# SEVERE ACUTE MATERNAL MORBIDITY

## RISK FACTORS IN THE NETHERLANDS AND VALIDATION OF THE WHO MATERNAL NEAR MISS TOOL

TOM WITTEVEEN

# SAFE MOTHERHOOD

Severe acute maternal morbidity: risk factors in the Netherlands and validation of the WHO Maternal Near Miss tool

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"There are things known and there are things unknown, and in between are the doors of perception"

**Aldous Huxley**
The Doors of Perception, 1954

# CONTENTS

# CHAPTER 1

## GENERAL INTRODUCTION

## BACKGROUND

Nowadays, maternal mortality during pregnancy, delivery and puerperium in high-income countries is low. In the majority of maternal deaths the situation or factors surrounding the event are specific and not generalizable to the larger population. Therefore, severe acute maternal morbidity (SAMM) has been introduced as an important and useful adjunct to maternal death inquiries [1]. The analysis of women sustaining SAMM, preferably on a nationwide scale, provides a more reliable indicator of the quality of maternal health care. After reliable surveillance is established, the ultimate goal is to identify substandard care, preferably through a systematic audit process. Recommendations from such audits are then implemented to prevent maternal morbidity and mortality. This thesis is conducted as a significant addition to the existing literature and research in the pursuit of a safe motherhood.

## AIM OF THESIS

The general aims of this thesis are to analyse several important risk factors for SAMM in the Netherlands and to validate the recently proposed WHO Maternal Near Miss (MNM) tool to detect and monitor SAMM worldwide, using a two-year nationwide prospective study (see end of this chapter). The ratio behind the different subjects selected in this thesis is explained by differences in economic disparity throughout the globe. Where the effect of poverty is undeniably present in maternal health care, we hypothesize that -in contrast- the consequence of 'wealth' in high resource settings might also have its effect on pregnancy outcome. In this thesis, we refer to obstetrics in affluent societies where such factors are common as maternal "wealth care" instead of health care. The aim is to focus on "wealth care" factors that are common in contemporary maternity care: the globally increasing problem of overweight, the increased use of assisted reproductive techniques, the increasing rates of multiple pregnancies, and the increasing caesarean section rates worldwide and the associated increase in peripartum laparotomies.

The second part of this thesis contributes to the international discussion regarding definitions of SAMM. The World Health Organization (WHO) has established a definition for SAMM and created an audit system of maternity care using the WHO MNM tool (including five disease-, four intervention- and seven organ dysfunction-based criteria) [2]. Our aim was to analyse potential difficulties in using the WHO MNM tool to detect SAMM in both low- and high-income countries. We hypothesized that it may be problematic to pursue cross-country comparisons across very different contexts. We sought to identify such challenges and recommend improvements.

## MAIN RESEARCH QUESTIONS

1. Is overweight an independent risk factor for severe acute maternal morbidity in the Netherlands?
2. What is the incidence of severe acute maternal morbidity in multiple pregnancies?
3. What is the relation between chorionicity in multiple pregnancies and severe acute maternal morbidity in the Netherlands?
4. What is the relation of assisted reproductive techniques and severe acute maternal morbidity in multiple pregnancies in the Netherlands?
5. What is the incidence of puerperal uterine inversion in the Netherlands?
6. What is the incidence of laparotomy after childbirth in the Netherlands in relation to mode of delivery?
7. Are the WHO Maternal Near Miss tool and the organ dysfunction criteria applicable in a high-income country?
8. Is the WHO Maternal Near Miss tool useful for cross-country application and comparison in high- and low-income settings?

## OUTLINE OF THIS THESIS

The first part of the thesis addresses a number of subsets of a population sustaining SAMM in search for associated risk factors.

**Chapter 2** addresses the consequences of the increasing proportion of overweight in the Netherlands by comparing women with overweight sustaining SAMM with a low-risk population containing women who did not sustain SAMM.

In **Chapter 3** women with multiple gestations are considered and the incidence for them to develop SAMM during pregnancy, delivery and puerperium is calculated using the Netherlands Perinatal Registry (PRN) as a reference. This chapter also searches for associated risk factors (such as chorionicity or assisted reproductive techniques) for women carrying multiple gestations who endured SAMM, to improve antenatal health care counselling.

**Chapter 4** describes the first population-based study for a very rare obstetric complication of yet unknown origin: uterine inversion, often leading to major haemorrhage. Associated risk factors will be presented in search for its etiology.

In **Chapter 5**, the largest study performed in the literature regarding laparotomy during pregnancy, childbirth and the puerperium is presented. This chapter gives the incidence and relative risks of laparotomy after childbirth in relation with mode of delivery.

The second part of the thesis addresses the international discussion regarding definitions of SAMM. Notwithstanding some controversy, the WHO has established a definition for pregnant women sustaining SAMM in general. These women are also called "maternal near misses" and are defined as "women who nearly died from a complication during pregnancy, childbirth or within 42 days after termination of pregnancy" [2].

Although consensus was reached for this general definition, there is worldwide debate which cases should be attributed the term "near miss". Main obstacles in this debate are the absence of robust definitions for different maternal morbidity conditions and the balance between under- and overreporting resulting from missed or included cases. WHO has created an audit system of maternal care using the WHO MNM tool, which should be used to detect severe maternal outcome nationwide as well as for international comparison. This part of the thesis includes studies that in **Chapter 6** validate the WHO MNM tool in the Netherlands and in **Chapter 7** analyse whether this tool is useful for cross-country application and comparison in one high- and two low-income countries without considering the different contexts of these countries.
To conclude this thesis, **Chapter 8** and **Chapter 9** contain a general discussion and conclusion and a summary of results. **Chapter 10** contains a list of publications, the authors' curriculum vitae and the acknowledgements or personal messages from the author of this thesis.

## ABBREVIATIONS AND DEFINITIONS

Severe acute maternal morbidity (SAMM) = all severe maternal morbidity during pregnancy, childbirth and puerperium meeting the inclusion criteria of the Dutch LEMMoN-study.

Maternal near miss (MNM) = all severe maternal morbidity which nearly led to death from a complication during pregnancy, childbirth or within 42 days after termination of pregnancy, meeting the inclusion criteria of the WHO MNM tool.

Severe maternal outcome (SMO) = maternal near miss and maternal mortality.

## THE LEMMON-STUDY

This thesis is part of a two-year nationwide prospective cohort study called the LEMMoN-study (from Dutch: Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland). Most important methodological considerations and aspects of this study have been published before. However, since it forms an important basis for this thesis, a short outline of this study is given [3,4].
This study assessed SAMM during pregnancy, delivery and puerperium in the Netherlands, including pregnant women with SAMM in the period 1st August 2004 until 1st August 2006. All Dutch hospitals with a maternity unit (98 facilities; of which 8 tertiary care hospitals, 35 non-academic teaching hospitals and 55 general hospitals) participated during this period.
Inclusion criteria for SAMM were categorized into five groups: intensive care unit (ICU) admission, uterine rupture, eclampsia or HELLP-syndrome (only when accompanied by liver haematoma or rupture), major obstetric haemorrhage (MOH, defined as ≥4 units of packed cells, peripartum hysterectomy or arterial embolization) and a miscellaneous group, containing rare cases of SAMM according to the treating obstetrician, which could not be included in any of the other four groups (for

definitions, see Figure 1). Maternal deaths reported to the national Maternal Mortality Committee of the Dutch Society of Obstetrics and Gynaecology by the attending obstetrician were also included. Detailed results regarding the performance, such as hospital participation or incidence of SAMM per hospital / region, have been described previously [4].

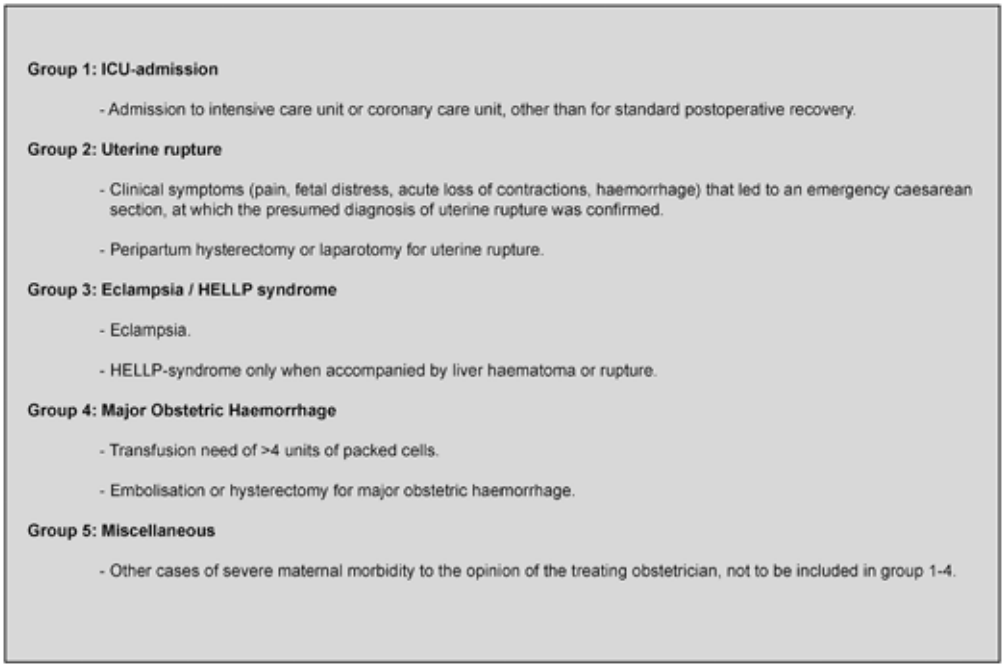


**Figure 1** | Inclusion criteria of the LEMMoN-study

## THE NETHERLANDS PERINATAL REGISTRY

In the first part of this thesis (Chapters 3-5) the Netherlands Perinatal Registry (PRN) is used as a reference population in search for associated risk factors for SAMM. The PRN is the result of the collaboration between four Dutch professional organisations (Royal Organisation of Midwives in the Netherlands (KNOV); National Organisation of General Practitioners (LHV); Dutch Society of Obstetrics & Gynaecology (NVOG) and the Paediatric Association of the Netherlands (NvK)). This national registration system is initiated and specialized to monitor the quality of maternity care and gives insight in perinatal care process and outcome. This registration system monitors a large set of parameters and results can be obtained on individual researchers' request or the yearly open access publications. In this thesis both methods have been used to obtain reference data for comparison to our SAMM population. The method section of each chapter contains an explanation as to which data are used in that specific study.

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# PART 1

## SEVERE ACUTE MATERNAL MORBIDITY AND RISK FACTORS IN THE NETHERLANDS

# CHAPTER 2

## OVERWEIGHT AND SEVERE ACUTE MATERNAL MORBIDITY IN A LOW-RISK PREGNANT POPULATION IN THE NETHERLANDS

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## ABSTRACT

**Objective:** To investigate the association between overweight and severe acute maternal morbidity (SAMM) in a low-risk pregnant population.

**Design:** Nationwide case-control study.

**Setting:** The Netherlands, august 2004 to august 2006.

**Population:** 1567 cases from initially primary care and 2994 women from primary care practices as controls, out of 371 012 women delivering in the Netherlands during the study period.

**Methods:** Cases were women with SAMM obtained from a nationwide prospective study. All women in this cohort who initially had low-risk pregnancies were compared with low-risk women without SAMM to calculate odd ratios (ORs) to develop SAMM by body mass index (BMI) category. We divided body mass index in three overweight categories and calculated the ORs (95% CI) of total SAMM and per specific endpoint by logistic regression, with normal weight as reference. We adjusted for age, parity and socio-economic status.

**Main Outcome Measures:** SAMM, defined as Intensive Care Unit (ICU)-admission, Uterine Rupture, Eclampsia or Major Obstetric Haemorrhage (MOH).

**Results:** SAMM was reported in 1567 women who started as low-risk pregnancies. BMI was available in 1097 (70.0%) cases and 2994 control subjects were included. Analysis showed a dose response relation for overweight (aOR, 1.3; 95% CI, 1.0-1.5), obese (aOR, 1.4; 95% CI, 1.1-1.9) and morbidly obese (aOR, 2.1; 95% CI, 1.3-3.2) women to develop SAMM compared to normal weight. Sub analysis showed the same dose response relation for ICU-admission, Uterine Rupture and Eclampsia. We found no association for MOH.

**Conclusion:** Overweight without pre-existent co-morbidity is an important risk-indicator for developing SAMM. This risk increases with an increasing body mass index.

## INTRODUCTION

The increasing prevalence of overweight and obesity is a dramatic trend all over the world, especially in western countries. The United States has taken the lead with more than one-third of adult women being obese [1]. In the United Kingdom the prevalence of obesity at the start of pregnancy has increased from 9,9% to 16% in a 15-year period [2]. In the Netherlands the prevalence of self-reported overweight and obesity in women increased from respectively 30% and 6% in 1981 to 42% and 12% in 2004 [3]. In many other western countries similar trends are observed [4-5]. Obesity is a risk factor for chronic diseases such as cardiovascular disease and type 2 diabetes [6-7]. In obstetrics, women with overweight have a higher risk for adverse neonatal outcomes [8-12] and many studies have reported an increased risk for gestational diabetes, pre-eclampsia and caesarean delivery [13-16]. As a consequence overweight leads to increased utilisation of healthcare during pregnancy and therefore to higher costs [17-19]. We hypothesize that the increased prevalence of overweight in the Netherlands contributes to the observed increase of maternal mortality [20]. This is difficult to investigate, because numbers are low. Therefore, we used severe morbidity as an outcome measurement. In the Netherlands overall SAMM occurred in 7.1 per 1,000 births with a case fatality rate of 1 in 53 [21]. The objective of this article is to report the association between overweight and severe acute maternal morbidity (SAMM) in a low-risk pregnant population.

## METHODS

### Ethics statement

The LeMMoN-study was centrally approved by the medical ethics committee of Leiden University Medical Center (P04-020; 8 March 2004). In this study only anonymous data is used and information cannot be related to individual women. In the Netherlands informed consent and ethical approval is not needed when all participant information is anonymous.

### Study design and study population

This is a nationwide case-control study investigating the association between overweight and SAMM. SAMM was defined as Intensive Care Unit (ICU)-admission, Uterine Rupture, Eclampsia, Major Obstetric Haemorrhage (MOH) or Miscellaneous (severe acute maternal morbidity according to the opinion of the treating obstetrician, which could not be included in the four other categories). Women could be included in more than one SAMM category. Cases were women with SAMM who started their pregnancy in primary care. Controls were women in primary care without SAMM. Cases were selected from the LEMMoN study, a nationwide prospective cohort study, detailed information of which was described previously [21]. In summary; all cases of severe acute maternal morbidity during pregnancy, delivery and the puerperal period were included from all 98 hospitals in the Netherlands with a maternity unit from august 1, 2004 until august 1, 2006. These hospitals consist of 8 tertiary care hospitals, 35 non-academic teaching hospitals and 55 general hospitals. We excluded cases that were referred to a secondary or tertiary care centre before 18 weeks of gestation

and cases with missing data on height and weight or BMI (i.e. weight not registered before 14 weeks of gestation). The referral cut-off point of 18 weeks of gestational age to secondary care includes at least two primary care visits for risk selection.

For the controls, we collected data of all pregnant women with known BMI, who delivered between August 1, 2004 and August 1, 2005 in eight primary obstetric care practices dispersed in the Netherlands. All controls could have developed SAMM. When this happened they have been referred to secondary care and included in the LEMMoN-study case group. We conveniently chose practices that had excellent registration of BMI. By selecting women from primary obstetric care practices, we were certain to only include women without co-morbidities due to the Dutch risk selection system [22].

The Dutch risk selection system is based on risk selection in primary obstetric care where pregnant women are guided through pregnancy and referred to secondary or third specialised obstetric care when higher risk for or a present complication exists, meaning that the low-risk women used in this study do not have any pre-existent co-morbidity [22]. By including only the initially low-risk cases we corrected for possible confounding co-morbidities as the initially high-risk cases have been referred. We used measured BMI at booking because self-reported BMI have shown to be unreliable.

### Data collection

Data available for the cases included maternal characteristics (age, BMI, zip-code, parity and ethnicity) and information regarding pregnancy, delivery and the corresponding specific complication(s). This data was extracted monthly from each hospital using a standardised web based form reported by a local coordinator.

Available data for the control subjects included age, BMI, parity, zip-code, occupation, birth weight, place of delivery and mode of delivery. All used data were continuous except BMI (see statistical analysis), parity (0, 1, 2 and ≥3), ethnicity (native or immigrant, only available for cases) and socioeconomic status (low, modest, high).

### Statistical analysis

We divided participants in categories according to their BMI based on the WHO-classification (underweight; BMI<18.5, normal; BMI 18.5-24.9, overweight; BMI 25.0-29.9, obesity; BMI 30.0-34.9 and morbid obesity; BMI≥35.0). We calculated the socio-economic status score per participant by combining residence value and average income with factor analysis. This score was divided into three categories of socio-economic status (SES); low, modest and high. Residence value and average income were based on the validated residence zip-code indicator list of Statistics Netherlands (CBS) [23,24].

We examined differences in characteristics between cases and control subjects and these were tested with a chi-square test or independent t-test where appropriate. Furthermore, we investigated whether cases with known BMI differed from cases without BMI by comparing other characteristics. We calculated crude odds ratios (OR) and their 95% confidence intervals (95% CI) of SAMM for women with a BMI<18.5, BMI≥25, (including BMI≥30 and 35), BMI≥30 (including BMI≥35) with normal weight (BMI 18.5-24.9) as a reference category. In a multivariable logistic regression analysis

we calculated adjusted odd ratios (aOR) for age, parity and socio-economic status. In this model data were only used if age, parity and socio-economic status were known.
We additionally calculated OR (95% CI) for the different categories of SAMM (i.e. ICU-admission, Uterine Rupture, Eclampsia, MOH) except for the Miscellaneous group which was a very heterogeneous category including many different complications. Cases could be included in more than one SAMM category. In the total SAMM analyses these cases were included once. Statistical analysis was performed using SPSS statistics, version 17.0 (SPSS, Chicago, IL).



## RESULTS

Between August 1, 2004 and August 1, 2006, 371 012 women delivered in the Netherlands according to Statistics Netherlands [23]. Out of 2552 reported SAMM cases we excluded the high-risk pregnancies at booking (N=985) and cases with missing data for BMI (N=470), 1097 cases were left for analyses. We collected data of 2994 controls with known BMI.

### Demographics

The case group included 356 (32.5%) women with ICU-admission, 71 (6.4%) with Uterine Rupture, 113 (10.2%) with Eclampsia, 704 (64.2%) with MOH and 142 cases reported as Miscellaneous (12.9%). All compared variables showed significant differences. Cases had a higher mean BMI (24.4 kg/m$^2$ versus 23.8 kg/m$^2$) and had overweight more frequently. The percentage of women with a normal weight was 62.0% in the cases compared to 65.2% in the control subjects. The prevalence of overweight, obesity and morbid obesity was respectively 248 (22.6%), 70 (6.4%) and 54 (4.9%) in the cases, compared to 619 (20.6%), 200 (6.7%) and 77 (2.6%) in the control group (Table 1).

### Main outcome

Table 2 shows the association between BMI categories and the risk to develop SAMM. Women with overweight had an aOR of 1.3 (95% CI, 1.0-1.5) to develop SAMM compared women with a normal weight. For obese women the aOR increased to 1.4 (95% CI, 1.1-1.9) and for morbidly obese to 2.1 (95% CI, 1.3-3.2). The sub analyses for the first three inclusion groups showed a dose response increase in aOR except for morbidly obese women with Uterine Rupture. Analysis for MOH showed no significant difference (Table 2). Detailed description of the Miscellaneous group has been published previously [21]. For example, this group also includes two extremely obese women with anaesthetic complications which did not fulfill the criteria of the other four categories.

**Table 1** | Characteristics of cases and control subjects

| | | Cases N=1097 | Control subjects N=2994 | P value |
|---|---|---|---|---|
| Age (y) | | 30.9 (4.7) | 30.1 (5.0) | <0.001 |
| SES (n, %) | Low | 272 (27.8) | 445 (17.7) | <0.001 |
| | Modest | 476 (48.7) | 1370 (54.4) | |
| | High | 229 (23.4) | 704 (27.9) | |
| Parity (n, %) | 0 | 647 (59.0) | 1463 (48.7) | <0.001 |
| | 1 | 333 (30.4) | 1048 (34.9) | |
| | 2 | 83 (7.6) | 345 (11.5) | |
| | ≥3 | 34 (3.1) | 122 (4.1) | |
| Birth weight (g) | | 3296 (834) | 3490 (550) | <0.001 |
| BMI (kg/m$^2$) | | 24,4 (5.0) | 23,8 (4.4) | <0.001 |
| BMI category[1] (n, %) | Underweight | 45 (4.1) | 145 (4.8) | .001 |
| | Normal | 680 (62.0) | 1953 (65.2) | |
| | Overweight | 248 (22.6) | 619 (20.7) | |
| | Obesity | 70 (6.4) | 200 (6.7) | |
| | Morbid obesity | 54 (4.9) | 77 (2.6) | |

Data are presented as mean (SD) or number (%). [1] BMI classification, see Method section. SES = Socio-Economic Status; BMI = Body Mass Index.

## DISCUSSION

This study shows that women with overweight had a 30% higher risk and women with obesity had a 40% higher risk to develop SAMM compared to women with a normal weight. The association between overweight and SAMM is even stronger for specific endpoints such as ICU-admission, uterine rupture and eclampsia. We found no increased risk for major obstetric haemorrhage. The increasing incidence of overweight and obesity seems to be one of the causal factors in the increasing trend in SAMM in western countries, other suggested factors being the increased age of women, the increased caesarean rate and the increased rate of multiple pregnancies through artificial reproduction techniques.

### Strengths and limitations

The incidence of SAMM is relatively low and therefore a case-control study is the most appropriate design. We were able to collect information on all cases of SAMM in the Netherlands during a two-year period and to include a large number of cases. This study also has some limitations that need to be considered. Due to the observational and retrospective aspect of data collection, residual confounding may remain. This is inherent to the study design. The missing values for BMI in the case group could have introduced selection bias. To explore this we compared cases with known BMI to cases with missing BMI (Table 3 and S1). This analysis shows that all the initially low-risk

**Table 2** | Primary and secondary analysis results

| | Underweight | | Overweight | | Obesity | | Morbid Obesity | |
|---|---|---|---|---|---|---|---|---|
| | **OR (95% CI)** | **aOR* (95% CI)** | **OR (95% CI)** | **aOR* (95% CI)** | **OR (95% CI)** | **aOR* (95% CI)** | **OR (95% CI)** | **aOR* (95% CI)** |
| **ICU-admission** N= 356 | 1.2 (0.7-2.0) | 1.4 (0.8-2.5) | 1.2 (1.0-1.6) | 1.4 (1.1-1.9) | 1.6 (1.1-2.2) | 1.7 (1.1-2.6) | 3.1 (1.9-4.9) | 3.2 (1.8-5.9) |
| **Uterine rupture** N=71 | # | # | 2.2 (1.4-3.5) | 2.0 (1.1-3.7) | 3.3 (1.8-6.1) | 3.6 (1.6-7.9) | 3.7 (1.4-9.8) | 3.2 (0.9-11.4) |
| **Eclampsia** N=113 | 1.4 (0.6-3.1) | 1.6 (0.6-4.1) | 1.3 (0.9-1.9) | 1.8 (1.1-3.0) | 1.4 (0.8-2.5) | 2.4 (1.2-4.8) | 3.4 (1.6-7.1) | 6.4 (2.8-14.7) |
| **MOH** N=704 | 0.8 (0.5-1.2) | 0.7 (0.4-1.2) | 1.0 (0.8-1.2) | 1.0 (0.8-1.3) | 0.9 (0.7-1.2) | 1.1 (0.8-1.5) | 1.2 (0.7-1.9) | 1.0 (0.5-2.0) |
| **SAMM Total** | 0.9 (0.6-1.3) | 0.9 (0.6-1.3) | 1.2 (1.0-1.4) | 1.3 (1.0-1.5) | 1.3 (1.0-1.6) | 1.4 (1.1-1.9) | 2.0 (1.4-2.9) | 2.1 (1.3-3.2) |

*Adjusted for age, parity and socio-economic status. #Not enough cases (n=3) for analysis. ICU = Intensive Care Unit; MOH = Major Obstetric Hemorrhage; CI = confidence interval; OR = odds ratio; aOR = adjusted odds ratio.

cases are similar in seven out of nine characteristics. Cases with missing BMI had a higher incidence of immigrants, and a higher incidence of women with low socio-economic status than the cases with known BMI. Both factors are associated with higher BMI and thus due to this exclusion our results are likely to be an underestimation. The exclusion of confounding of co-morbidities relies on the quality of the Dutch risk selection system in which women with co-morbidities should be referred to secondary care. Appropriate application of these guidelines has been confirmed by previous studies. For example, Zwart et al. showed that women delivering under the care of a Dutch primary care giver have a lower risk to develop SAMM (RR 0.1 95% CI: 0.1-0.2) [21]. Assuming that complications before 18 weeks are followed by referral to secondary care, the calculated risks are primarily the consequence of overweight without overt consequences of their overweight. The women selected initially as low-risk probably had underlying pathology, such as co-morbidities that were clinically not (yet) present. Referral indication primarily based on high BMI in the absence of any other known pathology was not advised in the national guideline used during the study period. To collect controls, we conveniently selected primary care practices that had an excellent registration of BMI. At the moment of selection, we were not aware of the actual BMI values in the practices. Furthermore, rates of BMI categories corresponded well with national incidence figures from Statistics Netherlands (CBS) during the study period (National: BMI≥25: 31.7% and BMI≥30: 9.1%; Control population: BMI≥25: 30.0% and BMI≥30: 9.3%) [21,23]. Ethnicity information was not available for the control group and therefore adjustment was not possible. Previous studies showed higher risks for immigrant women to develop adverse pregnancy outcomes [21,27-32]. Due to this limitation there could be residual confounding in our primary results caused by ethnicity. Our results also show wide confidence intervals for specific conditions of SAMM due to low numbers: for example, the OR of morbidly obese women with uterine rupture (N=5). This rare situation with non-significant OR could still be considered clinically relevant.

**Table 3** | Comparison of low-risk cases to excluded cases without BMI

| | | **BMI N=1097** | **BMI missing N=470** | **P value** |
|---|---|---|---|---|
| SES (n, %) | Low | 272 (27.8) | 153 (36.6) | <0.01 |
| | Modest | 476 (48.7) | 175 (41.9) | |
| | High | 229 (23.4) | 90 (21.5) | |
| Etnicity (n, %) | Native | 870 (79.5) | 333 (71.3) | <0.001 |
| | Immigrant | 225 (20.5) | 134 (28.7) | |

BMI = Body Mass Index; SES = Socio-Economic Status. Data are presented as number (%). For all compared characteristics: see supplemental information, see Table S1.

## Interpretation and comparison

Maternal overweight could have a harmful effect in different phases of pregnancy and the postpartum period; during risk assessment, pregnancy and labour monitoring and delivery. In the

antenatal phase ultrasonography on overweight women has shown to go with difficulties visualising fetal structures between 18 and 24 weeks and therefore assessing potential risks [33]. Also, the measurement of blood pressure has shown to be less accurate in women with overweight and this may lead to delayed detection of (pre-) eclampsia. If there is a potential risk detected at home, then the difficulty of transport arises in the extremely obese. Elevated risks during the perinatal phase can be the consequence of a delay in induction, a longer duration of labor, higher incidence of caesarean section and difficulty with anaesthesiology. For example, Pevzner et al. [34] showed an almost twice the amount of predelivery oxytocin units was needed in labour induction (BMI<30, 2.6 units; BMI>40, 5.0 units; p<0.001). They also showed a more than four hour (p<0.001) longer duration of labor for BMI>40 (27.0 hour) compared to women with a BMI<30 (22.7 hour) [34]. The elevated risk for emergency and elective caesarean section in overweight women is supported by many large studies [14,35,36]. This goes along with perioperative problems such as the placement of an epidural catheter or tracheal tube in obese patients [37]. For example, a six-year review of failed intubation in 36 obstetric patients out of 8970 (incidence 1:249) general anaesthetics, showed an average BMI of 33 in the UK [38]. Besides the procedural difficulties there are also risks for overweight women in the operation room. The physiological differences compared with a normal weight non-pregnant woman further complicate the whole process of delivery and anaesthesiology [39]. Adding to this, there are also increased infectious risks during and after delivery. Sebire et al. showed significant risks for overweight women to develop genital tract, urinary tract and wound infection compared to normal weight (BMI 20-<25) women [14]. The higher risk for infectious morbidities and the decreased performance in general can explain the increased risk for overweight women to be admitted to an intensive care unit. The high incidence of previous caesarean section in overweight women also explains the elevated risk for uterine rupture [40,41]. This is the reason that in this study caesarean section was not considered as a potential confounder. Also no adjustment was performed for birth weight because studies show a significant relation with overweight [14,25-28]. Interestingly, no significantly increased risk was observed for major obstetric haemorrhage as endpoint in this study. Large previous studies do not support this finding, although we mention that these studies did not study low-risk populations. Cedergren et al. [28] showed aOR's of 1.19 (BMI 29.1-35; 95% CI, 1.15-1.23), 1.36 (BMI 35.1-40; 95% CI, 1.25-1.48) and 1.70 (BMI>40; 95% CI 1.45-1.98) among vaginally delivered women to develop major postpartum haemorrhage [28]. Sebire et al. used a cut-off value of >1000 ml and found aOR's of 1.17 (BMI 25-30; 99% CI, 1.07-1.27) and 1.44 (BMI>30; 99% CI, 1.30-1.60) [14]. As blood loss is underestimated [42,43] and blood transfusion depends on local management these OR's are difficult to compare. In the LEMMoN study only cases needing transfusion of at least 4 units of packed red blood cells were included and we did not find a relation with overweight. As the prevalence of overweight increases rapidly, the incidence of SAMM and probably maternal mortality are likely to increase in the future. In our opinion morbidly obese women (BMI≥35) should be included in the national guidelines as "official risk factor" as reason for referral. For obese (BMI≥30) women, we advise midwives or obstetricians to thoroughly evaluate these patients with an individual perspective. When other SAMM risk factors such as a previous caesarean section or a previous severe preeclampsia are present these patients should also be referred. Only if the obesity epidemic will be put to a hold the consequences might be attenuated.

As weight loss during pregnancy is contraindicated, SAMM and life threatening complications can only be avoided by pre-conceptional counseling to stimulate weight loss and weight monitoring during pregnancy of overweight women.

## CONCLUSION

This study shows that maternal overweight without preexistent co-morbidities is an important risk factor for SAMM in a Dutch low-risk population. Obese and morbidly obese pregnant women should be regarded as high-risk pregnant women also in the absence of any overt co-morbidity.

**Table S1** | Characteristics of included and excluded low-risk cases

| | | **BMI N=1097** | **BMI missing N=470** | **P value** |
|---|---|---|---|---|
| Age (y) | | 30.9 (4.7) | 30.5 (5.2) | .177 |
| SES (n, %) | Low | 272 (27.8) | 153 (36.6) | <0.01 |
| | Modest | 476 (48.7) | 175 (41.9) | |
| | High | 229 (23.4) | 90 (21.5) | |
| Parity (n, %) | 0 | 648 (59.1) | 249 (53.2) | .118 |
| | 1 | 332 (30.3) | 154 (32.9) | |
| | 2 | 83 (7.6) | 44 (9.4) | |
| | ≥3 | 34 (3.1) | 21 (4.5) | |
| Etnicity (n, %) | Native | 870 (79.5) | 333 (71.3) | <0.001 |
| | Immigrant | 225 (20.5) | 134 (28.7) | |
| Hospital admission (d) | | 8,2 (8.9) | 7.6 (7.0) | .148 |
| Birth weight (g) | | 3179 (976) | 3155 (1044) | .668 |
| Blood pressure (mmHg)* | | 87 (18) | 88 (19) | .724 |
| Blood loss (ml) | | 2316 (2135) | 2268 (2071) | .698 |
| Gestational age (w) | | 35,8 (6,2) | 35,8 (6,3) | .917 |

BMI = Body Mass Index; SES = Socio-Economic Status. *Maximum diastolic blood pressure. Data are presented as mean (SD) or number (%).

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# CHAPTER 3

## SEVERE ACUTE MATERNAL MORBIDITY IN MULTIPLE PREGNANCIES: A NATIONWIDE COHORT STUDY

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## ABSTRACT

**Background:** Adverse neonatal outcomes in multiple pregnancies have been documented extensively, in particular those associated with the increased risk of preterm birth. Paradoxically, much less is known about adverse maternal events. The combined risk of severe acute maternal morbidity in multiple pregnancies has not been documented previously in any nationwide prospective study.

**Objective:** To assess the risk of severe acute maternal morbidity in multiple pregnancies in a high-income European country and identify possible risk indicators.

**Study Design:** In a population-based cohort study including all 98 hospitals with a maternity unit in the Netherlands, pregnant women with severe acute maternal morbidity were included in the period 1st August 2004 until 1st August 2006. We calculated the incidence of severe acute maternal morbidity in multiple pregnancies in the Netherlands using the Netherlands Perinatal Registry. Relative risks (RR) of severe acute maternal morbidity in multiple pregnancies compared to singletons were calculated. To identify possible risk indicators we also compared age, parity, method of conception, onset of labour and mode of delivery for multiple pregnancies using the Netherlands Perinatal Registry as reference.

**Results:** 2552 cases of severe acute maternal morbidity were reported during the two-year study period. Among 202 multiple pregnancies (8.0%), there were 197 twins (7.8%) and five triplets (0.2%). The overall incidence of severe acute maternal morbidity was 7.0 per 1000 deliveries, 6.5 and 28.0 per 1000 for singletons and multiple pregnancies respectively. The relative risk of severe acute maternal morbidity compared to singleton pregnancies was 4.3 (95% confidence interval [95% CI] 3.7-5.0) and increased to 6.2 (95% CI 2.5-15.3) in triplet pregnancies. Risk indicators for developing severe acute maternal morbidity in women with multiple pregnancies were age of ≥40 (RR 2.5 95% CI 1.4-4.3), nulliparity (RR 1.8, 95% CI 1.4-2.4), use of assisted reproductive techniques (RR 1.9, 95% CI 1.4-2.5), and non-spontaneous onset of delivery (RR 1.6, 95% CI 1.2-2.1). No significant difference was found between mono- and dichorionic twins (RR 0.8, 95% CI 0.6-1.2).

**Conclusions:** Women with multiple pregnancies in the Netherlands have a more than four times elevated risk of sustaining severe acute maternal morbidity as compared to singletons.

## INTRODUCTION

The incidence of multiple pregnancies is increasing in many parts of the world [1]. In the Netherlands, multiple pregnancy rates increased from 10.8 to 16.2 per 1000 births between 1980 and 2011 [2]. This result is amongst other factors attributed to delayed childbearing and more frequent use of assisted reproductive techniques (ART) [3-5].

Adverse neonatal outcomes in multiple pregnancies have been documented extensively, in particular those associated with the increased risk of preterm birth [6]. Paradoxically, much less is known about adverse *maternal* events, although an increased incidence has been described for preeclampsia, anemia, nutritional deficiencies, cesarean delivery and postpartum hemorrhage [7,8]. To our knowledge, the combined risk of severe acute maternal morbidity (SAMM) in multiple pregnancies has not been documented previously in any nationwide prospective study. Uncertainties with regard to the risk of SAMM and the possible effects of chorionicity on maternal morbidity are two important barriers to effective communication with women. The aim of this study was to assess incidence of SAMM in multiple gestations in the Netherlands, as well as risk indicators.



## MATERIALS AND METHODS

This study formed part of a two-year nationwide prospective cohort study to assess SAMM during pregnancy, delivery and puerperium in the Netherlands, called the LEMMoN-study. Pregnant women were included from all 98 hospitals with a maternity unit, in the period 1st August 2004 until 1st August 2006. These 98 facilities comprised eight tertiary care hospitals, 35 non-academic teaching hospitals and 55 general hospitals. Detailed information about the study and data collection was described previously [9].

Inclusion criteria for SAMM were categorized into five groups: intensive care unit (ICU) admission, uterine rupture, eclampsia, major obstetric hemorrhage (MOH, defined as ≥4 units of packed cells, peripartum hysterectomy or arterial embolization) and a miscellaneous group, containing rare cases of SAMM according to the treating obstetrician, which could not be included in any of the other groups. Women who developed HELLP-syndrome accompanied with liver hematoma or rupture were also included in the eclampsia category. It was possible for women to be included into more than one group of SAMM, but each woman was counted once in the overall analysis. The management of multiple pregnancies and severe maternal complications in the Netherlands is guided through national (open access) guidelines. Maternal mortality cases were reported to the national Maternal Mortality Committee of the Dutch Society of Obstetrics and Gynecology by the attending obstetrician and added to our database. We excluded those cases in which the number of fetuses was not known.

First, we calculated nationwide incidence of SAMM in multiple pregnancies using the number of multiple pregnancies in the Netherlands during the study period obtained from the Netherlands Perinatal Registry (PRN) [10]. The PRN is a national registration system specialized to monitor the quality of obstetric health care and gives insight in perinatal care process and outcome. For each

SAMM inclusion group (ICU-admission, uterine rupture, eclampsia, MOH and maternal mortality) we also compared nationwide incidence between singleton and multiple pregnancies. Due to the heterogeneity of the miscellaneous group no risk analysis was performed for this group.
Secondly, to identify possible risk indicators data from the LEMMoN-study were compared to data extracted from PRN. The following parameters were used for this comparison: age, parity, method of conception, onset of labour and mode of delivery [10]. All national reference data from PRN were corrected for the LEMMoN-study period. In the analysis of risk indicators, women with missing information were added to the same category as was usually done in the PRN reference database. For example, in the PRN database women with missing data for parity (N=1) and method of conception (N=20) were included into the 'nulliparous' and 'spontaneous' groups respectively, since these are the most likely outcomes. To analyze the possible effect of chorionicity we used Weinberg's differential rule (rate of dichorionic twins = two times the unlike-sex twins) to estimate the rate of mono- and dichorionic twins in the Netherlands [11]. Assisted reproductive technique (ART) was defined as in vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI). The numbers for mode of delivery were calculated by counting one method for each fetus. Due to the absence of individual case-linked data from the PRN, multi-variable analysis and therefore adjustment for possible confounders was impossible.
Finally, we compared multiple and singleton pregnancies within our (LEMMoN-study) cohort of women with SAMM. Compared characteristics included the following variables: age, body mass index (BMI), socio-economic status (SES), parity, ethnicity, method of conception, induction of labour, mode of delivery, gestational age, birth weight, blood loss, number of packed cells and hospital admission. We also analyzed the distribution of indications for ICU-admission and cause of MOH within the two main inclusion groups of the SAMM cohort.

### Statistical analysis

Relative risks (RR) with 95% confidence intervals (CI) were calculated where appropriate. Reference groups were depicted and are shown in the legend below the tables. For example age was compared <25 versus ≥25, ≥35 versus <35 and ≥40 versus <40. Differences in characteristics between women with singleton and multiple pregnancies were tested with a chi-square test or independent t-test. Statistical analysis was performed using SPSS statistics, version 20.0 (SPSS, Chicago, IL).

### Ethical statement

This study was exempt from Institutional Review Board approval as we used only anonymous data from the LEMMoN-study and the PRN that cannot be related to any individual. The LEMMoN-study was centrally approved by the medical ethics committee of Leiden University Medical Center (P04-020; 8 March 2004).

## RESULTS

During the study period there were 365 594 deliveries in the Netherlands: 358 369 singleton (98.0%) and 7225 multiple pregnancies (2.0%) [10]. In that period 2274 (97%) of 2352 monthly notification cards (98 hospitals, 24 months) were returned. A total of 2552 cases with SAMM were reported. Twelve cases (0.5%) were excluded due to an unknown number of fetuses. Of the remaining 2540 cases, there were 2338 singleton (92.0%) and 202 multiple pregnancies (8.0%), of which 197 twins (7.8%) and 5 triplets (0.2%). There were no higher order pregnancies. Out of the 202 women with multiple pregnancies, 153 (75.9%) were included with MOH, 70 (34.5%) with ICU-admission, 21 (10.3%) with eclampsia, 18 (8.9%) in the miscellaneous group and 3 (1.5%) with uterine rupture.
The overall incidence of SAMM was 7.0 per 1000 deliveries, 6.5 per 1000 for singletons and 28.0 per 1000 for multiple pregnancies. The relative risk was 4.3 (95% CI 3.7-5.0) for multiple pregnancies compared to singleton pregnancies, i.e. 4.3 (95% CI 3.7-4.9) for twins and 6.2 (95% CI 2.5-15.3) for triplets (Table 1). The comparison of the incidence of the four SAMM conditions (MOH, ICU-admission, eclampsia, uterine rupture) and maternal mortality for multiple and singleton pregnancies are shown in Table 2. Compared to singletons, the occurrence of SAMM was higher in each group for multiple pregnancies, except for uterine rupture. The case fatality rate (CFR) of SAMM in multiple pregnancies was 4/202 (2.0%) and 44/2338 (1.9%) for singletons.



**Table 1** | Population based relative risks for SAMM in multiple pregnancies in the Netherlands

| | | SAMM | Netherlands | RR (95% CI) |
|---|---|---|---|---|
| Total deliveries | | 2540 | 365 594 | |
| Singleton | | 2338 (92.0) | 358 369 (98.0) | Reference |
| Multiple | | 202 (8.0) | 7225 (2.0) | 4.3 (3.7-5.0) |
| | Twin | 197 (7.8) | 7102 (1.94) | 4.3 (3.7-4.9) |
| | Triplet | 5 (0.2) | 123 (0.03) | 6.2 (2.5-15.3) |

RR = relative risk; CI = confidence Interval. Data are presented as number (%).

**Table 2** | Comparison of multiple versus singleton pregnancies for each SAMM condition and maternal mortality

| The Netherlands | Multiple N=7225 | Singleton N=358 369 | RR (95% CI) |
|---|---|---|---|
| ICU-admission | 70 (1.0) | 771 (0.2) | 4.5 (3.5-5.8) |
| Uterine rupture | 3 (0.04) | 215 (0.1) | 0.7 (0.2-2.2) |
| Eclampsia | 21 (0.3) | 217 (0.1) | 4.8 (3.1-7.5) |
| MOH | 153 (2.1) | 1449 (0.4) | 5.2 (4.4-6.2) |
| Maternal mortality | 4 (0.1) | 44 (0.01) | 4.5 (1.6-12.5) |

ICU = intensive care unit; RR = relative risk; CI = confidence interval; MOH = major obstetric hemorrhage. Data are presented as number (%).

The risk for a woman with multiple pregnancy in the Netherlands to develop SAMM as compared to the general Dutch pregnant population was elevated for women aged 40 or above (RR 2.5, 95% CI 1.4-4.3), nulliparous women (RR 1.8, 95% CI 1.4-2.4), women who conceived through ART (RR 2.0, 95% CI 1.4-2.7) and women who did not deliver spontaneously (induced labour or elective cesarean) (RR 1.6, 95% CI 1.2-2.1). No significant difference in SAMM was found between mono- and dichorionic twins (RR 0.8, 95% CI 0.6-1.2). The rate of cesarean delivery compared to women with multiple pregnancies in the general Dutch population (51.1% versus 37.0%) indicates that cesarean delivery is also associated with SAMM (RR 1.8, 95% CI 1.5-2.2) in multiple pregnancies (Table 3).

**Table 3** | Risk indicators for severe acute maternal morbidity in multiple pregnancies in the Netherlands

| **Multiple** | | **SAMM N=202** | **Netherlands[¶] N=7225** | **RR (95% CI)** |
|---|---|---|---|---|
| Age | <25 | 7 (3.5) | 481 (6.7) | 0.5 (0.2-1.1)[1] |
| | ≥35 | 64 (31.8) | 1958 (27.1) | 1.3 (0.9-1.7)[2] |
| | ≥40 | 15 (7.5) | 226 (3.1) | 2.5 (1.4-4.3)[3] |
| Parity | 0 | 128 (63.4) | 3533 (48.9) | 1.8 (1.4-2.4)[4] |
| | 1 | 51 (25.2) | 2553 (35.3) | |
| | ≥2 | 23 (11.4) | 1140 (15.8) | |
| Chorionicity | Monochorionic | 49 (24.9)^ | 2034 (30.0)^ | 0.8 (0.6-1.2)[5] |
| | Dichorionic | 138 (70.1)^ | 4754 (70.0)^ | |
| Conception | Spontaneous | 136 (67.3) | 5233 (72.4) | |
| | IVF/ICSI | 52 (25.7) | 1018 (14.1) | 2.0 (1.4-2.7)[6] |
| | Other[#] | 14 (6.9) | 974 (13.5) | |
| Onset of labour | Spontaneous | 78 (38.6) | 2030 (28.1) | |
| | Induced/CS | 124 (61.4) | 5195 (71.9) | 1.6 (1.2-2.1)[7] |
| | **Deliveries** | **N=409** | **N=13843** | |
| Mode of delivery | Vaginal | 200 (48.9) | 8729 (63.0) | |
| | – Spontaneous | 157 (38.4) | 7429 (53.7) | |
| | – VE/Forceps | 34 (8.3) | 984 (7.1) | |
| | – Breech extraction | 9 (2.2) | 316 (2.3) | |
| | CS | 209 (51.1) | 5114 (37.0) | 1.8 (1.5-2.2)[8] |
| | – Elective | 84 (40.2) | 2778 (53.3) | |
| | – Emergency | 125 (59.8) | 2336 (45.7) | 1.7 (1.3-2.3)[9] |

RR = relative risk; CI = confidence interval; IVF = in vitro fertilization; ICSI = intra-cytoplasmic sperm injection; CS = cesarean section. Data are presented as number (%). [#] Intra uterine insemination, artificial sperm insemination, ovulation induction and other reproductive techniques. ^ Percentage of twins, included in relative risk calculation for chorionicity. [1] Age <25 versus ≥25, [2] ≥35 versus <35, [3] ≥40 versus <40, [4] Nulliparous vs. multiparous, [5] MC vs. DC, [6] IVF/ICSI vs. spontaneous, [7] Spontaneous vs. induced or elective CS, [8] CS vs. vaginal delivery, [9] Emergency vs. elective CS.

The comparison of the 202 women with multiple pregnancies to the 2338 singleton pregnancies within our SAMM cohort showed that women with multiple pregnancies had a higher mean age (32.3 versus 31.5 years, p<0.05), were more often nulliparous (63.2% versus 49.0%, p<0.001), were less likely to have a scarred uterus (7.4 versus 19.8%, p<0.001) and had more often conceived through ART (36.3% versus 5.1%, p<0.001) and labour had more often been induced (56.9% versus 46.3%, p<0.001). They also had a lower gestational age at delivery (34.9 versus 37.8 weeks, p<0.001), were less likely to deliver spontaneously (32.7% versus 44.7%, p<0.01), had more blood loss (2673 versus 2262 ml, p<0.05), received a higher number of packed cells (5.4 versus 4.3 units, p<0.01), were hospitalized longer (12.9 versus 8.4 days, p<0.001) and their neonates had a lower mean birth weight (2306 versus 3104 gram, p<0.001) as compared to singleton pregnancies (Table 4).
Distribution of indications for ICU-admission and causes of MOH for women with singleton and multiple pregnancies are shown in Supplemental Tables 4.1 and 4.2. The most prevalent reason for ICU-admission was postpartum hemorrhage in both singleton (40.3%) and multiple pregnancies (40.0%). For women sustaining MOH postpartum uterine atony was present in a larger proportion of multiple pregnancies (42.2%) compared to singletons (26.5%).



## COMMENT

With this nationwide study we showed that women with multiple pregnancies have a more than four times elevated risk of sustaining SAMM as compared to singletons. To our knowledge, this is the first prospective nationwide study of SAMM in multiple pregnancies. Because of its nationwide design with high coverage (97%), we managed to acquire a large, unselected sample size and were able to calculate population-based relative risks. Although there is no obligation for health care providers to report to the PRN database (some general practitioners and midwives do not report), all multiple pregnancies are referred to secondary or tertiary care centers and thus will always be reported. This means women with multiple pregnancies only deliver in hospital and PRN is likely to cover 100% of multiple pregnancies in the country.
This study has some limitations. Because chorionicity is not registered we applied Weinberg's rule for estimating the number of mono- and dizygotic twins in the Netherlands in order to calculate the relative risk of chorionicity. Multiple studies have validated this method in recent years [12,13]. Also, we were not able to perform logistic regression for known risk factors to develop SAMM (such as age, parity, SES or comorbidities such as hypertension and diabetes) as we only had aggregated data available for the nationwide reference group.
Previously, three large nationwide studies reported on severe maternal outcome in multiple pregnancies. Luke et al. (2007) found adjusted odds ratios (aOR) of 2.45 (95% CI 2.42-2.48) and 3.04 (95% CI 2.86-3.22) for pregnancy-associated hypertension in twins and triplets respectively. They also found increased risk for "excessive bleeding in labor and delivery" (abruption placentae, placenta previa and other causes of excessive bleeding) in twins (aOR 1.93, 95% CI 1.89-1.98) and triplets (aOR 3.85, 95% CI 2.57-3.12) [14]. Walker et al. (2004) found that pulmonary edema (RR 7.13, 95% CI 4.52-11.25), venous thromboembolic disease (RR 2.65, 95% CI 2.04-3.46), myocardial infarction

**Table 4** | Characteristics of multiple versus singleton pregnancies within SAMM population

| | | Multiple N=202 | Singleton N=2338 | P value |
|---|---|---|---|---|
| Mean age (yrs) | Unknown = 26 | 32.3 (4.7) | 31.5 (5.0) | 0.025 |
| Mean pre-pregnancy BMI | Unknown = 874 | 24.5 (5.1) | 24.8 (5.4) | 0.484 |
| SES | Low | 47 (27.0) | 654 (32.0) | 0.254 |
| | Modest | 88 (50.6) | 906 (44.4) | |
| | High | 39 (22.4) | 481 (23.6) | |
| | Unknown = 171 | | | |
| Parity | 0 | 127 (63.2) | 1137 (49.0) | <.001 |
| | 1 | 51 (25.4) | 818 (35.2) | |
| | 2 | 21 (10.4) | 242 (10.4) | |
| | ≥3 | 2 (1.0) | 125 (5.4) | |
| | Unknown = 29 | | | |
| Ethnicity | Native Dutch | 154 (76.6) | 1711 (74.2) | 0.451 |
| | Immigrant | 47 (23.4) | 595 (25.8) | |
| | Unknown = 5 | | | |
| Previous CS | | 15 (7.4) | 462 (19.8) | <.001 |
| | Unknown = 57 | | | |
| Method of conception | Spontaneous | 116 (63.7) | 1865 (94.9) | <.001 |
| | IVF/ICSI | 52 (28.6) | 68 (3.5) | |
| | Other[#] | 14 (7.7) | 33 (1.7) | |
| | Unknown = 404 | | | |
| Mean gestational age (wks) | | 34.9 (4.6) | 37.8 (4.5) | <.001 |
| | Unknown = 166 | | | |
| Start of labour | Spontaneous | 78 (38.6) | 1240 (53.1) | <.001 |
| | Induced | 115 (56.9) | 1082 (46.3) | |
| | Elective CS | 9 (4.5) | 15 (0.6) | |
| | Unknown = 1 | | | |
| Mode of delivery^ | Spontaneous* | 157 (38.4) | 1083 (46.3) | 0.001 |
| | VE/Forceps | 34 (8.3) | 279 (11.9) | |
| | Breech extraction | 9 (2.2) | 11 (0.5) | |
| | CS | 209 (51.1) | 964 (41.2) | |
| | – Elective | 84 (20.7) | 205 (8.8) | |
| | – Emergency | 125 (30.6) | 759 (32.4) | |
| | Unknown = 1 | | | |
| Mean blood loss (ml) | | 2673 (2488) | 2262 (2111) | 0.015 |
| | Unknown = 275 | | | |
| Mean number of packed cells (n) | Unknown = 75 | 5.4 (5.1) | 4.3 (5.0) | 0.003 |
| Mean birth weight (g) | | 2306 (765) | 3104 (1045) | <.001 |
| | Unknown = 233 | | | |
| Mean hospital stay (d) | | 12.9 (11.3) | 8.4 (9.4) | <.001 |
| | Unknown = 110 | | | |

BMI = body mass index; SES = socio-economic status; CS = cesarean section; IVF = in vitro fertilization; ICSI = intra-cytoplasmic sperm injection; VE = vacuum extraction;. Data are presented as mean (SD) or number (%). [#] Intra uterine insemination, artificial sperm insemination, ovulation induction and other reproductive techniques. * Including 13 cases with CS after first infant was born spontaneously. ^ For twins/triplet, two/three modes of delivery are counted per mother respectively.

(RR 3.70, 95% CI 2.34-5.83) and in-hospital death (RR 2.05, 95% CI 0.69-6.13, non-significant) had an increased incidence in women with multiple pregnancies. In line with the results of this study, Walker and coworkers also found a lower risk for uterine rupture (RR 0.51, 95% CI 0.32-0.80), which is probably due to a higher rate of elective cesarean section in multiple pregnancies, irrespective of the presence of a uterine scar [15]. In our SAMM cohort, a smaller proportion of women with multiple pregnancies had a previous cesarean delivery (7.4%) as compared to singletons (19.8%). Also, the cesarean section rate in multiples is much higher and both facts will have lowered the risk of uterine rupture in women with multiple pregnancies. Conde-Agudelo et al. (2000) found an adjusted relative risk of 3.0 (95% CI 2.9-3.3) for eclampsia and 2.0 (95% CI 1.0-2.0) for postpartum hemorrhage [8]. However, SAMM criteria in these studies are less robust. For example MOH was defined as "excessive bleeding" and "postpartum hemorrhage" in comparison to our study where MOH was defined as women having received ≥4 packed cells. Finally, our prospectively collected LEMMoN-database was exclusively designed to detect SAMM. In our opinion this leads to less underreporting compared to these retrospective studies which all used ICD-10 codes from national registration systems to detect SAMM.



One of the consistent outcomes was the elevated risk for hypertensive disorders, such as eclampsia in our study. This might be explained by the increased placental mass in multiple pregnancies and the correlating level of anti-angiogenic molecules in the maternal circulation [16,17]. We also confirmed a higher incidence of cesarean section, earlier delivery and higher age among women with multiple pregnancies. In contrast, chorionicity was not a significant maternal risk factor although we identified two women with SAMM related to twin-to-twin transfusion syndrome. We found no prior studies reporting on the relation between chorionicity and SAMM. This result is noteworthy since monochorionic twins clearly have a worse perinatal outcome [18-20].

The relative risk for maternal mortality in multiple pregnancies was 4.5 compared to singletons. In 63% of all direct maternal mortality cases in the Netherlands during the period from 1993 to 2005 substandard care was assessed to be present [21]. Also, in a subgroup audit of the LEMMoN-study substandard care was present in 79% of cases (n=67) of maternal morbidity [22]. With respect to these results, we would like to underline that women with multiple pregnancies should only deliver in hospitals with 24/7 acute interventions available.

We showed that risk indicators were age of ≥40, nulliparity and use of ART. We found no other studies reporting on ART as a possible risk factor for SAMM in multiple pregnancies. Higher incidence of pregnancy-induced hypertension [23], uterine bleeding [23], peripartum hemorrhage [24], postpartum anemia [24], and longer hospital stay [25], have been reported for women with ART. We found that the risk of SAMM was doubled in women with multiple pregnancies that were conceived through IVF or ICSI. A schematic overview of the distribution of ART in the Netherlands is shown in Figure 1. Since multiple embryo transfer is still widely practiced, the risk of multiple pregnancies after ART remains. Zegers-Hochschild et al. (2013) reported that the decreased use of multi embryo transfer with three or more embryos (36.7% to 34.2%) caused a worldwide decline in the proportion of twin (25.1% to 23.6%) and triplet (1.8% to 1.5%) pregnancies after ART. They also showed that the proportion of multi embryo transfer with three or four embryos still ranges from a maximum of 2% in countries where access to ART is restricted by national health policies to 47.5%

in the United States and up to 80% in low-income countries [26]. Further reduction of SAMM after ART will be achieved by making single embryo transfer the standard everywhere, as is already the case in the Netherlands.

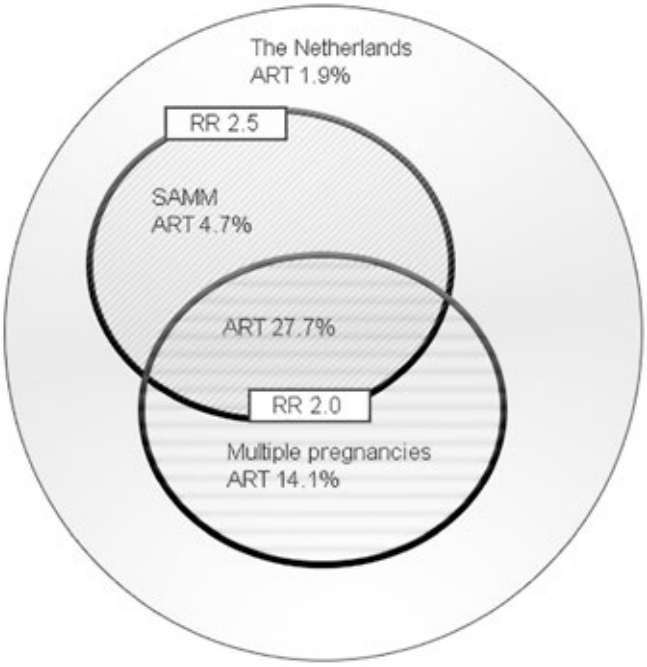


**Figure 1** | Proportion of pregnancies after ART in different populations. This figure shows the use of ART in the Netherlands and the RR for all pregnant women (RR 2.5) and multiple pregnancies (RR 2.0) to develop SAMM when conceived through ART

RR = relative risk; ART = artificial reproductive techniques. Nationwide reference data and relative risk were published before in the LEMMoN-study and implemented in this figure with approval [9].

We also found that non-spontaneous onset of delivery (induction or elective cesarean) and a higher CS rate were associated with multiple pregnancies. In other studies, cesarean section already appeared to be a significant risk indicator for developing SAMM [27]. And recently a large randomized trial of 2804 twin pregnancies also showed that there was no significant benefit in perinatal outcome when comparing planned cesarean section with planned vaginal delivery [28]. This implies that caesarean delivery with multiple pregnancy should not be performed on the indication of only a multiple pregnancy, since there is no benefit for the children and increased risk for the mother.

This study shows that women with multiple pregnancies have a more than four times elevated risk to develop SAMM, an increase that is highly relevant and requires measures to reduce avoidable risk factors. This should also be taken into account in multidisciplinary antenatal care of this high-risk group. A proportion of this risk increase seems to be caused by the use of ART in sub fertile older

women and the more liberal use of (elective) cesarean section. Indiscriminate use of ART, especially in older women, and unnecessary cesarean sections must be prevented. We recommend using only single embryo transfer. In case of multiple embryo transfer, women should be properly counseled about the possibility of multiple birth and its associated risks.

**Table S4.1** | Distribution of cases with ICU-admission in multiple and singleton pregnancies within SAMM population

| Diagnosis | Multiple N=70 | Singleton N=771 |
|---|---|---|
| PPH | 28 (40.0) | 311 (40.3) |
| PE/HELLP | 10 (14.3) | 169 (21.9) |
| Sepsis | 6 (8.6) | 40 (5.2) |
| Cardiac disease | 4 (5.7) | 50 (6.5) |
| Respiratory disease | 4 (5.7) | 24 (3.1) |
| Liver/pancreatic disease | 2 (2.9) | 10 (1.3) |
| Trombo-embolism | 0 (0.0) | 10 (1.3) |
| Other | 15 (21.4) | 149 (19.3) |
| Unknown | 1 (1.4) | 8 (1.0) |

PPH = post partum hemorrhage; PE/HELLP = preeclampsia/hemolysis elevated liver enzymes and low platelets.

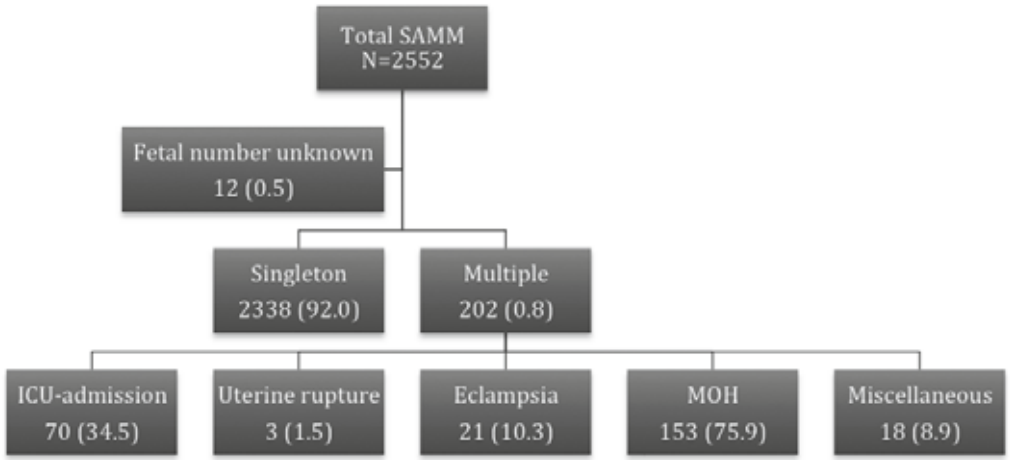


**Figure S2** | Flowchart of included SAMM cases

ICU = intensive care unit; MOH = major obstetric hemorrhage. Data are presented as number (%). Women could be included in more that one SAMM category.

**Table S4.2** | Distribution of causes of MOH in multiple and singleton pregnancies within SAMM population

| Number of events* | Diagnosis | Multiple N=204 | Singleton N=2019 |
|---|---|---|---|
| **Postpartum** | | 192 (94.1) | 1835 (90.9) |
| | Uterine atony | 81 (42.2) | 487 (26.5) |
| | Placentation defect | 6 (3.1) | 103 (5.7) |
| | Genital tract laceration | 6 (3.1) | 143 (7.8) |
| | Iatrogenic during surgery | 20 (10.4) | 163 (8.9) |
| | Uterine inversion | 0 (0.0) | 13 (0.7) |
| | Retained placenta | 51 (26.6) | 652 (35.6) |
| | Uterine rupture | 2 (1.0) | 42 (2.3) |
| | Coagulation disorder | 12 (6.3) | 114 (6.2) |
| | Cervical rupture | 1 (0.5) | 57 (3.1) |
| | Other | 10 (5.2) | 55 (3.0) |
| | Unknown | 3 (1.6) | 6 (0.3) |
| **Antepartum** | | 11 (5.4) | 124 (6.1) |
| | Abruption | 4 (36.4) | 57 (46.0) |
| | Placenta previa | 4 (36.4) | 51 (41.1) |
| | Other | 0 (0.0) | 9 (7.3) |
| | Unknown | 3 (27.3) | 7 (5.6 |
| **Early Pregnancy** | | 1 (0.5) | 50 (2.5) |
| | EUG | 0 (0.0) | 29 (58.0) |
| | Spontaneous abortion | 0 (0.0) | 10 (20.0) |
| | Induced abortion | 0 (0.0) | 7 (14.0) |
| | Other | 1 (100.0) | 4 (8.0) |
| **Unknown** | | 0 (0.0) | 10 (0.5) |

MOH = major obstetric hemorrhage; EUG = extra uterine gravidity. *Includes all hemorrhagic events sustained by singleton and multiple MOH cases.

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# CHAPTER 4

## PUERPERAL UTERINE INVERSION IN THE NETHERLANDS: A NATIONWIDE COHORT STUDY

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## ABSTRACT

Puerperal uterine inversion is a severe but rare obstetric complication of yet unknown origin. In this two-year study we determine the incidence of this complication and we describe associated risk factors to expose its etiology. All cases of uterine inversion were included from a nationwide cohort study which contained all 98 hospitals with a maternity unit in the Netherlands. We reviewed the medical records of 15 patients, resulting an incidence of approximately 1 in 20 000 vaginal births. Fourteen cases (93.3%) were classified as low-risk pregnancies at booking. Nulliparous women were not overrepresented and the main associated factors were signs of prolonged labor followed by third stage manipulation. This study is the first population-based study for uterine inversion. With the reported associated factors and occurrence in women with a low-risk profile, we show that every birth attendant should be able to detect this rare but severe complication.

## INTRODUCTION

Puerperal inversion of the uterus is a relatively rare, but serious, obstetric complication in which the corpus of the uterus is forced completely or partially through the uterine cervix. Uterine inversion presents itself after the third stage of labor with postpartum hemorrhage and severe shock. If untreated or not managed properly it can lead to maternal death. In the 1940s, Das [1] reported incidences ranging from 1 in 8537 deliveries in India to 1 in 23 127 in the USA and 1 in 27 992 in Great Britain. Mortality rates ranged from 13 to 41%. No maternal mortality is reported in recent studies from high-resource countries, probably as a consequence of early recognition and adequate management [2,3]. However, in low-income countries, maternal deaths due to uterine inversion are still reported [4]. In extremely rare cases it has also been described during cesarean section [5]. Non-puerperal inversion of the uterus is mainly caused by tumors of the uterus [1]. In the Netherlands only a few cases of uterine inversion during the puerperium have been reported [6,7]. Up to now, population-based studies on uterine inversion are lacking. Our aim was to determine the incidence of puerperal uterine inversion in the Netherlands and describe associated factors.



## MATERIAL AND METHODS

This study is part of a two-year nationwide cohort study to assess severe acute maternal morbidity during pregnancy, delivery and puerperium in the Netherlands – the LEMMoN-study. Pregnant women were included from all 98 hospitals with a maternity unit, in the period 1 August 2004 until 1 August 2006. This involved eight tertiary care hospitals, 35 non-academic teaching hospitals and 55 general hospitals. Detailed information about the data collection was described previously [8]. Inclusion criteria for severe acute maternal morbidity (SAMM) were categorized in five groups: intensive care unit admission, uterine rupture, eclampsia, major obstetric hemorrhage (defined as ≥4 units of packed cells or hysterectomy or embolization) and miscellaneous. The last group included rare cases of SAMM according to the opinion of the treating obstetrician.

All cases of uterine inversion during the two-year LEMMoN period were included. Main outcome measures were incidence and associated factors for uterine inversion. Statistics Netherlands (CBS) data was used as the source for denominator data to calculate the incidence. Clinical characteristics, delivery information, the degree of inversion and management were described in the search for predisposing factors. Clinical characteristics included age, parity, body mass index, gestational age, ethnicity, birthweight and Apgar-score. Delivery information included mode of delivery, duration of the second and third stage of labor, blood loss and duration of hospital admission.

Inversion of the uterus was classified according to the time of occurrence and degree of severity. The timing of inversion after delivery was divided in acute (within 24 hours), sub-acute (24 hours up to 30 days) or chronic (more than 30 days). The degree of inversion was classified as incomplete or complete (beyond the cervical ring).

Management information included hospital location, hemoglobin levels, presence of shock (as diagnosed by the attending physician), number of packed cells transfused, type of anesthesia

and the method of repositioning the inverted uterus. If possible, data were compared with the Netherlands Perinatal Registry data. If necessary, additional (follow-up) information for included cases was requested from the treating obstetricians by the first author.
The study was centrally approved by the medical ethics committee of Leiden University Medical Center (P04-020; 8 March 2004).

## RESULTS

During the LEMMoN-study there were 371 012 deliveries in the Netherlands [9]. In this two-year period, 97% of the 2352 monthly notification cards (98 hospitals, 24 months) were returned, representing 358 874 deliveries. The percentage of vaginal births during our study period was 84.9% [10]. A total of 2552 SAMM cases were reported and 16 (0.6%) of these concerned uterine inversion. All inversions occurred within 24 hours (acute). One occurred during cesarean section and was excluded from our analysis. The incidence of acute uterine inversion after vaginal birth was 1 in 20 312 deliveries. In this study there were no maternal deaths due to uterine inversion.
Fourteen women (93%) were classified as low risk at the start of pregnancy. At the onset of birth, eight of these (57.1%) were still classified as low risk: two women were referred for induction because of post maturity, two because of IUGR in history (one with suspicion of repeated IUGR), one because of pregnancy-induced hypertension and one because of an ovarian cyst. One woman was classified as high risk because of the use of selective serotonin re-uptake inhibitor (SSRI) medication. The reasons for referral before birth were not associated with an increased risk of uterine inversion.
Maternal age in the study group ranged from 24 to 36 years (mean 30.1 years) and the body mass index ranged from 17.6 to 25.4 kg/m$^2$ (mean 21.5 kg/m$^2$). The average maternal age of Dutch women at delivery in the Netherlands during the study period was 31.0 years [10]. Thirteen women (87%) were of Dutch origin and the two (13%) other women were from Surinam and Morocco. Twelve women (80%) delivered at term, one delivered preterm (36 weeks + 2 days) and there were two postterm (42 weeks and 42 weeks + 1 day) deliveries. Mean birthweight was 3585 g (range 2575–5120 gram), two (13%) with macrosomia (>4500 g). All newborns were healthy.
Clinical characteristics of uterine inversions are presented in Table 1. Thirteen (87%) women had a complete inversion and two (13%) had an incomplete inversion. In six (40%) women the uterine inversion was diagnosed before placental birth and in five (33%) of these cases the placenta was removed before reposition was performed. Hemoglobin levels during the complication dropped below 5.0 mmol/L in nine (60%) cases, with a minimum of 2.5 mmol/L. Shock was registered in seven women (47%). All women were transported to the operation room for repositioning and/or further management, which included blood transfusion. In 14 cases (93%) manually repositioning was performed under general anesthesia, in the other case the type of anesthesia and repositioning method is unknown. One case needed a Rusch balloon to prevent recurrence. Two (13%) inversions were reverted in primary health care by midwifes before transfer to secondary health care.

All inversions were repositioned successfully. Only partial follow-up data about consecutive pregnancies is available due to anonymous data collection of the LEMMoN study. At least two women delivered healthy babies after uterine inversion.

**Table 1** | Clinical characteristics of uterine inversion

| | **Cases N = 15** | **The Netherlands (PRN %) 2005** |
|---|---|---|
| Age (y) | 30.1 | 31.0 |
| Parity | | |
| 0 | 8 (53.3) | 45.5 |
| 1 | 6 (40.0) | 36.4 |
| 2 | 1 (6.7) | 12.8 |
| Socio-economic status | | |
| Low | 2 (13.3) | |
| Modest | 10 (66.7) | N/A |
| High | 3 (20.0) | |
| Blood loss (ml) | 2.857 [1.500-5.000] | N/A |
| Shock registered | 7 (46.7) | N/A |
| Number of packed cells | 5 [2-10] | N/A |
| Hospital stay (d) | 3.5 [1-7] | N/A |
| **Possible risk factors** | | |
| Low risk at booking | 14 (93.3) | 79.5 |
| Low risk at onset of birth | 8 (57.1) | N/A |
| Mode of delivery | | |
| Spontaneous | 10 (66.7) | 74.9 |
| Vacuum extraction | 5 (33.3) | 9.9 |
| Retained placenta, cord-traction or macrosomia (>4500 gram) | 11 (73.3) | |
| Controlled cord traction | 7 (46.7) | N/A |
| Retained placenta | 4 (26.8) | |
| Macrosomia | 2 (13.4) | |
| Birth stage duration | | |
| 2nd | 42 [5-108] | N/A |
| 3rd | 40 [8-90] | |
| Fundal implantation | 1 (6.7) | N/A |

Data are presented as means [range] or number (percentage).

Abbreviations: PRN, The Netherlands Perinatal Registry; N/A, Not Applicable.

## DISCUSSION

All previous studies in the literature have been performed in single institutions. The present study provides the first population-based results on puerperal uterine inversion in the Netherlands. The incidence for acute uterine inversion was around 1 in 20 000 vaginal deliveries, resulting in severe blood loss, drop of hemoglobin levels, the need for blood transfusion, and shock. It is a rare obstetric complication and most cases occurred in low-risk women. In some cases prolonged duration of second and third stages of labor, macrosomia, vacuum extraction and retained placenta were found to be associated factors.

One limitation of this study was that there was no specific category for uterine inversion, so to be included the women had to meet the LEMMoN criteria. Thirteen women were included due to major obstetric hemorrhage (and received four or more packed cells), one was admitted to an intensive care unit and the remaining woman was included in the miscellaneous category. Considering the serious consequences of puerperal uterine inversion it is very unlikely that cases could have been missed with these criteria. We are convinced that complete data has been gathered on the incidence of puerperal uterine inversion in the Netherlands. Many studies have described nulliparity as a risk factor for uterine inversion [2,11]. In this study, the proportion of nulliparous women is comparable to that in the Dutch population. We thus cannot confirm nulliparity as a risk factor. A case-control study performed by Watson et al. [3] supports our finding. Placental adherence [1,12], macrosomia [13] and precipitate labor [13] have previously been proposed as risk factors. Other risk factors less frequently described are maternal structural anomalies [2,12], connective tissue disorders, [14] fundal placenta implantation [2,12] and a short umbilical cord [12]. In our study, one case with fundal placenta implantation was registered and none with connective tissue disorders. Unfortunately, no data were available for the other factors. As a consequence of the low prevalence of associated factors regarding mother and/or child, factors in obstetric health care can be considered. Das et al. [1] described umbilical cord traction and improper method of expressing the placenta as the two main causes (after a spontaneous origin), representing 21 and 19% of all puerperal inversions. In 47% of the cases in our study, controlled cord traction was registered. It is difficult to examine possible iatrogenic factors (such as controlled cord traction in a non- or not fully contracted uterus) and we think this item is prone to be underreported. Spontaneous birth of the placenta without any manipulation was registered in only two cases; for the other six cases this remains unclear. Other studies support third stage manipulation of the umbilical cord and placenta in the developing of uterine inversion [2,12]. On the other hand, active management is needed to prevent other complications of the third stage. Combs et al. [15] report an increased risk for hemorrhage and blood transfusion if the third stage exceeds 30 minutes. Considering a mean duration of the third stage of 40 minutes in our study population, active management was indicated in most cases. It is likely that cord traction may become "less controlled" when the placenta is not easily delivered. Presumably there is an interaction between big babies and prolonged delivery followed by active management of the third stage by the midwife or obstetrician. Management of uterine inversion consists of two important therapeutic interventions, to prevent severe blood loss or shock and revert as soon as possible. Shock treatment consists of oxygen, intravenous 0.9% NaCl administration and, if necessary, plasma

or blood products. Successful repositioning can be reached by pushing the uterine fundus back through while applying pressure from the outside with the other hand (Johnson's maneuver). In five cases (33%) of our study the placenta was removed before the uterus was reverted; this is believed to increase blood loss and is contraindicated in this situation. The internal hand should remain until the uterus is contracted (sometimes reached after administering oxytocic agents) so that the risk of recurrence is as low as possible. As with one case in our study it is possible to use a Rusch balloon tamponade to prevent recurrence. When repositioning is not possible due contraction, tocolytic drugs are sometimes needed. Nowadays, laparotomy is not needed for successful repositioning. All these procedures should be performed under general anesthesia in the operation room. At the onset of birth, eight of our 14 (57.1%) initially low-risk booked cases were still low risk. This low-risk profile implies that every birth attendant should be able to detect this rare but severe complication. One should then proceed with adequate management as described to avoid the risk for acute severe maternal morbidity. To prevent the condition we advise to only perform controlled cord traction in the case of a well contracted uterus.

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# CHAPTER 5

## LAPAROTOMY AFTER CHILDBIRTH: A TWO-YEAR NATIONWIDE COHORT STUDY IN THE NETHERLANDS

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*Submitted for publication*

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## ABSTRACT

**Objective:** To identify national incidence rates for laparotomy concomitant with severe acute maternal morbidity and the relation with mode of delivery of laparotomy after childbirth..

**Design:** Prospective population based cohort study.

**Setting:** All 98 maternity units in the Netherlands.

**Population:** All women who sustained severe acute maternal morbidity between August 2004 and August 2006 during pregnancy, childbirth and puerperium in the Netherlands.

**Methods:** All women who had one or more laparotomies during the two-year study period were included. Women with laparotomy after childbirth were analysed in relation to mode of delivery using all deliveries in the country over the same period as reference.

**Main outcome measures:** Incidence rates for laparotomy during pregnancy, childbirth and puerperium and relative risk of laparotomy following emergency and planned caesarean in comparison with vaginal delivery.

**Results:** The overall incidence of laparotomy during pregnancy, delivery and puerperium in the Netherlands was 7.8 per 10 000 deliveries, and 6.0 per 10 000 deliveries for laparotomy after childbirth only. Considering different modes of delivery, incidences were 30.1 and 1.8 per 10 000 respectively after caesarean and vaginal delivery. Compared to vaginal delivery the relative risk for laparotomy after caesarean delivery was 16.7 (95% CI: 12.2-22.6). Relative risk was 21.8 (95% CI: 15.8-30.2) following emergency caesarean section and 10.5 (95% CI: 7.1-15.6) following planned caesarean section.

**Conclusions:** The risk of laparotomy is considerably elevated in women undergoing caesarean section. This must be considered in counselling and decision making regarding mode of delivery.

## INTRODUCTION

According to the World Health Organization (WHO), laparotomy is an intervention, which should only be performed for severe pregnancy complications. It may therefore be used as an indicator of severe maternal outcome and 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 centre studies with a limited number of cases.
Previous studies only address 're-laparotomy' after caesarean section (CS). Reported incidence rates of 're-laparotomy' are low, varying between 0.2 and 0.9% [2-11]. Although data on laparotomy after vaginal delivery (VD) are not reported it has been suggested that the incidence of laparotomy may be higher after CS, since operative delivery is associated with a higher risk of maternal morbidity and mortality [12,13].
In this paper we report nationwide incidence rates of laparotomy during pregnancy, childbirth and puerperium and test the hypothesis that the risk of pregnancy related laparotomy after birth differs by mode of delivery.

## METHODS



This study is part of a two-year nationwide cohort study to assess severe acute maternal morbidity during pregnancy, delivery and puerperium in the Netherlands, called the LEMMoN-study. Pregnant women 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 severe acute maternal morbidity (SAMM) were categorized in five groups: Intensive Care Unit (ICU) admission, uterine rupture, eclampsia, major obstetric haemorrhage (defined as ≥4 units of packed cells or hysterectomy or embolization) and a miscellaneous group with SAMM according to the opinion of the treating clinician that could not be included in the other four groups. Cases could be included into more than one group.
All women who had a laparotomy during pregnancy and after vaginal or caesarean delivery were included in the present study. Laparotomy was defined as a surgical procedure involving an incision through the abdominal wall to gain access into the abdominal cavity, other than routine caesarean section. Before risk analysis incidence of laparotomy during pregnancy, childbirth and the puerperium was calculated.
Subsequently, risk analysis with regard to mode of delivery was performed for only women who had a laparotomy after childbirth. In this analysis only women with a gestational age of at least 24 weeks during time of birth were included who had a laparotomy within six weeks after delivery. Women who had a caesarean hysterectomy were also excluded from this analysis.
Main outcome measure was the relative risk according to mode of delivery (with VD as reference) and associated risk factors. The Netherlands Perinatal Registry (PRN) was used as the source for background denominator data. Clinical characteristics and delivery data were analysed in search

for predisposing factors. Maternal characteristics included: age, body mass index, parity, gestational age, and previous caesarean section. Data concerning delivery included: mode of delivery, blood loss, number of units of blood transfused, indication for laparotomy, timing of laparotomy after birth (<24 hours, 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, (non-)obstetric sepsis, hematoma and miscellaneous (i.e. removal of purposely-left sterile gauze, bladder damage, rectovaginal fistula). Therapeutic interventions were clustered into: bleeding control 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.

Relative risks (RR) with 95% confidence intervals (CI) were calculated where appropriate. Differences in characteristics between modes of delivery 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).

In this study we used anonymous data from the LEMMoN-study that cannot be related to any individual. The LEMMoN study was approved by the medical ethics committee of the Leiden University Medical Centre (P04-020; 8 March 2004).

## RESULTS

During the two-year study period 355 841 deliveries were registered in the PRN, of which 302 689 (85.1%) were vaginal deliveries and 53 152 (14.9%) were CS (planned: 24 580, 46.2%; emergency 28 572, 53.8%).

Among a total of 2552 SAMM cases, 325 laparotomies were reported in 276 women. The incidence of laparotomy during pregnancy, delivery and puerperium concomitant with SAMM in the Netherlands was 7.8 per 10 000 deliveries. Out of these women, 37 (13.4%) had the (initial) laparotomy before birth, 15 (5.4%) during caesarean section with additional procedures (including 11 hysterectomies), 6 (2.2%) after delivery before 24 weeks of gestational age and 3 (1.1%) more than 6 weeks after delivery. In the analysis of the relation to mode of delivery these 61 women (22.1%) were excluded. The remaining 215 women were included for risk analysis, of whom 160 (74.4%) sustained laparotomies after CS and 55 (25.6%) after VD (Figure 1). The remaining 215 women were included for risk analysis, of whom 160 (74.4%) sustained laparotomies after CS and 55 (25.6%) after VD (Figure 1). These 215 women were originally included in the SAMM cohort by at least one criterion: ICU-admission 145 (67.4%), uterine rupture 22 (10.2%), eclampsia 8 (3.7%), MOH 192 (89.3%) and miscellaneous 6 (2.8%). The incidence of laparotomy after childbirth concomitant with SAMM was 6.0 per 10 000. Among those laparotomies that took place after delivery, incidence was 30.1 per 10 000 caesarean deliveries and 1.8 per 10 000 vaginal deliveries, RR 16.7 (95% CI 12.2-22.6). The absolute risk of laparotomy was 39.5 per 10 000 deliveries for emergency CS and 19.1 per 10 000 for

planned CS. Compared to VD, RRs for emergency and planned CS were 21.8 (95% CI 15.8-30.2) and 10.5 (95% CI 7.1-15.6) respectively (Table 1).

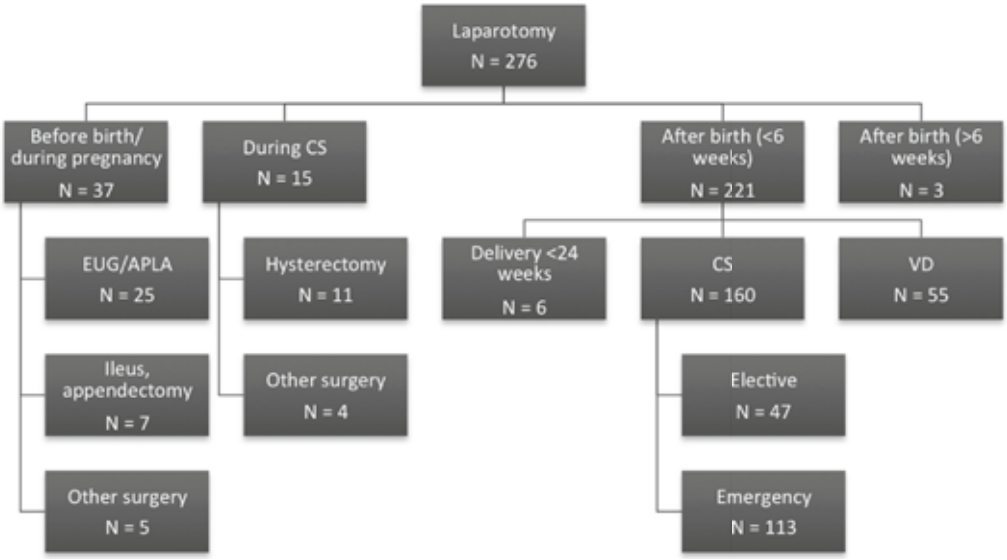


**Figure 1** | Overview of women enduring laparotomy during pregnancy, delivery and puerperium
EUG = extra uterine gravidity; APLA = provoked abortion; CS = caesarean delivery; VD = vaginal delivery.

**Table 1** | Incidence of laparotomy after childbirth

| | 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 CS, were more often nulliparous, had pregnancies of a lower gestational age and longer hospital admission compared to those who delivered vaginally (Table 2). Large proportions in both groups had 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 CS the proportion of women with a previous CS scar was larger in the planned CS group (emergency

20.4%, planned 61.7%; p<0.01). There were 113 women (52.6%) who needed nine or more packed cells. SAMM occurred before childbirth in 14 women (6.5%) and after childbirth in 198 (92.1%) women (Table 2).

**Table 2** | Maternal characteristics and delivery 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) | 4303 (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 delivery; RBC = red blood cells. Data is presented as mean (SD) or number (%).

In 46.0% of women the indication to perform laparotomy after birth was intra-abdominal bleeding, followed by severe postpartum haemorrhage (38.6%) (Table 3). For CS, the main indication was intra-abdominal bleeding (58.1%). For VD, the main indications to perform laparotomy were severe postpartum haemorrhage (61.8%) or suspected uterine rupture (21.8%).

A total of 147 (68.4%) laparotomies were performed within 24 hours after birth (CS 63.1% versus VD 83.6% ; p<0.05). Late laparotomies (within 2-7 days) were more likely to happen after CS (CS 26.9% versus VD 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 CS scar-related bleeding (34 women, 15.8%). In 21 (9.8%) women no therapeutic intervention was done during laparotomy.

Forty women (18.6%) had more than one laparotomy, of whom 32 (14.8%) two, 7 (3.3%) three and 1 (0.5%) had four laparotomies. In 21 (52.5%) of these women, the operation was due to intra-abdominal bleeding and in 5 (12.5%) women re-laparotomy resulted in hysterectomy.

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

**Table 3** | Detailed information of performed 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) | |
| Time* | <24h | 46 (83.6) | 101 (63.1) | **<0.05** | 71 (62.8) | 30 (63.8) | **<0.05** |
| | 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) | |
| | Unknown | 0 (0.0) | 4 (2.9) | | 1 (0.9) | 3 (6.4) | |
| Intervention* | Abdominal wall | 0 (0.0) | 13 (8.1) | **<0.001** | 10 (8.9) | 3 (6.4) | 0.591 |
| | 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-lynch 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) | |
| | Miscellaneous | 10 (18.2) | 24 (15.0) | | 18 (15.9) | 6 (12.8) | |
| | Unknown | 0 (0.0) | 6 (3.8) | | 3 (2.7) | 3 (6.4) | |
| Number | 1 | 43 (78.2) | 129 (80.6) | 0.26 | 88 (77.9) | 41 (87.2) | 0.44 |
| | ≥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 post partum haemorrhage. Data is presented as number (%). *considering 1st laparotomy.



## DISCUSSION

This study is the first to report a national incidence rate of laparotomy during pregnancy, delivery and puerperium. The risk of postpartum laparotomy was more than 16 times higher in women who delivered by CS compared to those who delivered vaginally. The risk for laparotomy is lower when CS is planned, but still 10 times higher compared with vaginal birth.

Our study shows that laparotomy after childbirth is an indicator of a life threatening condition. First, when applying the WHO Maternal Near Miss tool, defining life-threatening conditions by using the threshold of five or more units of blood, we found 183 of 215 women (85.1%) [1]. Secondly,

79 of 276 (28.6%) women ended up having hysterectomy (of which 11 during CS and 68 during first or subsequent laparotomy). Furthermore when calculating the risk of dying if massive blood transfusion would not be possible, as is the case in many countries in the world, 113 out of 215 women, (52.6%) would have died [15].

Available literature indicates that laparotomy is performed after 0.2 – 0.9% of all caesarean sections, mainly due to intra-abdominal haemorrhage [2-10]. Within this range, the rate in the Netherlands is relatively low (0.3%). Since laparotomy after vaginal birth has not been studied before the incidence of 1.8 per 10 000 deliveries (0.02%) we found in the current study cannot be compared to existing literature.

The largest study of laparotomy after CS was conducted in a single university medical centre in Israel and included 80 patients over a period of twenty years [4]. Our study is unique due to the large sample size (N=215) in a relatively short period and its prospective nationwide design. Postpartum haemorrhage, placental abruption, uterine rupture and previous CS have been described as the factors most frequently associated with re-laparotomy [2,4,5,10]. We confirmed that the main proportion (68.4%) of all laparotomies is performed within 24 hours after childbirth due to either intra-abdominal bleeding (46.0%) or postpartum haemorrhage (38.6%). Nearly one third of women (32.6%) had a previous CS. Although placental abruption was not an endpoint in this study, the majority of these cases are likely represented in the group of major obstetric haemorrhage since they generally receive at least four units of blood. Eleven (5.1%) women sustained laparotomy due to (suspected) uterine rupture. Infection or sepsis was no endpoint in any previous study. In our study sepsis was the indication for laparotomy in 11 cases (5.1%).

When analysing the three main modes of delivery (VD, emergency CS and planned CS) there are some noteworthy results. In contrast with what is commonly assumed, the proportion of intra-abdominal bleeding as an indication to perform re-laparotomy after planned CS was not different from emergency CS. Also, the timing to perform laparotomy does occur more often between two and seven days after CS than after VD, where laparotomy is performed earlier. This means that three or four days of clinical monitoring after CS are justified.

It should also be addressed that in our study there were 40 (18.6%) women who sustained more than one laparotomy (up to four times) after delivery and that exploration without any therapeutic intervention ('negative laparotomy') was performed 21 times (9.8% of all laparotomies). Finally, in 149 (93.1%) women who delivered by caesarean followed by laparotomy SAMM occurred only until after childbirth.

A limitation of this study is that laparotomy was not a separate inclusion criterion for the LEMMoN-study. Although this means that some relatively mild cases may have been missed, it is unlikely that this has affected the reported relative risks of laparotomy by mode of delivery. Cases that might not have been reported are cases with less than four units of blood transfused, without hysterectomy, embolization, uterine rupture or ICU admission. These cases were only included if the treating obstetrician considered it to be a case of severe maternal morbidity. This means our incidence of laparotomy during pregnancy could be underestimated, but we have no reason to believe that this has affected the relative risks for laparotomy after childbirth.

CS rates (especially in industrialized countries) have been increasing for the past decades [16]. They vary up to 32% in the United States, 39% in Italy and 50% in Brazil [16,17]. In the Netherlands, although rates are relatively low, the proportion of CS has risen from 11% to 16% between 1999 and 2012 [18]. A recent study in China showed a CS rate of 52% with 40% of caesarean sections being performed without medical indication [19].

Considering caesarean delivery and its elevated risk for laparotomy, this development may lead to unfavourable outcomes. This adds to the results of previous studies in which caesarean delivery 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 the short- and long-term adverse effects of performing CS: one of the most severe short-term complications of CS is an intraoperative surgical complication requiring laparotomy. Long-term complications occur in subsequent pregnancies and include abnormally adherent placentation and the risks of delivery in presence of a uterine scar [21-23]. Our study affirms this, since women with a vaginal birth after previous CS are over-represented (18/55 women, 34.0%) compared to the general Dutch pregnant population (6.0%) [14].

WHO has recently repeated their statement that national CS rates above 10% are not associated with a decrease in maternal or neonatal mortality [24]. It should be alarming therefore that 17 out of 22 industrialized countries reported rates of 20% or more in 2007 [16]. This increase of CS rates may be difficult to stop. It is, however, important to realize that every cut has its cost. Adverse maternal complications, including laparotomy, should be kept in mind when caesarean section is considered and when future mothers are counselled for mode of delivery, especially when maternal request is the only indication.

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# PART 2

## SEVERE ACUTE MATERNAL MORBIDITY AND VALIDATION OF THE WHO MATERNAL NEAR MISS TOOL

# CHAPTER 6

## VALIDATING THE WHO MATERNAL NEAR MISS TOOL IN A HIGH-INCOME COUNTRY

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## ABSTRACT

**Introduction:** This study was performed to assess the applicability of the WHO Maternal Near Miss tool (MNM tool) and the organ dysfunction criteria in a high-income country.

**Material and Methods:** The MNM tool was applied to 2552 women who died of pregnancy-related causes or sustained severe acute maternal morbidity (SAMM) between August 2004 and August 2006 in one of all 98 hospitals with a maternity unit in the Netherlands. Fourteen (0.6%) cases had insufficient data for application. Each case was assessed according to the three main 'MNM categories' specified in the MNM tool and their subcategory criteria: five disease-, four intervention- and seven organ dysfunction-based criteria. Potentially life threatening conditions (disease-based inclusions) and life threatening cases (organ dysfunction-based inclusions) were differentiated according to WHO-methodology. Outcomes were incidence of all (sub)categories and case fatality rates (CFR).

**Results:** Out of the 2538 cases, 2308 (90.9%) women fulfilled disease-based, 2116 (83.4%) intervention-based and 1024 (40.3%) the organ dysfunction-based criteria. Maternal death occurred in 48 women, of whom 23 (47.9%) fulfilled disease-based, 33 (68.8%) intervention-based and 31 (64.6%) organ dysfunction-based criteria. CFR was 33/2116 (1.6%) for cases fulfilling the disease-based criteria, 33/2116 (1.6%) for intervention-based criteria and 31/1024 (3.0%) for women fulfilling the organ dysfunction-based criteria.

**Conclusions:** In the Netherlands, where advanced laboratory and clinical monitoring are available, organ dysfunction-based criteria of the MNM tool failed to identify nearly two-thirds of SAMM cases and more than one-third of maternal deaths. Disease-based criteria remain important, and using only organ dysfunction-based criteria would lead to underestimating severe acute maternal morbidity.

## INTRODUCTION

Prevention of maternal deaths is one of the major goals in global maternity care [1,2]. Maternal mortality is used as a quality marker for obstetric care [3,4]. Fortunately, maternal deaths have become rare events in high-income countries [5,6]. Therefore, other markers including severe acute maternal morbidity (SAMM) have been introduced to monitor the quality of obstetric care [5]. SAMM is a stage in the continuum between complication and mortality, occurs more frequently than mortality [3,7] and may have similar associated factors [1].

In order to arrive at a universal and discriminatory definition of severe maternal morbidity, the World Health Organization (WHO) proposes the term 'Maternal Near Miss' (MNM). MNM is defined as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy [8]. With the aim of creating uniform criteria to detect and monitor MNM and enable cross-country comparisons [1], WHO developed the Maternal Near Miss tool (MNM tool) (Figure 1) [8]. This tool summarizes three main types of criteria to identify MNM: five disease-based criteria (A0-4, 'A-criteria'); four critical interventions (B0-3, 'B-criteria'), and seven organ dysfunction criteria (C0-6, 'C-criteria') [1,8]. According to WHO, C-criteria are the most promising marker to detect MNM, since organ dysfunction is the ultimate step in the continuum from complication to death [1,9,10]. WHO claims that C-criteria are sensitive enough to pick up severe (life-threatening) cases and specific enough not to include 'unnecessary' less severe (potentially life-threatening) complications, so as to arrive at a manageable workload for audit purposes.

The MNM tool applicability was previously studied in single institutions in a variety of settings, including Brazil, Malawi and Tanzania [10-12]. These studies indicate that the MNM tool in general and the organ dysfunction criteria in particular detect only a small proportion of all severe morbidity (Brazil 12%, Malawi 22%, Tanzania 42%). In addition, the largest assessment of the MNM tool to date, performed by WHO, did not include any high-income European country [13]. This means that the applicability of the MNM tool in these countries is currently not known.

Therefore, this study was performed to validate the MNM tool in the Netherlands, as an example of a high-income European country. Our aims were to investigate the MNM tool's applicability and to determine whether organ dysfunction criteria are suitable as markers to identify severe morbidity.



## MATERIAL AND METHODS

We applied the WHO MNM tool to a previously collected cohort of women who sustained severe morbidity in the Netherlands (LEMMoN-study) [14]. Data collection was done prospectively between 1 August 2004 and 1 August 2006. All 98 hospitals with a maternity unit participated: ten tertiary care centers, 33 non-university teaching hospitals and 55 general hospitals. Inclusion criteria were: ICU admission, uterine rupture, eclampsia or HELLP syndrome with liver hematoma or rupture, major obstetric hemorrhage (MOH; defined as a need of four and more units of blood for transfusion) and a miscellaneous group of cases of severe morbidity in the opinion of the treating obstetrician, which could not be included in group 1-4. Maternal deaths during the study period were also included.

More detailed information about data collection of the LEMMoN-study was described previously [14].

Group A: Severe complications/potentially life threatening conditions
- A0: Severe postpartum hemorrhage
- A1: Severe pre-eclampsia
- A2: Eclampsia
- A3: Sepsis or severe systemic infection
- A4: Ruptured uterus

Group B: Critical interventions or intensive care unit admission
- B0: Use of blood products (includes any blood transfusion)
- B1: Interventional radiology (uterine artery embolization)
- B2: Laparotomy (other than caesarean section)
- B3: Admission to Intensive Care Unit

Group C: Organ dysfunction/ life-threatening conditions
- C0: Cardiovascular dysfunction
  - Shock, cardiac arrest (absence of pulse/ heart beat and loss of consciousness), use of continuous vasoactive drugs, cardiopulmonary resuscitation, severe hypoperfusion (lactate >5 mmol/l or >45 mg/dl), severe acidosis (pH <7.1)
- C1: Respiratory dysfunction
  - Acute cyanosis, gasping, severe tachypnea (respiratory rate >40 breaths per minute), severe bradypnea (respiratory rate <6 breaths per minute), intubation and ventilation not related to anesthesia, severe hypoxemia (O2 saturation <90% for ≥60 minutes or PAO2/FiO2 <200)
- C2: Renal dysfunction
  - Oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, severe acute azotemia (creatinine ≥300 µmol/ml or ≥3.5 mg/dl)
- C3: Coagulation/ hematologic dysfunction
  - Failure to form clots, massive transfusion of blood or red cells (≥5 units), severe acute thrombocytopenia (<50 000 platelets/ml)
- C4: Hepatic dysfunction
  - Jaundice in the presence of pre-eclampsia, severe acute hyperbilirubinemia (bilirubin >100 µmol/l or >6.0 mg/dl)
- C5: Neurologic dysfunction
  - Prolonged unconsciousness (lasting ≥12 hours)/coma (including metabolic coma), stroke, uncontrollable fits/status epilepticus, total paralysis
- C6: Uterine dysfunction/ hysterectomy
  - Uterine hemorrhage or infection leading to hysterectomy

**Figure 1** | MNM-tool groups and subcategories [8]

The MNM groups and subcategories are shown in Figure 1. The MNM tool was applied to each LEMMoN-case. Fourteen (0.6%) cases were excluded due to insufficient data for application of the tool. Each case could be part of more than one MNM-group and fulfill several subcategories, which are called events. For example, a woman with major post-partum hemorrhage who received six units of packed cells, fulfilled disease based (event: severe postpartum hemorrhage), intervention

based (event: use of blood products) and organ dysfunction based (event: coagulation dysfunction defined as ≥5 units of blood) criteria. Based on WHO terminology, disease-based criteria are used to identify potentially life-threatening conditions, whereas organ dysfunction-based criteria identify life-threatening conditions.

For each woman the following parameters were available: maternal age, parity, BMI, smoking habits during pregnancy, socio-economic status indicator according to postal code [14], ethnic origin as defined by Statistics Netherlands [15], mode of delivery, quantity of blood loss and number of received blood products. If additional information was necessary, anonymized patient records were also available.

Two investigators (IK, HB) independently applied the MNM tool to all SAMM-cases. Afterwards, their results were compared. Differences in interpretation were discussed with the entire research team until consensus for categorization was reached. Cases with incomplete or missing information were discussed within the research team to prevent misclassification or unnecessary exclusion.

Primary outcomes were the number of women and events detected within the three main MNM groups and subcategories (A0-4, B0-3, C0-6). Based on these and numbers of maternal deaths case fatality rates were calculated. A comparison was made between women with potentially life-threatening conditions and those with life-threatening conditions.

### Statistics

The numeric parameters were compared using independent sample T-tests. Statistical analysis was performed using SPSS statistics, version 20.0 (SPSS, Chicago, IL).

### Ethics

In this study we used anonymous data from the LEMMoN-study that cannot be related to any individual. The LEMMoN-study was approved by the medical ethics committee of the Leiden University Medical Centre (P04-020; 8 March 2004) [14].



## RESULTS

In the study period of the LEMMoN-study, there were 371 623 deliveries in the Netherlands [15]. A total of 2552 SAMM-cases were reported (0.7% of all deliveries). General characteristics of the 2538 women assessed by the MNM tool are shown in Table 1. Of these 2538 women, 2308 (90.9%) fulfilled one or more disease based-criteria, 2116 (83.4%) one or more intervention based-criteria and 1024 (40.3%) one or more organ dysfunction-based criteria. In total there were 7007 events reported, of which 2638 (37.6%) were disease-based, 3190 (45.5%) intervention-based and 1179 (16.8%) organ dysfunction-based. Table 2 shows the number of events in each sub-category.

During the study period 48 deaths occurred. Of these, 23 (47.9%) fulfilled disease-based, 33 (68.8%) intervention-based and 31 (64.6%) organ dysfunction-based criteria. There were five maternal deaths (10.4%) that could not be classified into any MNM-group: suicide, acute asthma exacerbation, pancreas carcinoma, liver cirrhosis and massive pulmonary embolism, respectively. Case fatality rate

for cases that only fulfilled disease-based criteria was 23/2308 (1.0%), for cases that additionally fitted intervention-based criteria 33/2116 (1.6%) and for those with organ dysfunction criteria 31/1024 (3.0%).

**Table 1** | Characteristics of women in the study

| **Age (yrs)** | **N** | **%** | **Body Mass Index (BMI)** | **N** | **%** |
|---|---|---|---|---|---|
| <20 | 31 | 1.2 | <18,5 | 60 | 2.4 |
| 20-34 | 1770 | 69.8 | 18.5-24.9 | 969 | 38.2 |
| 35-39 | 589 | 23.2 | 25.0-29.9 | 386 | 15.2 |
| ≥40 | 122 | 4.8 | ≥ 30 | 238 | 8.6 |
| Unknown | 26 | 1.0 | Unknown | 905 | 35.6 |
| **Parity** | | | **Socio-economic status indicator** | | |
| 0 | 1259 | 49.6 | Low | 701 | 27.6 |
| 1 | 867 | 34.2 | Middle | 991 | 39.1 |
| ≥ 2 | 390 | 16.3 | High | 520 | 20.5 |
| Unknown | 22 | 0.9 | Unknown | 326 | 12.8 |
| **Mode of delivery** | | | **Received packed cells (n)** | | |
| Induction of labour | 1196 | 47.1 | 0 | 734 | 28.9 |
| Spontaneous | 1118 | 44.1 | <5 | 946 | 38.4 |
| Caesarean section | 1058 | 41.7 | 5-9 | 542 | 37.3 |
| Ventouse/forceps | 300 | 11.8 | 10-19 | 189 | 7.4 |
| Breech delivery | 10 | 0.4 | ≥20 | 50 | 2.0 |
| Unknown | 11 | 0.4 | Unknown | 77 | 3.0 |
| **Quantity of blood loss (l)** | | | **Ethnic origin** | | |
| <1 | 688 | 27.1 | Netherlands | 1862 | 73.4 |
| 1.0-4.9 | 1390 | 54.8 | Morocco | 116 | 4.6 |
| 5.0-9.9 | 159 | 6.3 | Surinam/Dutch Antilles | 111 | 4.3 |
| ≥10 | 31 | 1.2 | Sub-Sahara Africa | 93 | 3.7 |
| Unknown | 271 | 10.7 | Turkey | 87 | 3.4 |
| **Smoking during pregnancy** | N | % | Indonesia | 112 | 4.4 |
| Yes | 176 | 6.9 | South-America | 10 | 0.4 |
| No | 1294 | 51.0 | Other Western* | 113 | 4.5 |
| Unknown | 1068 | 42.1 | Unknown | 34 | 1.3 |

BMI = body mass index. *Japan, USA, Canada.

**Table 2** | Overview after application of the MNM-tool

| Category | SAMM cases (%) | Events (%) | Sub-category | Events (%) |
|---|---|---|---|---|
| **A: disease** | 2308 (90.9) | 2638 (37.6) | 0: PPH | 1635 (61.9) |
| | | | 1: Pre-eclampsia | 414 (15.7) |
| | | | 2: Eclampsia | 242 (9.2) |
| | | | 3: Infection/sepsis | 118 (4.5) |
| | | | 4: Ruptured uterus | 229 (8.7) |
| **B: intervention** | 2116 (83.4) | 3190 (45.5) | 0: Any blood products | 1738 (57.5) |
| | | | 1: Interventional radiology | 111 (3.7) |
| | | | 2: Laparotomy | 267 (8.8) |
| | | | 3: Admission to ICU | 909 (30.0) |
| **C: organ failure** | 1024 (40.3) | 1179 (16.8) | 0: Cardiovascular | 165 (12.5) |
| | | | 1: Respiratory insufficiency | 115 (8.7) |
| | | | 2: Renal | 26 (2.0) |
| | | | 3: Coagulation/ Hematologic | 846 (63.8) |
| | | | 4: Hepatic insufficiency | 27 (2.0) |
| | | | 5: Neurologic | 33 (2.5) |
| | | | 6: Hysterectomy | 113 (8.5) |
| **Total** | | 7007 | | |

PPH = postpartum hemorrhage; ICU = intensive care unit.



**Table 3** | Comparison of potentially life-threatening and life-threatening group

| | Life threatening | Potentially Life threatening | P value |
|---|---|---|---|
| Maternal age (years) | 31.9 (5.0) | 31.5 (4.9) | 0.043 |
| Duration of hospital stay (days) | 10.4 (12.0) | 7.4 (6.9) | 0.000 |
| BMI | 24.4 (5.2) | 25.1 (5.5) | 0.017 |
| Parity | 2.9 (11.1) | 2.2 (7.2) | 0.070 |
| Maximum DBP (mmHg) | 85.4 (16.9) | 89.8 (19.0) | 0.000 |
| Blood loss (mL) | 3415 (2715) | 1639 (1151) | 0.000 |
| Units of packed cells (n) | 7.5 (6.4) | 2.4 (2.0) | 0.000 |
| Birth weight infant (g) | 3034 (1031) | 3069 (1051) | 0.434 |

BMI = body mass index; DBP = diastolic blood pressure.

Comparison between potentially life-threatening (women fulfilling disease-based criteria) and life-threatening (women fulfilling organ dysfunction criteria) conditions is shown in Table 3. In the life-threatening group the following parameters were significantly different: higher maternal age, longer duration of hospital stay, lower BMI, lower maximum diastolic blood pressure, more blood loss and packed cells transfused.

## DISCUSSION

To our knowledge, this is the first study evaluating the application of the WHO MNM tool in a high-income European country. Our findings show that the organ dysfunction criteria failed to identify nearly 60% of severe maternal morbidity cases. In contrast, disease-based criteria detected more than 90% of the SAMM-cases.

Our results are comparable to other studies from different settings. A cross-sectional study in Brazil found that only 10 out of 84 (12%) MNM cases fulfilled organ dysfunction criteria. Two more recent studies (2013) in Malawi and Tanzania found organ dysfunction detection percentages of 22% (84 out of 386 women) and 42% (103 out of 248 women). Importantly, case fatality rates for the study populations in these countries were 3.2% (Brazil), 12% (Malawi) and 13% (Tanzania), which indicate that it is justified to state that all women with SAMM in these countries are actually sustaining 'life-threatening' conditions. The low detection results were attributed to absence of sophisticated laboratory diagnostics and lack of manpower to perform extensive clinical monitoring in low-income countries [10,12,16]. In the Netherlands, however, such laboratory diagnostics and human resources are available. Therefore, our nationwide results indicate that organ dysfunction-based criteria also underperform in a setting with sufficient resources.

The differentiation between 'potentially life-threatening' and 'life-threatening' conditions shows a significantly higher maternal age, longer duration of hospital stay, more units of packed cells, more blood loss and higher parity in the life-threatening group. These determinants are known factors associated with maternal morbidity or mortality [12,17]. Mean BMI and maximum diastolic blood pressure were higher in the potentially life-threatening group, which may be explained by the fact that obesity is a risk-factor for high blood pressure and (pre-)eclampsia [17,18].

Case fatality rate was highest for organ dysfunction criteria (potentially: 1.0%, life-threatening: 3.0%), which suggests that the WHO terminology 'life-threatening' may be justified. However, attributing this terminology to this relatively limited difference in case fatality rate can be considered highly arbitrary, since both (or neither) of these case fatality rates could be interpreted as 'life-threatening'. We also show that the MNM tool fails to detect 35% of all maternal deaths. This clearly shows that these criteria are not able to detect every life-threatening condition.

Finally, further analysis of women in each organ dysfunction subgroup (specifically C3; coagulation/hematologic dysfunction criteria, see Figure 1) indicates that 76% of all included women in the organ dysfunction group (781/1024) would have been included on the basis of a single criterion: massive transfusion of ≥5 units packed cells. This means that three quarters of all women included by the organ dysfunction criteria would have been detected with one relatively simple criterion. It stipulates the extreme importance of well-organized blood transfusion guidelines and services [19].

One limitation of our study is that we used data from a previous study, designed to detect SAMM according to different criteria and not designed to assess the MNM tool. An expert panel of obstetricians and the national Maternal Mortality Committee of the Dutch Society of Obstetrics and Gynecology defined the LEMMoN-study inclusion criteria, based on previous international studies. Considering the fact that the MNM-tool missed 60% of these differently defined SAMM-cases, the consequence can only be relative overreporting of MNM within the LEMMoN-study. This means it is

unlikely that cases that could have been detected by the MNM tool would have been missing from this nationwide study.

A second limitation was incomplete or missing information. Therefore, cases with incomplete information were discussed and assessed by our research group to prevent bias. As a consequence, the number of excluded cases (0.6%) could also be minimized. We believe that the large number of cases in this reliable dataset provides a unique and solid base for validating the MNM tool in a high-income country. A third limitation is the relatively old data set, but we have no reason to argue that our findings would be different in a cohort of more recent date.

Although the intervention-based criteria were able to identify a considerable number of SAMM and mortality cases, these criteria are not suitable for international comparison studies because of different criteria for transfusing blood products and indications to perform laparotomy. Admission into intensive care units and interventional radiology, such as embolization of the uterine arteries, are not present in all settings, and – where present- access depends on local protocols. Our advice would be to further refine the potentially life-threatening criteria of the WHO MNM tool, since these make early medical intervention possible with the intention of preventing life-threatening conditions and averting maternal deaths.

In the Netherlands, where advanced laboratory and clinical monitoring are available, organ dysfunction-based criteria of the WHO MNM tool fail to identify nearly two-third of SAMM cases and more than one-third of maternal deaths. Disease-based criteria remain important, and using only organ dysfunction-based criteria to detect MNM-cases would lead to an underestimation of severe maternal morbidity. Therefore, we propose to focus the discussion on potentially life-threatening conditions in the MNM tool in order to establish universal disease-based criteria to prevent life-threatening maternal morbidity

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# CHAPTER 7

## THE WHO MATERNAL NEAR MISS TOOL IN HIGH- AND LOW-RESOURCE SETTINGS: A CROSS-COUNTRY COMPARISON

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*Submitted for publication*

## ABSTRACT

**Objectives:** To apply the WHO Maternal Near Miss (MNM) tool in one high- and two low-resource settings and assess possibilities for cross-country comparison of severe maternal outcome (SMO).

**Methods:** Using three cohort studies that included SMO cases, during two-year time frames in the Netherlands, Tanzania and Malawi we reassessed all SMO cases (as defined by the original studies) with the WHO MNM tool (five disease-, four intervention- and seven organ dysfunction-based criteria). Main outcome measures were prevalence of MNM criteria and case fatality rates (CFR).

**Results:** A total of 3172 women were studied: 2538 (80.0%) from the Netherlands, 248 (7.8%) from Tanzania and 386 (12.2%) from Malawi. Total SMO detection was 2767 (87.2%) for disease-based criteria, 2504 (78.9%) for intervention-based criteria and 1211 (38.2%) for organ dysfunction-based criteria. Including every woman who received ≥1 unit of blood in low-resource settings as life-threatening, as defined by organ dysfunction criteria, led to more equally distributed populations. In one third of all Dutch and Malawian maternal death cases, organ dysfunction criteria could not be identified from medical records.

**Conclusions:** The organ dysfunction-based criteria are underreporting SMO. The WHO MNM tool, in its current form, is of limited use for cross-country comparison. In low-resource settings, lowering the threshold of transfused units of blood leads to a higher detection rate of MNM. We recommend refined disease-based criteria, accompanied by a limited set of intervention- and organ dysfunction-based criteria to set a measure of severity.

## INTRODUCTION

One of the Millennium Development Goals was to reduce global maternal mortality in 2015 by three quarters as compared to the level of 1990 [1]. In the summer of 2015, the United Nations reported an estimated 45% decline (using data up to 2013), indicating that this target will not be met. In the meantime, new Sustainable Development Goals have been set, including the reduction of the maternal mortality ratio below 70 per 100.000 live births by 2030 [2]. Assessment of pregnant women with severe maternal outcome (SMO), comprised of maternal near miss (MNM) and maternal death (MD), may contribute to accelerating this morbidity and mortality reduction [4].

The World Health Organisation (WHO) has defined a MNM as a 'woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy' [3,4]. WHO proposes an 'MNM approach' to monitor and improve quality of obstetric care using a tool that classifies women according to several (potentially) life-threatening conditions (Figure 1) [3]. The classification is based on three different types of criteria: disease-, intervention- and organ dysfunction-based. If any of the organ dysfunction-based criteria are met, the MNM approach defines that case as 'life-threatening', and therefore MNM [5].

According to WHO, uniformity of this MNM classification should make it possible to compare the quality of obstetric care between different settings in different countries, which would be useful in improving health care delivery. However, in some low-resource settings application of the WHO MNM tool showed underreporting of life-threatening maternal morbidity. This may be due to lack of blood for transfusion, absence of laboratory diagnostics and poor clinical monitoring, which are all needed to identify MNM [6-8].

In a nationwide cohort, we previously found that also in the Netherlands, a high-resource setting, organ dysfunction-based criteria failed to identify almost 60% of women with severe acute maternal morbidities as MNM [9]. If these women, who were not detected as having had 'life-threatening' conditions, had attended obstetric care in low-resource settings the majority would likely have died. Our previous studies have highlighted difficulties in finding universal criteria to identify MNM and raise questions about the applicability of the MNM tool in general, and its focus on organ dysfunction-based criteria in particular [6-9]. The aim of this present study is 1) to apply the WHO MNM tool in one high- and two low-resource settings and 2) to identify possibilities for cross-country comparison.



## METHODS

In the current study we used data available from SMO databases collected in the Netherlands, Tanzania and Malawi. Data for the Netherlands were extracted from a two-year nationwide cohort study (the LEMMoN-study), for Tanzania from a two-year cross-sectional study at Haydom Lutheran Hospital and for Malawi from a two-year study of maternal morbidity and mortality at Thyolo District Hospital (the '4M-study'). A general description of the three study populations can be found in Table 1. Details have been published previously [7-10].

Group A: Severe complications/potentially life threatening conditions
- A0: Severe postpartum hemorrhage
- A1: Severe pre-eclampsia
- A2: Eclampsia
- A3: Sepsis or severe systemic infection
- A4: Ruptured uterus

Group B: Critical interventions or intensive care unit admission
- B0: Use of blood products (includes any blood transfusion)
- B1: Interventional radiology (uterine artery embolization)
- B2: Laparotomy (other than caesarean section)
- B3: Admission to Intensive Care Unit

Group C: Organ dysfunction/ life-threatening conditions
- C0: Cardiovascular dysfunction
  - Shock, cardiac arrest (absence of pulse/ heart beat and loss of consciousness), use of continuous vasoactive drugs, cardiopulmonary resuscitation, severe hypoperfusion (lactate >5 mmol/l or >45 mg/dl), severe acidosis (pH <7.1)
- C1: Respiratory dysfunction
  - Acute cyanosis, gasping, severe tachypnea (respiratory rate >40 breaths per minute), severe bradypnea (respiratory rate <6 breaths per minute), intubation and ventilation not related to anesthesia, severe hypoxemia (O2 saturation <90% for ≥60 minutes or PAO2/FiO2 <200)
- C2: Renal dysfunction
  - Oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, severe acute azotemia (creatinine ≥300 µmol/ml or ≥3.5 mg/dl)
- C3: Coagulation/ hematologic dysfunction
  - Failure to form clots, massive transfusion of blood or red cells (≥5 units), severe acute thrombocytopenia (<50 000 platelets/ml)
- C4: Hepatic dysfunction
  - Jaundice in the presence of pre-eclampsia, severe acute hyperbilirubinemia (bilirubin >100 µmol/l or >6.0 mg/dl)
- C5: Neurologic dysfunction
  - Prolonged unconsciousness (lasting ≥12 hours)/coma (including metabolic coma), stroke, uncontrollable fits/status epilepticus, total paralysis
- C6: Uterine dysfunction/ hysterectomy
  - Uterine hemorrhage or infection leading to hysterectomy

**Figure 1** | WHO MNM tool groups and subcategories [3]

Women with SMO were included according to definitions established by the original studies (Table 2). We reassessed all cases in these three cohorts using the WHO MNM tool. Fourteen cases (0.4%) of the Dutch cohort were excluded due to insufficient data for application. All other 2538 SMO patients were assessed without the need for supplementation of any marker [9]. For the low-resource settings, identification of SMO did not only depend on relatively advanced laboratory tests, but could also happen on the basis of supplemented clinical markers as recommended by WHO [5].

**Table 1** | Demographics of the three study populations

| | The Netherlands | Tanzania | Malawi |
|---|---|---|---|
| Study type | Prospective cohort | Prospective cohort | Prospective cohort |
| Period | 2004-2006 | 2009-2011 | 2007-2009 |
| Population | Nationwide | Haydom Lutheran Hospital | Thyolo District |
| Maternity units | 98 | 1 | 29[†] |
| Reference area (km2) | 41 526 | 51 000 | 1715 |
| Live births* | 375 657 | 9136 | 31 838 |
| Deliveries* | 371 021 | 9471 | 33 254 |

Data is shown in numbers. *During study period. [†]Including Thyolo District Hospital and 28 smaller, government, mission and private facilities.

**Table 2** | Inclusion criteria of SMO used in the three study populations

| The Netherlands | Tanzania | Malawi |
|---|---|---|
| **ICU admission** | **Clinical criteria** | **Uterine rupture** |
| Admission to an ICU or coronary care unit, other than postoperative recovery | Acute cyanosis, gasping, respiratory rate >40 or <6/min, shock, oliguria non responsive to fluids or diuretics, failure to form clots, loss of consciousness lasting >12H, cardiac arrest, stroke, uncontrollable fit/total paralysis, jaundice in the presence of pre-eclampsia | Clinical symptoms or intrauterine foetal death that led to laparotomy, at which diagnosis was confirmed, laparotomy for uterine rupture after vaginal birth, rupture confirmed by autopsy or clinical symptoms with high suspicion of rupture after death |
| **Uterine rupture** | **Laboratory-based criteria** | **Eclampsia or severe pre-eclampsia with a maternal indication for termination of pregnancy** |
| Clinical symptoms that led to an emergency caesarean section, where uterine rupture was confirmed<br>Peripartum hysterectomy or laparotomy for uterine rupture | Oxygen saturation < 90% for ≥ 60 minutes<br>Acute thrombocytopenia (<50,000 platelets/ml) | |
| **Eclampsia/HELLP** | **Management-based criteria** | **Major obstetric haemorrhage** |
| HELLP syndrome only when accompanied by liver haematoma or rupture | Admission to an ICU, hysterectomy following infection or haemorrhage, transfusion of ≥ 1 unit of blood, intubation and ventilation ≥ 60 minutes not related to anaesthesia, cardio-pulmonary resuscitation | (including from complicated abortions and ectopic pregnancies)<br>Transfusion of units of ≥450 ml of blood or a haemoglobin level <6 g/dl measured after vaginal bleeding or estimated blood loss of > 1 litre. |

**Table 2** | *(Continued)*

| The Netherlands | Tanzania | Malawi |
|---|---|---|
| **Major obstetric haemorrhage (MOH)**<br>Transfusion of ≥4 units of packed cells<br>Embolization or hysterectomy for MOH | **Severe maternal complications**<br>Eclampsia, sepsis or severe systemic infection, uterine rupture | **Severe obstetric and non-obstetric peripartum infections**<br>All infections for which iv antibiotics or iv anti-malarials were prescribed or surgical treatment was performed.<br>Neoplasms resulting primarily from HIV-infections |
| **Miscellaneous**<br>SMO cases to the opinion of the treating obstetrician, not to be included in group 1-4 | **Severe maternal complications**<br>Eclampsia, sepsis or severe systemic infection, uterine rupture | **Other complication ≥ 2 senior clinicians considered the condition as severe** |

ICU = intensive care unit; HELLP = haemolysis elevated liver enzymes and low platelets; SMO = severe maternal outcome.

Data from the three studies were collected into a single database containing the following variables: age (<20, 20-35 and >35 years), parity (0, 1 and ≥2), units of blood given (0, 1, 2, 3, 4 and ≥5), duration of hospital stay, maternal mortality, and classification according to the three WHO MNM tool criteria groups (disease-, intervention- and organ dysfunction-based). If women had multiple conditions or interventions they were included into more than one criteria group, with each included criterion titled a separate 'event'. Case fatality rates (CFR) were calculated for the corresponding populations. All parameters were measured and compared between each country's population and those women who sustained life-threatening conditions as per WHO definition. Outcomes for the three countries were analysed individually and compared for differences. Finally, the life-threatening group was corrected by including every Tanzanian and Malawian woman (where giving five or more units is an exception even in life-threatening haemorrhage [11] who received one unit or more of blood for transfusion. Maintaining five units of blood as an organ dysfunction criterion would imply that in settings where the availability of blood products is highly limited, fewer MNM cases are included. Data were analysed using chi-square tests for categorical data and independent sample t-tests for numerical data. Statistical analysis was performed using SPSS statistics, version 20.0 (SPSS, Chicago, IL). All three initial studies had ethical approval and for present study anonymous data were used.

## RESULTS

A total of 3172 women were analysed: 2538 (80.0%) from the Netherlands, 248 (7.8%) from Tanzania, and 386 (12.2%) from Malawi. General characteristics of all three populations are shown in Table 3. All parameters significantly differed between the three countries.

**Table 3** | Basic characteristics of total study population

| | Netherlands (n=2538) | Tanzania (n=248) | Malawi (n=386) | P value |
|---|---|---|---|---|
| **Age (y)** | | | | |
| Data available | 2512 | 248 | 384 | |
| <20 | 31 (1.2) | 23 (9.3) | 83 (21.6) | * |
| 20-35 | 1945 (77.4) | 187 (75.4) | 267 (69.5) | † |
| >35 | 536 (21.3) | 38 (15.3) | 34 (8.9) | * |
| **Parity** | | | | |
| Data available | 2388 | 227 | 377 | |
| 0 | 1258 (52.7) | 52 (22.9) | 83 (22.0) | * |
| 1 | 867 (36.3) | 30 (13.2) | 56 (14.9) | * |
| ≥2 | 263 (9.9) | 145 (63.9) | 238 (63.1) | * |
| **Units of blood** | | | | |
| Data available | 2461 | 248 | 371 | |
| 0 | 734 (29.8) | 64 (25.8) | 201 (54.2) | * |
| 1 | 6 (0.2) | 108 (43.5) | 77 (20.8) | * |
| 2 | 88 (3.6) | 54 (21.8) | 65 (17.5) | * |
| 3 | 50 (2.0) | 12 (4.8) | 19 (5.1) | * |
| 4 | 802 (32.6) | 8 (3.2) | 5 (1.3) | * |
| ≥5 | 781 (31.7) | 2 (0.8) | 4 (1.0) | * |
| **Mortality** | | | | |
| Data available | 2538 | 248 | 386 | |
| CFR | 48 (1.9) | 32 (12.9) | 46 (11.9) | |

Data is shown in numbers (percentage). †= <0.05, *= <0.0001. CFR = case fatality rate.



After assessment with the WHO MNM tool, out of the 2538 Dutch women, 2308 (90.9%) fulfilled one or more disease-based criteria, 2116 (83.4%) any intervention-based criterion and 1024 (40.3%) any organ dysfunction-based criterion. In Tanzania there were 123 (49.6%) women fulfilling disease-based, 231 (85.9%) intervention-based, and 103 (41.5%) organ dysfunction-based criteria. For Malawi these numbers were 336 (87.0%), 175 (45.3%), and 84 (21.8%), respectively. The detection in the combined study population of 3172 women was 2767 (87.2%) women for disease-based, 2504 (78.9%) for intervention-based, and 1211 (38.2%) for organ dysfunction-based criteria. Only this final group sustained 'life-threatening conditions' according to WHO methodology. The CFRs were 48/2538 (1.9%) for the Netherlands, 32/248 (12.9%) for Tanzania and 46/386 (11.9%) for Malawi. Of these maternal deaths, 17 (35%) women in the Netherlands and 15 (33%) women in Malawi could not be identified as having had a 'life-threatening' condition. In Tanzania, all maternal deaths could be defined.

For the total population, analysis of the events detected by the WHO MNM tool subcategories is shown in Table 4. Postpartum haemorrhage (PPH) is the most commonly detected event among the disease-based criteria. Pre-eclampsia follows as an important second in the Netherlands, whereas in Tanzania and Malawi sepsis is more prominent. Giving blood products is the most frequent intervention and laparotomies (other than caesarean section) are more frequently performed in Malawi and Tanzania compared to the Netherlands. For the organ dysfunction-based criteria, coagulation or haematological dysfunction is the major reason for inclusion in the Netherlands, whereas in the low-resource settings this is cardiovascular dysfunction. Between countries all subcategories differed significantly except for the numbers of ruptured uterus (disease-based), admissions to ICU (intervention-based), and women who presented with renal dysfunction or ended up having hysterectomy (organ dysfunction-based).

**Table 4** | WHO MNM tool inclusions of the total study population

| Category | Subcategory | Events (n) | | | |
|---|---|---|---|---|---|
| **A: Disease** | | **Netherlands (N=2638)** | **Tanzania (N=139)** | **Malawi (N=394)** | **P value** |
| | 0: PPH | 1635 (62.0) | 66 (47.5) | 110 (27.9) | * |
| | 1: Pre-eclampsia | 414 (15.7) | 8 (5.8) | 20 (5.1) | * |
| | 2: Eclampsia | 242 (9.2) | 15 (10.8) | 69 (17.5) | * |
| | 3: Sepsis | 118 (4.5) | 30 (21.6) | 148 (37.6) | * |
| | 4: Ruptured uterus | 229 (8.7) | 20 (14.4) | 47 (11.9) | 0.11 |
| **B: Intervention** | | **Netherlands (N=3030)** | **Tanzania (N=334)** | **Malawi (N=224)** | |
| | 0: Blood products | 1743 (57.5) | 184 (55.1) | 165 (73.7) | * |
| | 1: Int. radiology | 111 (3.7) | N/A | N/A | |
| | 2: Laparotomy | 267 (8.8) | 59 (17.7) | 59 (26.3) | * |
| | 3: Admission to ICU | 909 (30.0) | 91 (27.2) | N/A | 0.78 |
| **C: Organ dysfunction** | | **Netherlands (N=1325)** | **Tanzania (N=167)** | **Malawi (N=96)** | |
| | 0: Cardiovascular | 166 (12.5) | 60 (35.9) | 35 (36.5) | * |
| | 1: Respiratory | 115 (8.7) | 35 (21.0) | 13 (13.5) | * |
| | 2: Renal | 26 (2.0) | 4 (2.4) | 1 (1.0) | 0.21 |
| | 3: C/H | 845 (63.8) | 16 (9.6) | 4 (4.2) | * |
| | 4: Hepatic | 27 (2.0) | 3 (1.8) | 11 (11.5) | † |
| | 5: Neurologic | 33 (2.5) | 33 (19.8) | 11 (11.5) | * |
| | 6: Hysterectomy | 113 (8.5) | 16 (9.6) | 21 (21.9) | 0.29 |

Data is shown in numbers (percentage). †= <0.05, *= <0.0001. PPH = postpartum haemorrhage; ICU = intensive care unit; Int. radiology = interventional radiology; C/H = coagulation/haematological; N/A = not applicable.

**Table 5** | WHO MNM tool inclusions of the (corrected) life-threatening population

| Category | Subcategory | Events (n) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **A: Disease** | | **Netherlands (N=1132)** | **Tanzania (N=77)** | *Corrected* (N=124) | **Malawi (N=86)** | *Corrected* (N=216) | **P value** | *Corrected* |
| | 0: PPH | 822 (72.6) | 28 (36.4) | 66 (53.2) | 21 (24.4) | 92 (42.6) | * | * |
| | 1: Pre-eclampsia | 160 (14.1) | 3 (3.9) | 5 (4.0) | 5 (5.8) | 7 (3.2) | * | * |
| | 2: Eclampsia | 52 (4.6) | 15 (19.5) | 15 (12.1) | 21 (24.4) | 25 (11.6) | * | * |
| | 3: Sepsis | 52 (4.6) | 20 (26.0) | 23 (18.5) | 21 (24.4) | 56 (25.9) | * | * |
| | 4: Ruptured uterus | 46 (4.1) | 11 (14.3) | 15 (12.1) | 18 (20.9) | 36 (16.7) | * | * |
| **B: Intervention** | | **Netherlands (N=1725)** | **Tanzania (N=153)** | (N=315) | **Malawi (N=66)** | (N=215) | | |
| | 0: Blood products | 895 (51.9) | 59 (38.6) | 184 (58.4) | 43 (65.2) | 165 (76.7) | * | * |
| | 1: Interv. radiology | 96 (5.6) | N/A | N/A | N/A | N/A | | |
| | 2: Laparotomy | 197 (11.4) | 27 (17.6) | 50 (15.9) | 23 (34.8) | 50 (23.3) | 0.06 | 0.21 |
| | 3: Admission to ICU | 537 (31.1) | 67 (43.8) | 81 (25.7) | N/A | N/A | | |
| **C: Organ dysfunction** | | **Netherlands (N=1325)** | **Tanzania (N=167)** | (N=337) | **Malawi (N=96)** | (N=257) | | |
| | 0: Cardiovascular | 166 (12.5) | 60 (35.9) | 60 (17.8) | 35 (36.5) | 35 (13.6) | * | * |
| | 1: Respiratory | 115 (8.7) | 35 (21.0) | 35 (10.4) | 13 (13.5) | 13 (5.1) | * | † |
| | 2: Renal | 26 (2.0) | 4 (2.4) | 4 (1.2) | 1 (1.0) | 1 (0.4) | 0.51 | 0.16 |
| | 3: C/H | 845 (63.8) | 16 (9.6) | 186 (55.2) | 4 (4.2) | 165 (64.2) | * | 0.70 |
| | 4: Hepatic | 27 (2.0) | 3 (1.8) | 3 (0.9) | 11 (11.5) | 11 (4.3) | * | † |
| | 5: Neurologic | 33 (2.5) | 33 (19.8) | 33 (9.8) | 11 (11.5) | 11 (4.3) | * | * |
| | 6: Hysterectomy | 113 (8.5) | 16 (9.6) | 16 (4.7) | 21 (21.9) | 21 (8.2) | * | 0.20 |

Data is shown in numbers (percentage). *= <0.0001; †= <0.05; PPH = postpartum haemorrhage; ICU = intensive care unit; C/H = coagulation/haematological; N/A = not applicable.



Among women with life-threatening conditions (as defined by the organ dysfunction-based criteria, Table 5), PPH is the most common event for inclusion in the Netherlands and Tanzania. In Malawi PPH, eclampsia, infection, and uterine rupture are almost equally represented. Eclampsia is significantly more common in both low-resource settings. Giving blood products is the commonest intervention-based criterion in the Netherlands and Malawi. In Tanzania this is ICU admission.

After correction for any blood transfusion in the low-resource settings the life-threatening group changed (Table 5). First, the MNM tool now identified 1458 (46.0%) women with organ dysfunction, instead of 1205 (38.2%). In addition, blood transfusion became a more frequent inclusion criterion in the low-resource settings as compared to the Dutch setting, and 'coagulation or hematologic dysfunction' was now equally represented in each setting. When including any blood transfusion, the position of PPH as major contributor to severe acute maternal morbidity becomes more prominent in Tanzania and Malawi (36.4% and 24.4% raised to 53.2% and 42.6%).

The general characteristics of women with life-threatening conditions (before and after correction for blood transfusion) can be seen in Table 6. In comparison with the total study population (Table 3) higher CFRs are seen among women with life-threatening conditions, and among women in low-resource settings.

**Table 6 |** Basic characteristics of the (corrected) life-threatening population

| | **Netherlands (N=1024)** | **Tanzania (N=103)** | *Corrected* (N=228) | **Malawi (N=84)** | *Corrected* (N=206) | **P value** | *Corrected* |
|---|---|---|---|---|---|---|---|
| **Age (y)** | | | | | | | |
| Data available | 1019 | 103 | 228 | 84 | 205 | | |
| <20 | 11 (1.1) | 15 (14.6) | 22 (9.6) | 16 (19.0) | 29 (14.1) | * | 0.15 |
| 20-35 | 760 (74.6) | 75 (72.8) | 170 (74.6) | 54 (70.2) | 157 (76.2) | 0.71 | 0.69 |
| >35 | 248 (24.3) | 13 (12.6) | 36 (15.8) | 9 (10.7) | 19 (9.2) | * | † |
| **Parity** | | | | | | | |
| Data available | 967 | 93 | 208 | 81 | 202 | | |
| 0 | 514 (53.2) | 28 (30.1) | 47 (22.6) | 19 (23.5) | 32 (15.8) | * | 0.08 |
| 1 | 333 (32.5) | 10 (10.8) | 27 (13.0) | 9 (11.1) | 28 (13.6) | * | 0.79 |
| ≥2 | 120 (12.4) | 55 (59.1) | 134 (64.4) | 53 (65.4) | 142 (70.3) | * | 0.21 |
| **Units of blood** | | | | | | | |
| Data available | 1000 | 103 | 228 | 82 | 202 | | |
| 0 | 123 (12.3) | 44 (42.7) | 44 (19.3) | 39 (47.6) | 49 (24.3) | * | 0.21 |
| 1 | 6 (0.6) | 22 (21.4) | 108 (47.4) | 14 (17.1) | 64 (31.7) | * | ‡ |
| 2 | 23 (2.3) | 25 (24.3) | 54 (23.7) | 17 (22.1) | 62 (30.7) | * | 0.10 |
| 3 | 16 (1.6) | 6 (5.8) | 12 (5.3) | 5 (6.1) | 17 (8.4) | * | 0.19 |
| 4 | 88 (8.8) | 4 (3.9) | 8 (3.5) | 3 (3.7) | 5 (2.5) | 0.07 | 0.53 |
| ≥5 | 744 (74.4) | 2 (1.9) | 2 (0.9) | 4 (4.9) | 4 (2.0) | * | 0.33 |
| **Mortality** | | | | | | | |
| Data available | 1024 | 103 | 228 | 84 | 206 | | |
| CFR | 31 (3.0) | 32 (31.1) | 32 (14.0) | 21 (25.0) | 28 (13.6) | | |

Data is shown in numbers (percentage). *= <0.0001, †= <0.05; ‡= <0.01; CFR = case fatality rate.

## DISCUSSION

Our results indicate that the WHO MNM tool, in its current form, is not useful for cross-country comparison. Detection differs between high- and low-income countries and organ dysfunction-based criteria detect only 38.2% of all women with SMO as defined by three cohort studies.
Moreover, in cases of maternal *mortality* and based on the specified criteria, organ dysfunction could not be identified from the medical records in 17 out of 48 cases (35%) in the Netherlands and

15 out of 46 cases (33%) in Malawi. We believe that a revision of the WHO MNM tool and specifically the organ dysfunction-based criteria is needed to enable meaningful cross-country comparisons.

A recent study by Menezes et al. states that the WHO criteria perform well [12]. In this study, conducted in two Brazilian reference hospitals, 77 out of 1196 (6.4%) women were identified as having life-threatening conditions based on the WHO MNM tool, compared to 33.8% and 80.2% by using Waterstone's or other literature-based criteria respectively. However, the authors do not clarify why the other 1119 (93.6%) women did not sustain MNM conditions or why these pregnant women did not 'nearly die, but survived' (according to WHO MNM definition). The reason for this omission appears that the current WHO criteria are mistakenly seen as the 'gold standard' for evaluation of severe maternal morbidity.

The underestimation of severe maternal outcome when applying the WHO MNM tool in its current form remains an important issue. Overall, disease-based criteria show the highest detection of SMO (87.2%) in each type of setting. An explanation for the low detection rate (49.6%) in the Tanzanian population could be the local SMO criteria used in that study. For example, this led to fewer women with PPH (according to the WHO MNM definition of blood loss above one liter) in this cohort, as PPH as such was no separate inclusion criterion in the Tanzanian cohort (in contrast with Malawi) and women were only included if they had received blood transfusion. The intervention-based criteria detected 78.9% of all SMO cases. An explanation for the low detection (45.3%) in the Malawian population is the absence of interventional radiology and an ICU. Both disease-based and intervention-based criteria show higher SMO detection in each setting compared to organ dysfunction-based criteria. The CFRs of the potentially life-threatening populations (fulfilling only disease-based criteria) in low-resource settings remain high (Tanzania 13/123, 10.6%; Malawi 35/336, 10.4% versus 23/2308, 1.0% in the Netherlands). This implies that there is hardly any 'over-inclusion' in such settings and that these women should be picked up as SMO in the 'potentially life-threatening phase' of their conditions.

The lack of laboratory and clinical diagnostics for detecting organ dysfunction explains under-reporting in low-resource settings [6-9]. Similar detection rates for Tanzania and the Netherlands may seem contradictory because advanced technology in the highly resourced Dutch setting would be expected to lead to a higher detection of SMO. An explanation could be found in the supplemented clinical criteria (such as acute cyanosis, gasping, loss of consciousness etc.) as part of the local Tanzanian inclusion criteria (Table 1). These compensate the lack of extensive intensive care monitoring needed for detection by organ dysfunction-based criteria. This would also explain the low detection numbers in Malawi due to the mainly disease- and intervention-based local inclusion criteria.

Different criteria for SMO used in the three cohorts are the most important limitation of this study. SMO cases, as identified differently by local criteria, are being compared according to a single WHO MNM tool. The consequence may be an underestimation of SMO in low-resource settings as Tanzania and Malawi due to limited available diagnostics. However, this limitation also stresses the fact that application of the WHO MNM tool may differ in different contexts.

Another major issue is that, although WHO uses a threshold of five units, there is no consensus about the number of units of blood transfused, which identifies organ dysfunction [6-9]. After including

every woman in a low-resource setting who received even one unit of blood, results show a more equally distributed 'life-threatening group' in all settings, emphasizing that the shortage of blood for transfusion remains a large problem in many low-resource settings [13]. Also, SMO detection increased from 38.2% to 46.0% of all SMO cases. This 7.8% increase consists of 228 Tanzanian women (91.9%) and 206 Malawian women (53.4%). This leads to a more realistic comparison between high- and low-resource settings, because PPH is an important cause of SMO and lack of blood compounds this problem [11,14]. Unfortunately, this is also due to unwillingness and impossibility of relatives to donate, and inadequacy or lack of blood bank storage facilities and transport [6, 7,11,15].

Although it is clear that there is an urgent need for monitoring health care delivery in both high- and low-resource settings, it remains difficult to determine which set of criteria should be used. In our opinion, disease-based criteria remain important in all settings, since detection is high and does not depend on local protocols. In contrast, for the same reason, intervention-based criteria (such as ICU admission) are of limited use. To prevent 'over-inclusion' for disease-based criteria, especially in high-income countries, more strict operational definitions (such as the blood loss threshold defining 'severe postpartum haemorrhage') are needed. For low-resource settings, supplemented clinical markers could be included and the threshold of received units of blood should be lowered for organ dysfunction-based criteria [8].

In conclusion, we have shown that the WHO MNM tool leads to underreporting of SMO and renders cross-country comparisons impossible and meaningless in its current form. We recommend refined disease-based criteria, accompanied by a limited set of (intervention- and organ dysfunction-based) criteria to set a measure of severity. We believe that with these adjustments, the MNM tool may be more valuable and could ultimately lead to more comparable assessments of the quality of obstetric health care across different settings.

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# CHAPTER 8

## DISCUSSION AND CONCLUSION

## DISCUSSION

Maternal health care in high-income countries has significantly improved over the years, however, multiple audit studies have shown that preventable severe acute maternal morbidity (SAMM) and maternal mortality are still present nowadays [1,2]. To prevent these, solutions can clearly be found in attempting to decrease risk factors derived from poverty. However, this thesis also shows a possible trend of 'wealth care', derived from increased availability of resources and opportunities, influencing maternal care worldwide. Below, the different maternal 'wealth care' subjects attended in this thesis will be discussed.

### Overweight

An important subject and consequence of higher availability of resources and socio-economic inequality is overweight (BMI≥25) worldwide. Obesity is currently considered the largest and fastest growing problem in medicine worldwide and more than doubled between 1980 and 2014. In 2014, more than 1.9 billion adults (≥18 years) were overweight and 600 million of these were obese (BMI≥30). When considering the world's female adult population, more than 40% is overweight [3]. It also has been predicted that 60% of the world's population could suffer from overweight or obesity (total of 3.3 billion people) by 2030 if current trends continue [4].

This thesis shows that obesity and the possible underlying metabolic syndrome also has an independent effect on pregnancy and delivery to develop SAMM. In chapter 2 it is shown that there is a dose-response relation between obesity and SAMM and that the origin of this elevated risk can be dissected into difficulties encountered during each phase of pregnancy and the puerperal period. For example, antenatal factors include difficulties during ultrasonography, delayed detection of (pre)eclampsia and venous tromboembolism [5-7]. And for the perinatal phase: delay in labor induction, a longer duration of labor, higher incidence of caesarean section and anaesthesiological difficulties (with the epidural catheter or tracheal tube), were raised as factors possibly causing this elevated risk of SAMM [8-11]. Adding to this, there are also increased infectious risks during and after delivery. For example, overweight women showed significant risks to develop genital tract, urinary tract and wound infection compared to women of normal weight (BMI 20-<25) [9]. This risk for infectious morbidities and the decreased performance in general can explain the increased risk for overweight women to be admitted to an intensive care unit. And the high incidence of previous caesarean section in overweight women also explains the elevated risk of uterine rupture [12,13].

Surprisingly, no increased risk was observed for major obstetric haemorrhage as endpoint in chapter 2. In this thesis only cases needing transfusion of at least 4 units of packed red blood cells were included. Large previous studies had different findings. For example, a 10-year nationwide study in Sweden showed adjusted odds ratios of 1.19 (BMI 29.1-35; 95% CI 1.15-1.23), 1.36 (BMI 35.1-40; 95% CI 1.25-1.48) and 1.70 (BMI>40; 95% CI 1.45-1.98) among vaginally delivered women to develop major postpartum haemorrhage [14]. Another study analysing 287 213 pregnancies in London used a cut-off value of >1000 ml blood loss and found adjusted odds ratios of 1.17 (BMI 25-30; 99% CI 1.07-1.27) and 1.44 (BMI>30; 99% CI 1.30-1.60) [9]. As blood loss is underestimated and blood transfusion depends on local management, these odd ratios are difficult to compare [15,16].

Obesity clearly has its effect on the mother, but it also impacts on the foetus with impaired fetal growth, macrosomia and an increased number of stillbirths [17-20]. Not surprisingly, as a consequence of neonatal and maternal morbidity, a recent study has also shown that overweight is associated with increasing maternal health service costs [21]. It showed that women who were overweight, obese and morbidly obese (BMI≥35) were associated with respectively 4%, 9% and 12% prolongations of hospital admission. They also estimated that a 2,5% decrease in both the proportion of overweight and obese pregnant women (with a corresponding increase of 5% for the normal weight proportion) leads to cost savings of almost 15 million euros as a consequence of fewer admissions alone [21]. It is has longer been known that obesity can cause subfertility due anovulation, however it also affects spontaneous pregnancy chances in regular ovulatory women [22,23]. Nowadays, and even more in the future, this again will affect health service costs due elevated use of expensive subfertility programs and assisted reproduction techniques (ART). The effect of ART itself on SAMM will be discussed in the next section.

As the prevalence of overweight increases rapidly, the incidence of obesity related SAMM and probably maternal mortality will likely increase in the future. However, it is clear that overweight already at this present time causes a considerable burden on pregnant women, their offspring, obstetric care workers and national health care services worldwide. Therefore, to prevent SAMM worldwide, intervention strategies should ideally be devoted to children and young girls, since they are the future mothers.

Nowadays, women with a BMI of 40 or higher are advised to be monitored at hospital according to the Dutch national guidelines. The Dutch Society of Obstetrics and Gynaecology also advises that local management protocols should be established for obese (no BMI cut-off mentioned) women in general [24]. For obese (BMI≥30) women, no specific pregnancy and delivery advise is mentioned in the Dutch guidelines. When other SAMM risk factors such as previous caesarean section or history of severe preeclampsia are present these patients are referred from midwife to the hospital, however this is independent of the presence of overweight [25]. Based on this thesis and current literature, countries using risk selection systems for referral (such as the Netherlands), morbidly obese women (BMI≥35) should be included in the national guidelines as "official risk factor" as reason for referral. For BMI≥30, midwives or obstetricians are advised to thoroughly evaluate these women with an individual perspective for co-morbidities.

However, in addition to recognizing these risks, obstetric health care workers also need to focus on preventing weight gain during and after pregnancy. For example, effectiveness has been shown with low cost web-based lifestyle intervention and also behavioural interventions have prevented postpartum weight retention [26,27]. Since maternal overweight during pregnancy has shown to affect the metabolic profile in children [18,28,29], and considering the magnitude of this problem, it is even conceivable that preventing childhood overweight, followed by preventing future maternal obesity starts during pregnancy.

### Assisted reproductive techniques

Nowadays, older and subfertile women in high-income countries are offered opportunities to become pregnant through artificial reproductive techniques (ART), which all showed to increase the risks to develop SAMM.

In contrast with overweight, which has a direct effect on obstetric outcome, ART also has indirect effects. From an evolutionary perspective, there might be protective reasons for subfertile women to not become pregnant. Although this is an very unethical hypothesis, in this situation ART might be counterproductive in these women as they are physically or condition wise not suited to carry or deliver new-borns. Although every woman should have the right to become pregnant, from this perspective questions could be raised if these developments are safe for every woman, especially with the risk of higher order pregnancies with its inherent risks. Pregnancies achieved through ART have shown to be at a higher risk for adverse perinatal and obstetric outcome compared with spontaneous pregnancies [30,31]. Both singleton and multiple pregnancies conceived through ART showed higher risk for low birth weight, preterm birth and even perinatal death [30]. A nationwide study analysing 13 261 pregnancies after in vitro fertilization (IVF) showed an elevated risk for pregnant women to sustain pre-eclampsia, placental abruption and post-partum haemorrhage compared to spontaneous pregnancies [31]. Interestingly, it is also known that women who became pregnant after IVF with oocyte donation have even more obstetric complications compared to the standard IVF procedure [32]. For example, recent meta-analysis showed an increased risk for preeclampsia and gestational hypertention compared to other ART and spontaneous conception [33]. In a large nationwide Australian cohort, Venn et al. were one of the first to show in 2001 that IVF more than doubles the risk for maternal mortality (25.7 deaths per 100 000 IVF pregnancies compared to 10.9 per 100 000 non-IVF pregnancies) [34]. Also in the Netherlands, maternal mortality following IVF was evaluated, showing an even higher risk with 42.5 deaths per 100 000 IVF pregnancies compared to the 12.1 deaths per 100 000 live born children from non-IVF pregnancies [35]. In this study the risk is attributed also to higher age, more multiple pregnancies and higher rate of caesarean sections. For this reason, in agreement with the elevated risks, there is a maximum limit of age of 45 years for offering IVF to women in the Netherlands and in 2002 the embryo law was introduced forbidding commercial oocyte donation. Considering the risks for maternal morbidity and mortality it is alarming that currently debate is taking place for raising this limit to 50 years of age.

The use of multi embryo transfer (MET) increases the risk of multiple pregnancies. Since this is still extensively practiced worldwide, the risk of multiple pregnancies after ART remains. In 2013, a worldwide report analysing 53 countries showed that the decreased use of MET with three or more embryos (36.7% to 34.2%) caused a decline in the proportion of twin (25.1% to 23.6%) and triplet (1.8% to 1.5%) pregnancies after ART. They also showed that the proportion of MET with three or four embryos still ranges from 47.5% in the United States up to 80% in low-income countries, compared to a maximum of 2% in those were ART is restricted by national health policies [36]. In 2015, a new report using updated data showed that the mean number of embryos transferred reduced from 2.35 in 2004 to 2.22 in 2006. On average these might be promising results, however it should be noted that there is still a great variation between countries ranging from <1.5 (Australia,

New Zealand, Sweden) to >3 embryos per transfer (Albania, South Korea). They also state that the decreased high order delivery rate is merely attributed to multifetal reduction rather than to the average number of embryos transferred [37]. Therefore, the ultimate method to avoid higher rates of multiple pregnancies is using only single embryo transfer (SET).

In current times the boundaries of nature are broken by science. In the case of ART it is most likely that when selecting the 'appropriate' subfertile women there is a large proportion of women where these techniques are an extraordinary solution and perhaps safe, but considering the mentioned risks counselling before pregnancy and closer monitoring is obligatory. And as multifetal reduction also raises significant professional and ethical issues, further reduction of SAMM after ART will only be achieved by making SET the standard everywhere, as is already the case in the Netherlands. And it is also important that access to these techniques are restricted by clear national health policies.

**Caesarean section**

Since 1985, WHO recommends an optimal population-based caesarean rate from 10-15% [38]. Ironically, this recommendation was established by an expert panel at a WHO-meeting in Brazil, which currently is considered one the caesarean capitals in the world. In 2015 this recommendation was revisited, using a worldwide country-level analysis and systematic review, concluding that at population level caesarean rates above 10% are not associated with reduction in maternal and neonatal mortality [39].

Caesarean section is a mode of delivery, but also still a major surgical procedure, which is always associated with short and long-term risks. It thus affects physical and psychological health of the mother, child and even future pregnancies. Increasing caesarean rates and especially those without medical indication can also be seen as a consequence of the more superfluous 'wealth care' access worldwide and 'standardising' of this surgical procedure.

In this thesis, caesarean section showed to be associated with increased maternal morbidity in multiple pregnancies and an increased risk for laparotomy after birth. Previous studies using the LEMMoN study already showed overall elevated risks for severe acute maternal morbidity after caesarean section in general (RR 5.2, 95% CI 4.8-5.6) [40]. This risk has also been shown for several maternal morbidities specifically, such as ICU-admission (RR 7.7, 95% CI 6.7- 8.8), eclampsia (RR 2.2, 95% CI 1.3-4.0) and hysterectomy/arterial embolization for major obstetric haemorrhage (RR 6.6, 95% CI 5.0-8.7) [41-43]. Besides the risk of the index caesarean section it also affects subsequent pregnancies as previous caesarean section has also been shown to elevate the risk for SAMM (RR 3.7, 95% CI 3.4-4.1) [40].

Besides maternal morbidity, multiple studies have shown elevated risk for maternal mortality when comparing caesarean and vaginal delivery [44,45]. Schuitemaker et al. showed that caesarean section was the direct cause of death three times more often compared to vaginal birth. They also estimated, after detailed analysis of all cases, that after adding also indirect causes of death, the associated fatality rate was 0.28 per 1000 caesarean sections [46]. This implicates that in every 3571 caesarean births one woman would die with caesarean section as a direct or indirect cause. If these Dutch figures apply to other countries, this is seriously alarming when considering the estimated 18,5 million caesarean sections performed yearly worldwide [47], implicating more than 5000 maternal deaths each year.

New recommendations of WHO include a statement that caesarean section should only be used when a medical indication is present. Since the procedure was used for the first time, technique has improved and adverse risks decreased significantly. However, obstetricians in some countries seem to have forgotten the fact that it is still an important risk factor for maternal morbidity and mortality compared to vaginal delivery. In 2010, WHO performed a population-based study considering 137 countries of the United Nations aiming to report the global numbers and costs of unnecessary caesarean sections in the year 2008. First, they showed that more than 50% (69 out of 137 countries) had national caesarean rates above the recommended 15%. Secondly, when using a threshold of 20% to define overuse, a total of 4 million caesarean sections were in excess in 46 countries that year [47]. Without regard to the discussion of the optimal caesarean rate, this again can be found very alarming.

Below (Figure 1), the leading five non-European and European countries with the highest caesarean rates are listed using most recent data [47,48], including the percentage on maternal request or without medical reason [49]. Unfortunately, the number of caesarean sections without medical indication is unknown or unpublished for many countries.

**Figure 1** | Caesarean rates of worldwide leading countries in comparison with the Netherlands

**Non-European**

| Country | Rate | Without medical indication |
|---|---|---|
| China | 47.6% | 40% |
| Mexico | 47.5% | Not published |
| Brazil | 47.0% | Not published |
| Paraguay | 46.8% | Not published |
| Ecuador | 45.5% | Not published |

**European**

| Country | Rate | Without medical indication |
|---|---|---|
| Cyprus | 52% | Not published |
| Italy | 39% | Not published |
| Portugal | 35% | Not published |
| Hungary | 33% | Not published |
| Switzerland | 32% | Not published |
| **Netherlands** | 17% | Not published |

Considering these rates, which clearly include significant numbers of 'unnecessary' caesarean sections, there is no doubt that this 'wealth care' factor also has its effect on economy. As it happens, WHO estimated that in 2008, when using the 15% threshold, 6.2 million unnecessary sections were performed, and that the cost of this global "excess" was estimated to amount to approximately 2.32 billion US dollars [47].

In the following years, the debate for the optimal caesarean rate will continue. In a perfect world of caesarean section, the optimal rate should be the lowest without adverse outcome for mother and child. Most recent large cross-sectional and review studies report that this rate is ranging between 9% to 19% of all deliveries [50-53]. Added to this, it must be stated that these rates cannot always be used at every hospital level due differences in case mix of the obstetric population, hospital capacity (especially in low-income countries) and clinical management protocols.
Although these rates might be seen as an impossible goal for many countries, it should be strived for. Because only then the caesarean section pandemic can be put to a hold. In the meantime, obstetricians should keep in mind that caesarean section should only be performed with a clear medical indication and that performing caesarean section on request only is not an option.

**International comparison and universal detection**

Both poverty and wealth care factors have their effect on international comparison for severe maternal morbidity in low-, middle- and high-income countries.
An example to explain these comparison difficulties is blood transfusion. Blood transfusion is an important intervention and proxy of severeness for major obstetric haemorrhage and therefore severe maternal morbidity. However, this thesis (chapter 7) already outlined that in low-income countries lack of availability has shown to give a distorted view of the intervention rate to detect severe maternal outcome. Unfortunately, in these countries the consequence is underreporting of severe maternal morbidity when using the number of blood transfusion units as a proxy of severeness. However, for high-income countries such as the Netherlands, more availability of blood leads to higher detection. And when using too low a threshold it might even cause overreporting. When carrying forward this situation to high-income countries it might be hypothesised that 'wealth care' factors decrease the value of this then 'less-morbid' intervention as proxy of severeness due to more readily access. This hypothesis can be justified with the still increasing incidence of postpartum haemorrhage in multiple studies, which at the same time observed an even higher increase of blood transfusion rates [54,55]. A population-based study including 52 151 women admitted (or readmitted) with postpartum haemorrhage showed an increase in admittance of 8.3% to 10.7% in the period 1994 to 2002, compared to a significantly higher increase in blood transfusion rates of 1.9% to 11.7% of all women [55]. Besides an increased blood transfusion rate, Ford et al also showed that this increase was unrelated to increased morbidity and also suggested that blood transfusions were used in women with less severe haemorrhage [54]. Although there is a rise in interventions observed, it obviously also has a positive effect on safe motherhood as postpartum haemorrhage is still underreported and always needs adequate blood loss management [15,16]. It is also important to state that in low-income countries there is much to improve related to blood transfusion. Because unfortunately availability is still affected by unwillingness or impossibility of relatives to donate, and inadequacy or lack of blood bank storage facilities and transport [56].
A comparable effect can be seen for ICU-admission (as also stated in chapter 7). This intervention also highly depends on availability or local protocols and is therefore also not always a reliable reflection of severe maternal morbidity [57].

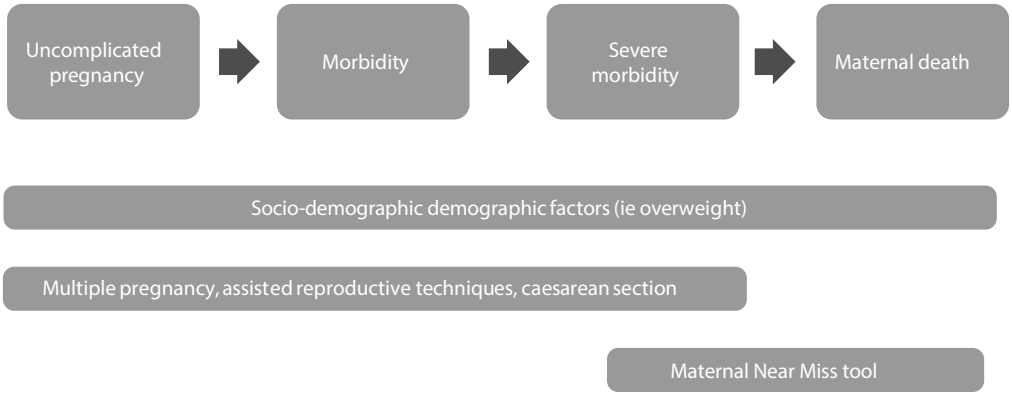
The most important lesson learned here is that besides differences in availability also a more permissive attitude to interventions used as proxy of severeness, will have future implications for universal classification of severe acute maternal morbidity. And although it is clear that there is an urgent need for monitoring health care delivery in both high- and low-resource settings, it remains difficult to determine which set of criteria should be used. Fortunately, WHO made the first steps in the quest for a worldwide universal classification, by composing the Maternal Near Miss (MNM) tool that includes both disease-, intervention- and organ dysfunction-based criteria [58]. Although it is causing underreporting in its current form in both settings (chapter 6 and 7), a foundation has been laid. Based on this thesis it is recommended to focus on refined disease-based criteria. Since detection is high in all settings and do not depend on local protocols, accompanied by a limited set of intervention- and organ dysfunction-based criteria to set a measure of severity.
To reach consensus, the debate on the WHO MNM tool will have to continue in search for balance between maximum detection and minimal over-inclusion.

## CONCLUSION

This thesis provides a valuable addition to the existing literature by describing important associated risk factors for SAMM and by validating the recently proposed WHO MNM tool. It showed that not only lack or absence of health care, but also 'wealth care' related factors have an impact on maternal care worldwide nowadays. The aetiology of wealth care can be found in two basic principles: the first originates from direct physical changes when increased resources become available, such as overweight. And the second indirectly originates from cultural and societal changes leading to the availability of and a more permissive attitude towards certain interventions, such as the use of ART and caesarean section. This permissive attitude to such interventions, combined with other interventions used as maternal morbidity indicators, also has implications for universal classification and detection of severe maternal morbidity. Considering this, questions can be raised if this is favourable. Without regard to these questions, it seems clear that women's autonomy and safety comes first. Obstetricians should be aware of these risks and all women and their partners should be counselled for these risks. And when informed consent is reached, women with elevated risks should be monitored more closely if necessary to prevent maternal morbidity.

**The continuum**

The flowchart shown below is a simplified illustration of the progression path to maternal mortality of pregnant women. It also shows the relation between the different stages of this continuum and subjects included in this thesis and possible points of action for preventing SAMM in the Netherlands.




Socio-demographic factors (such as age, overweight, parity) are usually already present before conception. And pregnant women carrying multiple gestations, when conceived spontaneously, generally start an uncomplicated pregnancy.

International 'wealth care' points of action:

1. Prevention of overweight in child- and (future) motherhood
2. Acknowledging maternal overweight as major risk factor for SAMM
3. Replacement of multi- for single embryo transfer worldwide
4. Restrict ART access through clear national health policies
5. Perform caesarean section only with clear maternal or fetal indication
6. Create universal disease-based criteria for severe maternal morbidity
7. In all cases, counsel pregnant women and their partners for known obstetric risks.

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# CHAPTER 9

## SUMMARY / NEDERLANDSE SAMENVATTING

## SUMMARY

Using the results from a two-year nationwide prospective study, this thesis shows numerous (risk) factors associated with severe acute maternal morbidity (SAMM) in the Netherlands and validates the WHO Maternal Near Miss (MNM) tool to detect and monitor SAMM worldwide. The ratio behind the different subjects selected in this thesis is explained by differences in economic disparity throughout the globe. Where the effect of poverty is undeniably present in maternal health care, we hypothesize that wealth might also have a negative impact on pregnancy outcome. We refer to maternal "wealth care" instead of health care, including factors that are common in contemporary maternal health care. Below, the main results of this thesis are outlined.

First, overweight has shown to be an independent risk factor for SAMM (chapter 2). This is seen in a initially low-risk population, which indicates that overweight without visible or measured comorbidities already has its effect on the physiology of pregnancy, causing a 30% elevated risk of SAMM. This effect shows a dose response relation with increasing body mass index.

Also, women carrying multiple gestations show to have a four times elevated risk to develop SAMM (chapter 3). Risk indicators are age ≥40, nulliparity and assisted reproductive techniques (ART). Also, non-spontaneous onset of labour and caesarean section are associated with SAMM. In contrast to the neonatal risks associated with monochorionicity, there is no difference in maternal risk between chorionicities.

The incidence of puerperal uterine inversion, a condition leading to major haemorrhage, is approximately 1 in 20 000 births (chapter 4). Main associated factors are signs of prolonged labor followed by third stage manipulation. However, even more important is that 93.3% of puerperal uterine inversions occurs in women with a low-risk profile. This means that all birth attendants, both midwives and obstetricians, should be able to detect this rare but severe complication at an early stage for adequate management.

The final chapter of the first section shows that the incidence of laparotomy performed after birth was 6.0 per 10 000 deliveries (chapter 5). Considering different modes of delivery, incidences are 30.1 per 10 000 caesarean sections and 1.8 per 10 000 vaginal deliveries. The risk of postpartum laparotomy is more than 16 times higher in women who delivered by caesarean section compared to those who delivered vaginally. The risk of laparotomy is lower when caesarean section is planned, but still 10 times higher compared with vaginal birth.

The second part shows that when the World Health Organization (WHO) Maternal Near Miss (MNM) tool is used in the Netherlands, SAMM cases are missed (chapter 6). And although advanced laboratory and clinical monitoring are available here, also organ dysfunction-based criteria of the MNM tool failed to identify nearly two-thirds of SAMM cases and more than one-third of maternal deaths. It shows that also in high-income countries, disease-based criteria remain important. Using only organ dysfunction-based criteria would lead to underestimating SAMM.

When comparing these results with two African low-income countries (Tanzania and Malawi) this same WHO MNM tool, in its current form, also shows to be of limited use for cross-country comparison (chapter 7). Based on our results it is recommended to refine the MNM tool, such as

lowering the threshold of transfused units of blood in low-resource settings, leading to a higher detection rate and to raise cross-country applicability.

Concluding, this thesis shows that not only lack or absence of health care, but also 'wealth care' related factors have an impact on maternity care worldwide nowadays. Obstetricians should be aware of such risks, counsel couples with the desire to have children and monitor pregnant women more closely if necessary to prevent maternal morbidity.

## NEDERLANDSE SAMENVATTING

Door middel van een twee jarige landelijke prospectieve studie brengt dit proefschrift een aantal risicofactoren naar voren voor ernstige acute maternale morbiditeit. Daarnaast wordt in dit proefschrift de zogenaamde 'WHO Maternal Near Miss tool' gevalideerd, welke ontworpen is om (internationaal) maternale morbiditeit te erkennen en monitoren.

De gedachte achter de gekozen onderwerpen in dit proefschrift is te verklaren op basis van economische verschillen welke nog steeds zichtbaar zijn wereldwijd. Aangezien armoede een duidelijk effect heeft op maternale gezondheidszorg, was de hypothese dat naast armoede ook welvaart zijn effect heeft op deze zorg. In het proefschrift wordt dit benoemd als 'wealthcare' in plaats van 'healthcare', waarbij de focus lag op factoren veelvoorkomend in welvarende landen. Deze factoren en het effect daarvan zullen hieronder per hoofdstuk worden uitgelegd.

Allereerst bleek overgewicht een onafhankelijke risico factor te zijn voor ernstige acute maternale morbiditeit (hoofdstuk 2). Dit is gezien in een populatie die op voorhand laag-risico was ingeschat door de eerstelijns verloskunde (op basis van de verloskunde indicatielijst). Dit geeft aan dat overgewicht zonder zichtbare co-morbiditeit al een effect heeft op de fysiologie van een zwangere vrouw. Overgewicht bleek daarmee een 30% verhoogd risico op ernstige acute maternale morbiditeit te geven. En dit risico neemt in gelijke trend toe naarmate de BMI van voor de zwangerschap hoger is.

Daarnaast is ook gezien dat vrouwen die zwanger zijn van meerlingen een vier keer verhoogd risico hebben op ernstige acute maternale morbiditeit (hoofdstuk 3). Risicofactoren zijn: leeftijd van boven de veertig, nulliparitеit en kunstmatige voortplantingstechnieken. Daarnaast zijn ook een niet-spontane start van de bevalling en keizersneden geassocieerd met deze morbiditeit. In tegenstelling tot bij neonaten, bleek monochorioniciteit niet geassocieerd met ernstige acute morbiditeit.

De incidentie van puerperale inversio uteri, een aandoening welke leidt tot ernstig bloedverlies, bleek ongeveer 1 op de 20 000 bevallingen (hoofdstuk 4). De belangrijkste factoren die een rol spelen bij het ontstaan hiervan is een langdurig partus gevolgd door het actief manipuleren van het derde tijdperk. Een belangrijke bevinding was dat 93.3% van de puerperale inversio uteri zich voordoet bij vrouwen met een laag risico profiel. Dit betekent dan ook dat elke parteur, zowel een verloskundige als de obstetricus, dit zeldzame en ernstige ziektebeeld in een vroeg stadium moet kunnen herkennen zodat adequate behandeling kan worden ingezet.

Het laatste hoofdstuk van het eerste deel van het proefschrift laat zien dat de incidente van laparotomie na de geboorte 6.0 per 10 000 bevallingen is (hoofdstuk 5). Wanneer specifiek gekeken wordt naar de verschillende wijzen van bevallen, bleek de incidentie 30.1 per 10 000 keizersneden en 1.8 per 10 000 vaginale bevallingen. Het risico op een laparotomie na de geboorte is 16 keer hoger na een keizersnede in vergelijking met een vaginale bevalling. Dit risico is lager op het moment dat de keizersnede gepland was, echter nog steeds 10 keer hoger dan een vaginale bevalling.

Het tweede deel van het proefschrift laat zien dat wanneer de Maternal Near Miss (MNM) tool van de World Health Organization (WHO) in Nederland wordt toegepast om maternale morbiditeit te detecteren, vrouwen met ernstige acute maternale morbiditeit worden gemist (hoofdstuk 6). En

alhoewel er in Nederland geavanceerde laboratoriumbepalingen en klinische monitoring mogelijk is, wordt bijna twee derde van de vrouwen met ernstige acute maternale morbiditeit en meer dan een derde van de maternale sterfte gevallen gemist door de 'orgaan dysfunctie-gebaseerde' criteria. Dit toont aan dat ook in hoge inkomenslanden, zoals Nederland, klinisch 'ziekte-gebaseerde' criteria zeer belangrijk blijven. En dat wanneer alleen 'orgaan dysfunctie-gebaseerde' criteria gebruikt worden, de incidentie van ernstige acute maternale morbiditeit zal worden onderschat.

Wanneer deze uitkomsten worden vergeleken met twee Afrikaanse lage inkomenslanden (Tanzania en Malawi), laat dit zien dat de WHO MNM tool in zijn huidige vorm niet geschikt is voor het vergelijken van landen onderling (hoofdstuk 7). Gebaseerd op de resultaten in dit hoofdstuk wordt aanbevolen om de WHO MNM tool aan te passen, zoals bijvoorbeeld voor de lage inkomenslanden de grens voor het aantal getransfundeerde eenheden bloed dat wordt gegeven te verlagen. Dit zal leiden tot een hogere detectie van morbiditeit en daarom ook een verbeterde toepasbaarheid voor het vergelijken van landen onderling.

Dit proefschrift laat zien dat niet alleen armoede een effect heeft op de gezondheidszorg, maar ook welvaart-gerelateerde factoren invloed hebben op de hedendaagse verloskundige zorg. Elke obstetricus moet zich bewust zijn van dergelijke risicofactoren, aanstaande ouders hierin adviseren en indien nodig ook zwangere vrouwen nauwer monitoren om maternale morbiditeit te voorkomen.

# CHAPTER 10

**PUBLICATIONS**

**CURRICULUM VITAE**

**ACKNOWLEDGEMENTS / DANKWOORD**

**SAFE MOTHERHOOD SERIES**

# PUBLICATIONS

Gosselink MJ, Witteveen T. Growth in empathy during clinical exchange. The Clinical Teacher. 2012;9:188–189.

Witteveen T, Zwart J, Gast KB, Bloemenkamp KW, van Roosmalen J. Overweight and severe acute maternal morbidity in a low-risk pregnant population in the Netherlands. PLoS One. 2013;8:9.

Witteveen T, Van Stralen G, Zwart JJ, Van Roosmalen J. Puerperal uterine inversion in The Netherlands: a nationwide cohort study. Acta Obstet Gynecol Scand 2013;92:334-7.

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Witteveen T, van den Akker T, Zwart J, Bloemenkamp KW, van Roosmalen J. Multiple pregnancies and severe acute maternal morbidity in the Netherlands: a nationwide cohort study. Am J Obstet Gynecol 2016;214(5):641.

Witteveen T, Bezstarosti H, de Koning I, van den Akker, van Roosmalen J, Bloemenkamp KW. The WHO Maternal Near Miss tool in high and low-resource settings: a cross-country comparison. *Submitted.*

Witteveen T, AF Kallianidis, van den Akker T, KW Bloemenkamp, van Roosmalen J. Laparotomy after childbirth: a nationwide cohort study. *Submitted.*

# CURRICULUM VITAE

Tom Witteveen werd op 1 januari 1987 geboren in Emmen. Binnen een jaar verhuisde hij onder de hoede van zijn ouders naar Zwolle, waar hij het grootste deel van zijn jeugd heeft doorgebracht. Hij is de tweede zoon van Rick en Dieke, en de broer van Bartjan (geboren in 1985) en Thijs (geboren in 1993). Na het doorlopen van het Atheneum op het Carolus Clusius College in Zwolle werd hij in eerste instantie niet toegelaten voor de studie geneeskunde. Dit heeft hem doen besluiten een jaar psychobiologie te studeren aan de Universiteit van Amsterdam alvorens het jaar erop wel toegelaten te worden voor geneeskunde aan de Universiteit Leiden.

Tijdens zijn studie geneeskunde heeft hij onder andere plaatsgenomen in de Leidse Studentenraad (advies orgaan van de Universiteit Leiden), de redactieraad van het tijdschrift Arts in Spe en het bestuur van de Medische Faculteit der Leidse Studenten. Naast studie-gerelateerde zaken vond hij zijn ontspanning ook als lid van basketbalvereniging L.U.S.V. Basketball en de band An Apple A Day. In zijn periode als student heeft hij internationale ervaring opgedaan in zowel Nepal als Tanzania. De basis voor zijn wetenschappelijke carrière werd in 2011 gelegd tijdens zijn wetenschapsstage op de afdeling Verloskunde en Gynaecologie, begeleidt door prof. dr. Jos van Roosmalen. Door een constante aanvoer van interessant onderzoek is hij tijdens zijn co-schappen wat betreft onderzoek niet meer afgeweken van deze afdeling. Dit heeft uiteindelijk geleid tot een solide basis voor dit proefschrift.

Op het moment dat hij in november 2013 zijn artsexamen behaalde en vervolgens 'de kliniek' in ging koos hij, zoals gepland, voor de kindergeneeskunde. Op zijn 27$^{e}$ verjaardag begon hij dan ook met een baan als arts-assistent kindergeneeskunde in het Medisch Centrum Haaglanden, locatie Westeinde (voorzitter vakgroep, dr. L.H.P.M. Filippini). Gedurende zijn arts-assistentschap heeft hij ook zijn promotietraject voortgezet. In 2015 heeft hij een periode van drie maanden fulltime aan zijn proefschrift kunnen werken, gecombineerd met een bezoek aan het 21$^{st}$ FIGO World Congress of Gynecology and Obstetrics in Vancouver om aldaar twee voordrachten te houden. Na deze periode is hij gestart met zijn huidige baan als arts-assistent kindergeneeskunde in het Reinier de Graaf Gasthuis in Delft (opleider, dr. B. Bakker) om tegelijkertijd de laatste meters voor dit proefschrift te maken. Eind dit jaar zal hij, na het in ontvangst nemen van zijn doctoraat, starten met de opleiding tot kinderarts.

# ACKNOWLEDGEMENTS / DANKWOORD

Alleen mijn naam staat op de cover van dit proefschrift, maar een proefschrift schrijf je niet zonder de (mentale) steun van velen. Een aantal hiervan zou ik dan ook heel graag willen bedanken door middel van onderstaande wellicht cliché (maar absoluut gemeende) teksten.

Allereerst mijn 'mentor' Jos dat je mij hebt aangesproken toen wij elkaar in 2011 tegen kwamen in het restaurant de Koetjes in Kalfjes: "heb je nou al een wetenschapsstage gevonden?". Zonder jou was er letterlijk geen letter op papier gekomen. Het is mij een eer om jouw laatste Leidse promovendus te zijn.

Alle co-auteurs van de verschillende hoofdstukken in dit proefschrift (op volgorde van verschijning): Joost Zwart, Karin Gast, Kitty Bloemenkamp, Jos van Roosmalen, Thomas van den Akker, Giel van Stralen, Athanasios Kallianidis, Ilona de Koning, Hans Bezstarosti en Ellen Nelissen. Het digitale en real-life contact met jullie is een aangename, leerzame en vanzelfsprekend zeer belangrijke inhoudelijke toevoeging van dit proefschrift geweest.

Iedereen die heeft meegewerkt om de LEMMoN-studie mogelijk te maken. Vele namen zijn mij niet eens bekend, maar ik hoop dat zij zich aangesproken voelen! Het is wederom een goudmijn gebleken.

Mijn promotiecommissie dank ik voor het beoordelen van mijn proefschrift.

Mijn maandagmatties en paranimfen Maarten en Esther. Dank dat ik jullie met mijn wellicht niet altijd zichtbare stress mocht lastig vallen. Elke maandag ontspannen zal nog lang onmisbaar blijken.

Mijn ouders en broers, omdat ze mij gevormd hebben tot wie ik ben.

Vera. Zonder jou was dit proefschrift wellicht ook wel tot stand gekomen. Maar dan was alles erom heen in elkaar gezakt.

# SAFE MOTHERHOOD SERIES

The safe motherhood series contains a more than 20-year old line of obstetric research that primarily focuses on maternal health care in both low- and high-income countries. Each of these theses has made its own and unique contribution in the pursuit of a safe motherhood.

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Safe motherhood: Confidential enquiries into Maternal Deaths in the Netherlands, 1983-1992. (Nico W.E. Schuitemaker), Leiden, 1998

Safe motherhood: Confidential enquiries into Maternal Deaths in Surinam. (Ashok S. Mungra), Leiden, 1999

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Safe Motherhood: Obstetric audit in Namibia and the Netherlands (Jeroen van Dillen), VU University Medical Centre, Amsterdam, the Netherlands, 2009

Safe Motherhood: Confidential enquiries into maternal deaths in the Netherlands 1993-2005 (Joke Schutte), VU University Medical Centre, Amsterdam, the Netherlands, 2010

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Safe Motherhood: Obstetric emergencies in primary midwifery care in the Netherlands (Marrit Smit), Leiden University Medical Center, the Netherlands, 2014

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Safe Motherhood: The aberrant third stage of labour (Giel van Stralen), Leiden University Medical Center, the Netherlands, 2015

Safe Motherhood: Severe acute maternal morbidity: risk factors in the Netherlands and validation of the WHO Maternal Near Miss tool (Tom Witteveen), Leiden University Medical Center, the Netherlands, 2016

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