

Expectant Management of Midtrimester Premature Rupture of Membranes: A Plea for Limits

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OBJECTIVE:

Our aim was to assess neonatal and maternal complications of the expectant management of pregnancies with preterm premature rupture of membranes (P-PROM) prior to 24 weeks of gestation and to delineate a patient consult strategy.

STUDY DESIGN:

We included all consecutive cases of early midtrimester P-PROM (16–24 weeks gestation). Information coded in our perinatal database was analyzed. Descriptive statistics, Student's *t*-test and Mann–Whitney test, and a logistic regression model were built accordingly.

RESULTS:

A total of 28 women presented with P-PROM at 16–24 weeks (mean 22.7 ± 1.0 weeks). Two patients declined conservative management and one was lost to follow-up (10.7%). In all, 25 (89.2%) were followed until the onset of labor or development of chorioamnionitis. Overall, 8/25 (32%) of the neonates survived. Pulmonary hypoplasia accounted for three deaths (3/25, 12%). Of 10 pregnancies with P-PROM before 22 weeks gestation, two (20%) neonates survived. The amount of amniotic fluid and gestational age at the time of diagnosis were crucial independent factors determining overall survival. Pulmonary hypoplasia (12%) and skeletal deformities (0%) were infrequent. The 21-day mean maternal antenatal hospital stay was further complicated by a high cesarean rate delivery (33.7%) and by postpartum infectious morbidity (32%).

CONCLUSION:

In cases of early midtrimester P-PROM (<24 weeks) expectantly managed, neonatal survival is positively associated with the amount of

amniotic fluid present and with the gestational age at the time of diagnosis. The mothers are at increased risk of prolonged antenatal hospitalization, cesarean delivery, preterm birth, and postpartum infection. In very early midtrimester P-PROM (<22 weeks), the maternal complication rate outweighs the poor neonatal outcome and expectant management should be reconsidered.

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INTRODUCTION

Premature rupture of membranes (P-PROM) occurring in the early second trimester (<24 weeks gestation) is associated with neonatal morbidity and mortality as well as significant maternal morbidity. Delivery at this time may result in a very low birth weight baby with an overall predicted survival rate ranging between 23 and 54%. Of the survivors, as many as 55% may be significantly neurologically and developmentally impaired on long-term follow-up.^{1,2} Conservative management leading to prolonged gestational age frequently provides the neonate with a greater chance of survival; however, this approach does not alleviate the lethal hazard of pulmonary hypoplasia. When expectant management is pursued, the incidence of maternal infection has been reported to be as high as 42%.¹

Despite these discouraging data, a consensus appears to have been formed in the last two decades regarding expectant management.^{1–3} A review of the English language literature^{2,7–15} revealed that studies diagnosed “midtrimester P-PROM” as late as 28–32 weeks of gestation and included only “eligible” patients. Our aim was to assess the neonatal survival and maternal complication rate in P-PROM cases prior to 24 weeks of gestation, at which time the remote chance of neonatal survival may be outweighed by the risk of maternal infection. Because of their religious beliefs, the ultraorthodox Jewish pregnant women delivering at our institution invariably refuse to terminate their pregnancies; using this population to test this management option allowed us to eliminate the selection bias.

Based on our critical review of the literature, we also formulated a patient consult strategy for cases of midtrimester P-PROM.

PATIENTS AND METHODS

This is a retrospective review of a case-cohort series using an in-house developed database. The study population consisted of

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consecutive patients with premature rupture of membranes occurring between 16 and 24 weeks gestation, who were managed at our institution from 1995 to 2001. Cases complicated by fetal malformation or chorioamnionitis at the time of diagnosis of P-PROM were excluded from the study. Premature rupture of membranes was diagnosed by visualization of amniotic fluid on speculum vaginal examination, positive nitrazine test, and amniotic fluid index (AFI) below the 5th centile for gestational age, and/or less than 5 cm.⁴ Our center principally serves a strictly religiously observant (Jewish Orthodox) population that will not consider terminating any pregnancy at any gestational age. Expectant management was implemented only after the couple had received a comprehensive detailed consultation from a specialist in perinatology, and in all cases requested to be observed unless maternal life hazard is to be expected. If contractions occurred before 34 weeks of gestation, tocolysis was attempted by administration of indomethacin for 48 hours in order to permit the fetus to benefit from antenatal steroid therapy. The patients received a combined antibiotic treatment of ampicillin and erythromycin from the time of admission until delivery (intravenously during the first week and orally thereafter). At 24 weeks of gestation, betamethasone (two doses of 12 mg i.m. at 24-hour intervals) was administered and repeated once if delivery was considered imminent between 28 and 34 weeks of gestation. Indication for delivery included: (a) suspected clinical acute chorioamnionitis; (b) non-reassuring fetal profile (≤ 4); (c) gestational age of ≥ 36 weeks. Unless obstetrically contraindicated, vaginal delivery was attempted. AFI was determined at admission and then twice weekly until delivery. The latency period was defined as the time interval between the rupture of membranes and delivery. Vaginal and urine bacterial cultures

were obtained at admission and then weekly until delivery. Placental cultures were obtained at delivery.

Neonatal pulmonary hypoplasia was diagnosed by radiologic and clinical criteria.⁵⁻⁷ The radiologic criteria included a small, bell-shaped chest with well-aerated lung fields and an elevated diaphragm up to the seventh rib. The clinical criteria consisted of a small chest circumference, severe pulmonary insufficiency necessitating high ventilatory settings and complicated by air leak or pulmonary hypertension. As a result of religious restrictions, the families refused postmortem examinations. Maternal and neonatal characteristics were obtained from our perinatal database and a database specifically designed for the patients included in the study.

Statistical analysis was performed by descriptive statistics, Student's *t*-test, Mann Whitney test, and a logistic regression model built for significant indicators of neonatal mortality and maternal infectious morbidity. Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 28 women presented with P-PROM between 16 and 24 weeks of gestation (mean 22.7+1.0). Two patients declined conservative management, and one was lost to follow-up (3/28, 10.7%). The overall perinatal survival was 8/25 (32%). The perinatal characteristics of the survivors and nonsurvivors are summarized in Table 1. Survivors differed significantly from the nonsurvivors with regard to the amniotic fluid index (AFI) at the time of admission, gestational age at delivery, and birth weight. Although not significantly different, a trend of differences between the groups was observed for the following factors: latency period, the use of antenatal steroids, and the occurrence of neonatal sepsis.

Table 1 Perinatal Characteristics of Neonatal Survivors Versus Nonsurvivors from Pregnancies Complicated by Early Midtrimester P-PROM

Characteristic	Survivors (N=8, 32%)	Nonsurvivors (N=17, 68%)	<i>p</i>
Maternal age (years) (median, range)	31.0 (19–43)	26.9 (23–38)	0.839
Parity (N [†] , median range)	4 (1–11)	3 (1–8)	0.257
GA at PROM (median, range)	22.4 (20–24)	22.1(18–24)	0.867
GA at delivery (median, range)	31.2 (22–36)	24.1(21–33)	0.005*
Days from PPRM to delivery (mean±SE [‡])	23.8±7.3	11.8±2.8	0.160
AFI at P-PROM (mean±SE)	4.6±5.3	1.5±4.3	0.000*
Birth weight (g) (mean±SE)	1449±218	906±116	0.051*
Antenatal steroids (N, %)	7 (87.5)	8 (47.1)	0.088
Tocolysis (N, %)	0	3 (17%)	0.515
Antibiotics (N, %)	8 (100)	14 (82.4)	0.527
Male gender (N, %)	5 (62.5)	7 (50)	0.675
Cesarean section (N, %)	4 (50)	3 (17.4)	0.156
Neonatal sepsis (N, %)	4 (50)	1 (7.7%)	0.047

*GA=gestational age (weeks).
[†]N=number of individuals included in the group.
[‡]SE=standard error of the mean.

In a multivariate logistic regression model (89.5% accuracy) applied to determine which of the variables independently affected mortality, we found that low AFI (significant oligohydramnios below the fifth percentile for gestational age) was the sole significant factor for this group. Pulmonary hypoplasia accounted for three deaths (3/28, 12%). The immediate complications of the group of survivors were as follows: five neonates (5/8, 63%) suffered from varying degrees of respiratory distress necessitating assisted ventilatory support, two (2/8, 25%) were diagnosed with intraventricular hemorrhage (IVH) graded III–IV, two (2/8, 25%) were diagnosed with retinopathy grade II and treated by laser therapy before discharge, one (1/8, 12.5%) had severe necrotizing enterocolitis (NEC) with bowel surgical intervention and five (5/8, 63%) had neonatal sepsis. Longer neonatal intensive care stay was significantly associated with the development of nosocomial infections ($p < 0.05$) and not with associated intrauterine infection. Antenatal and placental bacterial cultures showed no pathological growth.

The group of ten (40%) patients in whom the P-PROM occurred before 22 weeks of gestation was also analyzed separately. In this group, maternal characteristics were similar to those of the entire group. The mean gestational age at which P-PROM occurred was 19.0 ± 0.6 weeks. The mean latency period was 15.5 ± 4.3 days. There were two (20%) survivors; furthermore, at the time of P-PROM, the AFI for this group was also significantly different for the survivors than for the nonsurvivors ($p < 0.056$). Pulmonary hypoplasia accounted for one death in this group (10%). None of the neonates from this group had significant skeletal deformities.

We encountered no case of maternal mortality. All mothers were exposed to antibiotic treatment during the latent period between the diagnosis of P-PROM and delivery, and 8/25 (32%) had postpartum febrile morbidity related to the pelvic organs and thus required additional antibiotic therapy.

DISCUSSION

Early midtrimester P-PROM is an intriguing issue. An informed, educated management decision should consider both potential neonatal as well as maternal complications. The option of intentional delivery at the time of diagnosis should be weighed against the option of expectant management. Over the last two decades, 1059 pregnancies complicated by early midtrimester P-PROM and managed expectantly were reported (Table 2).^{2,6–16} The overall neonatal survival was 51.8% (549/1059). There were only rare occurrences of both pulmonary hypoplasia (11.2%) and skeletal deformities (7.2%). Each of these studies considered different primary outcomes for communicating the results: survival, pulmonary hypoplasia, or overall perinatal outcome. In all studies both neonatal mortality and/or lung hypoplasia were found to correlate positively with the degree of oligohydramnios

(defined by ultrasound), earlier gestational age on admission and delivery.^{6,13–15,17–19}

In the early 1990s, there were significant changes in the standards of perinatal care, including use of antenatal steroids in cases of P-PROM, use of antenatal prophylactic antibiotics, technical advances in neonatal respiratory support, and use of surfactant. In the light of these changes, we carried out a “re-analysis” of the literature (Table 3). Because the level of care had improved, we expected to observe a rise in the survival rate; in fact we observed a decrease in survival. However, the frequent use of ultrasound examination in determining gestational age and in defining oligohydramnios has led to stringent study inclusion criteria that may account for this trend. Also the clinical diagnosis of lung hypoplasia was strictly defined and not biased by inclusion of severe respiratory distress syndrome of prematurity, especially in neonates who had not received either antenatal steroids and/or postnatal surfactant. We believe that survival rates of 32% (our study) to 46% and a lung hypoplasia incidence of 10.4–12% would be a closer reflection of present-day standards. The mean gestational age at delivery was reported to be 27–28 weeks (as it was in our series), and had no independent influence on the neonatal outcome. Nevertheless, such an extremely early delivery represents an added burden to the neonate.

In the even more problematic group of very early midtrimester P-PROM (<24 weeks gestation) (“postamniocentesis drip” not included), only 153 cases were reported in the literature and the outcome was rarely reported separately. According to our study, the pregnancies complicated by P-PROM at less than 22 weeks gestation had a significantly higher neonatal mortality rate (80%), despite the 90% use of antibiotics and 40% use of antenatal steroid therapy. The survival in this group was positively influenced by the amount of amniotic fluid at diagnosis. Similar to our series, a study²⁰ on the neonatal short-term follow-up of the survivors of early P-PROM compared to control infants of matched gestational age also showed an increased risk for chronic lung disease (46% vs 17%, respectively), intracranial hemorrhage (31% vs 6%) and death (32% vs 8%). Generally, in the literature and in our series, the rate of skeletal deformities was low.

By the time the study was performed, there was minimal influence on the maternal outcome. The mean maternal antenatal hospitalization remained stable (20.9–17.8 days in our series) and the cesarean section rate also remained relatively high (28.4–33.7% in our series). The only decrease that was observed was in the postpartum febrile complication rate (47.3–26.9%, and 32% in our series), probably due to the more frequent use of antenatal antibiotics. In none of the series did we find any report of maternal mortality due to infectious morbidity.

During the two-decade survey period, we, along with the rest of the medical community, have witnessed a progressive decrease in the definition of neonatal “limit of viability”; over the same period, the survival rate has stabilized, but there has been a continuous rise in the neonatal morbidity.^{21–23}

Table 2 Summary of Studies on Midtrimester P-PROM in the English language Literature from 1985 to 2002

Authors	Study type	n/N cases analyzed (%)	Survivors N (%)	GA (weeks) at P-PROM (range, mean)	N ≤ 24 weeks	Latency (days, range, mean)	Steroids	Infection n/N (%)	CS n/N (%)	Lung hypoplasia n/N (%)	Skeletal deformities n/N (%)	Best predictor for survival/hypoplasia
Thibeault et al. (1985) ⁸	R*	76/76 (100)	45 (59.2)	<34 (30.6±1.8)	NA [§]	Complicated 30±17; no complications 18.4±14.5	Not used	NA	NA	20/76 (26.3)	21/76 (27.6)	Severe oligohydramnios for >5 days predictive for lung hypoplasia
Beydoun et al. (1986) ⁹	P [†]	70/70 (100)	36/70 (51.4)	20–27 (24.1)	23/70 (32.8)	2–124 (mean 19.1)	Not used	41/70 (58.6)	12/70 (17.1)	4/70 (5.7)	None	Gestational age at P-PROM influenced survival
Blott et al. (1988) ¹⁰	P	30/30 (100)	19/30 (63.3)	15–28 (21.3)	NA	14–133	Not used	2/30 (6.6)	6/30 (20.0)	8/30 (26.6)	1/30 (3.3)	Gestational age <26 weeks at P-PROM influenced survival
Rotschild et al. (1989) ⁷	R	88/88 (100)	70/88 (79.5)	15–29	NA	7–126	NA	43/88 (48.8)	NA	14/88 (16)	NA	Pulmonary hypoplasia was affected by GA at P-PROM and not by latency and Toligo-hydramnios severity Skeletal deformities correlated with latency and oligohydramnios severity
Bengston et al. (1989) ¹¹	R	63/59 (96.8)	31 (50.8)	15–26 (23.2)	9/59 (15.2)	0.5–161 (mean 21.5)	30/59 (50.8)	27/59 (45.8)	21/59 (35.5)	3/59 (5)	NA	Mortality correlated with GA at P-PROM and GA at delivery
Major and Kitymiller, (1990) ¹²	R	70/70 (100)	44 (63)	19–25 (23.7)	6/70 (8.5)	1–60 (mean 12)	34/70 (48)	30/70 (43)	17/70 (24.2)	1/70 (1.4)	None	Perinatal survival was dependent on the GA at P-PROM
Morales and Talley, (1992) ²	P	97/138 (0.2)	39/97 (40)	22 median	NA	0.5–126 (median 10.5)	21/97 (21.6)	28/97 (28.8)	5/20 (25.0)	24/97 (23)	NA	If P-PROM <22 weeks, survival drops to 10% from 40% overall
Hadi et al. (1994) ¹³	P	178/178 (100)	98/178 (55.0)	20–25 (median 22.3)	109 /178 (61.2)	1–94	NA	47/178 (26.4)	5/178 (2.8)	2/178 (1.1)	None	Perinatal outcome correlated with AFI at admission and GA at delivery. On admission 107(60.1%) had adequate AFI
Vergani et al. (1994) ⁶	P	54/63 (85.7)	24 (44.4)	15–28.6 (24.6)	NA	0.5–112 (16.9 +25.6)	Week-ly	16/63 (25.3)	33/53 (61)	12/25 (48)	None	AFI <2 and GA at P-PROM correlated with pulmonary hypoplasia
Kilbride et al. (1996) ¹⁴	P	108/120 (90)	68 (62.9)	<29 25.3 +2.1 survivors/22.7+3.3 nonsurvivors	NA	10.3±19.3 survivors/28.2+20.9 nonsurvivors	Not used	NA	40 (37)	7(6.4): 4(7) surv. 3(19) non-survivors	18(18.8): 14(25.5) survivors; 4(25) nonsurvivors	Latency >14 days duration and gestational age at P-PROM of <25 weeks only in cases of severe oligohydramnios (1 cm vertical pocket) affected neonatal mortality
Winn et al. (2000) ¹⁵	P	163/163 (100)	75 (46)	15–28	NA	29.0+22.7 no hypoplasia 8.5+12.9	NA	NA	38% without hypoplasia 48% with hypoplasia	21/163 (12.8)	NA	GA at P-PROM(15-22 weeks), latency period and initial and average AFI—risk for hypoplasia, perinatal mortality

*R=Retrospective.

†P=Prospective

§NA=Not Applicable

Table 3 Midtrimester P-PROM — Reviewed by Study Period

Study period	No of cases	<i>N</i> <24 weeks	Survival <i>N</i> (%)	GA at P-PROM (weeks, mean)	Latency (days, mean)	Cesarean section <i>N</i> (%)	Infection <i>N</i> (%)	Lung Hypoplasia <i>N</i> (%)
1985–1989	397	44	245 (61.7)	24.6	22.05	75/229 (32.8)	150/317 (47.3)	50/229 (21.8)
1990–2002	662	109	304 (45.95)	22.8	19.65	159/662 (24)	91/338 (26.9)	69/662 (10.4)

Pending a prospective, randomized, multicenter study of management options, we suggest that the long-term maternal hospitalization, antibiotic treatment before and after delivery, high rate of cesarean delivery rate, and the burden of neonatal morbidity should be presented to the pregnant patient facing the decision of electing expectant management when diagnosed with P-PROM before 24 weeks of gestation. Special consideration and different emphasis should be given to patients with pregnancies complicated by P-PROM at less than 22 weeks gestation. In this subgroup, the potential maternal complications may outweigh the chances of neonatal survival, and termination of pregnancy should be considered a balanced alternative to conservative management.

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