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Maternal, perinatal and childhood outcomes of the PPROMEXIL-III cohort: Pregnancies complicated by previable prelabor rupture of membranes

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ABSTRACT

Objective: Perinatal mortality after previable prelabor rupture of membranes (previable PROM) might be underestimated as most studies exclude patients with poor prognosis, or solely include patients in tertiary-care centers. We aimed to report perinatal, neonatal and long-term outcomes in a consecutive series of women with pregnancies complicated by previable PROM.

Study design: We conducted a prospective cohort study including women with singleton pregnancies and previable PROM $\leq 23^{+6}$ weeks gestational age (GA) from one tertiary hospital and eight affiliated secondary hospitals in the region of Amsterdam, the Netherlands (June 2012 until January 2016, PPROMEXIL-III cohort). Exclusion criteria were signs of active labor before onset of PROM or fetal structural anomalies visible at ultrasound. We assessed perinatal mortality. Furthermore, outcomes were maternal, perinatal, neonatal and long-term child characteristics.

Results: We included 98 pregnancies with previable PROM. Twelve women (12.2%) opted for termination of pregnancy, resulting in 86 pregnancies included in further analyses. Median GA at PROM was 20^{+2} weeks (interquartile range (IQR) 17^{+6}-22^{+0}). Median GA at delivery was 22^{+6} weeks (IQR 20^{+1}-26^{+4}). Delivery within 1 week occurred in 38.4% of women and 60.4% delivered before 24 weeks GA (viability). Perinatal mortality occurred in 73.3% of pregnancies. 23/33 (69.7%) live-born neonates survived to discharge, representing 26.7% of total. None of the children died after discharge. Developmental data at two and/or five years of age was available for 13/23 children (i.e. all children born before 32 weeks of gestation), with 69.2% of children reporting a normal neurodevelopment. However, more than half of children reported respiratory problems.

Conclusion: In women with previable PROM perinatal mortality was 73.3%, with a normal neurodevelopment in 69.2% of surviving children with follow-up data. Due to broad inclusion criteria, this cohort represents a population more generalizable to daily practice as compared to previous studies.

Introduction

Previable prelabor rupture of membranes (previable PROM), defined as PROM before 24 weeks of gestation, affects < 1% of all pregnancies [1,2]. Previable PROM severely compromises survival, and current reported mortality rate is 60% [2,3]. If immediate delivery does not occur, previable PROM is associated with severe perinatal and neonatal morbidities, such as (extreme) preterm birth, chorioamnionitis, and pulmonary hypoplasia [1–3].

Abbreviations: Bayley-III, Bayley Scales of Infant Development-III; CCS, Cognitive Composite Score; CI, Confidence Interval; CRP, C-reactive protein; GA, Gestational age; IQ, Intelligence quotient; IQR, Interquartile rage; MCS, Motor Composite Score; NICU, neonatal intensive care unit; Previable PROM, Previable prelabor rupture of membranes; SD, standard deviation; TOP, termination of pregnancy; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

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Previous cohort studies reporting on perinatal outcome after previable PROM show great heterogeneity in included patient characteristics and descriptive assessments of outcomes, making it difficult to interpret numbers of survival [2–4]. For example, previously performed studies include women with gestational ages ranging from 14^{+0} to 28^{+0} weeks [1–3]. Furthermore, the definition of gestational age (GA) at viability varies per country (>22^{+0} or > 24^{+0} weeks' GA), causing differences in the number of neonates treated with active or comfort care.

Moreover, most studies investigating outcome following previable PROM solely include patients presenting in tertiary hospitals with maternal-fetal care units or exclude patients with a dismal prognosis (e.g. patients who deliver within 24 h after PROM, who present with an intra-uterine infection, or who opt for termination of pregnancy). These factors could potentially contribute to an overestimation of survival and increased latency time after previable PROM.

The aim of this study was to report maternal, perinatal, neonatal and child outcomes of all pregnancies with previable PROM, with minimal exclusion criteria. These results can be used by clinicians in daily clinical practice to inform women about the numbers and percentages of possible outcomes after previable PROM.

Material and Methods

We conducted a prospective cohort study (PPROMEXIL-III cohort), including women with previable PROM in hospitals surrounding Amsterdam, the Netherlands. Participating centers were one tertiary academic care center (Amsterdam UMC – location AMC) and eight affiliated secondary care hospitals. In the Netherlands, women with suspected previable PROM were referred by their midwife to secondary hospitals providing obstetric care. In case further obstetric management was needed, women were referred to a tertiary care hospital. Pregnancy was managed expectantly until 23^{+5} weeks GA, with fetal heartbeat assessment using a Doppler monitor on regular basis. Corticosteroids to accelerate lung maturation was indicated from 23^{+5} weeks of gestation and onwards. Based on fetal presentation and maternal complaints women were admitted to the hospital for observation. Ultrasound examination to assess fetal growth occurred every fortnight after 24^{+0} weeks of gestation. Suspected intra-uterine infection was treated with antibiotics.

The manuscript is reported following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [5].

Selection of participants

Women with a singleton pregnancy complicated by previable PROM between 13^{+0} and 23^{+6} weeks of gestation were included. Diagnosis was confirmed by treating physician, based on a positive history of continuous vaginal fluid loss combined with the presence of fluid originating from the cervical os and/or confirmed by a fern or amnion test, and documented in electronic medical records. In the Netherlands, viability is set at 24^{+0} weeks of gestation. We included women with previable PROM opting for termination of pregnancy, women with PROM following iatrogenic rupture of membranes (PROM following amniocentesis, multifetal pregnancy reduction, or secondary cerclage because of asymptomatic shortening of cervical length), women with an acute infection (maternal or fetal) following PROM, and/or intrauterine fetal demise following previable PROM.

Exclusion criteria were signs of active labor before or at onset of previable PROM or fetal structural anomalies visible at ultrasound examination.

Outcomes were maternal, perinatal, neonatal and long-term child outcomes. Perinatal mortality was defined as all fetal deaths (antepartum and peripartum death, irrespective of gestational age) and all neonatal deaths (death of children born $\geq$ 24 weeks of gestation). The core outcome set for studies evaluating interventions to prevent preterm birth was used as a guideline to define outcomes in this study [6].

Data collection

Between June 15, 2012 and January 13, 2016 the multicenter open-label randomized controlled PPROMEXIL-III trial was conducted in the Netherlands (NTR3492) [7]. For inclusion purposes, all women with previable PROM were prospectively registered. Methods and results of this trial are described elsewhere [7,8]. Our cohort study included all women with previable PROM during this time period in the Amsterdam region, irrespective of trial participation.

To ensure completeness of this cohort, we searched electronic ultrasound databases (Astraia [9] and Mosos [10]) of the Amsterdam UMC and eight affiliated hospitals, including all women with previable PROM.

Maternal, perinatal and neonatal data until discharge from the hospital were extracted from (local) electronic medical records. Chorioamnionitis was defined as; suspected (maternal temperature > 37.8 Celsius, leukocytosis, uterine tenderness, maternal or fetal tachycardia or malodorous amniotic fluid) or proven (histopathological proven). If children were assessed for long-term follow-up in standardized follow-up visits, results were also obtained from medical records. Children born after 32 weeks of gestation were not included in any follow-up program, children born between 30 and 32 weeks of gestation were seen by a pediatrician by age two. Children born before 30 weeks gestational age were included in the national follow-up program [11], consisting of a consultation with a pediatrician and extensive, validated neurodevelopmental testing using the Bayley Scales of Infant Development-III (Bayley-III) [12] at two years of age and/or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) [13] at five years of age. Respiratory problems were extracted from medical reports, defined as use of any respiratory medication or any hospital admissions for respiratory reasons. We did not contact parents for additional information.

Statistical analysis

We calculated the rate of each outcome measure for the total group of women, and for women who experienced perinatal mortality or survival to discharge separately, expressed as number with percentage, mean with SD or median with interquartile rage (IQR) when appropriate. Time specific probability estimates of survival to discharge were calculated using a Kaplan Meier approach. This approach was similar to analyses performed by Manuck et al. in 2009 [14]. Both gestational age at previable PROM and gestational age at delivery were grouped per two weeks. For every two week increment of gestational age at previable PROM, the probability of survival was calculated. For every subsequent two week time period only the women at risk were included, excluding women who (at that time point) already delivered their babies or who experienced fetal death, calculating the percentage of children who survived to discharge at that time period and the corresponding 95% Confidence Interval (CI). If there were no deaths or deliveries, the risk from the earlier time interval was carried forward, consistent with the Kaplan-Meier approach. All analyses were done using RStudio Version 1.2.1335 [15].

Ethical approval

The Medical Ethics Committee of the Amsterdam UMC deemed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study (W20_040) and official approval was therefore not required.

Results

Baseline characteristics

We included 98 women with a singleton pregnancy and previable PROM (Fig. 1). Twelve women opted for termination of pregnancy (12.2%). Forty-one women (47.7%) were nulliparous and 45 women (52.3%) multiparous. Mean maternal age was 31.2 years (SD 5.7 years). Previable PROM was iatrogenic in two women (2.4%). Other maternal demographics and baseline characteristics are listed in Appendix Table A1. During the period in which this study was executed, approximately 56.000 pregnancies were registered in the Amsterdam region [16], resulting in an incidence of previable PROM of approximately 0.2%.

Perinatal outcomes

Perinatal outcomes are shown in Table 1. Median gestational age at previable PROM was 20^{+2} weeks (interquartile range (IQR) 17^{+6}–22^{+0}). Median GA at delivery was 22^{+6} weeks (IQR 20^{+1}–26^{+4}). Median latency was 9.0 days (IQR 2.6–52.3). Women with perinatal mortality had a median latency of 5.0 days (IQR 2.0–12.5) and for neonates who survived to discharge a median latency of 67.0 days (IQR 53–80.0) was shown. Delivery occurred within 24 h in 6/86 women (7.0%, 95% CI 2.6–14.6), most women delivered after more than seven days of latency (53/86 women (61.6%, 95% CI 50.5–71.9)).

Anhydramnios at onset previable PROM was seen in 34/80 women (42.5%, 95% CI 31.5–54.1). In 24/80 women (30%, 95% CI 20.3–41.3) normal amniotic fluid levels were seen, and 22/80 women (27.5%, 95% CI 18.1–38.6) had oligohydramnios at onset of PROM. In women with anhydramnios 30/34 children (88.2%, 95% CI 72.6–96.7) died perinatal. In women with normal amniotic fluid this were 15/24 children (62.5%, 95% CI 40.6–81.2) and in women with oligohydramnios 12/22 children died (54.6%, 95% CI 32.2–75.6). Median C-reactive protein (CRP) at onset previable PROM was 12.8 mg/L (IQR 9.0–44.5) in women whose child died perinatal and 5.0 mg/L (IQR 2.8–7.3) in women whose child survived to discharge. Furthermore, in pregnancies with a CRP > 10 mg/L at onset previable PROM perinatal mortality was seen in 25/29 pregnancies (86.2%, 95% CI 68.3–96.1).

Twelve women (12.2%) opted for termination of pregnancy (TOP), with a median gestational age at previable PROM of 16^{+1} weeks (IQR 15^{+3}-16^{+6}) and gestational age at TOP of 17^{+6} weeks (IQR 16^{+6}-18^{+2}). Additional characteristics of women who opted for TOP are described in Appendix Table A2.

Table 2, Figs. 1 and 2 give an overview of perinatal mortality and survival to discharge. Perinatal mortality occurred in 63/86 fetuses (73.3%, 95% CI 62.6–82.2). Fifty-two women (60.5%, 95% CI 49.3–70.9) delivered before 24 weeks of gestation. Most fetuses died intra uterine (44/86 fetuses, 51.2%, 95% CI 40.1–62.1). 33 neonates were live born after 24 weeks of gestation, and 23 of these neonates (69.7% of live-born neonates (95% CI 51.3–84.4), 26.7% of total (95% CI 17.4–36.1)) were alive at the moment of discharge from the hospital.

Results of the Kaplan Meier analysis showing the probability of survival per two weeks of gestation are shown in Table 3. In all groups of gestational age at previable PROM, the probability of survival was lowest in the first three to four weeks after onset of previable PROM. Women with gestational age at delivery of > 26 weeks have a high probability of survival, with 20/24 children (83.3%) alive at the moment of discharge from the hospital to home. Characteristics of these women are shown in Appendix Table A3.

Maternal morbidity rates were low (see Table 1). Chorioamnionitis was suspected in 31/80 women (38.8%, 95% CI 28.1–50.3) and proven in 38/50 women (76.0% 95% CI 61.8–86.9). Three

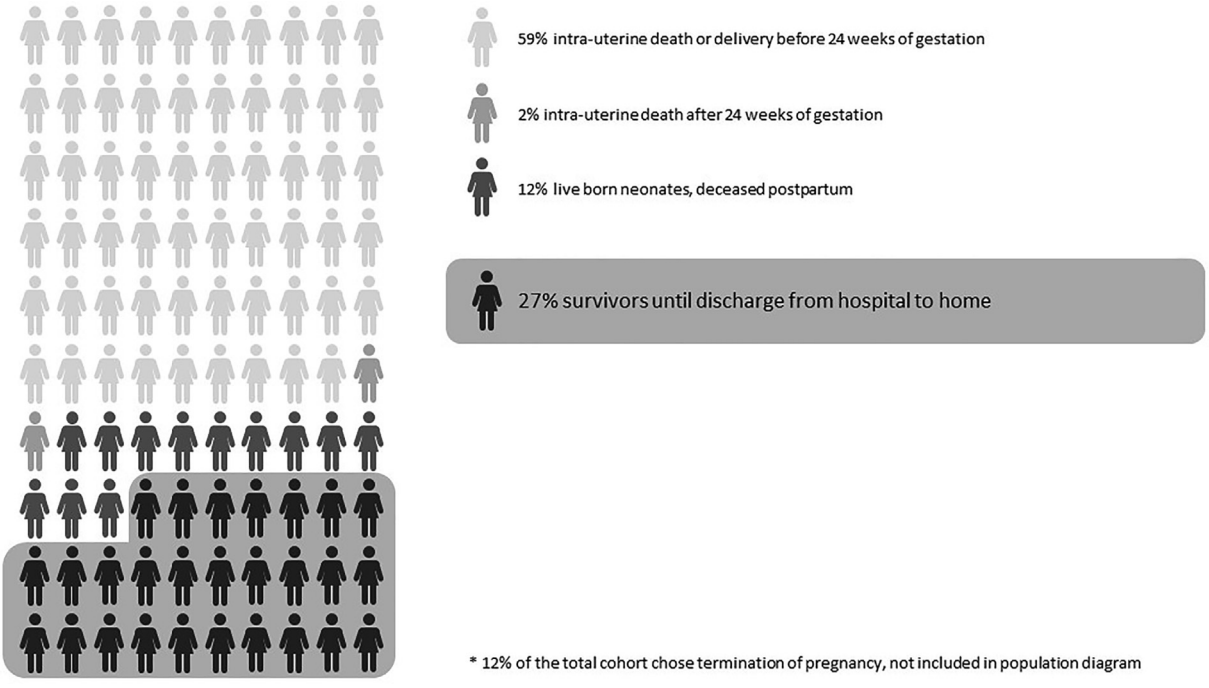

Fig. 1. Population diagram of outcomes after previable PROM.

Table 1
Perinatal outcomes.

Outcomes	N*	Number of women n(%) or median (IQR)		Number of foetus/children n (%) or median (IQR)
Gestational age at previable PROM median (IQR)	86	20^{+2} (17^{+6}-22^{+0})	† ○	19^{+5} (17^{+4}-21^{+5}) 21^{+1} (19^{+2}-22^{+6})
<16^{+0} weeks	86	4 (4.6)	† ○	4 (100) 0
16^{+0}–17^{+6} weeks	86	20 (23.3)	† ○	16 (80.0) 4 (20.0)
18^{+0}–19^{+6} weeks	86	16 (18.6)	† ○	13 (81.3) 3 (18.7)
20^{+0}–21^{+6} weeks	86	24 (27.9)	† ○	17 (70.8) 7 (29.2)
22^{+0}–23^{+6} weeks	86	22 (25.6)	† ○	13 (59.1) 9 (40.9)
Gestational age at delivery median (IQR)	86	22^{+6} (20^{+1}-26^{+4})	† ○	21^{+3} (19^{+2}–23^{+2}) 30^{+5} (27^{+4}–32^{+3})
<16^{+0} weeks	86	0	† ○	0 0
16^{+0}–17^{+6} weeks	86	9 (10.5)	† ○	9 (100) 0
18^{+0}–19^{+6} weeks	86	12 (14.0)	† ○	12 (100) 0
20^{+0}–21^{+6} weeks	86	18 (20.9)	† ○	18 (100) 0
22^{+0}–23^{+6} weeks	86	13 (15.1)	† ○	13 (100) 0
24^{+0}–25^{+6} weeks	86	10 (11.6)	† ○	7 (70.0) 3 (30.0)
26^{+0}–27^{+6} weeks	86	6 (7.0)	† ○	3 (50.0) 3 (50.0)
28^{+0}–29^{+6} weeks	86	5 (5.8)	† ○	0 5 (100)
>30^{+0} weeks	86	13 (15.1)	† ○	1 (7.7) 12 (92.3)
Latency (days) median (IQR)	86	9.0 (2.6–52.3)	† ○	5.0 (2.0–12.5) 67.0 (53.0–80.0)
Delivery < 1 day		6 (7.0)	† ○	6 (100) 0
Delivery 1–2 days		8 (9.3)	† ○	8 (100) 0
Delivery 2–7 days		19 (22.1)	† ○	19 (100) 0
Delivery 1–2 weeks		16 (18.6)	† ○	15 (93.8) 1 (6.2)
Delivery > 2 weeks		37 (43.0)	† ○	15 (40.5) 22 (59.5)
Amount of amniotic fluid at onset previable PROM				
Anhydramnios	80	34 (42.5)	† ○	30 (88.2) 4 (11.8)
Oligohydramnios	80	22 (27.5)	† ○	12 (54.5) 10 (45.5)
Normal	80	24 (30.0)	† ○	15 (62.5) 9 (27.5)
Aspect of amniotic fluid at any time	75			
Transparent		66 (88.0)	† ○	48 (72.7) 18 (27.3)
Meconium		9 (12.0)	† ○	5 (55.6) 4 (44.4)
Received amnioinfusion *(PPROMEXIL-III)*	86	5 (5.8)	† ○	4 (80.0) 1 (20.0)
CRP onset previable PROM (mg/L) Median (IQR)	60	9.5 (4.3–25.0)	† ○	12.8 (9.0–44.5) 5.0 (2.8–7.3)
>10 mg/L n (%)		29 (48.3)	† ○	25 (86.2) 4 (13.8)
CRP delivery (mg/L) Median (IQR)	52	18.1 (8.8–48.4)	† ○	26.0 (15.0–56.7) 9.0 (3.6–16.0)
>10 mg/L n (%)		36 (69.2)	† ○	29 (80.6) 7 (19.4)
Vaginal culture at onset PPROM				
None	53	37 (69.8)	† ○	20 (54.1) 17 (45.9)
GBS	52	7 (13.5)	† ○	6 (85.7) 1 (14.3)
Bacterial vaginosis	47	5 (10.6)	†	4 (80.0)

(*continued on next page*)

Table 1 (*continued*)

Outcomes	N*	Number of women n(%) or median (IQR)		Number of foetus/children n (%) or median (IQR)
			○	1 (20.0)
Other	46	5 (10.9)	†	4 (80.0)
			○	1 (20.0)
Chorioamnionitis				
Suspected	80	31 (38.8)	†	24 (77.4)
			○	7 (22.6)
Proven	50	38 (76.0)	†	32 (84.2)
			○	6 (15.8)
Corticosteroids	83	30 (36.1)	†	8 (26.7)
			○	22 (73.3)
Maternal sepsis	79	3 (3.8)	†	3 (100)
			○	0
Umbilical cord prolapse at any time	79	12 (15.2)	†	12 (100)
			○	0
Mode of delivery	85			
Vaginal		72 (84.7)	†	58 (80.6)
			○	14 (19.4)
Caesarean scheduled		4 (4.7)	†	0
			○	4 (100)
Caesarean emergency		9 (10.6)	†	5 (55.6)
			○	4 (44.4)
Placenta retention†	81	28 (34.6)		
Post-partum haemorrhage	80	12 (15.0)		

Abbreviations: CRP, c-reactive protein; IQR, interquartile range; previable PROM, previable prelabor rupture of membranes.
*N number of women/children with reporting of this outcome in electronic medical record; † number of children that died perinatal; ○ number of children that survived until discharge. Table 3 shows the rate of each outcome measure for the total group of included women. Per outcome the percentage (or IQR) of children who died perinatal (†) and the percentage (or IQR) of children who survived until discharge (○) are calculated. Example: in 20/86 (23.3%) women gestational age at previable PROM occurred between 16 and 18 weeks gestational age. Of this group in 16 cases perinatal mortality occurred (16/20 (80.0%)) and 4 children survived until discharge (4/20 (20.0%)).
‡ Suspected chorioamnionitis: clinical maternal temperature > 37.8 Celsius, leukocytosis, uterine tenderness, maternal or fetal tachycardia or malodorous amniotic fluid. Proven chorioamnionitis: histopathological proven.

Table 2
Perinatal mortality.

Outcomes	Total n(%) n = 86
Perinatal mortality	63 (73.3)
Survival to discharge	23 (26.7)
Perinatal mortality	
Fetal death	53 (61.6)
<24 weeks GA	51
o Intrauterine death	o 42
o Peripartum death	o 9
≥24 weeks GA	2
o Intrauterine death	o 2
Neonatal	10 (11.6)
o <24 h after birth*	o 4
o 1–7 days after birth	o 2
o >7 days after birth	o 4
Infant	0

Abbreviations: GA, gestational age.
*One neonate was born GA 24^{+4} weeks and did not receive active life support, this neonate died within 24 h after birth.

women were diagnosed with sepsis. Placenta retention requiring manual removal, was seen in 35%.

The main objective of our study was to be able to inform women with numbers and percentages generalizable to daily practice. We therefore provided apprehensible figures to use in daily practice (Figs. 1 and 2).

Neonatal outcomes

33 children were live-born at viable gestational age, and we could collect additional neonatal outcomes of 32 children. Nearly all live-born children were admitted to the neonatal intensive care unit (NICU) (30/32 children, 92.8%, 95% CI 79.2–99.2) with a median NICU duration of 13.5 days (IQR 4.3–39.5). One neonate (>24 weeks gestational age) did not receive active life support and was therefore not admitted at the NICU, the other neonate was born gestational age 37^{+0} weeks and admitted at the children's ward. 25/28 live-born children (89.3%, 95% CI 71.8–97.8) required respiratory support, with a median duration of 45.0 days (IQR 10.3–88.5). Pulmonary hypoplasia was diagnosed in 4/10 deceased children (40.0%, 95% CI 12.2–73.8). Other neonatal outcomes are reported in Table 4.

Childhood outcomes

Out of 23 children who survived to discharge, long-term follow-up data was available for 13 children (13/23 children, 56.5%), with a median gestational age at delivery of 28^{+2} weeks (IQR 26^{+5}-30^{+6}), see Table 5. The mean index score of the Bayley-III cognitive composite score was 102 points (SD 17.9) and the mean motor composite score was 94.2 points (SD 9.2). Five children were assessed with the WPPSI [13] at five years of age. The mean WPPSI Total IQ score was 102 points (SD 16.9). Based on the Bayley-III and/or WPPSI test or as reported in the medical electronic record by the treating pediatrician, 9/13 children (69.2%, 95% CI 38.6–90.9) had a normal neurodevelopment at age two and/or five. At two years of age 6/12 children (50%) and at 5 years of age 4/7 children (57.1%) were experiencing respiratory problems requiring respiratory medication.

Discussion

In this prospective cohort study, we included 98 women with a singleton pregnancy and previable PROM, of which twelve women (12.2%) terminated pregnancy. A total of 86 women with previable PROM were included in analysis, with a perinatal mortality of

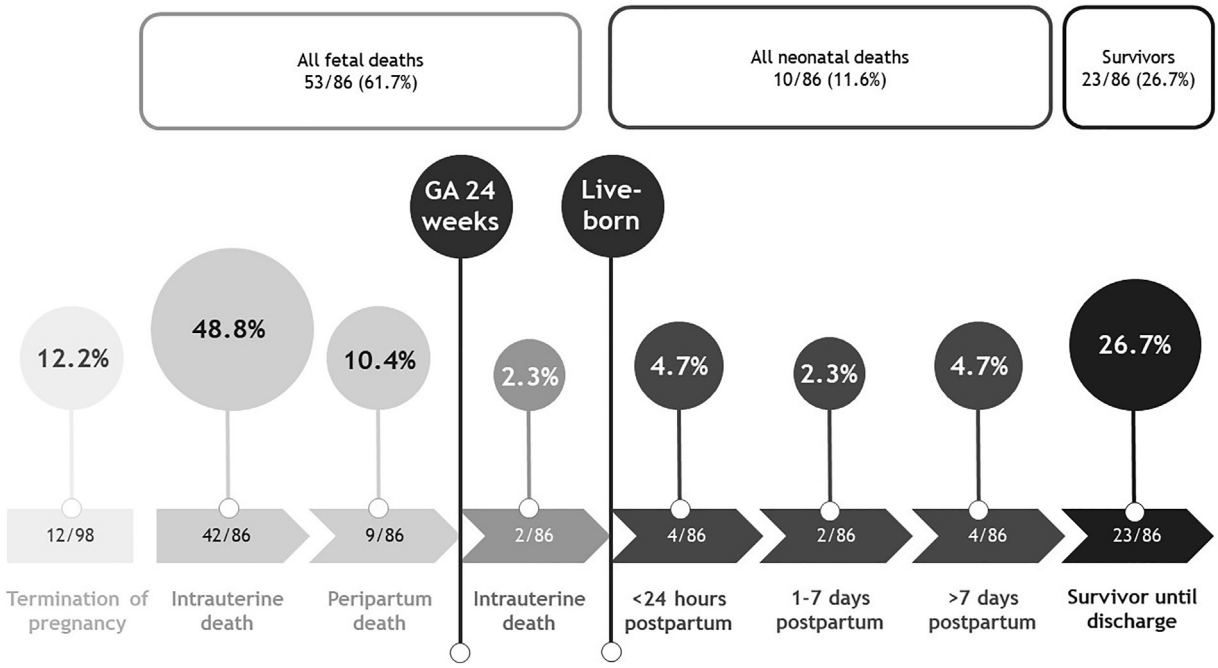

Fig. 2. Overview of perinatal mortality.

73.3%, and a survival at discharge from the hospital of 26.7%. Delivery before 24 weeks of gestation (viability) occurred in 60.5% of women. Survival rates increased with higher gestational age at previable PROM and longer latency period. Perinatal mortality was high in women with anhydramnios or with high CRP at onset previable PROM. Follow-up data was available for all surviving children born before 32 weeks of gestation (13/23 of surviving children), of which 69% had normal neurodevelopment at age two and/or five years. However, we did find a high percentage of children with any respiratory problems (50–57.1%). Results from this cohort study, summarized in our apprehensible figures and tables, should be used when counseling parents with this severe complication.

This study shows some important differences with recent studies. This Dutch cohort study shows that previable PROM occurs in 0.2% of pregnancies. This is slightly lower than the incidence of 0.33–1%, which has been frequently mentioned in previously performed cohort studies [2,3]. Furthermore, we found a survival rate of 26.7%, which is lower than the mean survival rate in a recent systematic review of 39.2% [3], range reported in literature: 25.9% to 83.3%. Possibly, this can be explained by the relatively low gestational age at PROM in our study (20^{+2} weeks GA). Comparable to other studies, perinatal mortality was highest in women with previable PROM < 20 weeks of gestation (82.5%) versus women $\geq$ 20 weeks of gestation (65.0%) and none of the fetuses born to women with previable PROM before 16 weeks of gestation survived to discharge. We included women who opted for termination of pregnancy in our cohort, since they represent nearly 12% of the total population of women with previable PROM. Outcomes such as median gestational age at previable PROM and/or at delivery did not change including or excluding women opting for TOP.

We found a high perinatal mortality in women with anhydramnios (88.2%). This is comparable to other studies investigating previable PROM and residual amniotic fluid [17–20]. A recent systematic review showed that pregnancies with reduced amniotic fluid had shorter mean latency intervals, increased risk of chorioamnionitis and higher neonatal death in the first days after birth [18]. However, even though perinatal mortality is high in women with anhydramnios, 12% of children born to these women survived to discharge.

Normal neurodevelopment at age two and/or five was seen in 69.2% of children assessed for follow-up, and almost half reported no respiratory problems. This is comparable to the long-term outcomes of the PPROMEXIL-III trial and to other preterm birth studies [8,21,22]. Due to retrospective data collection we have no additional information about the severity of the respiratory problems.

The main limitation of this cohort study is that not all outcomes could be collected for all women and children. This may be due to the heterogeneity of our cohort, including women from nine different hospitals and data collection from electronic medical records. In addition, some outcome measures were predominantly obtained in case of certain clinical indications (e.g. determining CRP at onset previable PROM in women with clinical signs of infection). However, due to the retrospective data collection, data unavailability could also be the reason of missing outcomes. This could have been prevented by using a prospective data collection model.

Another limitation of this study is that even though we have long-term follow-up data of all children born before 32 weeks of gestation, this was not available for children born at later gestational age (43%). We can presume that children born after 32 weeks' do not have major neurodevelopmental disabilities.

We included women with very limited exclusion criteria, mimicking the situation for caregivers and women in daily clinical practice. Our main goal was to present a survival rate that indicates a close reflection to common practice. With our findings, we will be able to provide numbers that can be used to inform women and their partners about possible outcomes after previable PROM, using a low biased sample of data. Most importantly, due to the national follow-up program in the Netherlands we could collect very valuable information on long-term development of surviving children born before 30 weeks of gestation, tested with internationally validated neurodevelopmental tests (Bayley-III and WPPSI test [12,13]).

Table 3
Probability of survival to discharge based on gestational age at previable PROM and gestational age at delivery. N = 86 pregnancies.

Gestational age at previable PROM		Number pregnancies with previable PROM (n = 86)	Gestational age at delivery								
			<16^{+0}	16^{+0}-17^{+6}	18^{+0}-19^{+6}	20^{+0}-21^{+6}	22^{+0}-23^{+6}	24^{+0}-25^{+6}	26^{+0}-27^{+6}	28^{+0}-29^{+6}	>30^{+0}
<16^{+0}	n = 4	**Probability of survival (%) (95% CI)**	0% (0–60)	0% (0–60)	0% (0–84)	0% (0–84)	0% (0–84)	0% (0–98)			
		Number of surviving children/Number of pregnancies	0/4	0/4	0/2	0/2	0/2	0/1			
		Number of births		2	0	0	1	1			
		Number of children who survived (n = 0)		0			0	0			
		Number of children who died (n = 4)		2			1	1			
16^{+0}-17^{+6}	n = 20	**Probability of survival (%) (95% CI)**		20% (6–44)	31% (9–61)	50% (16–84)	67% (22–96)	80% (28–99)	100% (40–100)	100% (16–100)	100% (16–100)
		Number of surviving children/Number of pregnancies		4/20	4/13	4/8	4/6	4/5	4/4	2/2	2/2
		Number of births		7	5	2	1	1	2	0	2
		Number of children who survived (n = 4)		0	0	0	0	0	2		2
		Number of children who died (n = 16)		7	5	2	1	1	0		0
18^{+0}-19^{+6}	n = 16	**Probability of survival (%) (95% CI)**			19% (4–46)	33% (7–71)	60% (15–95)	60% (15–95)	60% (15–95)	100% (29–100)	100% (3–100)
		Number of surviving children/Number of pregnancies			3/16	3/9	3/5	3/5	3/5	3/3	1/1
		Number of births			7	4	0	0	2	2	1
		Number of children who survived (n = 3)			0	0			0	2	1
		Number of children who died (n = 13)			7	4			2	0	0
20^{+0}-21^{+6}	n = 24	**Probability of survival (%) (95% CI)**				29% (13–51)	58% (28–85)	70% (35–93)	83% (36–100)	100% (40–100)	100% (29–100)
		Number of surviving children/Number of pregnancies				7/24	7/12	7/10	5/6	4/4	3/3
		Number of births				12	2	4	2	1	3
		Number of children who survived (n = 7)				0	0	2	1	1	3
		Number of children who died (n = 17)				12	2	2	1	0	0
22^{+0}-23^{+6}	n = 22	**Probability of survival (%) (95% CI)**					41% (21–64)	69% (39–91)	89% (52–100)	89% (52–100)	86% (42–100)
		Number of surviving children/Number of pregnancies					9/22	9/13	8/9	8/9	6/7
		Number of births					9	4	0	2	7
		Number of children who survived (n = 9)					0	1		2	6
		Number of children who died (n = 13)					9	3		0	1

Abbreviations: previable PROM, previable prelabor rupture of membranes; CI, confidence interval.
This table shows the chance of survival to discharge (95% confidence interval (CI)), depending on gestational age at previable PROM and gestational age at delivery. For example, when membranes rupture between 18^{+0}–19^{+6} weeks of pregnancy, and delivery does not occur immediately, the chance of survival to discharge is 33% (95% CI 7–71). When pregnancy continues to 22^{+0} weeks, the change of survival to discharge increases to 60% (95% CI 15–95), and subsequently to 100% (95% CI 29–100) chance of survival when pregnancy continues until 28^{+0} weeks of gestation.

Table 4
Neonatal outcomes.

Outcomes	N*	Number of liveborn n(%) or median (IQR)		Number of foetus/children n (%) or median (IQR)
Gestational age at delivery median (IQR)	33	28^{+2} (25^{+1}-31^{+5})	†	24^{+5} (24^{+4}-26^{+3})
			○	30^{+0} (27^{+2}-32^{+0})
Birthweight median (IQR)	32	1070 (743–1840)	†	740 (678–793)
			○	1450 (1020–1960)
<p5		6 (18.8)	†	1 (16.7)
			○	5 (83.3)
P5-P95		26 (81.3)	†	9 (34.6)
			○	17 (65.4)
>p95		0	†	0
			○	0
NICU admission n(%)	32	30 (93.8)	†	9 (30.0)
			○	21 (70.0)
Days median (IQR)	30	13.5 (4.3–39.5)	†	5.0 (0–14.0)
			○	21.0 (7.0–46.0)
Total length of hospitalisation (days) median (IQR)	25	40.0 (20.0–96.0)	†	13.0 (6.8–18.5)
			○	67.0 (31.5–102.0)
Respiratory support n(%)	28	25 (89.3)	†	6 (24.0)
			○	19 (76.0)
Days median (IQR)	22	45.0 (10.3–88.5)	†	12.0 (5.8–17.5)
			○	81.5 (13.0–98.8)
Pulmonary hypoplasia	32	4 (12.5)	†	4 (100)
			○	0
IRDS	32	12 (37.5)	†	5 (41.7)
			○	7 (58.3)
PPHN	32	8 (25.0)	†	4 (50.0)
			○	4 (50.0)
Pneumothorax	32	2 (6.3)	†	2 (100)
			○	0
Sepsis				
Suspected	28	14 (50.0)	†	4 (28.6)
			○	10 (71.4)
Proven	28	8 (28.6)	†	3 (37.5)
			○	5 (62.5)
Meningitis	28	1 (3.6)	†	0
			○	1 (100)
Intraventriculair haemorrhage	29	10 (34.5)	†	5 (50.0)
			○	5 (50.0)
Necrotising enterocolitis	29	7 (24.1)	†	3 (42.9)
			○	4 (57.1)
Circulatory insufficiency requiring inotropic support	30	14 (46.7)	†	8 (57.1)
			○	6 (42.9)
Persistent ductus arteriosus	29	8 (27.6)	†	4 (50.0)
			○	4 (50.0)
Anemia requiring erythrocyte transfusion	30	18 (60.0)	†	8 (44.4)
			○	10 (55.6)
Hyperbilirubinaemia in need of phototherapy	28	24 (85.7)	†	5 (20.8)
			○	19 (79.2)

Abbreviations: IQR, interquartile range; IRDS, idiopathic respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the newborn; NICU, neonatal intensive care unit.
*N number of women/children in which this outcome was reported in electronic medical record; † number of children that died perinatally; ○ number of children that survived until discharge. Pulmonary hypoplasia defined as: Lethal pulmonary hypoplasie, neonatal death within 24 h after birth caused by respiratory failure, unresponsive to postpartum ventilation, not attributable to other causes, or confirmed by autopsy.
Table A6 shows the rate of each outcome measure for the total group of included live-born neonates. Per outcome the percentage (or IQR) of children who died perinatal (†) and the percentage (or IQR) of children who survived until discharge (○) are calculated Example: 25/28 (89.3%) neonates required respiratory support, in 6 cases perinatal mortality occurred (6/25 (24.0%)) and 19 children survived until discharge from home to hospital (19/25(76.0%)).

Conclusion

This study finds that previable PROM occurs in 0.2% of pregnancies in the Netherlands. The termination of pregnancy rate in this population was 12.2%. Perinatal mortality rates in pregnancies complicated by previable PROM are high. Survival to discharge from the hospital is seen in 26.6% of pregnancies. Normal neurodevelopment at two and/or five years of age was seen in two third of survivors with follow-up data, however, more than half of these children reported respiratory problems at follow-up.

Results from this cohort study, summarized in the apprehensible figures and tables of this paper, could be used by clinicians when counseling patients and their partners regarding the incidence of previable PPROM, possible prognostic factors and (long-term) outcome. Performing larger studies by merging several previously performed cohort studies at individual patient data level might help to further establish risk factors and calculate prognosis models of women with previable PROM.

Presentations

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Key message

In a cohort of 86 singleton pregnancies with previable PROM perinatal mortality was 73.3%. Normal neurodevelopment was seen in 69.2% of surviving children with follow-up data.

Table 5
. Childhood outcomes (age two and five years)

	n(%) or mean (SD)
Survival up to discharge from hospital to home	23 children
Death after discharge (known)	0/13
Any childhood outcome	13/23 (56.5)
Children assessed with Bayley-III and/or WPPSI	9/23 (39.1)
Children assessed with Bayley-III and WPPSI	3/9 (33.3)
2 years of age	
GA at delivery median (IQR)	28^{+2} (26^{+5}-30^{+6})
Bayley-III Cognitive composite score	6 children
Mean (SD)	102 (17.9)
−1SD n(%)	1 (16.7)
−2SD n(%)	0
Bayley-III Motor composite score	6 children
Mean (SD)	94.2 (9.2)
−1SD n(%)	1 (16.7)
−2SD n(%)	0
Fine motor skills mean (SD)	11.0 (2.1)
Gross motor skills mean (SD)	6.7 (1.37)
Normal development at age two* n(%)	9/12 (75.0)
5 years of age	
GA at delivery median (IQR)	27^{+0} (25^{+5}-28^{+2})
WPPSI Total IQ	5 children
Mean (SD)	102 (16.9)
−1SD n(%)	1 (20.0)
−2SD n(%)	0
Normal development at age two and/or five* n(%)	9/13 (69.2)
Respiratory problems* n(%)	
Respiratory problems at 2 years of age†	6/12 (50.0)
Respiratory problems at 5 years of age†	4/7 (57.1)

Abbreviations: Bayley-III, Bayley Scales of Infant and Toddler Development – third edition Dutch version; IQ, intelligence quotient; SD, standard deviation; WPPSI, Wechsler Preschool and Primary Scale of Intelligence – third edition Dutch version. The Bayley-III reports two subscales: the Cognitive Composite Score (CCS) and the Motor Composite Score (MCS). The WPPSI test reports a Total intelligence quotient (IQ) score. Both tests use a mean of 100 points and standard deviation (SD) of 15 points.[12, 13] A score ≤ 85 points (≥−1 SD below the mean score) was considered as a mild neurodevelopmental delay, and ≤ 70 points (≥-2 SD) as a severe delay.

* Development reported in medical electronic record by treating paediatrician (total n = 8 children of which 6 children had normal developmental) or a cognitive or motor Bayley-III score above 85 (total n = 7 children of which 4 children scored above 85); †Respiratory problems defined as: use of any medication for respiratory morbidity or any hospital admissions for respiratory reasons.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Ben Willem Mol is supported by a NHMRC Practitioner Fellowship (GNT1082548). Dr. Ben Willem Mol reports consultancy for ObsEva, Merck Merck KGaA and Guerbet. The other authors do not report any potential conflicts of interest.

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Statement of Ethics

The Medical Ethics Committee of the Amsterdam UMC deemed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study (W20_040) and official approval was therefore not required.

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Author contributions

NS, AdR and LvdW participated in protocol development, data collection, data analysis, interpretation and writing. BK, AvWL, AvT, EvL, BM, JvtH and EP participated in protocol development, data analysis, data interpretation and writing. All collaborators saw and approved the final version. All collaborators were sent the paper as prepared for submission and given the opportunity to comment on the draft manuscript.

Appendix

Table A1
Baseline characteristics, showing results from the total group of women and women who experienced perinatal mortality or survival to discharge separately.

Outcomes	N*	Number of women n(%) or median (IQR)		Number of foetus/children n (%) or median (IQR)
Maternal age (years) mean (SD)	86	31.2 (5.7)	†	31.6 (5.6)
			○	30.0 (5.8)
BMI (kg/m2) median (IQR)	81	24.7 (22.0–30.4)	†	25.2 (22.3–32.4)
			○	23.0 (21.4–27.7)
Smoker	83	12 (14.5)	†	7 (58.3)
			○	5 (41.7)
Parity				
Nulliparous	86	41 (47.7)	†	33 (80.5)
			○	8 (19.5)
Multiparous	86	45 (52.3)	†	30 (66.7)
			○	15 (33.3)
History of preterm birth	45	13 (28.9)	†	7 (53.4)
			○	6 (46.6)
History of PPROM	44	6 (13.6)	†	5 (83.3)
			○	1 (16.7)
Cervix insufficiency	83	12 (14.5)	†	10 (83.3)
			○	2 (16.7)
Iatrogenic PPROM	84	2 (2.4)	†	2 (100)
			○	0
Uterus anomaly	86	2 (2.4)	†	1 (50.0)
			○	1 (50.0)
Male gestation	84	52 (61.9)	†	38 (73.1)
			○	14 (26.9)

Abbreviations: BMI, Body mass index; IQR, interquartile range; PPROM, prelabour preterm rupture of membranes; SD, standard diviation.
*number of women/children in which this outcome was reported in electronic medical record; † number of children that died perinatally; ○ number of children that survived until discharge. Table S1 shows the rate of each outcome measure for the total group of included women. Per outcome the percentage (or IQR) of children who died perinatal (†) and the percentage (or IQR) of children who survived until discharge (○) are calculated. Example: in 41/86 (47.7%) women had a nulliparous pregnancy, in 33 cases perinatal mortality occurred (33/41 (80.5%)) and 8 children survived until discharge (8/41 (19.5%)).

Table A2
Characteristics of women who opted for termination of pregnancy.

Outcomes	N*	Total n(%) n = 12
Maternal age mean (SD)	12	33.9 (5.8)
Gestational age at PPROM median (IQR)	12	16^{+1} (15^{+3}-16^{+6})
Gestation age at TOP median (IQR)	12	17^{+6} (16^{+6}-18^{+2})
Anhydramnios n(%)	12	10 (83.3)
Oligohydramnios n(%)		2 (16.7)
Normal amniotic fluid n(%)		0
Latency median (IQR)	12	11.5 (3.6–17.5)
CRP at onset PPROM	5	
Median (IQR)		11.0 (9.0–43.0)
>10 mg/L n(%)		3 (60)
Leukocyte count at onset PPROM n(%)	5	10.4 (3.6)
Chorioamnionitis		
Suspected n(%)	11	2 (18.2)
Proven n(%)	7	6 (66.7)
Iatrogenic PPROM n(%)	11	2 (18.2)

Abbreviations: CRP, c-reactive protein; IQR, interquartile range; PPROM, prelabour preterm rupture of membranes; SD, standard deviation.
*N number of women/children in which this outcome was reported in electronic medical record

Table A3
Characteristics of women with delivery ≥ 26 weeks of gestation.

Outcomes	N*	Total n(%) n = 24
Maternal age mean (SD)	24	31.5 (27.3–34.3)
Gestational age at PPROM median (IQR)	24	20^{+4} (19^{+3}-22^{+3})
Gestation age at delivery median (IQR)	24	30^{+3} (27^{+6}-32^{+2})
Anhydramnios n(%)	24	2 (8.3)
Oligohydramnios n(%)		10 (41.7)
Normal amniotic fluid n(%)		12 (50.0)
Latency median (IQR)	24	66.5 (55.3–79.5)
CRP at onset PPROM	21	
Median (IQR)		5.8 (2.9–8.0)
>10 mg/L n(%)		4 (19.0)
Chorioamnionitis		
Suspected n(%)	23	8 (34.8)
Proven n(%)	7	6 (85.7)
Survived to discharge	24	20 (83.3)

Abbreviations: CRP, c-reactive protein; IQR, interquartile range; PPROM, prelabour preterm rupture of membranes; SD, standard deviation.
*N number of women/children in which this outcome was reported in electronic medical record.

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