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ORIGINAL RESEARCH ARTICLE

Maternal mortality in women with pre-viable premature rupture of membranes: An analysis from the French confidential enquiry into maternal deaths

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Abstract

Introduction: Pre-viable premature rupture of membranes (pre-viable PROM) is a rare event occurring in less than 1% of pregnancies. Nevertheless, it can be responsible for severe maternal complications, the risk of which needs to be balanced with the possibility to prolong the pregnancy up to viable gestational age. Maternal sepsis was reported in 1%–5% of women who received conservative management and prophylactic antibiotics, but information on maternal mortality is lacking. Our objective was to identify maternal deaths in women who had pre-viable PROM, describe the characteristics of the women, explore preventability factors within the care they received, and estimate the lethality of pre-viable PROM.

Material and methods: We identified all maternal deaths associated with pre-viable PROM from the 2001–2015 French National Confidential Enquiry into Maternal Deaths (NCMM). Data on women's characteristics and the care they received were extracted from the ENCMM database. The lethality was determined after estimating the total number of pregnant women with pre-viable PROM from the national hospital discharge database.

Results: Between 2001 and 2015, we identified seven maternal deaths associated with pre-viable PROM, representing 0.6% of all maternal deaths over this period (ie, maternal mortality ratio 0.06/100000 live births). Six maternal deaths were attributed to sepsis after genital infection by Gram-negative bacilli and one to postpartum hemorrhage due to placenta accreta. Four of these seven cases were considered preventable. The main preventability factors were delayed diagnosis, delayed fetal extraction, and inappropriate antibiotic treatment. The estimated lethality was 4.5/10000 women with pre-viable PROM.

Conclusions: Maternal death associated with pre-viable PROM is rare but possible. Most of these deaths seem preventable, with areas for improvement related to earlier diagnosis and better treatment of uterine infections, which can evolve rapidly.

Abbreviations: ENCMM, Enquête Nationale Confidentielle sur les Morts Maternelles; PROM, premature rupture of membranes.

KEYWORDS
maternal mortality, preventability, pre-viable premature rupture of membranes, suboptimal care

1 | INTRODUCTION

Pre-viable premature rupture of membranes (pre-viable PROM) is a rare event that concerns less than 1% of pregnancies[1] but can be responsible for maternal morbidity.[2] For women with pre-viable PROM managed conservatively (no fetal extraction), the literature reports a wide heterogeneity of maternal morbidity, 16%–71% intrauterine infection[3–5] and 0.8%–4.8% maternal sepsis in most recent studies with systematic use of prophylactic antibiotics.[2,6] Maternal sepsis in this context may evolve acutely and lead to severe maternal morbidity and even death.

Few maternal deaths in women with pre-viable PROM have been reported. One was reported in the 1980s, due to septic shock after chorioamnionitis.[7] In the 2006–2008 report of the UK Confidential Enquiries into Maternal Deaths, 4 of 155 maternal deaths were due to chorioamnionitis after spontaneous pre-viable PROM in the second trimester of pregnancy.[8] In 2012 in Ireland, the death of a woman after mid-trimester pre-viable PROM raised national and international public awareness of the key role of terminating the pregnancy in some emergency obstetric situations, which led to increased legislation on the matter.[9] To our knowledge, no other case has been reported since.

Although this event is very rare, maternal death after pre-viable PROM may be under-reported in the literature. Nonetheless, characterizing the maternal vital risk associated with pre-viable PROM is important to inform decision-making at a pregnancy term when maternal risk must be balanced with the possibility of prolonging pregnancy up to viable gestational age.

The aim of our study was to identify maternal deaths in women who had pre-viable PROM, describe the characteristics of women, explore preventability factors within the care they received, and estimate the lethality of pre-viable PROM.

Key message

Over a 15-year period, seven maternal deaths associated with pre-viable premature rupture of membranes, mainly due to intrauterine infection, were identified in France. The estimated lethality was 4.5/10000 women with pre-viable premature rupture of membranes.

2 | MATERIAL AND METHODS

We identified maternal deaths from the database of the French National Confidential Enquiry into Maternal Deaths (Enquête Confidentielle sur les Morts Maternelles [ENCMM]) for the 2001–2015 period.[10–12] Since 1996, this permanent system has studied all pregnancy-associated deaths of women who were pregnant or within 1 year of the termination of pregnancy. Deaths are identified from three sources: (a) death certificates with any cause of death coded in the pregnancy chapter of the International Classification of Diseases, 10th revision (ICD-10), or any mention of pregnancy or puerperium in the text, or when the pregnancy checkbox was ticked; (b) computer-based national linkage of the death and birth registers to identify women who died within a year after a pregnancy; and (c) hospital discharge database identifying hospitalizations of women with at least one diagnostic code in the ICD-10 O00–O99 range or a code related to pregnancy, delivery, or the postpartum period and who died during the hospitalization. For each pregnancy-associated death identified, a team of assessors (an obstetrician or midwife and an anesthesiologist) conducts a confidential enquiry, using a standardized questionnaire to collect relevant clinical information about the woman and her death via interviews and a review of hospital records and autopsy reports. When a confidential enquiry is not possible, information from the death certificate and hospital discharge summary is analyzed. Deaths are then anonymously reviewed by the national expert committee of the ENCMM, which reaches a unanimous determination of the underlying cause of death, whether it was a maternal death (defined as a woman's death during pregnancy or within 1 year of its end, regardless of its duration and site, from any cause related to or aggravated by the pregnancy or its management, but not accidental or incidental), and its preventability. A maternal death is considered preventable if one or more changes in the care provided or in the patient behavior might have prevented the fatal outcome. Each case is determined as "probably preventable", "possibly preventable", "not preventable" or "not enough information to conclude." The factors contributing to preventable deaths are classified as "Factors associated with care provided" (late diagnosis, delayed treatment, inadequate treatment), "Factors associated with the organization of care" (inadequate unit of care, delayed transfer, inadequate communication, insufficient human resources, insufficient material resources), and "Factors associated with the interaction between the patient and health care" (inadequate observance of treatment, "no show" in consultation or refused hospitalization, social vulnerability, mental vulnerability).

For this analysis, we reviewed all maternal deaths up to 42 days after pregnancy that occurred between 2001 and 2015 (most recent completed year at the time of our analysis) and selected those that occurred in women with pre-viable PROM defined as PROM between 14^{+0} and 24^{+6} weeks of gestation. For each

included woman, we collected data on age, citizenship, parity, pre-pregnancy body mass index, allergies, obstetrical history, number of fetuses, pregnancy monitoring, gestational age at PROM, clinical signs on day of admission, initial blood tests, antibiotics initiated, vaginal swab results, planned initial management decision regarding termination or pursuit of pregnancy, delay between admission for PROM and first infectious clinical signs (hyperthermia, uterine contractions, leukorrhea, metrorrhagia), first antibiotic switch, actual management regarding termination of pregnancy, final infectious agent identification, antibiotic resistance profile, delay between first clinical signs and admission to the intensive care unit, delay between first clinical signs and death, the cause of death, and preventability factors determined by the national expert committee.

Before 2018, and thus for the period relevant to our study, there were no guidelines for the management of pre-viable PROM in France, and practices for management were likely heterogeneous as suggested by the heterogeneous rates of termination of pregnancy, neonate survival, and perinatal morbidity.[13] In 2018, national guidelines on the management of PROM included specific recommendations on pre-viable PROM, which include initial hospitalization, empirical antibiotic treatment by amoxicillin and information on the risk associated with pre-viable PROM and the management options.[14] First-line antibiotic treatment includes lactam group agents and macrolides, in agreement with the international literature.[15–17] In France, termination of pregnancy can take place at "any point during the pregnancy" in accordance with the strict conditions set forth in Public Health Code article L2213-1: "either the continuation of the pregnancy seriously threatens the woman's health, or there is a strong probability that the child to be born is affected by a very severe condition recognized as incurable at the time of diagnosis." The criteria considered in the decision-making process leading to termination of pregnancy include clinical (hyperthermia, uterine contractions) and laboratory results (vaginal swab, blood inflammation markers).[14] Induction of labor in second trimester of pregnancy is usually performed medically with mifepristone, misoprostol and oxytocin. Since 2013, primary cervical dilatation using Dilapan-S® (Medicem) patented aquacryl hydrogel rods is proposed.

The specific maternal mortality ratio was defined as the number of maternal deaths associated with pre-viable PROM per 100 000 live births. The number of live births was determined from the French national birth register.[18]

The lethality was defined as the number of maternal deaths with pre-viable PROM divided by the number of women hospitalized with pre-viable PROM (between 14^{+0} and 24^{+6} weeks of gestation) estimated from the national hospital discharge database (the *Programme National de Médicalisation des Systèmes d'Information*), including all hospital stays in France. Because hospital data earlier than 2011 were not available, the lethality was estimated for the 2011–2015 period.

Descriptive statistics are presented as mean (standard deviation) and median (range) for continuous variables and frequency (percentage) for categorical data.

2.1 | Ethics statement

Ethical approval for the ENCMM was granted by the French Commission on Information Technology and Liberties on June 26, 2018, DR-2018-157.

3 | RESULTS

Over the 15-year study period (2001–2015), we identified 1093 maternal deaths up to 42 days after pregnancy end in France (maternal mortality ratio 8.9/100 000 live births). Seven deaths were associated with pre-viable PROM (ie, 0.64% of maternal deaths up to 42 days; specific maternal mortality ratio 0.06/100 000 live births).

The estimated number of women with pre-viable PROM in the national hospital discharge data was 8853 during 2011–2015, representing 0.22% of pregnancies. The estimated lethality of pre-viable PROM was 4.5/10 000 cases (95% confidence interval 1.4–9.2).

Table 1 describes the characteristics of the seven women whose death was associated with pre-viable PROM. Women were 21 to 37 years old, and four were nulliparas. One woman had two late miscarriages, and another had three previous cesarean sections. Two women had spontaneous twin pregnancies, and one had amniocentesis at 15 weeks for risk of Down syndrome.

Pre-viable PROM occurred at 17 (two women), 18 (two women), 20, 22, and 23 weeks of pregnancy. None of the seven women showed clinical signs of infection at admission. Conservative management was initially decided in five cases, and medical termination of pregnancy was decided before any sign of infection in two cases. All women received prophylactic antibiotics: amoxicillin for five, amoxicillin/clavulanic acid for one and erythromycin for one because of allergy to penicillin. At admission, all women had vaginal swab analysis, which revealed infection with *Escherichia coli* in two and group B streptococcus in two and was negative in three. At admission, laboratory tests revealed moderately elevated C-reactive protein level in three women (10, 11, and 26 mg/L). One woman (patient 2) was discharged after 4 days of uneventful hospitalization and was readmitted the next day for fever.

The median delay between pre-viable PROM and the first signs of intrauterine infection, hyperthermia in all women, was 5 days (range 1–10 days); between the first signs and admission to the intensive care unit was 10 hours (range 9–36 hours); and between the first signs and death was 18 hours (range 12–120 hours) (Figure 1).

When intrauterine infection was diagnosed, the termination of pregnancy was medically induced with misoprostol in three women, followed by intravenous oxytocin if necessary (one woman). After a variable delay, all women were switched to another antibiotic after the first signs of infection: cephalosporin in three women, amoxicillin/clavulanic acid in two, tazobactam in one and ofloxacin in one. Aminosides were added to the antibiotic treatment in five women (inadequate dose in one). One woman with severe sepsis was transferred from a local clinic to a university hospital. One woman (in a

TABLE 1 Characteristics and care of the seven women whose death was associated with pre-viable premature rupture of membranes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Triennum of death	2001–2003	2007–2009	2007–2009	2010–2012	2013–2015	2013–2015	2013–2015
Age (years)	26	27	37	21	28	25	35
Citizenship	France	France	France	France	France	France	Not France
Parity	0	0	3	0	1	0	1
Body mass index (kg/m^2)	30.1	19.6	35.1	31.0	N/A	23.0	22.0
Obstetric history	0	0	Cesarean section ×3	0	0	2 Late miscarriages	0
Allergy	0	0	0	Penicillin	0	0	0
Number of fetuses	1	2	1	1	1	2	1
Prenatal care provider	General practitioner	Level 3 hospital	Level 1 hospital	Level 3 hospital	Level 2 hospital	Level 1 private clinic	General practitioner
Gestational age at PROM (weeks)	17^{+3}	22^{+0}	18^{+5}	20^{+5}	23^{+6}	17^{+0}	18^{+0}
Infectious clinical signs on day of admission for PROM[a]	none	none	none	none	none	none	none
Initial blood tests[b]	negative	negative	negative	CRP = 11	CRP = 26	negative	CRP = 10
Antibiotics initiated	Amoxicillin/CA	Amoxicillin	Amoxicillin	Erythromycin	Amoxicillin	Amoxicillin	Amoxicillin
Vaginal swab result	Group B streptococcus	*Eshcerichia coli*	negative	*E. coli*	Group B streptococcus	negative	negative
Planned initial management decision at admission	TOP (planned at 17^{+5})	Conservative	TOP (planned at 19^{+0})	Conservative	Conservative	Conservative	Conservative[c]
Delay between admission for PROM and first infectious clinical signs (days)	1	5	6	2	10	2	6
First antibiotic switch	Ofloxacine	Cefotaxime + gentamycin	Amoxicillin/CA + gentamycin	Cefotaxime + metronidazole	Ceftriaxone + gentamycin	Amoxicillin/CA + amikacin[d]	Tazocilline + amikacin
Course of events	Spontaneous abortion	Spontaneous	Induction of labor	Induction of labor	Death in utero	Spontaneous	Induction of labor
Final microbiology	*E. coli*	*E. coli*	Negative	*E. coli*	*E. coli*	*Klebsiella pneumoniae*	*E. coli*
Antibiotic resistance profile	Amoxicillin/CA-R Ofloxacine-R	Amoxicillin-R Cefotaxime-S Gentamycin-S	N/A	0	0	Amoxicillin/CA-R amikacin-S	Amoxicillin-R tazocilline-R amikacin-S

TABLE 1 (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Delay from first signs to ICU (h)	10	12	N/A	9	36	20	10
Delay from first signs to death (h)	18	17	N/A	12	38	5 days	13
Cause of maternal death	Genital tract infection	Genital tract infection	Postpartum hemorrhage due to placenta accreta	Genital tract infection	Genital tract infection	Genital tract infection	Genital tract infection

CA, clavulanic acid; CRP, C-reactive protein; ICU, intensive care unit; TOP, termination of pregnancy.

[a]Infectious clinical signs: hyperthermia, uterine contractions, leukorrhea, metrorrhagia.

[b]Blood tests at initial evaluation included complete blood count, C-reactive protein, urine culture and vaginal swab.

[c]Termination of pregnancy was not allowed by CPDPN commission.

[d]Patient 6 had more than one antibiotic switch during critical care: ceftriaxone + metronidazole + dalacine + amikacin on day 2, amoxicillin + tazocilline + amikacin on day 4.

type 1 maternity hospital) had an emergency hysterectomy for uncontrolled hemorrhage (placenta accreta not previously suspected), with several intestinal and vesical traumatic lesions.

The underlying cause of death was genital tract infection in six of seven women, and one death was due to placenta accreta with postpartum hemorrhage. No autopsy was performed. For the six cases of intrauterine infection, final microbiology analysis of hemocultures, amniotic fluid, or placental culture revealed *E. coli* infection in five cases and *Klebsiella pneumoniae* infection in one case. Among the six cases with identified Gram-negative bacilli, four showed antibiotic resistance to amoxicillin, which had been administered as first-line empirical antibiotic treatment.

For one woman (patient 5), pre-viable PROM occurred at 23^{+6} weeks; the woman received amoxicillin for 1 week and had the first clinical signs of infection at 25^{+3} weeks. The signs initially included hyperthermia and coughing without uterine contractions and led to an initial diagnosis of frontal sinusitis treated by spiramycine. This associated diagnosis delayed the diagnosis and management of the intrauterine infection and led to worsening condition. Severe sepsis and septic shock developed rapidly, and the woman died the next day before labor could be induced, which illustrates how rapidly this situation can evolve.

The ENCMM expert committee considered four of the seven deaths preventable and one non-preventable; preventability could not be concluded in two deaths (Table 2). In three of four cases of preventable deaths, delayed management (particularly delayed fetal extraction) and inadequate treatment (inadequate antibiotic type or dosage) were identified. Also identified were late diagnosis and miscommunication between professionals (eg, delayed antibiotic switch while transferring the patient from the delivery ward to the intensive care unit).

4 | DISCUSSION

Our 15-year national study confirms that pre-viable PROM is a rare but still possible context of maternal death, accounting for less than 1% of maternal mortality, with a lethality of 4.5/10 000 women with pre-viable PROM. Death is almost always due to genital tract infection with bacteriological evidence of infection with Gram-negative bacilli. Preventability factors were identified in four of the seven cases, mainly related to delayed diagnosis, delayed fetal extraction, and inadequate antibiotic treatment.

Our study, based on national data, provides population-based estimates of maternal mortality and lethality associated with pre-viable PROM, about which data are scarce in the international literature. The ENCMM data collection uses a rigorous method that guarantees registration of all maternal deaths in France in the studied period. However, because data collection is retrospective for maternal deaths, we cannot exclude that some maternal deaths in women with pre-viable PROM were not included in our analysis if death was not due to maternal infection and PROM was not reported in medical files. Because the medical management of pre-viable PROM may have changed between

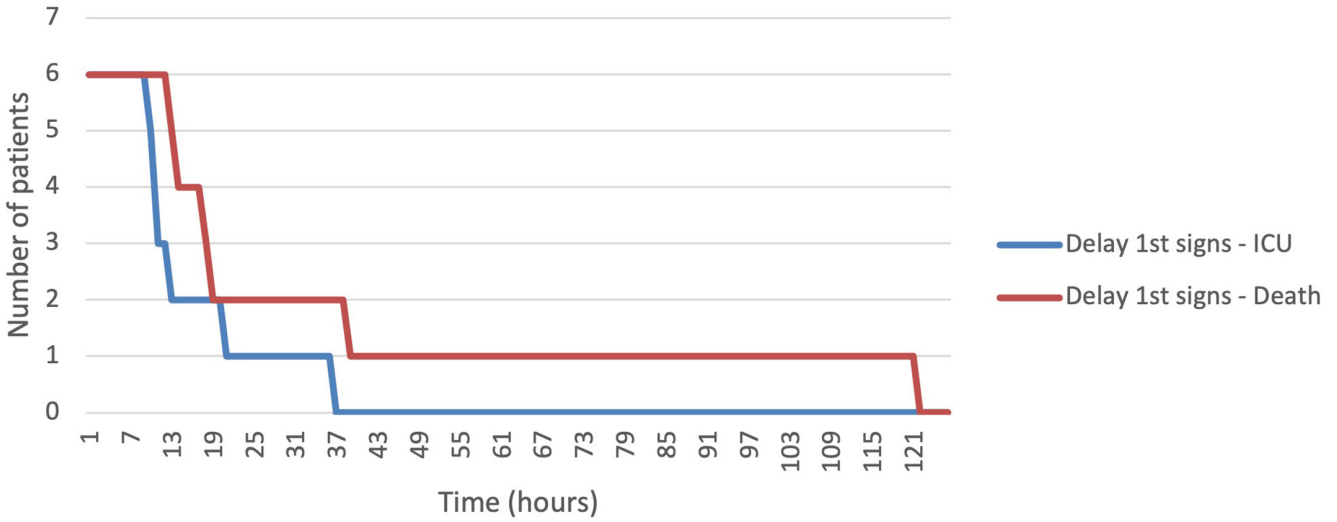

FIGURE 1 Delay (hours) between first signs of infection and transfer to the intensive care unit (ICU) and death associated with pre-viable premature rupture of membranes ($n = 6$)

TABLE 2 Preventability of death associated with pre-viable premature rupture of membranes in the seven women

Preventability	Patient 1 Possibly preventable	Patient 2 Probably preventable	Patient 3 Probably preventable	Patient 4 Cannot conclude	Patient 5 Cannot conclude	Patient 6 Probably preventable	Patient 7 Not preventable
Preventability factor							
Inadequate care							
Late diagnosis	–	–	–			×	
Late management	×	×	–			×	
Inadequate treatment	–	×	×			×	
Inadequate organization of care							
Inadequate site of care	–	–	×			×	
Miscommunication	–	–	–			×	
Inadequate interaction between patient and health care	–	–	–			–	

the beginning of the study period and the time of the analysis, the calculated rates may not reflect the current context.

The definition of viability varies in different countries. In France, this definition is classically between 24 and 25 weeks of gestation.[14] Because no case of PROM occurred between 24 and 25 weeks of gestation in our study, a more inclusive definition would not have affected the estimates we provide. Regarding the lethality estimate, pre-viable PROM may be under-reported in the hospital data; the 0.2% prevalence of pre-viable PROM among pregnant women we found is indeed slightly lower than the 0.3%–1% range reported in the literature[2,4,19]; this might slightly overestimate the lethality of pre-viable PROM that we report.

Finally, our estimates are relevant for high-income countries, and mortality after pre-viable PROM is likely higher in lower-income countries with more difficult access to antibiotic treatment and obstetrical care, although numbers are lacking. Nevertheless, preventability factors identified in our study may still be informative for the decision-making process for women with pre-viable PROM in all settings.

Maternal sepsis was due to intrauterine infection by Gram-negative bacilli in six women: *E. coli* in five, and *K. pneumoniae* in one. In the last case, maternal death was due to postpartum hemorrhage, and no pathogen was found on microbiological analysis. These findings are consistent with previous studies identifying *E. coli* and Gram-negative bacilli as some of the most common and virulent pathogen agents in intrauterine infections, particularly in the second trimester. However, β-hemolytic streptococcus causes severe sepsis more frequently in the third trimester and in the early postpartum period.[20,21] In the 2006–2008 UK Report of the Confidential Enquiries into Maternal Deaths, one maternal death due to chorioamnionitis after spontaneous pre-viable PROM in the second trimester involved infection with *Morganella*

morganii, another Gram-negative bacterium commonly present in the intestinal flora.[8] *Escherichia coli* resistance to amoxicillin has been found to be as high as 60% in community-acquired infections, which is consistent with our findings.[22] Of note, in national guidelines, first-line probabilistic antibiotic treatment remains amoxicillin, clindamycin, or erythromycin, regardless of the term at PROM.[15–17,23] The likelihood of amoxicillin and other antibiotic resistance profiles in *E. coli* infection must be considered for antibiotic upgrade in case of signs of infection after initial antibiotic therapy.

In our study, four of the seven maternal deaths were considered preventable, mostly due to delayed diagnosis, delayed fetal extraction, and inadequate antibiotic treatment. In a large study including 28 150 non-obstetric patients with severe sepsis and septic shock, Ferrer et al showed a linear increase in risk of mortality for each hour delay in antibiotic administration.[24] In our study, severe sepsis was diagnosed less than 12 hours after first signs of infection, and in four of six cases, death occurred less than 18 hours after the first signs of infection. This observation underlines the key role of time in these potentially rapidly evolving situations, and the importance of close surveillance during hospitalization, recognition, quick response to first signs of intrauterine infection, and rapid decision to actively evacuate intrauterine content by terminating the pregnancy.

5 | CONCLUSION

As expected, maternal deaths associated with pre-viable PROM are extremely rare but still exist and are mostly preventable. Relevant empirical antibiotics, patient information on the maternal risks of intrauterine infection, close monitoring of the first signs of intrauterine infection, and uncontrolled sepsis are areas for improvement to avoid maternal mortality associated with worsening condition. Specific national or international guidelines on monitoring and treatment strategies for pre-viable PROM might help to avoid these preventable maternal deaths. The estimated lethality of pre-viable PROM reported in our study is a new piece of information that may help in the individual decision-making process and the design of such guidelines.

AUTHOR CONTRIBUTIONS

YA and MS contributed to the conception, design, data collection, and drafting the manuscript. AR contributed to drafting the manuscript. CD-T and EA contributed to the conception, design and drafting the manuscript. All authors approved the final version for submission.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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