Outcome of prelabor rupture of membranes before or at the limit of viability: systematic review and meta-analysis

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OBJECTIVE: Counseling of pregnancies complicated by pre- and periviable premature rupture of membranes to reach shared decision-making is challenging, and the current limited evidence hampers the robustness of the information provided. This study aimed to elucidate the rate of obstetrical and neonatal outcomes after expectant management for premature rupture of membranes occurring before or at the limit of viability.

DATA SOURCES: Medline, Embase, CINAHL, and Web of Science databases were searched electronically up to September 2023.

STUDY ELIGIBILITY CRITERIA: Our study included both prospective and retrospective studies of singleton pregnancies with premature rupture of membranes before and at the limit of viability (ie, occurring between 14 0/7 and 24 6/7 weeks of gestation).

METHODS: Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale for cohort studies. Moreover, our study used meta-analyses of proportions to combine data and reported pooled proportions. Given the clinical heterogeneity, a random-effects model was used to compute the pooled data analyses. This study was registered with the International Prospective Register of Systematic Reviews database (registration number: CRD42022368029).

RESULTS: The pooled proportion of termination of pregnancy was 32.3%. After the exclusion of cases of termination of pregnancy, the rate of spontaneous miscarriage or fetal demise was 20.1%, whereas the rate of live birth was 65.9%. The mean gestational age at delivery among the live-born cases was 27.3 weeks, and the mean latency between premature rupture of membranes and delivery was 39.4 days. The pooled proportion of cesarean deliveries was 47.9% of the live-born cases. Oligohydramnios occurred in 47.1% of cases. Chorioamnionitis occurred in 33.4% of cases, endometritis in 7.0%, placental abruption in 9.2%, and postpartum hemorrhage in 5.3%. Hysterectomy was necessary in 1.2% of cases. Maternal sepsis occurred in 1.5% of cases, whereas no maternal death was reported in the included studies. When focusing on neonatal outcomes, the mean birthweight was 1022.8 g in live-born cases. The neonatal intensive care unit admission rate was 86.3%, respiratory distress syndrome was diagnosed in 66.5% of cases, pulmonary hypoplasia or dysplasia was diagnosed in 24.0% of cases, and persistent pulmonary hypertension was diagnosed in 40.9% of cases. Of the surviving neonates, the other neonatal complications included necrotizing enterocolitis in 11.1%, retinopathy of prematurity in 27.1%, and intraventricular hemorrhage in 17.5%. Neonatal sepsis occurred in 30.2% of cases, and the overall neonatal mortality was 23.9%. The long-term follow-up at 2 to 4 years was normal in 74.1% of the available cases.

CONCLUSION: Premature rupture of membranes before or at the limit of viability was associated with a great burden of both obstetrical and neonatal complications, with an impaired long-term follow-up at 2 to 4 years in almost 30% of cases, representing a clinical challenge for both counseling and management. Our data are useful when initially approaching such patients to offer the most comprehensive possible scenario on short- and long-term outcomes of this condition and to help parents in shared decision-making.

Key words: maternal, neonatal, perinatal, periviability, preterm, premature rupture of membranes, preterm premature rupture of membranes, previability, viability

Introduction

Periviability is usually defined as the earliest stage of fetal maturity and is associated with the highest incidence of short- and long-term morbidity and mortality. In terms of gestational age

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The data that support the findings of this study are available from the corresponding author on reasonable request.

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AJOG MFM at a Glance

Why was this study conducted?

Counseling of pregnancies complicated by pre- and periviable premature rupture of membranes (PROM) to achieve shared decision-making is challenging, and the current limited evidence hampers the robustness of the information provided.

Key findings

PROM before or at the limit of viability was associated with a great burden of either obstetrical or neonatal complications, with one-third of pregnancies opting for termination of pregnancy, and a rate of live birth of 67.2% in the remaining pregnancies. In addition, long-term follow-up at 2 to 4 years was impaired in almost 30.0% of cases.

What does this add to what is known?

Our data are useful when initially approaching such patients to offer the most comprehensive possible scenario on short- and long-term outcomes of this condition and to help parents in shared decision-making.

(GA), unequivocal consensus is lacking; however, the 25 weeks of gestation threshold is generally accepted to define periviability.[1]

Premature rupture of membranes (PROM) before or at the limit of viability is one of the most common causes of pre- and periviable births and complicates up to 0.4% of pregnancies, mostly because of spontaneous pathogenesis or iatrogenic causes, such as invasive procedures (ie amniocentesis or cervical cerclage).[2]

In this scenario, 2 main options are usually offered to the patient: expectant management with antibiotic prophylaxis and close monitoring of both maternal and fetal well-being or elective termination of pregnancy (TOP), according to the national law. Although recent studies have evaluated the potential role of experimental interventions, such as amniopatch or serial transabdominal amnioinfusion, these procedures are still limited to research contexts and are currently not recommended by clinical guidelines.[3–4]

Expectant management after PROM before or at the limit of viability is associated with a great burden of severe perinatal complications.[5] A recent study reported a neonatal survival rate of 51.7%, with 38.8% of neonates without severe morbidity at discharge and 46.4% survivors at 2 years without cerebral palsy in pregnancies complicated by PROM between 22 and 25 weeks of gestation.[6]

Moreover, PROM before or at the limit of viability is associated with several maternal complications, including chorioamnionitis, endometritis, placental abruption, postpartum hemorrhage, and, although very rarely, maternal death.[2,7–10]

Therefore, the counseling of pregnancies complicated by pre- and periviable PROM is intuitively challenging. Physicians are required to discuss the various possible outcomes associated with expectant management to facilitate shared decision-making, but the small sample size of several published cohorts and the inclusion of both singleton and twin pregnancies at wide GA ranges often hamper the robustness of the available information.

Thus, this systematic review and meta-analysis aimed to elucidate the rate of obstetrical and neonatal outcomes in the case of expectant management for PROM occurring before or at the limit of viability (ie, occurring between 14 0/7 and 24 6/7 weeks of gestation).

Materials and Methods

Protocol, information sources, and literature search

This study was conducted according to the designed protocol recommended for systematic reviews and meta-analyses.[11–13] Medline, Embase, CINAHL, and Web of Science databases were searched electronically up to September 2023, using combinations of relevant Medical Subject Headings terms, key words, and word variants for "previable premature rupture of membranes," "periviable," "midtrimester," "early," "before viability," "maternal outcomes," "perinatal outcomes," "obstetric outcomes," "neonatal outcomes."

The search and selection criteria were restricted to the English language and year of publication (from 2000 onward). The reference lists of relevant articles and reviews were manually searched for additional reports. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.[14–16] The study was registered with the International Prospective Register of Systematic Reviews database (registration number: CRD42022368029).

Outcomes measures, study selection, and data collection

Our systematic review and meta-analysis outcomes were divided into obstetrical (both perinatal and maternal) and neonatal outcomes.

Obstetrical outcomes included the following:

- TOP
- Spontaneous miscarriage or fetal demise
- Live birth
- Mean GA at delivery (considering both the total group of cases and only the live-born cases)
- Latency time between PROM and delivery (considering both the total group of cases and only the live-born cases)
- Cesarean delivery (considering both the total group of cases and only the live-born cases)
- Oligohydramnios
- Placental abruption
- Chorioamnionitis
- Endometritis
- Postpartum hemorrhage
- Need for hysterectomy
- Need for blood transfusion
- Sepsis
- Maternal death

Neonatal outcomes included the following:

- Birthweight
- Admission to the neonatal intensive care unit (NICU)
- Respiratory distress syndrome (RDS)
- Pulmonary hypoplasia or dysplasia
- Persistent pulmonary hypertension
- Necrotizing enterocolitis (NEC)
- Retinopathy of prematurity (ROP)
- Intraventricular hemorrhage (IVH)
- Neonatal sepsis
- Neonatal mortality

When available, normal long-term follow-up at 2 to 4 years was considered as an outcome. The outcomes were included in the analysis only if they were reported by at least 2 studies.

The selection criteria included both prospective and retrospective studies of singleton pregnancies with PROM before and at the limit of viability (ie, occurring between 14 0/7 and 24 6/7 weeks of gestation).

Case reports, case series with fewer than 20 cases, review articles, letters to the editor, and editorials were excluded. In addition, studies that included both singletons and twin pregnancies were excluded. Finally, we excluded studies evaluating a specific intervention for preterm PROM (ie, amniopatch or amnioinfusion).

Of note, 2 authors (S.S. and F.Z.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full-text copies of articles were obtained, and the same 2 reviewers independently extracted relevant data regarding study characteristics and outcomes. Inconsistencies were resolved through discussion between the 2 reviewers until a consensus was reached or by consulting a third author (D.D.M.). Data not presented in the original publications were requested by e-mail from the authors.

Quality assessment, risk of bias, and statistical analysis

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies.[17] According to the NOS, each study is judged on 3 broad perspectives: selection of study groups, comparability of groups, and ascertainment of the outcome of interest. Assessment of the selection category includes evaluation of the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability category includes evaluation of the comparability of cohorts based on design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest and length and adequacy of follow-up. According to the NOS, a study can be awarded a maximum of 1 star for each numbered item within the selection and outcome categories. A maximum of 2 stars can be given for comparability.[17]

Data extraction and statistical analysis

We used meta-analyses of proportions to combine data and reported pooled proportions. Funnel plots were performed with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was <10. In this case, the power of the tests is too low to distinguish chance from real asymmetry.

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation because of heterogeneity rather than chance. An I^2 value of 0% indicates no observed heterogeneity, whereas I^2 values >50% indicate a substantial level of heterogeneity. Given the clinical heterogeneity, a random-effects model was used to compute the pooled data analyses. All proportion meta-analyses were performed using Comprehensive Meta-Analysis (version 4; Biostat, Englewood, NJ).

When the median values were available, the mean and standard deviation (SD) estimates were obtained using the equation proposed by Hozo et al[18] according to their recommendations. When the sample size was >25, the sample's median was considered the best estimate of its mean, and the SD was calculated as range divided by 4. When the outcome was reported by <3 studies, heterogeneity (I^2) was not reported.

Results

Study selection and characteristics

A total of 2201 articles were identified, of which 105 were assessed concerning their eligibility for inclusion and 19 were included in this systematic review (Table 1 and Figure 1).[19−37]

These 19 studies included 1640 singleton pregnancies. Moreover, 18 studies[19−28,30−37] were retrospective, and 1 study[29] was a secondary analysis of a randomized controlled trial.

Of note, 3 studies[19,26,30] included cases of PROM after an invasive procedure (ie, amniocentesis); moreover, 7 studies[20,24,28,31,32,34,37] only reported cases of spontaneous preterm PROM. In the 9 remaining studies,[21−23,25,27,29,33,35,36] the potential cause of PROM was not reported.

The characteristics of the study groups are outlined in Table 1.[19−37] The lower GA limit of the included studies was 14 weeks, whereas the upper GA limit was 25 weeks. In most of the included studies, PROM was treated with antibiotic prophylaxis. At the limit of viability, antenatal corticosteroid therapy to reduce the incidence and severity of RDS and intrapartum magnesium sulfate for neuroprotection were administered in most of the included studies (Table 2[19−37]).

The results of the quality assessment of the included studies using NOS are presented in Table 3.[19−37]

Synthesis of the results

The results were synthesized as obstetrical and neonatal outcomes presented in Tables 4[19−37] and 5[19−37] as both raw and pooled proportions. Moreover, the results are summarized as infographics in Figures 2 and 3.

In the overall population of pregnancies complicated by PROM before or at the limit of viability, the pooled proportion of TOP was 31.5% (176/559; 95% confidence interval [CI], 18.3−50.3),

TABLE 1
Characteristics of the included studies and study population

First author	Year	Study period	Study location	Study design	Sample size	Included cases after invasive procedures	Maternal age (y)	Nulliparous	GA at PPROM (wk)
Kraft et al[19]	2022	2008–2018	Germany	Retrospective	51	Yes	NR	19/51 (37.2%)	14 0/7 to 19 6/7
Herzlich et al[20]	2022	2014–2019	Israel	Retrospective	24	No	29.0±5.0	NA	17 0/7 to 23 6/7
Knupp et al[21]	2022	2011–2015	United States	Retrospective	94	NR	NR	44/94 (46.8%)	16 0/7 to 23 6/7
Günes et al[22]	2022	2012–2017	Turkey	Retrospective	192	NR	28.4±5.5	NR	20.45±2.87
Pendse et al[23]	2021	2006–2016	Australia	Retrospective	82	NR	NR	NR	<22 6/7
LeMoine et al[24]	2020	2012–2019	United States	Retrospective	81	No	28.8±5.7	38/81 (46.9%)	15 5/7 to 22 6/7 (mean, 20.6±1.9)
Sorano et al[25]	2020	2007–2017	Japan	Retrospective	66	NR	32.5±6.1	37/66 (56.1%)	20 0/7 to 23 6/7 (mean, 22.0+5.0±6.0)
Cobo et al[26]	2018	2000–2013	Spain	Retrospective	104	Yes	NR	NR	<24 0/7 (median, 18.5; IQR, 15.7–21.3)
Linehan et al[27]	2016	2007–2012	Ireland	Retrospective	42	NR	32.0 (19.0–42.0)	12/42 (28.6%)	14 0/7 to 23 6/7 (median, 18 (15 5/7 to 23 6/7)
Wagner et al[28]	2016	2005–2015	Germany	Retrospective	101	No	NR	NR	<24 0/7
Manuck et al[29]	2014	1997–2004	United States	Secondary analysis of RCT	275	NR	27.0±5.9	NR	15.1–24.9 (mean, 23.7±1.2)
Acaia et al[30]	2013	2000–2009	Italy	Retrospective	85	Yes	NR	NR	14 0/7 to 23 6/7
Azria et al[31]	2012	2003–2007	France	Retrospective	113	No	NR	59/113 (52.2%)	15 0/7 to 24 6/7
Storness-Bliss et al[32]	2012	2002–2011	Canada	Retrospective	31	No	NR	NR	<24 6/7
Shah et al[33]	2011	2000–2008	Australia	Retrospective	26	NR	NR	NR	<24 6/7 (mean, 19.3±2.8)
Manuck et al[34]	2009	2001–2007	United States	Retrospective	159	No	NR	48/159 (30.2%)	<24 0/7
Williams et al[35]	2009	2006–2008	Belgium	Retrospective	23	NR	NR	NR	18 0/7 to 24 6/7
Verma et al[36]	2006	1997–1999	United States	Retrospective	66	NR	28.3 (15.0–43.0)	NR	<24 0/7
Grisaru-Granovsky et al[37]	2003	1995–2001	Israel	Retrospective	25	No	NR	NR	16 0/7 to 24 0/7 (mean, 22.7±1.0)

GA, gestational age; *IQR*, interquartile range; *NR*, not reported; *PPROM*, preterm premature rupture of membranes; *RCT*, randomized controlled trial.

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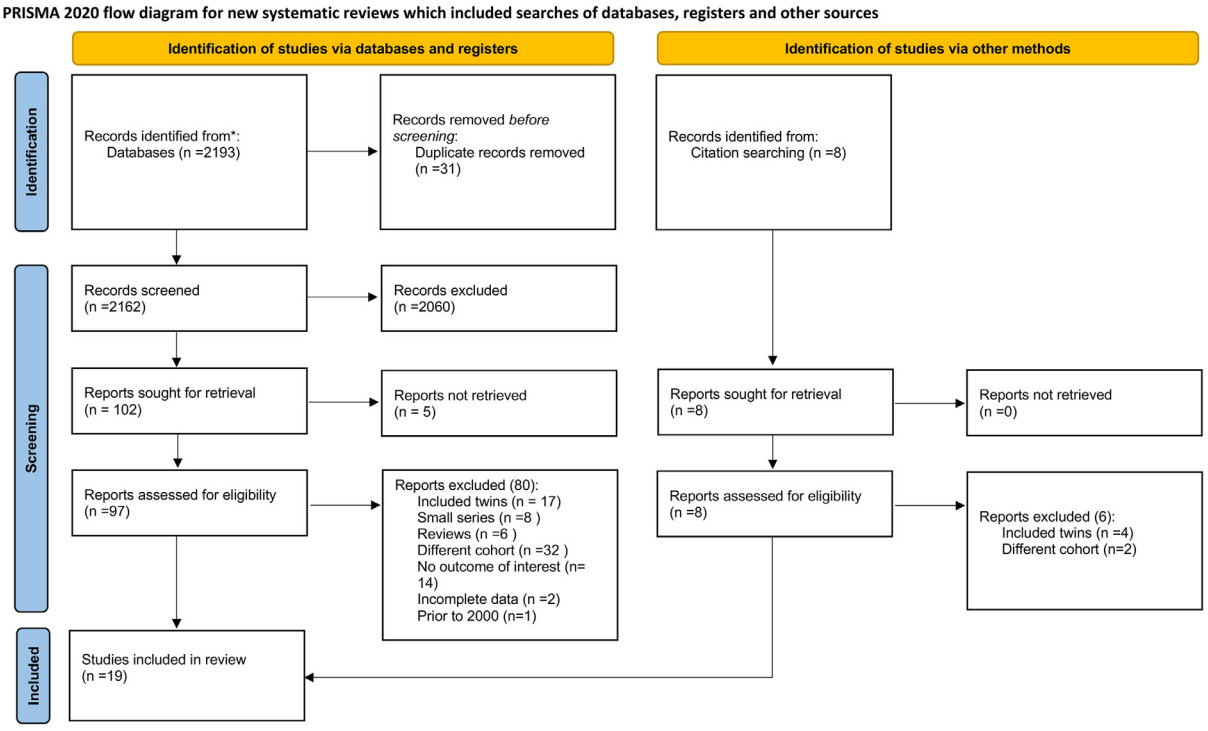
FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

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although not all studies reported this outcome.

After the exclusion of cases of TOP, the rate of spontaneous miscarriage or fetal demise was 20.1% (176/889; 95% CI, 11.8−32.0), whereas the rate of live birth was 65.9% (550/803, 95% CI, 50.9 −78.3).

The mean GA at delivery among the live-born cases was 27.3 weeks (95% CI, 25.8−28.7), whereas the GA at delivery among cases of fetal demise and perinatal death was 25.8 weeks (95% CI, 20.2 −31.3). The mean latency estimates between PROM and delivery were 39.4 days (95% CI, 23.4−55.4) in live-born cases and 24.3 days (95% CI, 1.0 −49.6) in cases of fetal demise and perinatal death.

The pooled proportions of cesarean deliveries were 282 of 687 cases (35.6%; 95% CI, 23.4−50.1) of the whole group, including cases of fetal demise, and 207 of 469 cases (47.9%; 95% CI, 33.1−63.1) of the live-born cases. Oligohydramnios occurred in 162 of 334 cases (47.1%; 95% CI, 25.6−69.7).

Concerning maternal complications, chorioamnionitis occurred in 439 of 1330 cases (33.4%; 95% CI, 24.8−43.2), endometritis in 46 of 641 cases (7.0%; 95% CI, 4.3−11.2), placental abruption in 109 of 990 cases (9.2%; 95% CI, 5.2 −15.9), and postpartum hemorrhage in 14 of 303 cases (5.3%; 95% CI, 2.2 −12.1); moreover, blood transfusion was needed in 4 of 93 cases (4.8%; 95% CI, 1.4−14.6). Hysterectomy was necessary in 3 of 293 cases (1.2%; 95% CI, 0.3 −4.2). Maternal sepsis occurred in 12 of 811 cases (1.5%; 95% CI, 0.5−4.2), whereas no maternal death was reported in the included studies (0/511).

When focusing on neonatal outcomes, the mean birthweights were 1022.8 g (95% CI, 888.4−1157.3) in live-born cases and 1070.9 g (95% CI, 538.8−1603.0) in all cases, including stillbirths. The admission rate to the NICU was 86.3% (141/186; 95% CI, 63.2−95.8), RDS was diagnosed in 223 of 345 cases (66.5%; 95% CI, 45.6 −82.4), pulmonary hypoplasia or dysplasia was diagnosed in 230 of 762 cases (24.0%; 95% CI, 14.8−36.5), and persistent pulmonary hypertension was diagnosed in 46 of 113 cases (40.9%; 95% CI, 32.2−50.2). Of the surviving neonates, other neonatal complications included NEC in 90 of 796 cases (11.1%; 95% CI, 8.1−15.0), ROP in 237 of 601 cases (27.1%; 95% CI, 15.8 −42.5), IVH in 173 of 788 cases (17.5%; 95% CI, 11.4−25.9). Neonatal sepsis complicated 30.2% (258/761, 95% CI, 22.9−38.8) of cases and the overall neonatal mortality was 23.9% (247/1058, 95% CI, 17.6−31.7). The long-term

TABLE 2
Management of singleton pregnancies complicated by PPROM

Study	Antibiotic therapy	Tocolysis	RDS prophylaxis	Magnesium sulfate for neuroprotection
Kraft et al,[19] 2022	NR	NR	NR	NR
Herzlich et al,[20] 2022	24/24 (100.0% of cases); Mercer protocol	NR	Almost all mothers received corticosteroids	22/24 (91.7%)
Knupp et al,[21] 2022	94/94 (100%); 57/94 (61%) received antibiotics within 24 h of PROM; 37/94 (39%) received antibiotics 24 h after PROM: 10-d course of 1 g oral azithromycin on days 1 and 5, 500-mg amoxicillin 3 times daily for 10 d, or ampicillin intravenous 2 g every 6 h in place of oral amoxicillin	NR	71/94 (75.5%)	64/94 (68.1%)
Günes et al,[22] 2022	174/192 (90.6%) 2 d of intravenous ampicillin-sulbactam, followed by 5 d of oral amoxicillin-sulbactam): administered for 1 wk to patients hospitalized for chorioamnionitis	Not routinely given in cases of PPROM before 24 wk 13/192 (6.8%)	Completed in 131/192 (68.3%)	NR
Pendse et al,[23] 2021	NR	NR	81/82 (99.0%)	6/82 (7.3%)
LeMoine et al,[24] 2020	57/81 (70.4%)	Not administered in any patients	12 mg intramuscularly administered every 24 h for a total of 2 doses	6-g loading dose, 6 g in 100 mL infused over 15-20 min, followed by maintenance dose
Sorano et al,[25] 2020	Ampicillin 1 g every 6 or 8 h and oral azithromycin 1 g	Tocolysis with intravascular ritodrine hydrochloride or magnesium sulfate performed in the existence of uterine contraction	2 doses of intramuscular 12 mg betamethasone 24 h apart administrated when delivery was anticipated within a week	Administered in the existence of uterine contraction
Cobo et al,[26] 2018	A course of 5-d intravenous ampicillin (1 g/6 h) and gentamicin (80 mg/8 h) systematically given to all women with PPROM and as a single dose of oral azithromycin (1 g) at admission	NR	2 intramuscular doses of betamethasone 12 mg administered 24 h apart beyond 24 wk when risk of early delivery	Administered if labor started between 24 and 32 wk
Linehan et al,[27] 2016	All women received oral antibiotics, usually oral erythromycin	NR	Corticosteroids routinely administered at 24 wk of gestation	NR
Wagner et al,[28] 2016	Administration of antibiotics for 5–7 d	Not routinely administered	2 administrations of 12 mg betamethasone administered 24 h apart intramuscularly at 24 wk	NR
Manuck et al,[29] 2014				133/275 (48%)

(continued)

TABLE 2
Management of singleton pregnancies complicated by PPROM *(continued)*

Study	Antibiotic therapy	Tocolysis	RDS prophylaxis	Magnesium sulfate for neuroprotection
	1326 (86.6%) received ampicillin, amoxicillin, or penicillin; 914 (59.7%) received erythromycin	Only few women received tocolysis	272/275 (98%) received corticosteroids	
Acaia et al,[30] 2013	2 d of intravenous ampicillin 1 g/8 h and clarithromycin 500 mg/12 h, followed by 5 d of oral amoxicillin 1 g/8 h and oral clarithromycin 500 mg/12 h, administered to all women	Tocolysis (indomethacin, ritodrine, atosiban) given for imminent risk of preterm labor or during the administration of steroids (24–34 wk)	Steroids only prescribed beyond 24 wk	NR
Azria et al,[31] 2012	Ampicillin or erythromycin given to most patients	Tocolytic agents not recommended, but short courses allowed during course of steroids after 24 wk	NR	NR
Storness-Bliss et al,[32] 2012	NR	NR	NR	NR
Shah et al,[33] 2011	NR	NR	NR	NR
Manuck et al,[34] 2009	Most women given antibiotics (ampicillin with or without erythromycin for a total of 7 d)	Not routinely administered (only if necessary during transport from an outlying facility)	NR	NR
Williams et al,[35] 2009	Antibiotic course given	8/15 (53.3%); atosiban or ritodrine	13/15 (86.7%)	NR
Verma et al,[36] 2006	Intravenous ampicillin or penicillin or the combination of ampicillin or amoxicillin and erythromycin, given to all patients	NR	NR	NR
Grisaru-Granovsky et al,[37] 2003	22/25 (88.0%) given a combined antibiotic treatment of ampicillin and erythromycin from the time of admission until delivery	In case of contractions before 34 wk, administration of indomethacin for 48 h to permit antenatal steroid therapy	At 24 wk of gestation betamethasone (2 doses of 12 mg intramuscularly at 24-h interval) administrated	NR

NR, not reported; *PPROM*, preterm premature rupture of membranes; *PROM*, premature rupture of membranes; *RDS*, respiratory distress syndrome.

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TABLE 3
Quality assessment of the included studies according to Newcastle-Ottawa Scale for cohort studies

Study	Selection	Comparability	Outcome
Kraft et al,[19] 2022	★★★	★	★★
Herzlich et al,[20] 2022	★★★	★	★★
Knupp et al,[21] 2022	★★★	★	★★
Günes et al,[22] 2022	★★★	★	★★
Pendse et al,[23] 2021	★★★	★	★★
LeMoine et al,[24] 2020	★★★	★	★★
Sorano et al,[25] 2020	★★★	★	★★
Cobo et al,[26] 2018	★★★	★	★★
Linehan et al,[27] 2016	★★★	★	★★
Wagner et al,[28] 2016	★★★	★	★★
Manuck et al,[29] 2014	★★★	★	★★
Acaia et al,[30] 2013	★★★	★	★★
Azria et al,[31] 2012	★★★	★	★★
Storness-Bliss et al,[32] 2012	★★★	★	★★
Shah et al,[33] 2011	★★★	★	★★
Manuck et al,[34] 2009	★★★	★	★★
Williams et al,[35] 2009	★★★	★	★★
Verma et al,[36] 2006	★★★	★	★★
Grisaru-Granovsky et al,[37] 2003	★★★	★	★★

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follow-up at 2 to 4 years was normal in 218 of 381 cases (74.1%; 95% CI, 52.9−87.9).

Comment

Principal findings

Our findings in this systematic review confirmed that PROM before or at the limit of viability is associated with a great burden of either obstetrical or neonatal complications. In particular, one-third of pregnancies complicated by this condition opted for TOP. In the remaining pregnancies, the rate of live births was 65.9%, with a mean GA at delivery of 27.3 weeks and a mean latency between PROM and delivery of 39.4 days. The most common maternal complications were chorioamnionitis (occurring in one-third of cases), endometritis, and postpartum hemorrhage. Neonatal mortality occurred in 23.9% of cases, whereas the most frequent neonatal complications were respiratory disorders (ie, RDS, pulmonary hypoplasia, or pulmonary hypertension), ROP, sepsis, and IVH. Finally, the long-term follow-up at 2 to 4 years was impaired in almost one-quarter of cases.

Clinical and research implications

PROM occurring at pre- and periviable GAs is a serious complication of pregnancy that is frequently associated with an adverse pregnancy outcome and a poor prognosis in terms of short- and long-term neonatal morbidity and mortality.

One of the main determinants of both short- and long-term adverse outcomes is GA at delivery, with the rate of both immediate survival and survival at 2 years without significant neurodevelopmental impairment gradually improving as GA increases from 22 to 28 weeks.[38]

Our findings showed that, among the live-born cases, the mean GA at delivery was 27.3 weeks, thus falling into the most severe degree of prematurity based on GA (<28 weeks).

The time interval between PROM and delivery is another important factor that affects the outcome of pregnancies complicated by PROM before or at the limit of viability. Here, we reported a mean latency between PROM and delivery of 39.4 days when focusing only on live-born cases and 24.3 days if fetal deaths were also included, which is a slightly longer latency than that reported in previous, older studies.[39,40] In this scenario, it is not surprising that PROM at 23 to 25 weeks of gestation might be associated with better outcomes than PROM occurring before 23 weeks of gestation. However, latency from PROM to delivery is also affected by other parameters that physicians should consider when trying to define the prognosis, such as the amount of residual amniotic fluid, with a residual deepest vertical pocket

TABLE 4
Pooled proportions of obstetrical outcomes

Outcomes	Studies	Raw proportion (%)	Pooled proportion (95% CI)	I^2
Termination of pregnancy	6[19,26,28,31,32,34]	176/559 (31.5%)	32.3 (18.3–50.3)	93%
Spontaneous miscarriage or fetal demise	12[19,21,22,25–28,30,31,33–35]	176/889 (19.8%)	20.1 (11.8–32.0)	91%
Live birth	12[19,21,22,25–28,30,31,33,35,36]	550/803 (68.5%)	65.9 (50.9–78.3)	92%
GA at delivery (wk)[a]	4[22,25,27,33]	—	25.8 (20.2–31.3)	99%
GA at delivery in liveborns (wk)	7[19,20,24,26–29]	—	27.3 (25.8–28.7)	97%
Latency between PPROM and delivery (d)[a]	3[22,25,27]	—	24.3 (1.0–49.6)	99%
Latency between PPROM and delivery in liveborns (d)	4[19,20,24,29]	—	39.4 (23.4–55.4)	95%
Cesarean delivery (overall)[a]	7[21,22,25,30,34,36,37]	282/687 (41.0%)	35.6 (23.4–50.1)	91%
Cesarean delivery in live births	5[19,20,23,24,29]	207/469 (44.1%)	47.9 (33.1–63.1)	84%
Oligohydramnios	4[23,25,28,30]	162/334 (48.5%)	47.1 (25.6–69.7)	94%
Placental abruption	9[20,22,24,25,27,29,30,34,36]	109/990 (11.0%)	9.2 (5.2–15.9)	86%
Chorioamnionitis	13[19–25,27,29–31,34–36]	439/1330 (33.0%)	33.4 (24.8–43.2)	91%
Endometritis	4[21,29,31,34]	46/641 (7.2%)	7.0 (4.3–11.2)	56%
Postpartum hemorrhage	4[21,27,28,36]	14/303 (4.6%)	5.3 (2.2–12.1)	59%
Need for hysterectomy	2[22,28]	3/293 (1.0%)	1.2 (0.3–4.2)	NE
Need for blood transfusion	2[19,27]	4/93 (4.3%)	4.8 (1.4–14.6)	NE
Sepsis	9[19,22,24–27,30,32,34]	12/811 (1.5%)	1.5 (0.5–4.2)	60%
Maternal death	5[22,26,32,34,37]	0/511 (0%)	0.6 (0.2–2.2)	0%

CI, confidence interval; *GA*, gestational age; *PPROM*: preterm premature rupture of membranes; *NE*, not estimable.

[a] Includes cases of fetal demise.

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TABLE 5
Pooled proportions of neonatal outcomes and data on long-term follow-up at 2 to 4 years

Outcomes	Studies	Raw proportion (%)	Pooled proportion (95% CI)	I^2
Birthweight (g)[a]	3[22,25,33]	—	1070.9 (538.8–1603.0)	98%
Birthweight in liveborns (g)	5[20,26–29]	—	1022.8 (888.4–1157.3)	90%
Admission to the NICU	3[27,33,34]	141/186 (75.8%)	86.3 (63.2–95.8)	48%
Respiratory distress syndrome	8[19,22,23,26,27,30,31,36]	223/345 (64.6%)	66.5 (45.6–82.4)	88%
Pulmonary hypoplasia or dysplasia	10[19,20,22,23,28–31,34,37]	230/762 (30.2%)	24.0 (14.8–36.5)	89%
Persistent pulmonary hypertension	3[19,20,23]	46/113 (40.7%)	40.9 (32.2–50.2)	0%
Necrotizing enterocolitis	12[19,20,22,23,26–31,34,36]	90/796 (11.3%)	11.1 (8.1–15.0)	39%
Retinopathy of the preterm	8[19,20,22,23,28–30,36]	237/601 (39.4%)	27.1 (15.8–42.5)	89%
Intraventricular hemorrhage	11[20,22,23,26–31,34,36]	173/788 (21.9%)	17.5 (11.4–25.9)	82%
Neonatal sepsis	11[19,22,23,26,27,29–31,34,36,37]	258/761 (33.9%)	30.2 (22.9–38.8)	77%
Neonatal mortality	17[19–23,25–31,33]	247/1058 (23.3%)	23.9 (17.6–31.7)	81%
Normal long-term follow-up at 2 to 4 y	5[19,23,25,29,30]	218/381 (57.2%)	74.1 (52.9–87.9)	86%

CI, confidence interval; *NICU*, neonatal intensive care unit.

[a] Includes cases of fetal demise.

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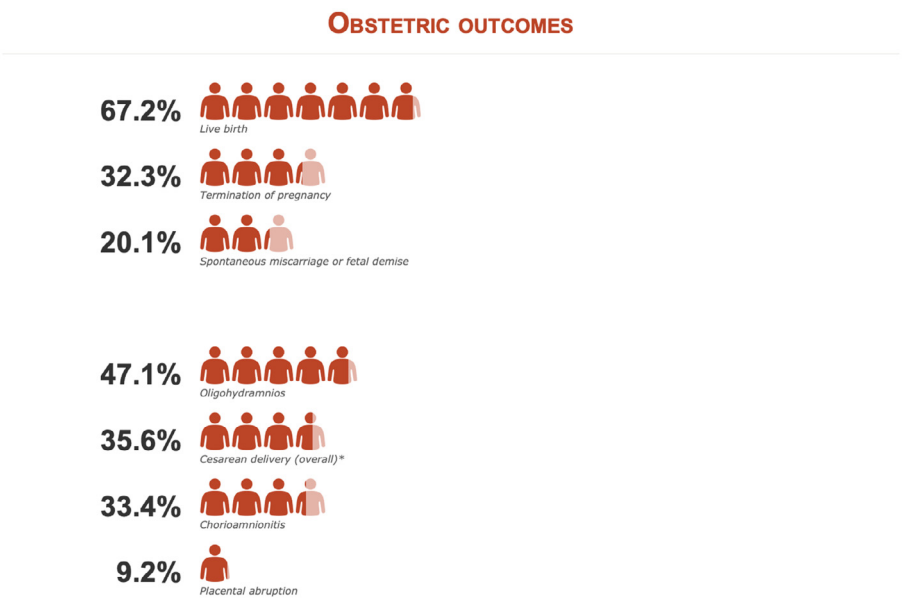
FIGURE 2
Infographics for the main obstetrical outcomes



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of ≥1 cm associated with higher chances of fetal survival and increased latency to delivery.[32]

In addition to mortality, PROM before or at the limit of viability is complicated by significantly higher rates of short- and long-term morbidity.

Our systematic review showed that respiratory morbidity is the most common short-term complication, with RDS, persistent pulmonary hypertension, and pulmonary hypoplasia or dysplasia occurring in 66.5%, 40.9%, and 24.0% of cases, respectively. Pulmonary hypoplasia is a well-known complication of prolonged oligohydramnios in the second trimester of pregnancy, with the risk increasing as the severity of oligohydramnios increases.[41] In addition, the risk of pulmonary hypoplasia is significantly related to earlier GAs and is

FIGURE 3
Infographics for neonatal outcomes

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the highest before 26 weeks of gestation, during the canalicular stage of lung development, after which the acinar structure is considered less sensitive to external stressors.[42]

Therefore, PROM before or at the limit of viability seems to be significantly associated with the risk of pulmonary hypoplasia, being frequently the cause of both prolonged oligohydramnios and extremely preterm birth.

Another important issue when dealing with PROM before or at the limit of viability is survival at 2 years of age without neurodevelopmental impairment. Of note, GA at delivery is commonly considered as the main predictor of long-term neurodevelopmental outcome, but PROM before or at the limit of viability may be itself an independent predictor of childhood morbidity, defined as moderate or severe cerebral palsy, Bayley Mental Development Index and Bayley Psychomotor Development Index scores >2 standard deviation below the mean, and/or death.[29]

However, our findings reported an abnormal follow-up at 2 to 4 years in approximately 30% of cases, which is lower than that reported from previous studies on this topic (approximately 50%).[29,43]

In this scenario, accurate and comprehensive counseling with evidence-based data on the magnitude of complications associated with expectant management is of paramount importance to inform shared decision-making and help parents make preference-sensitive and value-laden decisions.

Strengths and limitations

To the best of our knowledge, this is the most updated and comprehensive meta-analysis reporting the obstetrical, maternal, and neonatal outcomes in pregnancy complicated by PROM before or at the limit of viability. The robust methodology, the thorough literature search, and the large number of outcomes assessed represent additional study strengths.

We have to acknowledge that this systematic review and meta-analysis has also several limitations, mainly involving the retrospective nature of the included studies, the small sample size of some studies, and different GAs when PROM occurred.

In addition, there is significant heterogeneity among the studies, particularly when considering the lack of standardized criteria for antenatal surveillance and the use of different protocols for tocolysis, antibiotic prophylaxis, antenatal corticosteroid therapy for RDS prophylaxis, and intrapartum magnesium sulfate for neuroprotection.

Moreover, we acknowledge that, in this GA window, the outcomes considerably improve from 1 week of gestation to another. However, as this was not an individual patient meta-analysis, we could not stratify the analysis according to the progressive increase of the GA.

Another limitation concerns the different etiologies of PROM before or at the limit of viability, with some studies including cases following invasive procedures, some others excluding these cases, and some others not mentioning whether they were included or not. The different underlying conditions might somehow influence the natural course and, thus, the outcome of these pregnancies.

Finally, different hospitals in different settings worldwide have different policies regarding resuscitation and intensive care measures (ie, how and when to start), and this may intuitively affect the rate of perinatal or neonatal deaths among the included studies and ultimately our meta-analysis.

Conclusions

PROM before or at the limit of viability is associated with high overall rates of obstetrical and neonatal complications, thus representing a clinical challenge for both counseling and management. These data are useful when initially approaching such patients to offer the most comprehensive possible scenario on short- and long-term outcomes of this condition, but they need to be confirmed by larger prospective studies sharing objective protocols, mostly in terms of antenatal surveillance and management. ■

CRediT authorship contribution statement

Sara Sorrenti: Writing – original draft, Conceptualization. **Daniele Di Mascio:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Asma Khalil:** Writing – review & editing. **Francesco D'Antonio:** Methodology. **Giuseppe Rizzo:** Conceptualization. **Fabrizio Zullo:** Formal analysis. **Elena D'Alberti:** Data curation. **Valentina D'Ambrosio:** Data curation. **Ilenia Mappa:** Methodology. **Ludovico Muzii:** Supervision. **Antonella Giancotti:** Writing – review & editing.

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