVTG). The activities that are undertaken under the umbrella of the Working Party can be grouped into four pillars: education, patient care, research and advocacy.

Research activities are undertaken by (medical) students, Medical Doctors International Health and Tropical Medicine and many others. Some research activities develop into PhD-trajectories. PhD- candidates all over the world, Dutch and non-Dutch, work on finding locally acceptable and achievable ways to improve the quality of maternal health services, supervised by different members of the Working Party. Professor Jos van Roosmalen initiated the Safe Motherhood Series, which started in 1995.

THE SAFE MOTHERHOOD SERIES

- The role of oral (methyl)ergometrin in the prevention of postpartum haemorrhage. (**Akosua de Groot**), Radboud UMC, Nijmegen, the Netherlands, 1995
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