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Perinatal Outcomes of Pre-viable Preterm Premature Rupture of Membranes

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Abstract

Objective: To assess the maternal and neonatal outcomes after expectant management of pre-viable preterm premature rupture of membranes (PPROM).

Data Sources: We searched PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Scopus, and Web of Science databases for publications from 2008 to 2018 and ClinicalTrials.gov.

Methods of Study Selection: All studies that reported pregnancy outcomes of pre-viable PPROM were included. Excluded were the review articles, case reports, and studies that exclusively included patients with a particular characteristic (oligohydramnios/prolonged latency), those evaluating the effect of a specific intervention, or the ones providing aggregate data from which information for patients with PPROM <24 weeks could not be delineated.

Tabulation, Integration, and Results: Eighteen studies were reviewed that examined the outcomes of 1,372 pre-viable PPROM women following expectant management. Data was extracted in the form of predesigned tables. We used Microsoft Excel to integrate the results of included studies. The overall neonatal survival to discharge was 41.5%. Of these, 48.8% neonates survived without a major morbidity. Respiratory morbidity was the most common morbidity among surviving neonates: 49.5% neonates suffered from respiratory distress syndrome, 30% from bronchopulmonary dysplasia, and 10.7% from pulmonary hypoplasia. Chorioamnionitis was the most frequently observed maternal morbidity, complicating 49.3% pre-viable PPROM. The predictors for favorable outcomes included a later gestational age at PPROM and delivery, absence of oligohydramnios, and iatrogenic PPROM. Of note, 21.6% of pre-viable PPROM women opted for the termination of pregnancy.

Conclusion: The neonatal survival rate of pre-viable PPROM after expectant management is 4 of 10 affected neonates, and nearly half of them survive without any major morbidity. Maternal morbidity remains substantial, however, serious maternal complications are rare.

Keywords: Premature rupture,Prelabor rupture, PPROM, Fetal membranes rupture, Extremely premature, Midtrimester, Second trimester, Previable gestation, Before viability, Near viability, < 24wk, Pregnancy outcome.

Introduction

Premature rupture of membranes (PROM) prior to the limit of fetal viability i.e. before 24 weeks gestation is known as "pre-viable PPROM"[1]. The incidence of pre-viable PPROM is low i.e. 4 per 1000 pregnancies[2], but it is associated with a high rate of maternal and neonatal morbidity and poor neonatal survival.

Pulmonary hypoplasia is a major cause of mortality in pre-viable PPROM neonates. It is known that the canalicular phase of lung development, characterized by the terminal bronchioles development, occurs during 16-25 weeks of gestation[3]. Oligohydramnios during this critical period may result in pulmonary hypoplasia[4].

The management of pregnancies with pre-viable PPROM remains controversial. Typically, most women with pre-viable PPROM are presented the option of termination of pregnancy (TOP) given the poor neonatal survival and the potential high rate of maternal and neonatal morbidity. Recent publications have shown that the overall survival rates of the pre-viable PPROM neonates have improved due to recent advances in antenatal and neonatal intensive care[2]. This has shifted the trend towards expectant management. There are no clear guidelines that exist regarding the management of pre-viable PPROM. Of note, the American College of Obstetrics and Gynecology does recommend that

pre-viable PPROM patients should be counseled regarding the benefits and the risks of expectant management versus TOP. The patient should be provided with the most current data and then encouraged to make an individualized decision[5].

The purpose of this study was to outline the most up-to-date data on the pregnancy outcomes of pre-viable PPROM following expectant management. In addition, we also tried to describe the predictors for favorable pregnancy outcomes of pre-viable PPROM following expectant management and to determine the proportion of women opting for TOP instead of expectant management when both options were available. This document aims to serve as a guide for counseling of pre-viable PPROM patients and support them to make an individualized decision regarding their choice of expectant management or TOP.

Sources

Four databases were searched: PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Scopus, and Web of Science. With assistance of an experienced medical librarian, we designed a separate search strategy for each of these databases (Appendix 1). We collected the studies published in English language from January 2008 through March 2018. We also searched ClinicalTrials.gov for completed trials using the keywords "Preterm" and "Rupture." Furthermore, we hand-searched the reference lists of the included studies to find out the additional studies missed by the database search. We followed MOOSE guidelines to report our systematic review [6].

Study Selection

The identified studies were imported into bibliographic software (EndNote Web). After duplicates were deleted, we screened the titles and abstracts of the identified studies. The full text articles of the screened studies were retrieved using University of California Irvine library system and studies fulfilling the eligibility criteria were selected.

Studies reporting the maternal and neonatal outcomes of PPROM occurring before 24 weeks gestation published in past ten years were included. We excluded review articles and single case studies. We also excluded the studies that exclusively included women with a particular characteristic [e.g. oligohydramnios, prolonged latency (>5 days), or delivery at a particular gestation] or evaluated the effect of a particular intervention (antibiotics, corticosteroids, Amnioinfusion). Among the studies reporting pregnancy outcomes of mid-trimester PPROM (occurring at 14-28 weeks), we excluded those that provided the aggregate data, from which the subjects having PPROM at <24 weeks gestation could not be distinguished.

The selected studies were retrospective cohort studies. We assessed the quality of the selected studies by using Newcastle-Ottawa Quality Assessment Scale for Cohort Studies[7]. This scale assesses the studies in selection, comparability and outcome categories and awards a maximum of 9 stars. As our selected studies did not have any control group, they were not assessed for comparability. In selection category we excluded two items: "selection of non-exposed cohort" (there was no non-exposed group) and "demonstration the outcome was not present at start of study" (perinatal outcomes could not be present before PPROM). So, the maximum number of stars for our review was 5. All of our selected studies had >3 stars and therefore were included.

One author (F.M.) thoroughly read each of the included studies and collected data for the basic characteristics of these studies and primary and secondary outcomes using the predesigned tables. In addition, data was also collected for latency period, predictors for better pregnancy outcomes after expectant management, and the proportion of patients opting for TOP. A second author (A.B.H.) reviewed the collected data for its accuracy. Any disagreement between two authors was resolved by consensus. The study authors were contacted for missing data.

The primary outcome of our research was "neonatal survival to discharge". The secondary outcomes were neonatal and maternal morbidity. Neonatal Morbidity included pulmonary hypoplasia, bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), neonatal sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and limb contractures. Maternal Morbidity included chorioamnionitis, endometritis, maternal sepsis, cord prolapse, retained placenta, placental abruption, and caesarean delivery. Microsoft Excel was used to integrate the results of included studies. Results were presented in the form of tables and graphs.

Results

Total 1015 articles were identified (PubMed: 443, CINAHL: 200, Scopus: 165, Web of Science: 138, ClinicalTrials.gov: 47, Hand-search: 22). Of these, 38 were selected for full text article review. Finally, 18 articles [8-25] were included in the review. Figure 1 shows the whole process of study selection, using PRISMA flow diagram[26].

All of the included studies were conducted at tertiary care centers in 10 developed countries and reported the perinatal outcomes of 1,372 pre-viable PPROM women followingexpectant management. The summary of the basic characteristics of all of these studies is shown in Appendix 2. The range of GA at PPROM being studied varied across the studies (0-24, 14-24, 16-24, 18-24, 20-24, 13-20, 18-26, or 13-27 weeks). For two studies[15,25] that also included patients with higher gestations (18-26, or 13-27 weeks), data was extracted only for the subjects with PPROM at <24 weeks. In the reviewed studies, PPROM was diagnosed by a typical history of fluid leakage and speculum examination followed by ultrasound and PROM test. Except two studies where the option of TOP was not available, patients were allowed to choose between TOP and expectant management after counseling. Among women that underwent expectant membrane latency period varied across the studies (Appendix 3).

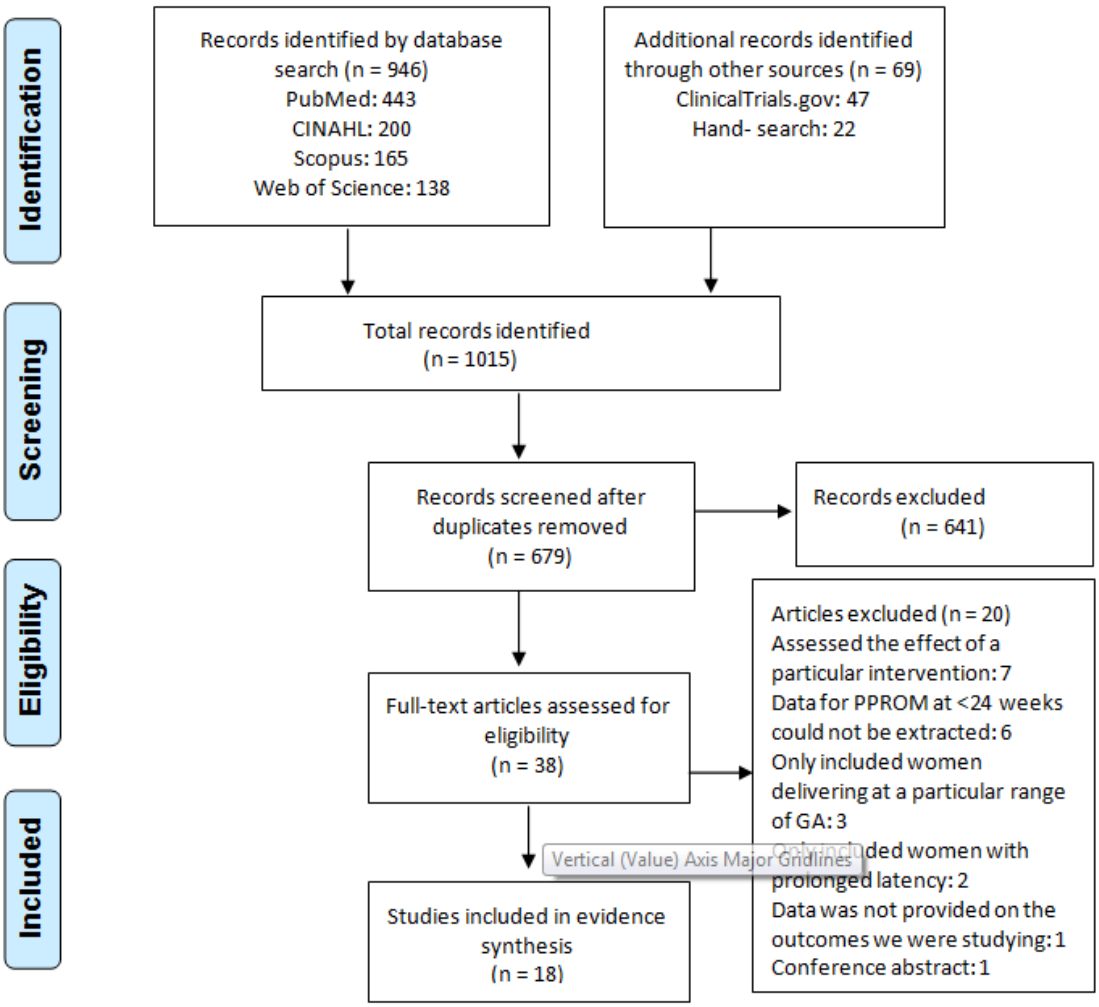

Figure 1: Flow diagram shows the stages of study selection process

Neonatal Survival to Discharge

Our reviewed articles studied 1,428pre-viable PPROM fetuses following expectant management. Among them, 923neonates were born alive. Some of these neonates died during their stay in NICU. The overall neonatal survival to discharge rate was 41.5 % (592/1428), with a range of 5-83% among studies (Table 1, Figure 2).

Most of the included studies showed that the survival to discharge rate improved significantly with increasing GA at PPROM[14,15,17-19,25]. van der Marel et al.[14] reportedthat the neonatal survival was significantly better for PPROM at >20 weeks than at <20 Weeks(46.9 vs. 22.7 %, p=0.008). This association remained significant after adjusting for potential confounders (adjusted OR: 9.78, 95% CI: 1.85-51.66). Similar association of improved survival with PPROM at >20 weeks was demonstrated by two other studies as well[18,19]. However, a recent study[8] demonstrated that there was no significant association between neonatal survival and GA at PPROM. This might be the result of type II error due to sample size of the study.

Four studies described oligohydramnios as a predictor of poor neonatal survival[17,18,20,24]. Storness-Bliss et al. reported that the survival rate was seven times lower inoligohydramnios group than non-oligohydramnios group (8.3% vs. 60 %, P=0.02). On contrary, Kibel et al. did not find any significant difference in survival between two groups. Two studies[17, 23] described a positive association of neonatal survival with iatrogenic PPROM and one[17] with CRP<1mg/dl on first admission.

Neonatal Morbidity

The most frequently observed neonatal morbidities were: RDS (49%, range: 26-100%) and BPD (30%, range: 14-48%). Sepsis, IVH, and joint contractures were also observed in a significant proportion of neonates (22.7%, 17.4%, and 17.5% respectively) (Table 2).

Overall, 49 percent (range: 27-64%) neonates survived without a major morbidity (Table 2, Figure 3). Wagner et al. demonstrated that GA at delivery was the only factor significantly associated with intact survival in a multivariable analysis (adjusted OR: 2.09, 95% CI: 1.20-3.63)(13). Two other studies also observed a similar association (16, 25). No other factor was demonstrated to contribute towards intact survival.

Among live born neonates, the rate of the pulmonary hypoplasia varied between 0-30 percent, with a mean of 10.7 (Appendix 4). The predictors of lower rate included later GA at PPROM (20, 25) and higher amniotic fluid index (AFI) levels (25).

Table 1: Neonatal Survival to Discharge of Pre-viable PPROMafter Expectant Management

Study (PPROM, week.)	n	Live born, n (%)	Survival to Discharge, n (%)
Kiver (<24)	70	44(62.8)	35(50)
Kibel (20-24)	104	66 (63.5)*	51 (49.0)
Linehan (14-23^{+6})	42	10 (23)	2(4.76)
McLaughlin (<24)	106	75(70.7)	39(37)
Wagner (<24)	69	40(58)*	38(55)
Wagner (<24) PPROM Twins Non-PPROM Twins	54 27 27	34(63) 17(63) 17(63)	31(57.4) 15(55) 16(59)
van der Marel(<24) <20 wk >20 wk	125 44 81	87(69.6) 24(54.5) 63(77.8)	48 (38.4) 10 (22.7) 38 (46.9)
Esteves (18-24) 18-20 20^{+1}-22 22^{+1}-24	30 16 10 14	22(73.3) 4(25.0) 5(50.0) 13(92.8)	11(36.7) 3(18.7) 2(20.0) 6(42.8)
van der Heyden(13-23^{+6}) 13-19^{+6} 20-23^{+6}	198 97 101	121(61.1) 50(51.5) 71(70.3)	67(33.8) 28 (28.9) 39 (38.6)
Verspyck (14-24)	83	46 (55.4)	38† (45.8)
Acaia (14-23^{+6})	85	49(57.6)	42† (49.4)
Hunter‡ (16^{+0}-24^{+0}) 16^{+0}-20^{+0} 20^{+1}-24^{+0}	106 24 82	57(53.8) 09(38) 48(58)	36(34) 04 (17) 32(39)
Margato (<24) 14-19 20-24	32 17 15	18(56.2) 07(41.2) 11(73.3)	11 (34.4) 03 (18) 08 (53)
Storness-Bliss (<24) AFI<1cm AFI≥1cm	22 12 10	22(100) 12(100) 10(100)	07(31.8) 01 (8.3) 06(60.0)
Deutsch (18-23^{+6})	108	98(90.7)	28 (25.9)
Zajicek (13-20)	6	5(83.3)	5(83.3)
Chauleur (14-23^{+6}) Spontaneous Iatrogenic	29 13 16	17(59) 06(46.1) 11(68.7)	14 (48) 03(23.1) 11(68.7)
Manuk (<24)	159	112(70.4)	89 (56)
Overall survival	1,428	923(64.6)	592(41.5)

*Does not include neonates delivered at <24 weeks and were alive, †Survival beyond neonatal period, ‡Data obtained only from singleton pregnancies

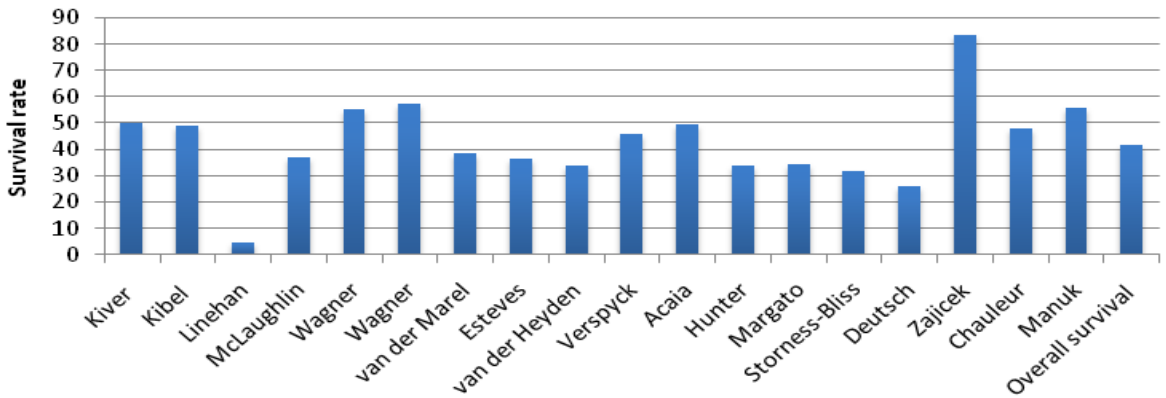

Figure 2: Neonatal survival of pre-viable PPROM following expectant management

Table 2: Neonatal Morbidity after Expectant Management of Pre-viable PPROM*

First Author	n	BPD	RDS	Sepsis	IVH	PVL	NEC	ROP	Contractures	Intact Survival
Kiver†	44	21(47.7)	44(100)	NA	10(22.7)	NA	NA	NA	NA	20(45)
Kibel‡	51	11(21.6)	NA	7(13.7)	NA	NA	3(5.9)	6§(11.8)	15(29.4)	27(53)
Linehan†	10	NA	7(70.0)	3(30.0)	3(30.0)	NA	2(20.0)	NA	NA	0(0)
McLaughlin‡	39	19(47)	NA	17(43.6)	0§(0.0)	0(0.0)	1(2.6)	2§(5.1)	NA	NA
Wagner†	40	13(32.5)	NA	NA	NA	1 (2.5)	3 (7.5)	7||(17.5)	NA	22 (55)
Wagner† **PPROM** **Non PPROM**	 17 17	 5(29.4) 0(0.0)	NA	NA	 1(5.9) 1(5.9)	 1(5.9) 0(0.0)	 6(35.5) 1(5.9)	 3(17.6) 3(17.6)	NA	 7(41.2) 12(71)
Marel† **<20 wk.** **>20 wk.**	68¶ 18¶ 50¶	(41.7) (38.9) (42.9)	(59.1) (66.7) (56.2)	NA	(7.3) (0.0) (10.0)	NA	(6.0) (0.0) (8.0)	(16.2) (0.0) (20.6)	(21.2) (58.8) (8.2)	NA
Esteves‡	11	NA	NA	NA	NA	NA	NA	NA	NA	3(27.3)
Heyden# **13-19**+6 **20-23**+6	69 28 41	10(14.5) 3(10.7) 7(17.1)	20(29.0) 3(10.7) 17(41.5)	5(7.2) 1(3.6) 4 (9.8)	8(11.6) 0(0.0) 8(19.5)	NA	2(2.9) 1(3.6) 1(2.4)	NA	NA	44(64) 24(86) 20(49)
Verspyck†	44¶	(48.3)	(72.7)	NA	(0.0)§	(0.0)	(9.7)	(0.0)§	(22.9)	NA
Acaia**	42	7(16.7)	11(26.2)	6 (14.2)	3 (7.1)	NA	6||(14.2)	3§ (7.1)	NA	23(55)
Margato††	32	NA	NA	7 (21.9)	3 (9.4)	NA	NA	NA	NA	NA
Deutsch†	45	12(26.7)	NA	31(68.9)	10(22.2)	NA	5 (11.1)	10(22.2)	NA	NA
Zajicek‡	5	NA	5 (100)	NA	NA	NA	NA	NA	2 (40.0)	NA
Chauleur†	17	4(23)	12(71)	NA	5(29)	NA	NA	NA	NA	9(52.9)
Manuk†	112	NA	NA	15(13.4)	47(42.0)	NA	12(10.7)	NA	8(7.1)	43(38)
Total	663	141/470 (30)	138/279 (49.5)	91/400 (22.7)	96/552 (17.4)	2/144 (1.4)	48/540 (8.9)	41/329 (12.5)	47/269 (17.5)	210/430 (48.8)

*All variables are no (%), † Among live born neonates; NA, Not available; ‡ Based on neonates survived to discharge; § ≥ stage III; || > Stage I; ¶ Different variables had different denominators as the data was not available for certain number of neonates; # Based on survivors beyond early neonatal period;** Among survivors beyond neonatal period; †† among total neonates following expectant management

Of the surviving neonates that were followed up during their childhood, 25% (range: 19-50%) suffered from some long-term morbidity (Appendix 5). The long-term sequelae included neurological impairment (most common), developmental problems, limb defects, chronic bronchitis, patent ductusarteriosus, pulmonary hypertension, and chronic lung disease.

Maternal Morbidity

Out of 802 pre-viable PPROM women being studied, almost half (49.3%) suffered from clinical chorioamnionitis. Cesarean delivery (34%), placental abruption (30%), and retained placenta (20%) were also frequently observed (Table 3). There was no significant predictor of maternal morbidity described in these studies. Oligohydramnios is generally thought to have an association withchorioamnionitis. Storness-Bliss et al. demonstrated that although the rate of chorioamnionitis was higher in women with oligohydramnios than those without oligohydramnios (70%vs.50%), the difference was not statistically significant (p=0.63).

Termination of Pregnancy

Overall, 21.6% (234/1083) of pre-viable PPROM women opted for TOP (Table 4). The decision to choose TOP was influenced by: GA at PPROM[12,14,18,25], AFI levels[12,17,23], and iatrogenic etiology of PPROM[18,23].

Table 3: Maternal Morbidity after Expectant Management of Pre-viable PPROM*

First Author	No of women	Chorioamnionitis		Endometritis	Sepsis	Cord prolapse	Retained placenta	Placental Abruption	Cesarean Delivery
		Clinical	Histological						
Kiver	53	NA	NA	NA	0	NA	NA	NA	27 (51)
Kibel	90	44 (49)	NA	NA	5 (5.5)	6 (6.7)	NA	18 (20)	37 (41.1)
Linehan	42	5 (12)	22 (52)	NA	1 (2.4)	NA	9 (21)	1 (2.4)	NA
McLaughlin	106	46 (43)	90 (85)	NA	NA	NA	NA	NA	38 (36)
Acaia	85	27 (32)	32 (38)	NA	8 (9.4)	NA	NA	4 (4.7)	28 (32.9)
Hunter† 16^{+0}-20^{+0} 20^{+1}-24^{+0}	106 24 82	58 (55) 13 (54) 45 (55)	77 (73) 15 (63) 62 (76)	NA	NA	10 (9) 1 (4) 9 (11)	NA	NA	21(20) 4 (17) 17 (21)
Margato	31	22 (71)	9 (29.0)	1 (3.2)	2 (6.5)	NA	NA	1 (3.2)	NA
Storness-Bliss AFI<1cm AFI≥1cm	22 12 10	13(59.1) 8 (70) 5 (50)	NA	1 (4.5) 1 (9) 0 (0)	0(0) 0 0	NA	4 (18.2) 2 (20) 2 (22)	11 (50.0) 5 (45) 6 (63)	NA
Deutsch	105	68(64.8)	NA	20(19)	1(0.9)	6(5.7)	NA	26(24.8)	23(21.9)
Zajicek	3	1 (33.3)	0 (0.0)	NA	NA	NA	NA	NA	2 (66.6)
Manuk	159	85(53.5)	NA	8 (5.0)	0 (0.0)	NA	NA	97 (61.0)	68 (42.8)
Total	802	369/749 (49.3)	230/373 (61.7)	30/317 (9.5)	17/587 (2.9)	22/301 (7.3)	13/64 (20.3)	158/534 (29.6)	244/707 (34.5)

*All variables are no (%); NA, not available; † Data obtained only from singleton pregnancies

Table 4: Pre-viable PPROM Women Opting for TOP

Reference	Total no of women	TOP no(%)
Kiver	73	20(27.4)
Kibel	115	11(9.6)
Wagner	101	32(31.7)
Wagner	29	02(6.9)
van der Marel <20 >20	160 74 86	39(24.4) 32(43.2) 07(8.1)
Verspyck	94	11(11.7)
Acaia	132	47(35.6)
Hunter	143	17(11.8)
Margato 14-19 20-24	36 20 16	05(13.9) 03(15.0) 02(12.5)
Storness-Bliss AFI<1cm AFI≥1cm	31 18 13	09(29.0) 06(33.3) 03(23.1)
Deutsch	133	28(21.0)
Chauleur Spontaneous Iatrogenic	38 22 16	13(34.2) 10(45.5) 03(18.7)
Total	1,085	234(21.6)

Discussion

Our review demonstrates that although 49% pre-viable PPROM women suffered from chorioamnionitis after expectant management, serious complications like sepsis occurred only in 2.9% and no maternal death was reported. Among these women, 41% took home a live baby. Neonates of 20% women survived without a major morbidity. Survival rate improved with increasing GA at PPROM and AFI levels. In light of these findings, women may be counseled regarding expectant management particularly when PPROM occurs after 20 weeks gestation and oligohydramnios is absent. Another important message is that neonatal survival has primarily improved due to advances in maternal and neonatal care, and therefore, all pre-viable PPROM patients should be managed at tertiary care facilities with higher level of NICU care.

The strength of our review is that whole of our data was exclusively collected for PPROM at <24 weeks gestation (age of fetal viability). Sixteen of the reviewed articles solely included women with PPROM at <24 weeks. Although we reviewed two studies that also included women with higher GA at PPROM, but from those we only extracted data for the subjects with PPROM at <24 weeks gestation. Therefore, our results are a true estimate of the maternal and neonatal outcomes after expectant management of pre-viable PPROM. Although some previous reviews tried to calculate pre-viable PPROM outcomes after expectant management, but at that time most of the available studies had focused on mid-trimester PPROM (at 14-28 weeks) instead of the pre-viable PPROM exclusively. Therefore, those reviews also included the studies evaluating PPROM outcomes at higher gestational age (for example: PPROM at <26, 22-25, 16-25+5, etc.) that clouded the results. Moreover, we also reported the proportion of pre-viable PPROM women who opted for TOP instead of expectant management when both options were available.

There are several limitations of our study. We did not include the studies published in non-English language. All of the included studies were retrospective in nature, so accuracy of their data was dependent on the accuracy of available records. These studies were conducted at tertiary care referral centers that may have led to pre-admission selection bias. In the selected studies several women underwent TOP and were excluded from data analysis. Most of these women had risk factors for poor neonatal survival. This may have resulted in overestimation of the survival rate after expectant management. Furthermore, there was great heterogeneity across the selected studies regarding: operational definitions of many study variables (pulmonary hypoplasia, survival without major morbidity, etc.); range of the GA at PPROM of the included patients; exclusion of twin pregnancies and iatrogenic PPROM; and expectant management protocols, which may have affected our results.

In conclusion, the neonatal survival rate after expectant management of pre-viable PPROM is poor, but not zero. Four of every 10 affected neonates do survive and half of them are without any major morbidity. Maternal morbidity remains high, but serious maternal complications are rare.

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Appendices

Appendix 1: Search Strategies

Date of last search: March 2018

Publication status: Published

PUBMED SEARCH STRATEGY

#1: Pregnancy outcomes OR pregnancy outcome OR outcomes OR outcome OR neonatal outcome OR neonatal outcomes OR maternal outcomes OR maternal outcome

#2: Preterm premature rupture of membranes OR Premature rupture of membranes OR Preterm prelabour rupture of membranes OR preterm prelabor rupture of membranes OR Preterm premature rupture of fetal membranes OR Premature rupture of fetal membranes OR Preterm prelabour rupture of fetal membranes OR preterm prelabor rupture of fetal membranes OR Preterm premature rupture of amniotic membranes OR Premature rupture of amniotic membranes OR Preterm prelabour rupture of amniotic membranes OR preterm prelabor rupture of amniotic membranes OR prelabour rupture of membranes OR prelabor rupture of membranes OR prelabour rupture of amniotic membranes OR prelabor rupture of amniotic membranes OR prelabour rupture of fetal membranes OR prelabor rupture of amniotic membranes OR PPROM

#3: Midtrimester OR midtrimesters OR mid-trimester OR second trimester OR second trimesters OR Pregnancy Trimester, Second OR pre-viable OR previable OR pre-viable gestation OR previable gestation OR before viability OR near viability OR before 24 weeks OR <24wk OR "24 weeks"

#1 AND #2 AND #3

Filters: Publication dates, last 10 years; Language, English

CINAHL Search strategy

(Premature Rupture* OR prelabor rupture* OR PPROM) AND (midtrimester* OR "mid trimester" OR "second trimester*" OR trimester* OR "previable Gestation" OR "before viability" OR "near viability" OR <24wk OR "24 weeks")

Limiters: Published Date, 2008-2018; Language, English

Scopus Search strategy

#1: ("Premature Rupture" OR "prelabor rupture" OR PPROM) AND ("Pregnancy outcome" OR "neonatal outcome" OR "maternal outcome")

#2: (midtrimester OR "mid trimester" OR "second trimester" OR "Pregnancy trimester" OR "second pregnancy trimester" OR "previable Gestation" OR "before viability" OR "near viability" OR "before 24 weeks" OR <24wk OR "24 weeks")

#1 AND #2

Limit to: Published Date, 2008-2018; Document Type, Article/review; Language, English

Web of Science Search strategy

(Premature Rupture* OR prelabor rupture* OR PPROM) ("Pregnancy outcome*" OR "neonatal outcome*" OR "maternal outcome*") AND (midtrimester* OR "mid trimester" OR "second trimester*" OR trimester* OR "previable Gestation" OR "before viability" OR "near viability" OR <24wk OR "24 weeks")

Refined by: Time-span, 2008-2018; Document type, article/review; Language, Englis

Appendix 2: Basic Characteristics of Included Studies

First Author, Publication year (PPROM, wk.)	Study period (Country)	Expectantly Managed Women (fetuses)	Iatrogenic PPROM	Multiple gestation	**Exclusion criteria**
Kiver, 2017 (<24)	2010-2016 (Germany)	53(70)	Nil	13+2*	Active labor, Iatrogenic PPROM, IUFD, Brisk vaginal bleeding
Kibel, 2016 (20-24)	2004-2014 (Canada)	90(104)	NA	14	Fetal anomaly, Fetal distress, Active labor, Chorioamnionitis, TOP, Placental abruption
Linehan, 2016 (14-23^{+6})	2007-2012 (Ireland)	42(42)	NA	Nil	Delivery within 24 hours of membranes rupture
McLaughlin, 2016 (<24)	2007-2011 (Australia)	106(106)	5	NA	Termination of pregnancy
Wagner, 2016 (<24)	2005-2015 (Germany)	69(69)	Nil	Nil	Fetal anomaly, Iatrogenic PPROM, Multiple gestation
Wagner, 2016 (<24)	2005-2015 (Germany)	27(54)	Nil	27	Fetal anomaly, Iatrogenic PPROM, Monochorionic Twins, Unclear chorionicity
van der Marel, 2016 (<24) <20 wk. >20 wk.	2002-2011 (Netherland)	121(125) 42(44) 79(81)	NA	25†‡	Fetal anomaly
Esteves, 2016 (18-26) 18-20 20^{+1}-22 22^{+1}-24	2005–2011 (Brazil)	61(61) 16(16) 10(10) 14(14)	NA	Nil	Multiple gestation, infection, Fetal anomaly, IUFD, TOP, Previous abortion attempts, active labor
van der Heyden, 2013 (13-27) 13-19^{+6} 20-23^{+6}	1994-2009 (Netherland)	305(336) 89(97) 96(101)	33	25+3* 08+0* 05+0*	Lethal Fetal anomaly, Active labor, Cervical insufficiency
Verspyck, 2013 (14-24)	2000-2010 (France)	83(83)	NA	Nil	Fetal anomaly, Multiple gestation
Acaia, 2013 (14-23^{+6})	2000-2009 (Italy)	85(85)	27†	Nil	Multiple gestation, Active labor, Severe PV Bleeding, Delivery within 24 hours, chorioamnionitis
Hunter, 2012 (16-24)	2001-2007 (Australia)	126(146)	NA	20	Preterm labor before PPROM Fetal anomaly, IUFD
Margato, 2012 (<24) 14-19 20-24	1996-2008 (Brazil)	31(32) 17(17) 14(15)	NA	1 0 1	NA
Storness-Bliss, 2012 (<24) AFI<1cm AFI≥1cm	2002-2011 (Canada)	22(22) 12 10	Nil	Nil	Fetal anomaly, chorioamnionitis, Iatrogenic PPROM, IUFD, Multiple gestation, Active labor, Delivery within 48 hours
Deutsch, 2010 (18-23^{+6})	2000-2007 (USA)	105(108)	NA	3	Fetal anomaly, chorioamnionitis, TOP, Active labor, Delivery within 12 hours
Zajicek, 2010 (13-20)	2003-2009 (Israel)	3(6)	1	All	Termination of pregnancy
Chauleur, 2009 (14-23^{+6}) Spontaneous Iatrogenic	1999-2004 (France)	25(29) 12(13) 13(16)	13	4	NA
Manuck, 2009 (<24)	2001-2007 (Canada)	159(159)	Nil	Nil	Fetal anomaly, IUFD, Iatrogenic PPROM, TOP, Multiple gestation, chorioamnionitis, Delivery within 12 hours

* Triplet pregnancies; NA, Not available; † Based on total pre-viable PPROM women, undergoing either expectant or active management; ‡ Among co-twins, the data was recorded only for the twin, whose gestational sac was ruptured

Appendix 3: Latency of Pre-viable PPROM Women after Expectant Management

Study	GA at PPROM (Weeks)	GA at Delivery (Weeks)	Latency period (Days)
Kiver*	19^{+6}(15-23^{+5})	22^{+4}(16^{+2}-34^{+0})	0-126
Kibel†	22.6±1.0	24.8±2.6	15.3±18.3
Linehan‡	18(15^{+5}-23^{+6})	20^{+5}(17^{+4} – 29^{+4})	13(1.1–85)
McLaughlin*	22^{+1}(13^{+1}-23^{+6})	24^{+2}(17^{+4}-38^{+4})	09(0-157)
Wagner§ Delivered <24wk. Delivered >24wk.	 20.0(18.0 – 21.7) 22.3(20.1 – 23)	 21.4(19.3 – 22.6) 27.7(25.3 – 30.9)	 04(1.0 – 9.0) 49.5(24.3-74.5)
Wagner§ Delivered <24wk. Delivered >24wk.	20.4(17.9-22.4) 20.1(18.7-22.0) 22.1(17.9-23.4)	NA 26.4(25.4-30.0) NA	19.0(3.0-43.0) 1.5(0.0-8.0) 35.0(21.0-73.0)
van der Marel* <20 wk. >20 wk.	20.3(12.4 – 23.9) 17.7(12.4 – 19.9) 22.5(20.0 – 23.9)	25.1 23.1(15.3 – 36.7) 25.3(21.0 – 35.9)	17.5 35(0 – 136) 12(0 – 103)
Esteves* 18-20 20^{+1}-22 22^{+1}-24	 NA	 21^{+6}(18^{+1}-30^{+0}) 22^{+6}(20^{+4}-30^{+7}) 25^{+5}(22^{+2}-28^{+6})	 19(1-77) 14(1-75) 16(1-44)
van der Heyden§ 13-19^{+6} 20-23^{+6}	 NA	 24.1±6.8 26.1±3.4	 NA
Verspyck||	20.3	26.5	NA
Hunter§¶ 16-20 20^{+1}-24	 19^{+2}(18^{+4}-19^{+6}) 22^{+4}(21^{+2}-23^{+3})	 21^{+5}(20^{+4}-27^{+1}) 23^{+5}(22^{+1}- 25^{+2})	 18(5-56) 7(2-14)
Margato‡ 14-19† 20-24†	19(14-23) 16.9±1.67 22.1±1.5	24(16-39) 22±6 27±5.5	35(0-137) 39±40 40±34
Storness-Bliss|| AFI<1cm AFI≥1cm	18.5 18 19	25 22.9 27.5	43 32 57
Deutsch||	NA	NA	(5.5-24.3)
Zajicek||	14	28.8	15.3
Chauleur* Spontaneous Iatrogenic	21(15-23^{+6}) 21+1(15-23^{+6}) 21(15-23^{+5})	NA 24(17-28^{+3}) 28(18^{+4}-39^{+1})	35(1-163) 23.5(1-94) 43(1-163)
Manuk†	20.7±2.6	25.6±4.3	NA

* Median (range); † Mean ± SD; ‡ mean (range); § median (IQR); NA, not available; || mean; ¶ Data was obtained only from singleton pregnancies

Appendix 4: Pulmonary Hypoplasia of Pre-Viable PPROM after Expectant Management

Reference	Live born neonates (n)	Pulmonary Hypoplasia n (%)
Kiver	44	13(30)
Linehan	10	1(10.0)
McLaughlin	75	6(8.0)
Wagner	40	2(5.0)
van der Heyden	121	11(9.1)
Verspyck	46	2(4.3)
Acaia	49	8(16.3)
Zajicek	05	0(0.0)
Manuk	112	14(12.5)
Total	534	57(10.7)

Appendix 5: Neonatal Long-term Morbidity after Expectant Management of Pre-Viable PPROM

Study	**Follow-up period (Months)**	**Fetuses (n)**	**Long -term Morbidity, n(%)**
Kibel	18–21	43	10 (23.3)
Linehan	48	02	01 (50)
Acaia	24	42	08(19)
Zajicek	18	05	02(40)
Chauleur	66	14	05(35.7)
Total	Range (18-66)	106	26(24.5)