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Factors associated with previable delivery following second trimester rupture of membranes

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Abstract

Objective: To identify factors associated with previable delivery in second trimester preterm rupture of membranes (PROM).

Methods: We conducted a single-center retrospective cohort study of women with pregnancies complicated by second trimester PROM (14.0-21.9 weeks gestation) from 2000-2015, who elected expectant pregnancy management and achieved at least 24 hours latency. Maternal characteristics and clinical factors were compared among pregnancies that reached viability (≥23.0 weeks) and pregnancies delivered before viability (<23.0 weeks), using appropriate statistical methods.

Results: Of 73 pregnancies complicated by second trimester PROM, 49 (67%) delivered before viability. Maternal race, history of preterm birth, and tobacco use were similar between women who delivered <23 weeks versus ≥23 weeks. Gestational age at PROM, cervical dilation >1cm, Group B streptococcus carrier status, bacterial vaginosis, and chlamydial infection during pregnancy were similar between groups. Median time to delivery was significantly shorter in women who delivered <23 weeks compared to those who reached ≥23 weeks (6 vs 46 days, $p<0.01$).

Conclusions: Previable delivery occurred in the majority of women with second trimester PROM. No maternal or clinical factors were associated with delivery prior to viability. Counseling women with second trimester PROM should include the inability to determine which pregnancies will reach viability.

Précis:

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There are no maternal or clinical factors associated with previable delivery in women with second trimester rupture of membranes.

Keywords

midtrimester; rupture of membranes; viability

Introduction

Preterm rupture of membranes (PROM), defined as rupture of membranes at less than 37 weeks' gestation, occurs in 3% of pregnancies.[1] Approximately 0.4% of pregnancies are complicated by PROM before 24 weeks' gestation, or second trimester PROM.[2] Gestational age at time of PROM is a significant predictor of perinatal outcome. Second trimester PROM often has devastating consequences, including fetal demise, complications of extreme prematurity, and maternal complications.[2-4] The neonatal prognosis for second trimester PROM is poor. With expectant management of PROM occurring between 14-24 weeks the reported neonatal survival rate to discharge is only 26.3%.[5] The range of neonatal survival in cases of PROM occurring before 20 weeks gestation has been reported as 0-33%, with the range of survival for PROM occurring between 20-23 weeks gestation reported as 8-50%.[6]

The broad range of possible outcomes, as well as the overall poor prognosis, for second trimester PROM presents a challenge for patient counseling and management decision making. One study of 143 pregnancies affected by second trimester PROM found that the most important factors influencing neonatal survival to discharge were gestational age at time of PROM and duration of latency.[7] There is currently evidence in the literature concerning factors associated with latency period for PROM occurring after viability (>24 weeks). In PROM occurring between 24-34 weeks gestation, length of latency is inversely associated with gestational age at time of rupture and a short latency period (defined as <48 hours) is associated with higher degree of cervical dilatation at admission, nulliparity, evidence of fetal growth restriction, and oligohydramnios.[8,9] Other factors that have been associated with shorter latency following PROM after 24 weeks include twin gestation, as compared to singleton gestation, as well as a clinical diagnosis of chorioamnionitis.[10] There is a paucity of data, however, regarding whether these clinical factors are also associated with latency following second trimester PROM. We sought to identify clinical factors that may be associated with delivery prior to viability following second trimester PROM, in the hope of being able to predict at time of presentation whether a patient may be able to achieve a long enough latency period to deliver beyond viability.

Materials and Methods

We conducted a retrospective cohort study at a single institution from June 2000 until June 2015. We identified women with prelabor rupture of membranes between 14 weeks 0 days and 21 weeks 6 days by searching the University of North Carolina Women's Hospital delivery log and by querying the billing records using codes of premature rupture of membranes, previable preterm premature rupture of membranes, and spontaneous abortion

from the 9th Edition of International Classification of Diseases codes (635, 634, & 637). To identify eligible pregnancies we then reviewed electronic medical records of patients identified from either source. REDCap electronic data capture was used to house study data, and a second researcher independently verified the data that was collected. This study was approved by the University of North Carolina's Institutional Review Board.

Women with a singleton or twin pregnancy complicated by second trimester PROM were included if rupture of membranes occurred between 14 weeks 0 days and 21 weeks 6 days and they achieved at least 24 hours latency. PROM had to be established via documentation in the medical record of history, vaginal pooling of fluid with positive fern testing or positive nitrazine testing, or low amniotic fluid volume by ultrasound. Women were excluded from this analysis if there was clinical evidence of chorioamnionitis on presentation, if labor occurred within 24 hours of rupture, if the pregnancy was complicated by a major fetal anomaly, or if PROM occurred within 2 weeks of chorionic villus sampling/amniocentesis. Women who elected immediate delivery at the time of PROM diagnosis were also excluded from this analysis.

We defined delivery after fetal viability as delivery after 23 weeks 0 days. Latency was defined as the duration in days from PROM until delivery. Leukocytosis was defined as a white blood cell count at or above the 75th percentile for the cohort, which was >14 $x10^3/mm^3$. Infectious placental pathology was defined as the presence of acute chorioamnionitis, acute funisitis, or both on placental pathology report. At our institution, no standard practice exists for management of women with previable PROM, thus management, specifically admission, administration of antibiotics (and which regimens), was at the discretion of the provider. Oligohydramnios was defined as amniotic fluid index of <5cm.

Maternal demographics, pregnancy characteristics, and other clinical factors were compared among women who reached fetal viability (23 weeks and greater) and those delivering before viability, using chi-square, Fisher's exact, or t-test, as appropriate. A sub-analysis of twin pregnancies was conducted given the elevated risk for PROM in multiple gestations. Finally, secondary analysis was performed comparing women with latency > 14 days to those with latency < 14 days. Analyses were performed using Stata (version 14.0; Stata Corporation, College Station, TX). Statistical significance was defined as $p<0.05$.

Results

From 2000-2015 at our institution there were 263 cases of PROM between 14 weeks 0 days and 21 weeks 6 days. Of 263, 89 (33.8%) did not meet inclusion criteria; 69 (26.2%) opted for immediate delivery, and 32 (12.2%) were expectantly managed but delivered within 24 hours of PROM. Of the 73 pregnancies included in this analysis (Figure 1), 50 were singleton and 23 were twin gestations. Overall, 49 (67%) of 73 women delivered before 23 weeks' gestation. In women delivered <23 weeks, the median gestational age at rupture was 19.1 (IQR 17.6, 20.6) and at delivery was 20.4 weeks (IQR 19.1, 21.6) and in those delivered ≥23 weeks, the median gestational age at rupture was similar 19.5 (IQR 18.7, 20.9), but that at delivery was later, 25.9 weeks (IQR 23.6, 27.4).

Demographic characteristics, including age, race, and insurance status, were similar between groups (Table 1). No significant differences in medical or obstetrical history were identified between groups (Table 2). The median gestational age at time of PROM was similar between women who delivered before 23 weeks and those who delivered at 23 weeks or later [19.1 weeks (IQR 17.6, 20.6) versus 19.5 weeks (IQR 18.7, 20.9), p=0.27]. Infectious characteristics, including group B streptococcus carrier status, bacterial vaginosis during pregnancy, and chlamydia infection during pregnancy, were also similar between groups (Table 2). Multiple gestation itself was not associated with a decreased likelihood of reaching viability. However, in a sub-analysis including only multiple gestations (n=23), women were more likely to deliver after viability if WBC count was lower at the time of PROM (median WBC 11.4 (IQR 10.4, 12.3). vs 13.9 (IQR 12.7, 15.6) (p=0.02)). There were no other clinical factors associated with reaching viability in this subgroup.

Placental pathology was available for 46 of 73 pregnancies, including 18 (75%) of 24 pregnancies that delivered 23 weeks or greater and 28 (57%) of 49 women who delivered prior to 23 weeks. As shown in Table 3, compared to women who delivered at 23 weeks or greater, those who delivered prior to 23 weeks were more likely to have infection on placental pathology, (82% vs. 50%, p=0.05), and less likely to have their placental pathology reported as “normal”, (0 vs, 22%, p=0.02).

For the entire study population, the median latency period was 14 days (IQR 3, 32). Compared to women who delivered at or beyond 23 weeks’ gestation, those who delivered prior to 23 weeks’ gestation had a shorter median latency, [6 days (IQR 3, 14) v 46 days (IQR 31, 64), p<0.001]. Given this difference, we performed a post-hoc secondary analysis assessing for factors associated with latency greater than median (14 or more days). Compared to women with latency < 14 days, those with latency of 14 days or longer had a lower median white blood cell count on admission, 10.5 $x10^3/mm^3$ vs 13.6 $x10^3/mm^3$ p=0.03. Though infectious placental pathology was less common in these women, this did not reach statistical significance (59% vs 84%, p=0.11).

Discussion

In this study, two out of three women whose pregnancies were complicated by second trimester PROM (<22 weeks gestation) delivered prior to viability (defined as 23 weeks). Women who delivered prior to viability had a significantly shorter latency period, than women who delivered after viability. However, none of the maternal demographic characteristics or specific antenatal factors examined were associated with delivery prior to viability. However, women who delivered prior to 23 weeks were more likely than those who delivered after 23 weeks to have infectious placental pathology. When looking only at latency, we found that women with latency at or above the median have lower white blood cells counts at the time of membrane rupture. Lower white blood cell count at the time of membrane rupture was also associated with reaching viability among women with twin gestations and second trimester PROM. However leukocytosis was not associated with delivery prior to viability in the cohort as a whole.

One of the first questions a patient will ask when diagnosed with second trimester PROM is ‘what is the chance of delivering a baby that could survive.’ There is currently little data in the literature to inform counseling women on the likelihood of reaching viability, and what if any clinical factors are associated with previable delivery. Hunter et al studied 143 women with PROM occurring at <24 weeks’ gestation and found that neonatal survival was associated with increasing gestational age at time of rupture and length of latency.[7] Kibel et al noted that rupture latency at greater than 7 days were associated with reaching viability.[11] These findings are consistent with our results that women who reached viability had significantly longer latency periods; however, in our study, gestational age at time of rupture was similar between those who reached viability and those who did not. In a study of 46 women with PROM <24 weeks, the median latency period was 13 days, which is consistent with our overall median latency of 14 days.[12] Van der Hyden et al studied women with PROM at <27 weeks gestation and found earlier gestational age at rupture to be associated with perinatal mortality, as well as long latency and any positive bacterial vaginal culture.[13] In our study however, vaginal infections including group B streptococcus carriage, chlamydia, and bacterial vaginosis were not associated with previable delivery. Interestingly, factors that have been associated with previable PROM, such as tobacco use or prior preterm delivery, did not appear to impact latency in this cohort.[14]

Several authors have identified factors associated with shorter latency in PROM occurring after viability, including twin gestation, nulliparity, maternal age <35, and oligohydramnios.[8,10,15] However, in our cohort, none of these were associated with delivery prior to viability. Others have examined placental pathology in women with second trimester PROM. Linehan et al examined placental pathology among women with PROM between 14 and 24 weeks’ gestation and noted that 69% had chorioamnionitis on placental pathology.[16] This finding, in conjunction with our finding that 82% of women who delivered before viability had infection on placental pathology, suggests that infection may result in previable delivery. The association between lower white blood cell count and longer latency as well as the association between lower white blood cell count and reaching viability among multiple gestations also lend credence to this theory. This potential explanation is further supported by the findings of Gopalani et al, who identified lower white blood cell count as an independent predictor of latency in women with PROM >24 weeks.[17] Further study, incorporating the presence of a left shift would also help support this data.

Our study is, to our knowledge, the first to specifically examine factors associated with delivery prior to viability in women with second trimester PROM. Additionally, it is strengthened by inclusion of an economically and ethnically diverse population of women, allowing for improved generalizability of our results. However, our study does have several limitations. First, we are limited by our relatively small sample size, which may restrict generalizability to the larger population. Similarly, we had small numbers of women with infection and medical co-morbidities, which limits our ability to examine the effect of these exposures on delivery prior to 23 weeks. Due to the retrospective nature of this study, we could not control for factors that might impact duration of latency, such as use of antibiotics, tocolytics, corticosteroids, or other interventions. Additionally, due to the rarity of this outcome, we extracted data from a long period of time, during which the limits of viability changed. The standard management for patients who elected expectant management

changed over the course of the study; for the majority of the study this was to be followed as outpatients until 23 weeks 6 days, at which time patients presented for admission to receive steroids. However, for the last few years, where a large number of cases came from, this changed to 22 weeks 6 days. However, in order to be in tune to today's standards, we used the limit of viability today, 23 weeks and 0 days. Steroids were not given until within 24 hours of viability. No patients in this analysis received tocolytics. In addition, the clinical factors chosen for evaluation were restricted to information available in the electronic medical record. This specifically limits our analysis of twin pregnancies. For example, data on WBC counts was only available for 14 patients with twin pregnancies. This small sample size makes drawing any conclusions challenging, but does allow for hypothesis generation.

Second trimester PROM, though uncommon, is a condition that raises many challenges for patients, their families, and providers. Counseling these patients is challenging as data are limited and often extrapolated from studies of women who had membrane rupture after viability. While we did not identify any specific maternal or obstetric characteristics available at the time of diagnosis that predicted the likelihood of achieving infant viability, our data did suggest that a higher WBC count at that point may be associated with shorter latency. Larger, prospective studies are needed to further clarify factors associated with previable delivery in order to better counsel women when they are faced with this challenging situation.

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References

1. Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. JAMA 1997;278(12):989–995 [PubMed: 9307346]
2. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. Am J Obstet Gynecol 2009;201(3):230–240 [PubMed: 19733274]
3. Schucker JL, Mercer BM. Midtrimester premature rupture of the membranes. Semin Perinatol 1996;20(5):389–400 [PubMed: 8912993]
4. Waters TP, Mercer B. Preterm PROM: prediction, prevention, principles. Clin Obstet Gynecol 2011;54(2):307–312 [PubMed: 21508700]
5. Falk SJ, Campbell LJ, Lee-Parritz A, et al. Expectant management in spontaneous preterm premature rupture of membranes between 14 and 24 weeks' gestation. J Perinatol 2004;24(10):611–616 [PubMed: 15254557]
6. Dewan H, Morris JM. A systematic review of pregnancy outcome following preterm premature rupture of membranes at a previable gestational age. Aust N Z J Obstet Gynaecol 2001;41(4):389–394 [PubMed: 11787910]
7. Hunter TJ, Byrnes MJ, Nathan E, Gill A, Pennell CE. Factors influencing survival in pre-viable preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2012;25(9):1755–1761 [PubMed: 22339558]
8. Melamed N, Hadar E, Ben-Haroush A, Kaplan B, Yogev Y. Factors affecting the duration of the latency period in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2009;22(11):1051–1056 [PubMed: 19900043]

9. Aziz N, Cheng YW, Caughey AB. Factors and outcomes associated with longer latency in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2008;21(11):821–825 [PubMed: 19031278]

10. Dagklis T, Petousis S, Margioula-Siarkou C, et al. Parameters affecting latency period in PPROM cases: a 10-year experience of a single institution. J Matern Fetal Neonatal Med 2013;26(14):1455–1458 [PubMed: 23488655]

11. Kibel M, Asztalos E, Barrett J, et al. Outcomes of Pregnancies Complicated by Preterm Premature Rupture of Membranes Between 20 and 24 Weeks of Gestation. Obstet Gynecol 2016;128(2):313–320 [PubMed: 27400016]

12. Dinsmoor MJ, Bachman R, Haney EI, Goldstein M, Mackendrick W. Outcomes after expectant management of extremely preterm premature rupture of the membranes. Am J Obstet Gynecol 2004;190(1):183–187 [PubMed: 14749657]

13. van der Heyden JL, van der Ham DP, van Kuijk S, et al. Outcome of pregnancies with preterm prelabor rupture of membranes before 27 weeks' gestation: a retrospective cohort study. Eur J Obstet Gynecol Reprod Biol 2013;170(1):125–130 [PubMed: 23845169]

14. Kilpatrick SJ, Patil R, Connell J, Nichols J, Studee L. Risk factors for previable premature rupture of membranes or advanced cervical dilation: a case control study. Am J Obstet Gynecol 2006;194(4):1168–1174; discussion 1174-1165 [PubMed: 16580325]

15. Test G, Levy A, Wiznitzer A, et al. Factors affecting the latency period in patients with preterm premature rupture of membranes. Arch Gynecol Obstet 2011;283(4):707–710 [PubMed: 20306063]

16. Linehan LA, Walsh J, Morris A, et al. Neonatal and maternal outcomes following midtrimester preterm premature rupture of the membranes: a retrospective cohort study. BMC Pregnancy Childbirth 2016;16:25 [PubMed: 26831896]

17. Gopalani S, Krohn M, Meyn L, Hitti J, Crombleholme WR. Contemporary management of preterm premature rupture of membranes: determinants of latency and neonatal outcome. Am J Perinatol 2004;21(4):183–190 [PubMed: 15168316]

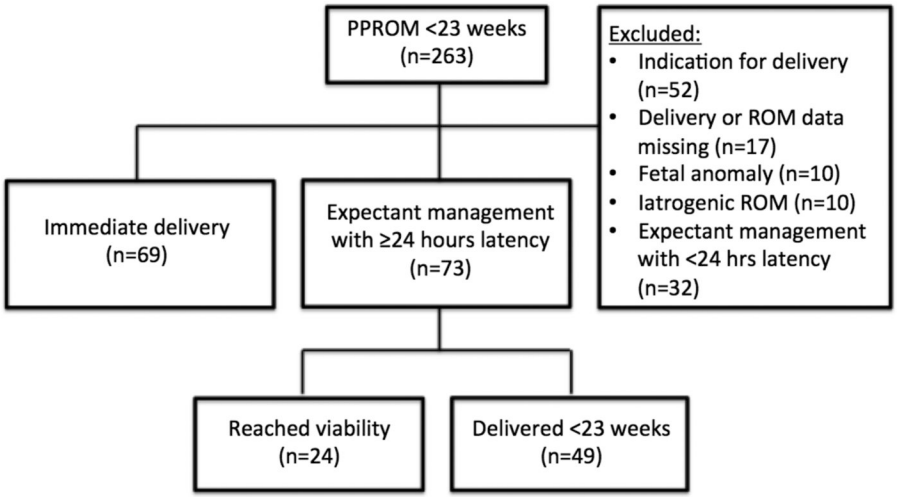

Figure 1:
Diagram of study population

Table 1:

Demographic characteristics associated with reaching viability for women with previable prelabor rupture of membranes (2000-2015)

Clinical Factor	Reached viability n=24 (%)	Delivered prior to viability n=49 (%)	p-value
Mean maternal age ± SD, years	30.5 ±7.8	29.2 ±6.2	0.76
Private insurance	13 (54)	26 (53)	0.93
Nulliparity	7 (29)	15 (31)	0.90
Black race	11 (46)	24 (49)	0.80
Twin gestation	9 (38)	14 (29)	0.59
History of prior preterm birth	6 (25)	12 (25)	0.96
Tobacco use	3 (13)	7 (14)	>0.99
Prepregnancy diabetes	2 (8.3)	3 (6.1)	>0.99
Chronic hypertension	5 (21)	7 (14)	0.51

Abbreviations: SD standard deviation

Table 2:

Antepartum and admission characteristics associated with reaching viability for women with previable prelabor rupture of membranes (2000-2015)

Clinical Factor	Reached viability n=24 (%)	Delivered prior to viability n=49 (%)	p-value
Median gestational age @ ROM, wks (IQR)	19.5 (18.7, 20.9)	19.1 (17.6, 20.6)	0.27
Oligohydramnios at presentation *	9/9 (100)	14/17 (82)	0.53
GBS carrier	4 (17)	5 (12)	0.72
Bacterial vaginosis in pregnancy	3 (13)	4 (8.5)	0.68
Chlamydia infection during pregnancy	2 (8.3)	1 (2.1)	0.26
Elevated WBC (>14) at admission *	1/10 (10)	12/32 (38)	0.10
Hct <32.0 *	3/17 (18)	13/39 (33)	0.25
Dilation @ ROM ≥ 1cm	14 (58)	32 (65)	0.56
Median Length of latency, days (IQR)	46 (31, 64)	6 (3, 14)	<0.001
Received latency antibiotics	10 (42)	17 (35)	0.56

Abbreviations: ROM rupture of membranes, IQR interquartile range, GBS group B streptococcus, WBC white blood cell count

* For variables where data was not available, the “n” is presented as a fraction, with the denominator denoting the number of subjects with that data point available.

Table 3:

Placental Pathology among women with previable prelabor rupture of membranes (2000-2015)*

Clinical Factor	Reached viability n=18 (%)	Delivered prior to viability n=28 (%)	p-value
Any Infection	9 (50)	23 (82)	0.047
Chorioamnionitis	2 (11)	7 (25)	0.45
Funisitis	0	1 (4)	>0.99
Chorioamnionitis and Funisitis	7 (39)	15 (54)	0.38
Abruption	4 (22)	8 (29)	0.74
Small for gestational age	3 (17)	4 (14)	>0.99
Normal	4 (22)	0	0.02

* Placental pathology was only available on 46 patients