



POPULATION STUDY OF MATERNAL MORTALITY DUE TO SEPSIS IN ANTIOQUIA, COLOMBIA, BETWEEN 2004 AND 2014: AN OVERVIEW OF THE CHALLENGE OF TIMELY IDENTIFICATION AND TREATMENT

Estudio de mortalidad materna por sepsis en Antioquia, Colombia, entre los años 2004-2014: una mirada al desafío de la identificación y el tratamiento oportunos

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ABSTRACT

Objective: To describe the characteristics of women who died as a result of sepsis and to identify the care-associated factors contributing to those deaths in the Department of Antioquia, Colombia.

Materials and methods: Case series study of maternal deaths caused by infection between the years 2004 and 2014. Maternal deaths were analysed based on the recommendations of the “Surviving Sepsis Campaign” and on clinical practice guide-

lines for specific infections. Judgements were made by consensus. The variables evaluated were timeliness of the diagnosis of sepsis, antibiotic treatment, septic shock, culture sampling, pregnancy termination, performance of surgery for controlling the source of the infection, admission to the intensive care unit, referral to a higher complexity level, and overall quality of management. Descriptive analysis.

Results: Out of 476 maternal deaths in 11 years, 47 (9.87%) were non-obstetrical cases of sepsis and 11 (5.2%) were obstetrical. Pneumonia was the leading cause of death. All the cases were associated with at least one consideration of poor care quality. The main factors influencing the outcome were delays in symptom identification and antibiotic initiation; inadequate treatment of septic shock; care of women at levels with low resolution capacity; and failure to modify therapeutic measures, even in the face of patient decline.

Conclusion: Maternal deaths from sepsis were mainly associated with non-obstetric causes. There

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are critical factors that can be modified, such as delay identifying the syndrome and timely initiation of adequate antibiotic therapy.

Key words: Maternal mortality, sepsis, infection.

RESUMEN

Objetivo: describir las características de las mujeres e identificar los factores de la atención que contribuyeron a las muertes maternas por sepsis en el departamento de Antioquia, Colombia.

Materiales y métodos: serie de casos de las muertes maternas causadas por infección entre los años 2004 y 2014. Se analizaron las muertes maternas con base en las recomendaciones de la “Campaña para sobrevivir a la sepsis”, y en guías de práctica clínica de infecciones específicas. Los juicios se realizaron por consenso. Se evaluaron la oportunidad del diagnóstico de sepsis, el tratamiento antibiótico, el choque séptico, la toma de cultivos, la terminación del embarazo, la realización de la cirugía para control del foco infeccioso, el ingreso a unidad de cuidados intensivos, la remisión a un nivel de complejidad mayor y la calidad global del manejo. Análisis descriptivo.

Resultados: de 476 muertes maternas, 47 (9,87 %) mujeres fallecieron por sepsis de origen no obstétrico y 11 (5,2 %) por infecciones propias del embarazo o puerperio. La neumonía fue la principal causa de muerte. Los principales factores que influyeron en el desenlace fueron las demoras en identificar el síndrome, en iniciar los antibióticos, asumir el manejo en niveles con baja capacidad resolutive, tratamiento inadecuado del choque séptico y la falta de modificación de las conductas terapéuticas ante el deterioro de las pacientes.

Conclusión: las muertes maternas por sepsis estuvieron principalmente asociadas a causas no obstétricas; hay factores críticos tales como el retraso en la identificación del síndrome, y el inicio oportuno y adecuado de los antibióticos que son susceptibles de intervención.

Palabras clave: mortalidad materna, sepsis, infección.

INTRODUCTION

Sepsis must be understood as the inflammatory response to an infection, characterised by life-threatening organ and systemic compromise (1). Despite the implementation of measures such as changes in asepsis techniques, the use of broad-spectrum antibiotics, hospital care during childbirth, and the analysis of all cases of maternal death as part of epidemiological surveillance, sepsis is still among the five leading causes of maternal death (MD) in the world (2, 3). In the pregnancy-related mortality report for the period between 2011 and 2013 in the United States, sepsis appears as the third cause of maternal mortality, accounting for 12,7% of the deaths (4) and 15% of admissions of pregnant women to intensive care units (ICU) (5). Maternal deaths due to sepsis are more frequent in Africa, Asia, Latin America and the Caribbean than in developed countries (3).

Infections accounting for 18% of the cases were the third cause of MD after bleeding and hypertensive complications during the period between 2010 and 2012 in Colombia and, among them, the most frequent were pneumonia, uterine infection and urinary tract infection. In Colombia, deaths due to septic miscarriage are classified under the category of miscarriage complications and are not added to the number of deaths attributed to sepsis (6).

Sepsis being a progressive phenomenon, it needs to be identified and treated promptly, considering that any delay in care is catastrophic. Unfortunately, the criteria for diagnosing sepsis in pregnant women are extrapolated from the general population, but many times they are equivocal as they are mistaken for the physiological changes of pregnancy (7-9), making diagnosis a true challenge for the clinician. It was only until 2012 that specific guidelines for the treatment of sepsis in pregnancy were published (2, 10), based on a syndromic approach to identification and treatment, supported on the guidelines for the general population, specifically on the “Surviving Sepsis Campaign,” which has been updated every four years since 2004 (11-13).

In Colombia, and specifically in the department of Antioquia, there are no studies regarding care-related factors that may be associated with maternal death. Therefore the objective of this study is to describe the characteristics of maternal deaths due to infection and to identify those that might influence the outcome of maternal death due to sepsis, in order to gain objective information that may lead to the development of focused strategies that can have a positive impact on maternal mortality due to this cause.

MATERIALS AND METHODS

Descriptive case series study of pregnant women coming from the department of Antioquia, who died from obstetric and non-obstetric sepsis during the time period between 2004 and 2014. Cases of tuberculosis were excluded because the recommendations for the syndromic approach to the management of sepsis do not apply in this disease, and the cases were insufficient data to perform an analysis.

The department of Antioquia is located in central Colombia, it has six million inhabitants distributed in 126 municipalities, with 75.000 births per year, 98% in institutions under the care of general practitioners or specialists. A consecutive sampling of all maternal deaths as defined by the World Health Organisation (WHO) was performed (14).

Procedure. Cases were identified based on search and comparisons in the following sources: database of deaths of the Single Affiliates Registry (RUIAF), or printed death certificates of the group of women between 10 and 54 years of age, plain files of the Public Health Surveillance System (Sivigila) (event 550: maternal mortality) and, after 2013, the web-based Maternal Mortality Surveillance System, the system currently used in Colombia for on-line reporting and analysis of maternal mortality cases. The Primary Data Generation Units (UPGD), or the healthcare institutions where the event takes place, are responsible for reporting immediately in accordance with the case definitions contained in the protocol of the National Health Institute. The Antioquia Health and Social Protection Secretariat

is in charge of screening and verifying the data. Duplicate records, records that did not meet the case definition, records of women living in a different department, and those discarded in the data sources were excluded.

The documents were reviewed by a committee consisting of obstetricians and gynaecologists with additional training in epidemiology, public health and obstetric intensive care and ten years of experience analysing cases of maternal deaths. The purpose of this review was to identify and assess the clinical factors that influenced the outcome. The documents consisted of the clinical record kept by each institution where women received care, the family interview or verbal autopsy, necropsy, analyses conducted by the healthcare institutions, and the reports of the epidemiological surveillance committee of the department.

A factor was considered to have had an influence on death based on a significant discrepancy between the care provided to the patient and the recommendations contained in the clinical practice guidelines, or the clinical reasoning. Judgement regarding care was arrived at by consensus of the research team, using a questionnaire built on the basis of the main recommendations for the identification and treatment of sepsis, in particular the "Surviving Sepsis Campaign" (12, 13), but also different management guidelines for sepsis in pregnancy, and specific guidelines for the management of pneumonia (15, 16), urinary tract infection (17) and obstetric infection (18, 19). The questionnaire was designed to be used as a checklist to document whether a recommendation was followed or not, and to help the evaluators judge whether in the specific clinical situation under evaluation failure to comply with the recommendation influenced the outcome of death.

Because of the complexity of the situations encountered, it is impossible to standardise the judgement of the team, for example, when rating care quality and timeliness. Timely care for women with the same diagnosis and disease severity

classification may vary substantially depending of the values of another characteristic that may be a relevant prognostic factor, even if it is not part of the diagnosis or its classification. In order to solve this issue, the research group used “clinical reasoning” understood as the “careful, analytic approach based on the scientific method that brings together all the relevant information in order to find the best method to reach a diagnosis and provide therapy to individual patients,” in contrast to the intuitive approach to problem solving and decision-making, understood as the “fast, generally subconscious, experience-driven approach” (20).

Variables measured

Referral. Timely referral was deemed to have occurred if the patients seen in a Level I healthcare institution were referred to a higher complexity institution (within the next 12 hours) as soon as the presence of the diagnostic criteria for sepsis was identified; also, if women seen in a level II institution were referred to a higher complexity level after identifying the need for intensive care for the mother as well as the baby (and if it was done within the first 12 hours). For women seen directly at a level III institution, the variable evaluated was whether the institution did not have the necessary resources to ensure care and transfer to a different institution was warranted.

Timely diagnosis. The number of visits prompted by a clinical picture suggestive of infection before admission, the time between the documentation in the clinical record of one (13) or two clinical signs of systemic inflammatory response (SIRS) (12), and the diagnosis of sepsis were all considered. SIRS criteria taken into consideration included temperature ≥ 38.3 °C o ≤ 36 °C, heart rate > 90 per minute, respiratory rate > 20 per minute, leukocytosis $> 12,000$, leukopenia $< 4,000$ or the presence of bands $> 10\%$. Diagnosis was considered timely when made immediately after documenting in the clinical record two signs of SIRS and suspicion of a source of infection.

Timely and adequate antibiotic treatment. The time between the diagnosis of sepsis and the administration of the first dose of antibiotic was evaluated, and treatment was considered timely if administered within the first hour after the diagnosis was made. The choice of the correct antibiotic was evaluated based on guideline recommendations for each aetiological diagnosis (2, 16, 19, 21).

Treatment of septic shock. Septic shock was defined as persistent hypotension: mean arterial pressure (MAP) < 65 mm/Hg and clinical or laboratory signs of hypoperfusion after the use of intravenous fluids. The evaluation included sufficiency of the administered amount, considered to be at least one 20 ml/kg bolus of crystalloids; the correct use of vasopressors; the choice of medication; and the dose and timeliness of the administration (2, 11).

Culture samples. A 24-hour limit was assigned for timely culture samples, considering non-availability of culture technology at the basic level of care, as well as patient transfer issues. This time period was determined by consensus of the research team, although it is recognised that the time period recommended is within the first 45 minutes (13). In those cases in which culture samples did not apply, as in the case of endometritis, this parameter was not assessed and those cases were not included in the respective denominators of the quality compliance calculations.

Pregnancy termination. The research team assessed the timeliness of the decision to terminate pregnancy as a maternal rescue strategy in order to improve the haemodynamic and respiratory parameters; a 72-hour period was used for patients in dual vasopressor/inotropic support or high ventilation parameters (e.g., PEEP > 10 mm/Hg, FiO₂:100%). This variable was built by consensus, based on the experience of the research team, and through the application of indirect evidence (management of cardiorespiratory arrest and acute respiratory distress syndrome in pregnancy) (22, 23).

Surgery for controlling the source of infection. Performance of surgery for controlling the source

of infection was evaluated on the basis of whether it was required in accordance with the aetiological diagnosis, the clinical picture and the diagnostic tests ordered. It was rated as timely if the procedure was done within the 12 hours following diagnosis (14, 24).

Admission to the intensive care unit. Based on consensus of the research team, it was considered timely if the woman was admitted to the intensive care unit within the first 24 hours of showing the following clinical and laboratory criteria: need for vasopressor or inotropic support; need for invasive or non-invasive mechanical ventilation; involvement of more than one organ; need for renal replacement therapy; and orotracheal intubation for airway protection in patients with altered state of consciousness (25).

Overall management rating. Care was given an overall rating as “quality care” if it met all the criteria mentioned above, as long as the parameter under assessment was applicable.

Statistical analysis. The results for the qualitative variables are presented as absolute numbers and proportions in relation to the number of cases with information or the number of cases for which the evaluation is relevant (subject to the presence of the factor under study). Age is presented as mean plus standard deviation because a normal distribution was confirmed, and discreet quantitative variables are presented as medians with their 25th and 75th percentiles, or as minimum and maximum (range). The ratio of maternal mortality due to sepsis over the 11-year period was calculated based on the number of deaths due to this cause and the number of babies born during this period.

Ethical considerations. This research study was approved by the Bioethics Committee of Antioquia University Medical School. For publication purposes and in order to maintain confidentiality of the analyses, the names of the institutions where care was provided to the women who died are omitted. Approval from the Antioquia Health Secretariat was also obtained. The way in which

the information is presented ensures confidentiality regarding patients and institutions.

RESULTS

Between 2004 and 2014 there were 476 maternal deaths and 936,008 live births in Antioquia, for a maternal mortality ratio of 51 x 100,000 live births. Overall, 58 cases associated with obstetric and non-obstetric sepsis were analysed, for a MM ratio due to sepsis of 6.21 x 100,000 live births. Tuberculosis cases were excluded from the factor analysis because the guidelines do not apply. Also excluded were cases with insufficient information for the analysis.

Sepsis was the fourth cause of maternal death after obstetric haemorrhage, hypertensive disorders and non-pregnancy-related complications. Patients who died had a gestational age under term, most of them came from the urban area, were in the lower limit for adequate attendance to prenatal control visits, and the most frequent comorbidity was anaemia (Table 1).

Overall, 47 women (81%) died from non-obstetric sepsis and 11 (19%) died from pregnancy or postpartum-related infections. Pneumonia was the main cause of non-obstetric sepsis, while both urinary tract infection and endometritis were second (Table 2).

The following determinations were made regarding compliance with the recommendations considered during the quality assessment: in terms of referral, a total of 36 women (62%) were seen initially in a Level I healthcare institution; there were delays in transfer to an institution with a higher ability to solve the problem in 58.6% of the cases, the main reason for this delay being diagnostic error or underestimation of the clinical picture. There were delays in administrative paperwork in 4 cases; 42 women (72.4%) presented to a healthcare institution between one and five times complaining of symptoms of infection before a definitive diagnosis was made; when they presented the first time, 50 women (86%) already had at least one sign of SIRS, 41 (70%) had two or more, and 10 (17.2%)

Table 1.
Sociodemographic characteristics of pregnant women who died from sepsis in Antioquia, Colombia, 2004-2012

Characteristic	Value
Maternal age (mean weeks \pm SD)	27.2 (7.4)
Gestational age (mean weeks \pm SD)	29.64 (6.3)
Parity. Median (25-75th percentile)	1 (0-2)
Number of prenatal visits. Median (25-75th percentile)	4 (2-5)
Area of residence*	
• Rural	19 (35.2%)
• Urban	35 (64.8%)
Anaemia*	7/56 (12.5%)
Human Immunodeficiency Virus*	2/53 (3.8%)
Diabetes*	
• Gestational	2/45 (4.4%)
• Pre-gestational	1/51 (2.0%)
PROM*†	4/52 (7.7%)

* Median (25th-75th percentile).

†Premature rupture of membranes.

had criteria consistent with septic shock from the first visit to the healthcare institution.

When one SIRS criterion was used at the time of presentation, the median time until the diagnosis of sepsis was made was 24 hours; when two criteria for sepsis were used, time to diagnosis was 6.5 hours. Once the diagnosis of sepsis was made, the median time elapsed before antibiotic therapy initiation was 2 hours, and the choice of the therapy was incorrect in 62% of cases. No culture samples were made within the adequate time period in 49% of patients. In 49%, the clinical practice was not changed despite evidence of patient decline. In 23% of patients found with signs of shock, the quantity of fluids administered was insufficient, and in a similar proportion, vasopressor support was managed inadequately. Admission to the ICU was considered untimely in 51% of the patients. Surgical removal of the source of sepsis was not performed in 38% of the patients in whom it was indicated (5 out of 13). In 49% of patients, treatment was

Table 2.
Aetiology of sepsis in pregnant women who died from this cause in Antioquia, Colombia, 2004-2012

Aetiology	n (%)
Pneumonia	30 (51.7)
Urinary tract	9 (15.5)
Endometritis	9 (15.5)
Meningoencephalitis	3 (5.2)
Unidentified source of infection	3 (5.2)
Chorioamnionitis	2 (3.4)
Peritonitis	1 (1.7)
Colangitis	1 (1.7)

not modified despite evidence of clinical decline. Early termination of pregnancy as a resuscitation strategy was delayed in 12 out of 26 patients. Table

3 shows the management characteristics of the deceased patients.

DISCUSSION

This case series of maternal mortality in Antioquia shows that sepsis from non-obstetric causes is the most frequent, in particular due to pneumonia and urinary tract infection. The main healthcare-associated factors that influenced the outcome were delays in recognising the syndrome and initiating antibiotic therapy because of failure to make the diagnosis, leading to delay in initiating the right antibiotic, and inadequate resuscitation and use of vasopressors in patients with signs of shock, and failure to modify clinical practice in view of evident deterioration of patient status.

The rise in mortality due to sepsis observed between 2009 and 2012 might be attributed to the 2009 H1N1 pandemic (26), explaining why pneumonia was the primary cause of death due to sepsis in our case series. Our data are consistent with the latest report on maternal mortality in the United Kingdom, where influenza accounted for 43% of the deaths due to sepsis between 2009 and 2012, similar to the finding reported in the United States between 1998 and 2008, when influenza accounted for 29.7% of maternal deaths (27).

Regarding healthcare-associated deficiencies that influenced the outcome, one potential explanation for these delays might be lack of knowledge of the management guidelines for sepsis in pregnant women. This situation was described by Rivers in 2001 (28). The explanation could perhaps be related to lack of compliance with the recommendations, a problem that has been identified throughout the world when it comes to the management of sepsis (29-33), and to the difficulty in making the diagnosis because signs and symptoms of infection tend to be mistaken for the physiological changes of pregnancy (8-10, 34).

Regarding the delay in recognising SIRS according to the clinical suspicion criteria, it is important to bear in mind that there was a change in the

definition of SIRS and the way to diagnose it during the time of data collection for the study. Before 2008, at least two criteria (clinical or laboratory) were required (11, 12), while only one criterion was required after 2012 (13). Had this new approach been applied, identification of nine patients could have been accomplished faster because the mere suspicion of an infectious origin would have triggered all the actions for the management of sepsis in those patients with uncertain predisposition for progression to septic shock (35).

Timely initiation of antibiotic therapy and the right choice of antibiotic are critical for improving prognosis and survival of patients with sepsis. It has been shown that for every hour that antibiotic administration is delayed after the start of hypotension, mortality increases by 7.6% (36). The study found delay in the initiation of antibiotic therapy and inadequate selection in 62% of cases. International recommendations point to antibiotic selection based on local sensitivity studies (37). Although progress has been made in Colombia in this regard (38), availability may be a problem in Level I hospitals, where more than half of the patients in our study received care.

In terms of inadequate fluid resuscitation and use of vasopressors in patients with septic shock, it has been described that optimal fluid replacement to maintain a mean arterial pressure (MAP) of > 65 mm/Hg was critical in reducing mortality (28). The normal drop in arterial blood pressure during the second trimester blurs the line between normalcy and the criterion for severe sepsis, leading to potential underestimation or confusion on the part of the clinician. This means that there is a need to assess other clinical and laboratory markers of hypoperfusion such as lactate (13); however, these tests were not ordered in more than half of our patients.

Failure to recognise patient decline has already been described in non-obstetric populations in our country (39). As for pregnancy termination, it is worth noting that no studies or specific recommendations regarding the adequate timing

Table 3.
Characteristics of the management provided to pregnant women who died from sepsis in Antioquia, Colombia, 2004-2012

Parameter	Value
Overall management rating (inadequate management)	58 (100%)
Number of visits to the emergency service before diagnosis. Median (range)	1 (0-5)
Time between documentation of a sign of SIRS and diagnosis. Median (25-75th p)	24 (5-72)
Time between documentation of two signs of SIRS and diagnosis. Median (25-75th p)	6.5 (0.7 – 48)
Time between diagnosis and antibiotic administration. Median (25-75th p)	2 (0.5 - 3.4)
Reasons why timely referral did not happen when it was necessary	24/34 (58.6%)
• Diagnostic error or underestimation of the clinical picture	19 (79.2%)
• Delay in implementing the order	2 (8.3%)
• Paperwork	2 (8.3%)
• No data	1 (4.2%)
Inadequate choice of the antibiotic for the suspected source of infection	31/50 (62.0%)
Failure to monitor vital signs continuously after the diagnosis	28/52(53.8%)
No timely admission to the ICU	24/47 (51.1%)
• Delay in administering the antibiotic	29/58 (50.0%)
• Delay in implementing the order	9 (31.0%)
• Diagnostic error or underestimation of the clinical picture	20 (69.0%)
No pregnancy termination as a necessary strategy for maternal resuscitation	12/26 (46.2%)
No cultures taken within the next 24 hours after diagnosis	26/53 (49.1%)
Inadequate intravenous fluid volume in patients with signs of shock	9/38 (23.7%)
Treatment not modified although changes in the patient's clinical condition required it	27/55 (49.1%)
No surgeries or procedures performed for controlling the source of infection within the first 12 hours following diagnosis	5/13 (38.5%)
Failure to order the paraclinical tests required for the clinical condition	22/55 (40.0%)
No use of vasopressors when the clinical conditions required it	4/45 (8.9%)
Delay in the use of vasopressors	10/48 (20.8%)
Inadequate dose of vasopressors	7/37 (18,9%)

*Median (percentil 25-75th percentile intervals).

were found. Plante *et al.* recommend interrupting pregnancy when there is no improvement of the clinical picture and the physiological changes of gestation prevent optimal resuscitation (40).

The strengths of this study include the exhaustive search for cases and the detailed individual analysis

leading to the identification of factors that have been found to be directly associated with the risk of dying. The main limitations include its retrospective character, lost information about some cases, and loss of 10% of the patients due to insufficient data. On the other hand, a key

issue with this type of analysis, faced by all groups doing this type of work in the world, is the lack of objective, reproducible and validated criteria for defining some of the categories for rating the quality of care. This situation results creates the need of establishing subjective criteria; however, resorting to clinical reasoning and discussion among several specialists, and making decisions on the basis of consensus, reduces arbitrary actions and diminishes the influence of individual experience on the clinical judgement (20). The reader must bear in mind the definitions agreed upon by the group at the time of interpreting and extrapolating the results of this study.

CONCLUSIONS

Maternal deaths due to sepsis were associated mainly with non-obstetric causes; there are critical, though modifiable factors such as delays in identifying the syndrome and timely initiation of adequate antibiotic therapy. Training for all healthcare practitioners providing care to pregnant women is necessary, particularly in the so-called low-risk environments where staff is perhaps less experienced in early identification of these situations.

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