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ORIGINAL RESEARCH

Maternal deaths from sepsis in the Nordic countries during 2005–2021: A descriptive study

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Abstract

Introduction: Maternal sepsis is a heterogenous condition which can arise from several different infections during and after pregnancy. Common for all etiologies is a high mortality rate. In a global perspective, maternal sepsis is an important contributor to maternal death. This study aimed to evaluate the clinical management of maternal deaths from sepsis in the Nordic countries and identify areas for improved clinical handling.

Material and Methods: We used data from the Nordic Maternal Mortality Collaboration including maternal deaths from the five Nordic countries from 2005 till 2021, identified through linked registers. The national audit groups assessed each maternal death based on hospital records and classified it according to cause and quality of management. We formulated learning points to improve future clinical care in cases of maternal sepsis.

Results: In total, 267 maternal deaths were identified, equaling a maternal mortality rate of 5.9 per 100 000 live births (95% CI 5.25–6.62). Maternal sepsis accounted for 9.7% of the maternal deaths ($n = 26$), ranking sepsis the fifth leading cause. Nongenital sepsis and genital tract sepsis numbers were almost equal. Substandard care was identified in 57% of cases with nongenital infections, and in 83% of genital tract sepsis cases. Improvements in care that possibly could have influenced the outcome were noted in 29% and 67% of cases, respectively. In nongenital sepsis, delayed recognition of sepsis and delayed administration of antimicrobial therapy were the commonest elements in substandard care. Delayed recognition of sepsis, delayed administration of antimicrobial therapy, and postponed or lacking surgical source control were the main elements in substandard care of genital tract sepsis.

Conclusions: In the Nordic countries, sepsis was the fifth leading cause of maternal deaths during 2005–2021. In one-third of maternal deaths from nongenital sepsis and two-thirds of maternal deaths from genital tract sepsis, clinical measures could have

Abbreviations: CI, confidence interval; MMR, maternal mortality ratio; UK, United Kingdom.

reduced the risk of fatal outcome, emphasizing the need for maximal awareness and improved clinical handling.

KEYWORDS
genital tract sepsis, maternal morbidity, maternal mortality, maternal sepsis, obstetric infection

1 | INTRODUCTION

The World Health Organization (WHO) Global Maternal Sepsis Study Research Group announced in 2020 that sepsis accounts for about half of in-hospital maternal deaths worldwide, higher than previously assumed.[1] Over the last three decades, the global burden of maternal infectious morbidity and mortality has declined. Alarmingly, a rise has been observed in the United States of America, where the maternal mortality ratio (MMR) due to sepsis increased from 12 to 21 per 100 000 live births from 2000 to 2020.[2–5] Sepsis contributed with a 9–10% annual increase to the MMR during 2001–2010.[6,7] In the United Kingdom (UK), maternal mortality has remained stable around 10–11 per 100 000 live births during 2000–2020 without the reduction observed in several other European countries.[2,3,8] The Nordic countries consistently report some of the world's lowest MMRs, averaging between 6 and 7.2 per 100 000 live births between 2005 and 2017.[2,9] Sepsis was ranked as the fifth leading cause of maternal deaths during this period. In contrast, in the UK during the years 2006–2008, sepsis was reported as the leading cause of direct maternal deaths for the first time since reporting started in 1952, resulting in a doubled MMR from genital tract sepsis from 0.65 to 1.13 per 100 000 maternities during 2000–2008.[8] More than half the sepsis deaths were attributed to *Streptococcus pyogenes* (group A *Streptococcus*; GAS), a trend that has also been described in the Netherlands.[10] Following the UK report, concerns were raised because substandard care was identified in approximately half the maternal deaths from sepsis.

Fatalities from maternal sepsis are high in comparison to other obstetric complications. It has been reported that up to 10% of all pregnant and postpartum women diagnosed with sepsis do not survive.[4,11,12] Approximately, 20 % of maternal sepsis cases evolve to septic shock, and up to 28% result in death where multiorgan failure is present.[13] Moreover, a recent study on streptococcal sepsis reported mortality rates between 10% and 30% in obstetric populations.[14] Contributing factors are multifaceted and complicate our understanding of maternal sepsis. The normal physiologic adaptations in pregnancy can both predispose the pregnant, parturient or newly delivered woman to development of organ failure in the course of infection, but also mimic clinical signs of sepsis.[15–17] Further, none of the sepsis screening tools such as the systemic inflammatory response syndrome (SIRS), the quick sequential organ failure assessment score (qSOFA) or the sequential organ failure assessment score (SOFA), are validated for obstetric populations. The progression of maternal sepsis to septic shock may be partially attributed to delayed case recognition following nonstandardized clinical management. Furthermore, a challenge in conducting studies of maternal sepsis has been a lacking definition of the condition until 2017, when WHO defined maternal sepsis as a "*life-threatening condition with organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period.*"[18] There is no unique diagnostic code in the International Statistical Classification of Diseases and Health Related Problems (ICD-10) for maternal sepsis throughout the entire pregnancy. The code O85 defined as puerperal fever, encompasses three infections: endometritis, peritonitis, and puerperal sepsis.[19] In a Norwegian university hospital, this code's ability to predict both puerperal and maternal sepsis was calculated to be 20%, making the code unsuited for the identification and surveillance of maternal sepsis.[20]

Key message

Sepsis is a significant contributor to maternal deaths in the Nordic countries, with substandard care identified in two-thirds of genital tract sepsis cases.

The Nordic Maternal Mortality Collaboration was established in 2010 with the aim to collect and analyze information in a population of almost 28 million people in the five Nordic countries, where health care systems are quite similar and antenatal care is universally available and free of charge.

The current study aimed to provide information on the impact of sepsis on maternal deaths in this region. Based on case reviews, we additionally aimed to identify areas for improvement of clinical handling in maternal sepsis cases.

2 | MATERIAL AND METHODS

In accordance with the 10th revision of the International Statistical Classification of Diseases and Health Related Problems (ICD-10), maternal death is defined as the death of a woman while pregnant or within 42 days following the end of pregnancy.[21] Maternal deaths are categorized as either direct, resulting from the pregnancy itself, or indirect, stemming from preexisting morbidities aggravated by pregnancy. In this context, direct maternal deaths are those caused by genital tract sepsis, while maternal deaths from sepsis caused by infections outside the genital tract are categorized as indirect. This

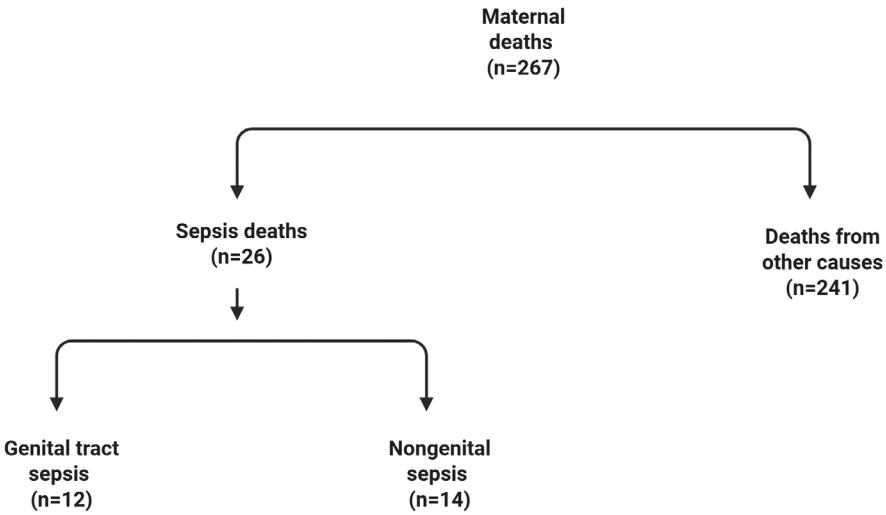

FIGURE 1 Flow chart of the study population with maternal deaths in the Nordic countries 2005–2021, $n=267$. The maternal deaths from sepsis ($n=26$) are further classified into direct (genital tract sepsis) and indirect (nongenital sepsis).

study reports both direct and indirect maternal deaths from sepsis during the years 2005–2021 in Sweden, 2005–2020 in Iceland and Norway, 2005–2018 in Finland, and 2005–2017 in Denmark. Cases from Denmark, Iceland and Norway were identified through register linkage between birth and cause-of-death registers, in combination with direct reporting from hospitals. In Finland, these linkages include the register for induced abortions and the hospital discharge register. Data linkages were executed prior to data collection from hospitals. Before 2016, Swedish data were collected by hospital reporting only. The register linkage in all Nordic countries is based on a unique personal identification number consisting of date of birth and control number. Register data on maternal deaths among visitors, undocumented migrants and asylum seekers not yet registered with a personal identification number, were not available. In-patient registers were used to obtain relevant diagnoses in pregnancy. Denominator data from the respective countries were acquired from the national birth registers, which provide comprehensive information regarding women giving birth to a living child, or a stillbirth with a gestational age ≥22 weeks. Experienced clinicians, including obstetricians, gynecologists, and anesthesiologists, comprised the national audit group in each country. These groups classified the maternal deaths into direct and indirect, and determined the underlying causes. To standardize classification of the cause(s) of death, we applied a modified version of the form developed by the Confidential Enquiry into Maternal and Child Health (CEMACH), later maintained by the UK Maternal, Newborn and Infant Clinical Outcome Review Program (MBRRACE-UK), with permission.[22] Furthermore, we classified the quality of care as: (1) good care—no improvements identified, (2) improvements to care identified which would have made no difference to the outcome, (3) improvements to care identified which may have made a difference to the outcome, or (4) insufficient data. Contemporary clinical care guidelines for each country constituted the reference standard for satisfactory clinical care.

2.1 | Statistical analyses

We calculated the MMR with a 95% confidence interval (CI) using the continuity corrected score method as the number of deaths by the number of live births.[23] To explore whether women who died from sepsis or other causes had different characteristics, we performed Pearson's Chi-squared test or Fisher's exact test for each characteristic considered. The statistical analyses were performed using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp).

3 | RESULTS

In total, we identified 267 maternal deaths in the Nordic countries during 2005–2021 (Figure 1). The MMR was calculated as 5.9 per 100 000 live births (95% CI 5.25–6.62). The intercountry MMR differences were small (Table 1).

The underlying causes of death are presented in Figure 2. There were 26 deaths from maternal sepsis, accounting for 9.7% of the maternal deaths (Table S1). The MMR due to maternal sepsis was 0.6 per 100 000 live births (95% CI 0.39–0.84). In Table S2, sepsis MMRs for the respective Nordic countries are presented. There were no maternal sepsis deaths in Iceland during the study period.

Sociodemographic, obstetric, and clinical characteristics are presented in Table S3. Table 2 shows that compared with Nordic women who died of other causes, women who died of maternal sepsis had more class II and III obesity with pregestational BMI 35 or higher. These women also received more antibiotics during pregnancy. In addition, the women who died of maternal sepsis, had more infections requiring hospital care during pregnancy, and more often postpartum infection.

Fourteen of the maternal sepsis deaths resulted from nongenital infections, while twelve deaths resulted from genital tract

TABLE 1 Maternal deaths and maternal mortality ratios (MMRs) in the Nordic countries, 2005–2021.

Country	Live born (*n*)	Maternal deaths (*n*)	MMR per 100 000 live births	95% CI
Denmark[a]	799 443	47	5.9	4.45–7.73
Finland[b]	799 928	57	7.1	5.55–9.13
Iceland[c]	70 962	2	2.8	0.78–9.71
Norway[c]	944 318	56	5.9	4.60–7.63
Sweden	1 908 663	105	5.5	4.57–6.62
In total	4 523 314	267	5.9	5.25–6.62

[a]2005–2017, data for 2018–2021 not collected.
[b]2005–2018, data for 2019–2021 not collected.
[c]2005–2020, data for 2021 not collected.

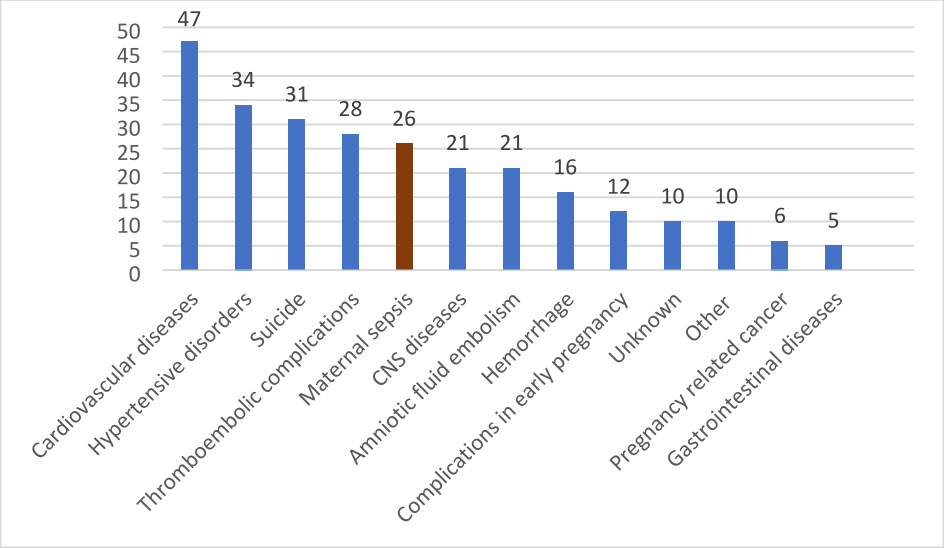

FIGURE 2 Causes of maternal deaths in the Nordic countries 2005–2021, n = 267 (Denmark from 2005 to 2017, Finland from 2005 to 2018, Iceland and Norway from 2005 to 2020).

TABLE 2 Significant differences in Nordic women who died from genital and nongenital sepsis, compared with Nordic women who died of other causes during 2005–2021.

Characteristic	Sepsis (*n* = 26) percentage (95% CI)	Other causes (*n* = 241) percentage (95% CI)	*p*-value
Pregestational BMI ≥35.0	26.9 (13.7–46.1)	7.9 (5.1–12.0)	0.05
Antibiotic use during pregnancy	11.5 (4.0–29.0)	0.0 (0.0–1.6)	<0.001
Infections requiring hospital care during pregnancy	15.4 (6.2–33.5)	0.4 (0.1–2.3)	<0.001
Puerperal infection	26.9 (16.5–50.0)	2.5 (1.2–5.3)	<0.001

Note: In Table S3 a complete list of demographic, pregnancy and labor characteristics examined are presented.
Abbreviations: BMI, body mass index; CI, confidence interval.

sepsis (Figure 1). Tables 3A, 3B and S4 provide a summary of the 26 cases with maternal sepsis, including the clinical and microbiological causes.

Among women who died of nongenital sepsis, more than half died in the antepartum period. Most women who died postpartum were delivered on maternal indication due to infection which started antepartum. Seven of the women had respiratory tract infection as the underlying infectious focus leading to sepsis (Table 3A). In five of these, a viral infectious agent was identified (influenza virus and SARS-Cov2), while in two of the women a bacterial agent was recovered, identified as GAS and *Staphyococcus aureus*, respectively. Three women died of intraabdominal sepsis, two of them with gastrointestinal pathology and one due to complications following cesarean section. Two women died of CNS infection with *Mycobacterium tuberculosis*. One woman died of sepsis with methicillin-resistant *Staphylococcus aureus* and one woman died of urosepsis. Substandard care was identified in 57% of the cases with nongenital infections. In almost 30% of cases, the audits concluded that improvements to care could have made a difference to the outcome. In the women

TABLE 3A Overview of maternal deaths from nongenital sepsis ($n = 14$).

No.	Clinical and microbiological cause of death	Classification of death	Timing of sepsis	Substandard care	Quality of care[a]
1	Intraabdominal sepsis with *Escherichia coli*	***Indirect*** maternal death due to intraabdominal sepsis from gastrointestinal focus	Antepartum	Delayed recognition and treatment of sepsis	3
2	Urosepsis, insufficient data regarding microbiology	***Indirect*** maternal death due to urosepsis	Antepartum	Insufficient data	4
3	Acute respiratory distress syndrome following *influenza virus* infection	***Indirect*** maternal death due to lower respiratory tract infection.	Postpartum	Suboptimal communication contributed to delayed awareness of the severity of respiratory infection. No use of professional translator.	2
4	CNS infection with *Mycobacterium tuberculosis*	***Indirect*** maternal death due to CNS infection	Postpartum	No multidisciplinary approach in the follow-up of the patient while hospitalized	2
5	CNS infection with *Mycobacterium tuberculosis*	***Indirect*** maternal death due to respiratory tract infection	Postpartum	Neurological symptoms were interpreted as migraine the first time the patient presented them, leading to delayed neuroimaging and delayed diagnosis	2
6	Intraabdominal sepsis, *no microbiological agent* recovered	**Indirect** maternal death due to intraabdominal sepsis following obstetric surgery	Postpartum	Delayed surgical source control	3
7	MRSA sepsis	**Indirect** maternal death	Antepartum	Insufficient data	4
8	Pneumonia with *staphylococcus aureus*	***Indirect*** maternal death due to lower respiratory tract infection	Antepartum	Good care	1
9	Septic shock after intrabdominal abscess, *no microbiologic agent* recovered	***Indirect*** maternal death due to intraabdominal sepsis	Antepartum	The patient was discharged with oral antibiotics without infection source control. Sepsis was not recognized until the patient went into cardiac arrest.	3
10	Pneumonia, *Streptococcus pyogenes*	***Indirect*** maternal death due to lower respiratory tract infection	Antepartum	The patient was not examined and did not receive adequate treatment for respiratory tract infection	3
11	Influenza virus	***Indirect*** maternal death due to lower respiratory tract infection	Missing data	Insufficient data	1
12	COVID-19. SARS-Cov2	***Indirect*** maternal death due to lower respiratory tract infection	Antepartum	Good care	1
13	COVID-19. SARS-Cov2	***Indirect*** maternal death due to lower respiratory tract infection	Antepartum	Late referral to hospital care	2
14	COVID-19. SARS-Cov2	***Indirect*** maternal death due to lower respiratory infection	Postpartum	Good care	1

Abbreviations: CNS, central nervous system; MRSA, Methicillin-resistant *Staphylococcus aureus*; SARS-Cov2, severe acute respiratory syndrome-corona virus 2.

[a]Quality of care: 1 – good care; 2 – improvements to care that would have made no difference to the outcome; 3 – improvements to care that may have made a difference to the outcome; 4 – insufficient data.

who died of nongenital sepsis where substandard care was identified, the main aspect of missing care was the lack of infection recognition, or inadequate infection control. The latter was due to either inappropriate antibiotics with narrow-spectrum antimicrobial coverage, delayed administration of broad-spectrum antibiotics and delayed or insufficient surgical source control.

A clinical course with rapid progression from the recognition of sepsis to the development of septic shock, and death within hours,

TABLE 3B Overview of maternal deaths from genital sepsis ($n = 12$).

No.	Clinical and microbiological cause of death	Classification of death	Timing of sepsis	Substandard care	Quality of care[a]
1	Septic shock, *Escherichia coli*	***Direct*** maternal death from genital tract sepsis	Antepartum	Administration of rescue cervical cerclage due to exposed fetal membranes and threatening labor. Temperature rise the second day after surgery. Given antibiotics, but not in accordance with sepsis guidelines. Sepsis was not recognized until the patient was in septic shock. Delayed removal of rescue cervical cerclage.	3
2	Septic shock, *no microbiological agent* recovered	***Direct*** maternal death due to genital tract sepsis	Postpartum	Pain out of proportion and hypothermia were not interpreted as infection. Sepsis was not recognized until the patient was in septic shock, at which point antibiotics were administered. No surgery was undertaken.	3
3	Septic shock, *Streptococcus pyogenes*	***Direct*** maternal death due to genital tract sepsis	Postpartum	Treatment was delayed for several hours after the suspicion of sepsis was raised. Septic shock was present at time of treatment initiation.	3
4	Septic abortion withshock, *Streptococcus pyogenes*	***Direct*** maternal death due to genital tract sepsis	Antepartum	Sepsis was not recognized until the patient was in septic shock. Delay in antibiotic administration and surgery for source control.	3
5	Septic shock, *Clostridium sordellii*	***Direct*** maternal death due to genital tract sepsis	Postpartum	Infection was missed the first time the patient presented with symptoms	2
6	Septic abortion with septic shock. *No microbiological agent* recovered	***Direct*** maternal death due to genital tract sepsis	Antepartum	Administration of narrow-spectrum antibiotics only. There was no source control with removal of cervical rescue cerclage undertaken. Septic shock was missed.	3
7	Septic shock arising from genital infection. *No microbiological agent* recovered	***Direct*** maternal death due to genital tract sepsis	Antepartum	Sepsis went undiagnosed for several hours without transfer to higher surveillance unit. The source of infection was not evacuated.	3
8	Septic abortion. *No microbiologic agent* recovered	***Direct*** maternal death due to genital tract sepsis	Antepartum	Insufficient data	1
9	Septic shock, *Streptococcus pyogenes*	***Direct*** maternal death due to genital tract sepsis	Postpartum	Insufficient data	3
10	Septic shock, *Clostridium sordellii*	***Direct*** maternal death due to genital tract sepsis	Postpartum	Suboptimal communication between hospitals. Possible contribution to delayed surgical source control.	2
11	Postpartum infection. *No microbiologic agent* recovered	***Direct*** maternal death due to genital tract sepsis	Postpartum	NA	3
12	Intrapartum infection. *No microbiologic agent* recovered	***Direct*** maternal death due to genital tract sepsis	Antepartum	Insufficient data	4

Abbreviations: NA, not applicable.

[a]Quality of care: 1 – good care; 2 – improvements to care that would have made no difference to the outcome; 3 – improvements to care that may have made a difference to the outcome; 4 – insufficient data.

was common for the women who died of genital tract sepsis. In the 10 cases where septic shock was the cause of death, all but one case resulted from genital tract sepsis. In six of the twelve cases with genital tract sepsis, a microbiological agent was recovered. In three cases the etiological microbe was *Streptococcus pyogenes*, in two *Clostridium sordellii*, and in one case *Escherichia coli*. In six cases, no microbiological agent was recovered. Two deaths were associated with the placement of a rescue cervical cerclage.

Among cases of genital tract sepsis, substandard care was identified in 83%, and in 67% of cases improvements to care could have made a difference to the outcome. Three elements of substandard care were identified in the handling of genital tract sepsis; (1) delayed

recognition of sepsis until the development of septic shock, (2) delayed administration of broad-spectrum antibiotics, and (3) delayed or inadequate performance of surgical source control.

4 | DISCUSSION

In this study, we found that sepsis accounted for 10% of maternal deaths in the Nordic countries in the period 2005–2021, ranking it the fifth leading cause of mortality. The numbers of lethal nongenital sepsis and genital tract sepsis were almost equal. In one-third of deaths from nongenital sepsis and two-thirds of deaths from genital tract sepsis, improved care may have made a difference to the outcome. In both the nongenital and genital tract sepsis cases, substandard care consisted of delayed recognition of sepsis and delayed administration of appropriate antimicrobial therapy, while in most cases of genital tract sepsis, surgical source control was either postponed until septic shock arose or not undertaken at all.

In our study, 14/26 or 53.8% of maternal deaths resulted from different nongenital infections. Half of the infections originated from the respiratory tract and the majority of these were caused by viral agents such as influenza virus and COVID-19. According to previous studies, pregnancy predisposes to complications such as secondary bacterial pneumonia, need for intensive care and mortality in the course of viral infections compared with nonpregnant individuals.[24,25] Also, the MBRRACE report covering 2019–2021 showed that none of the women who died due to influenza or COVID-19 were vaccinated during pregnancy.[26] Unfortunately, information on vaccination status could not be provided in the current study.

Our findings align with studies from the UK and Ireland, where maternal sepsis has been ranked the fifth leading cause of maternal deaths in the last 10 years.[22,27] In contrast, according to the MBRRACE report from the UK and Ireland covering 2019–2021, severe infection was the leading cause of maternal death, equaling 23% with a reported MMR of 2.5 per 100 000 maternities.[26] However, when deaths related to COVID-19 infection were excluded, sepsis accounted for 9.5% of all maternal deaths, estimating sepsis the fifth leading cause. Direct maternal deaths caused by genital tract sepsis constituted 29% in the UK study.

The same UK report on maternal deaths during 2019–2021 demonstrated that none of the women who died of genital tract sepsis received adequate care, with 75% of cases showing potential improvements that might have altered the outcome.[26] In the current study, we identified potential improvements to care that may have made a difference to the outcome in 67% of cases. Alarmingly, satisfactory care was registered in only 8.3% of women with genital tract sepsis. Both studies thus uncovered a need for improvement of clinical handling in genital tract sepsis. For every maternal sepsis death, an estimated 50 women survive life-threatening, severe antepartum and postpartum sepsis requiring higher surveillance (level 2 or intensive care unit), highlighting that the incidence of serious infections is many times higher than numbers of deaths.[11]

Consistent with the findings in a previous UK report from 2006 to 2008 where sepsis was the leading cause of direct maternal deaths,[8] the women who died of maternal sepsis arising from the genital tract were often not diagnosed in time, as sepsis was not considered until clinical deterioration occurred. Signs and symptoms of sepsis were misinterpreted as typical for pregnancy or postpartum complaints. Administration of broad-spectrum antibiotics was delayed from several hours to days after the onset of sepsis, and in most cases, often administered after septic shock was identified. In a study from 2019 it was demonstrated that mortality in obstetric sepsis increased from 8.3% in patients who received antibiotics within 1 h of diagnosis to 20% in those who received antibiotics after more than 1 h.[28]

In an American study covering maternal deaths in 1999–2006, sepsis was found to be the cause of death in 15% of cases. The sepsis MMR was calculated to be 2.1/100 000, which is more than three times higher than in the current study. Consistent with the findings in the current study, delayed care with inappropriate antibiotic therapy or delayed escalation of care was identified in the majority of cases.[29]

Sepsis studies from the general adult population illustrate that patient outcomes and survival are directly linked to early identification and timely intervention in the first hours after the development of sepsis. A core element in the identification of sepsis is the use of screening tools designed to identify acute illness resulting from infection, followed by rapid interventions consisting of fluid resuscitation and administration of broad-spectrum antimicrobials immediately or within 1 h where shock is present, and within 3 h if concern for infection persists in the absence of shock.[30]

We found that *Streptococcus pyogenes* was the most frequent microbial etiology in genital tract sepsis. The impact of *S. pyogenes* is supported by studies suggesting that postpartum women have a 20-fold increased risk for invasive *S. pyogenes* compared with nonpregnant women.[31] Also, a recent systematic review from several high-income countries showed a pooled incidence of invasive *S. pyogenes* infection in pregnant and postpartum women of 0.12/1000 live births, which is 89 times higher than in nonpregnant women.[32] Although *S. pyogenes* is a documented cause of maternity ward outbreaks, community-acquired acquisition probably plays a more important role than nosocomial in the spread of *S. pyogenes*, supported by studies from the USA and Israel, where ~80% of peripartum cases were community-acquired.[33,34]

Sepsis caused by *S. pyogenes* typically manifests as postpartum fever (90%) in combination with abdominal pain and tenderness (30%). In a few cases, purulent uterine discharge might be present (8%).[14] Endometritis and necrotizing soft tissue infection are the two most common clinical presentations leading to invasive infection, complicated by streptococcal shock syndrome in one-fifth to one-third of pregnancy-related cases.[8]

The postpartum uterus is often the portal of infection. In our study, women with genital tract sepsis were not properly handled regarding evacuation of an infectious focus. This includes timely surgical source control by expedited delivery in cases with antepartum

sepsis which presented with abdominal pain, vaginal bleeding and a dead fetus. Optimally, a search for infectious sources and intervention should be performed as soon as possible following the initial assessment and after administration of antimicrobial therapy and fluid resuscitation.[30] There are no studies comparing outcomes following conservative and surgical approaches. However, there is a unanimous agreement that confirmed infection with *S. pyogenes* in the presence of organ dysfunction, also should be managed surgically, including by hysterectomy that can be lifesaving in the presence of obstetric toxic shock syndrome.[35]

Clostridium sordellii was the confirmed etiology in two cases of genital tract sepsis and suspected in a third case. *C. sordellii* causes gas gangrene of the uterus and is described following spontaneous abortion, normal vaginal delivery, and traumatic injury in the birth canal. In recent years, fatal *C. sordellii* infections have been described after induced abortions with synthetic prostaglandins.[36] The case fatality rate associated with genital tract sepsis arising from this microbe was 100% in one case report from the USA.[36] Recommended antimicrobial treatment is clindamycin in combination with either piperacillin/tazobactam or carbapenem. However, antibiotics alone are not sufficient in the case of gas gangrene. In one of the women in this study with confirmed *C. sordellii* infection, radical surgery was performed after septic shock was established. The patient died in the operating room.

There were two cases of maternal death from genital tract sepsis following the placement of a rescue cervical cerclage with the purpose of preventing preterm delivery. In both cases, the cerclage was administered transvaginally due to shortening of the uterine cervix in combination with exposed fetal membranes. Whether intrauterine infection was considered prior to the procedure is unknown. However, both women developed sepsis shortly after the cerclage placement. The removal of the cerclage was performed 10 h after the onset of infection or not performed, respectively. In a study by Bauer et al. in an American pregnant population, the placement of a rescue cerclage was an independent risk factor for severe sepsis with an odds ratio of 9.8.[4] These cases provide two important learning points. The first is to assess the possibility of intrauterine infection when shortening of the cervix and exposed fetal membranes are present, while the second is to lower the threshold for removal of a rescue cerclage in the presence of clinical infection. This is in accordance with the good practice recommendations from the International Federation of Gynecology and Obstetrics.[37]

Based on the cases presented and existing recommendations for handling of maternal sepsis, the Nordic Maternal Mortality Collaboration has derived the following learning points to improve future clinical care in cases of maternal infections and sepsis:

1. Infection should be considered in patients who present with threatening preterm labor with shortened uterine cervix and/or exposed fetal membranes. Patients should be repeatedly evaluated for infection.
2. Sepsis should be considered in all pregnant or newly delivered women who present with persistent fever. In the absence of fever, sepsis should be suspected in pregnant or newly delivered women with nausea, vomiting, or other signs of toxin production.[8]
3. In postpartum women, sepsis should be considered in women presenting with heavy vaginal bleeding and pain out of proportion.[8,38]
4. Screening tools for vital parameters in the obstetric population should be applied to assess the continuous development of infection.[38,39]
5. Blood cultures should be drawn prior to treatment in suspected sepsis. Other appropriate microbial cultures from urine and potential infected sites should preferably precede the administration of antimicrobials, but testing should not postpone treatment.[39]
6. Where sepsis is suspected or confirmed, broad-spectrum antimicrobials in accordance with antibiotic guidelines for obstetric sepsis should be administered within 1 h (with or without the presence of septic shock), followed by intravenous fluids.[38,39]
7. Surgical source control should be considered in cases of maternal sepsis and undertaken as soon as possible. Evacuation of the uterus or other potential infectious sites should be highly prioritized in the early stages of sepsis.[39]
8. After placement of an emergency rescue cerclage in women with shortened cervix and/or exposed fetal membranes, the threshold for removal of the cerclage should be low if suspicion of infection arises.[37]
9. Pregnant and postpartum women with sepsis should be handled by a multidisciplinary team consisting of senior consultants in obstetrics and other relevant specialties.[8]
10. The level of surveillance must be in accordance with the clinical course. Obstetric patients with sepsis and organ failure should be monitored in the intensive care unit.[39]

The greatest limitation to our study was the inability to compare the deceased women to women who survived maternal sepsis and evaluate which differences in clinical handling prove to be decisive for detrimental outcome. Our finding of no antibiotic use in the women who died of other causes than sepsis could be due to lacking registration of this information in women where infection was not the focus. There could be cases we missed due to underreported deliveries to any register or missing obstetric diagnoses to the cause-of-death registers. Furthermore, unregistered deaths during early gestation and before pregnancy was confirmed, could have been missed. In some cases, we had no information about the clinical courses that lead to death, and had to rely on the conclusions regarding quality of care from the audit groups in the respective countries. Another weakness is that infectious diseases specialists were not part of the audit groups. Also, the time spent concluding on the quality of care was limited. The Nordic collaboration has not compared our conclusions to the conclusions of health care supervision authorities.

The strength of the study is an expert review of maternal sepsis deaths during a broad time interval in five countries with quite similar

health care systems, making the results representative for the entire Nordic area. Our learning points are thus valuable for the handling of maternal sepsis in general, and outside of the Nordic countries too.

5 | CONCLUSION

We found sepsis to be the fifth leading cause of maternal deaths during 2005–2021 in the Nordic countries. Delayed recognition of sepsis was the main element in substandard care in cases of maternal deaths from nongenital sepsis. Delayed recognition of sepsis, delayed administration of antimicrobial therapy and insufficient surgical source control were the main elements in substandard care of genital tract sepsis. There is need for increased awareness of sepsis and for improved clinical handling with early recognition and prompt antimicrobial and surgical approach to reduce the risk of serious maternal morbidity and mortality from sepsis.

AUTHOR CONTRIBUTIONS

Sedina Atic Kvalvik: conceptualization, formal analysis, investigation, methodology, visualization, writing – original draft, writing – review and editing. Hanna Åmark: writing – review and editing. Rikke Beg Helmig: writing – review and editing. Mika Gissler: data curation, writing – review and editing. Lill Trine Nyfløt: conceptualization, methodology, writing – review and editing. Steinar Skrede: conceptualization, methodology, supervision, writing – review and editing. Siri Vangen: writing – review and editing. Svein Rasmussen: methodology, supervision, writing – review and editing. Elham Baghestan: conceptualization, methodology, supervision, writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The Regional Committee for Medical and Health Research Ethics—Norway in Tromsø, approved the study for Norway (Ref: 2010/2854–6) on December 16, 2010. The Danish Data Protection Agency and the National Board of Health, The Icelandic National Bioethics Committee in addition to the Data Protection Authority, and the Finnish Institute for Health and Welfare and Statistics Finland, gave their concessions to use the confidential health data imported for this study. No ethical approval was needed in Sweden, as the study comprised deceased individuals.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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