

# The Relative Proportion of Preterm Births Complicated by Premature Rupture of Membranes in Multifetal Gestations: A Population-Based Study

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## Abstract

**Objective** To compare the relative contribution of premature rupture of membranes (PROM) to preterm births in singleton compared with multifetal gestations.

**Study Design** A population-based retrospective cohort study of 291,782 nonanomalous live births in the state of Ohio from January 1, 2006, to December 31, 2007, identified through birth certificate data. Frequency of PROM was compared between singleton and multifetal gestations and then stratified by gestational age at birth. Multivariate regression analysis estimated the risk of PROM by plurality in each gestational age group, accounting for influential risk factors.

**Results** The frequency of PROM increased with increasing plurality of gestation. The relative proportion of preterm birth <37 weeks complicated by PROM increased with gestational plurality 13.2% singletons, 16.8% twins, 20.0% triplets, 19.6% quadruplets, and 100% for higher-order multiples ( $p < 0.001$ ). The frequency of PROM increased with earlier gestational age at birth, regardless of plurality. The increased risk of PROM in multifetal gestation persisted even after adjustment for influential concomitant risk factors.

**Conclusion** The proportion of preterm birth attributable to PROM increases by plurality of gestation, with its most significant contribution in higher-order multiples and at earliest gestational ages when outcomes are the poorest.

## Keywords

- ▶ PROM
- ▶ preterm/premature birth
- ▶ multifetal gestation
- ▶ preterm rupture of membranes
- ▶ preterm labor

Preterm birth is a profound public health issue. Despite a decrease in the mortality rate after extremely preterm birth, the morbidity is increasing.<sup>1</sup> Preterm births contribute to 75% of all perinatal mortality and more than half the long-term morbidity in infant survivors.<sup>2</sup> It has been estimated that ~30 to 35% of preterm births are medically indicated, 40 to 45% are attributed to spontaneous preterm labor, and 25 to 30% follow preterm premature rupture of membranes (PROM).<sup>3</sup>

Based on U.S. birth records, Martin et al found that in 2006, one of every eight twins and one of three triplets were born at less than 32 weeks compared with 1 of 50 singletons.<sup>4</sup> The

rates of preterm birth at <37 weeks of gestation and at <32 weeks of gestation are 11.1% and 1.6% for singletons, 92.6% and 12.1% for twins, 92.6% and 36.3% for triplets, 94.9% and 79.2% for quadruplets, and 89.6% and 79.1% for quintuplet pregnancies, respectively.<sup>4</sup>

PROM is defined as rupture of the amniotic membranes before the onset of labor. Preterm PROM occurs at less than 37 weeks of gestation. PROM occurs in 1 to 2% of pregnancies nationally and is reported to recur in 21% of cases.<sup>5</sup> It is well known that PROM is associated with an increase in complications of pregnancy such as cord prolapse, placental

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abruption, chorioamnionitis, and preterm birth. A Swedish study examining the role of preterm delivery and neonatal outcome in a population of infants born at <28 weeks of gestation reported that infant survival was significantly lower when preterm delivery was secondary to PROM versus spontaneous preterm labor with intact membranes or indicated delivery.<sup>6</sup> Another study examining PROM between 17 to 30 weeks of gestation demonstrated a significant increase in pulmonary hypoplasia and symptomatic chronic lung disease when compared with a control group of infants born secondary to spontaneous preterm labor.<sup>7</sup> These studies highlight the importance of recognizing the risk of PROM especially at early gestational ages when preterm neonates are the most vulnerable to complications of prematurity.

Some studies have noted that multifetal gestation is a risk factor for PROM, and it is hypothesized that uterine overdistension is the probable cause of PROM in these pregnancies.<sup>8,9</sup> Although some studies have described an increase in the incidence of PROM in twin gestations in comparison with singleton pregnancies, there are no current large population-based epidemiological studies that have examined the relative proportion of preterm births attributed to PROM, stratified by plurality of gestation.

## Methods

The protocol for this study was approved by the Ohio Department of Health and Human Subjects Institutional Review Board, and a deidentified data set was provided by the Child Policy Research Center of Cincinnati Children's Hospital Medical Center. This study was exempt from review by the Institutional Review Board at the University of Cincinnati, Cincinnati, Ohio.

We performed a population-based retrospective cohort study using the Ohio Department of Health's birth certificate database to study the relative contribution of PROM to preterm birth in multifetal gestations (twins, triplets, quadruplets, and higher-order multiples) compared with singleton births. PROM was defined as premature rupture of membranes >12 hours, as coded in the birth certificate. The relative frequency of PROM was stratified for each group with respect to gestational age at birth (term, 34 to 37 weeks, 28 to 34 weeks, and <28 weeks). When comparing by plurality, singletons were the referent category, and for

gestational age comparisons, births occurring at term (37 to 42 weeks) were used as the reference group for comparison.

Births with gestational age <20 weeks, pregnancies complicated by major congenital anomalies, and fetal deaths were excluded from this study. After exclusions, there were 291,782 births remaining for this analysis. The primary outcome measure was PROM with the plurality of gestation as the exposure. The secondary outcomes studied were preterm birth, frequency and proportion of preterm births complicated by PROM, stratified by gestational age. For each of the variables included in this study, there was minimal missing data. There were no missing data on gestational age at birth. There was a single birth in the data set coded as being born to a gestation with plurality >6. This birth was dropped from the data set prior to analysis due to the likelihood of coding error, after taking into consideration characteristics of the birth that excluded the possibility it was indeed a higher-order multifetal gestation. There were only 16 births with missing data on plurality of the gestation (<0.01% missing) and 4873 births with missing information on PROM (1.7%). Likewise, there were minimal missing data on demographic characteristics studied ( $\leq 3\%$  for all variables except no prenatal care with 11% missing data).

Statistical analysis was performed using STATA (Stata Statistical Software: Release 10. College Station, TX: StataCorp LP). Demographic characteristics between the groups were compared using the analysis of variance test for continuous variables and chi-square test for categorical variables. Comparisons with  $p$  value <0.05 or 95% confidence interval (CI) not inclusive of the null were considered statistically significant. Multivariate logistic regression estimated the risk of PROM by gestational age at birth and plurality. Covariates were chosen for the final regression model by differences noted in bivariate analysis, significance testing through backward elimination, and parsimony within the model.

## Results

There were 291,782 live births included in this analysis. Of those, 280,882 (96.3%) were singletons, 10,293 (3.5%) twins, 539 (0.2%) triplets, 46 (0.02%) quadruplets, and 6 (0.01%) higher-order multiples. The frequency of PROM by gestational plurality is illustrated in **Table 1**. PROM occurred more frequently in twins (11.2%), triplets (19.3%), quadruplets

**Table 1** Distribution of PROM by Gestational Plurality ( $n = 291,782$ )

	PROM <sup>a</sup> ( $n = 9876$ ; 3.4%)	No PROM ( $n = 277,017$ ; 96.6%)
Singletons, $n$ (%)	8607 (3.1)	267,584 (96.9)
Twins, $n$ (%)	1150 (11.2)	8,970 (88.8)
Triplets, $n$ (%)	104 (19.3)	426 (79.7)
Quadruplets, $n$ (%)	9 (19.6)	37 (79.4)
Higher order (>4), $n$ (%)	6 (100)	0 (0)

PROM, premature rupture of membranes.

<sup>a</sup>The difference in rate of PROM, stratified by plurality of the gestation, was statistically significant,  $p < 0.001$ .

There were 4873 (1.7%) births with missing data on PROM and 16 (<0.01%) with missing data on plurality, resulting in  $n = 286,893$  for this comparison.

**Table 2** Maternal Characteristics of Pregnancies Complicated by PROM, by Gestational Plurality (n = 9876)

	Singleton	Twin	Triplet	Quadruplet	Higher Order	p Value
Parity	1.8 ± 1.3	2.3 ± 1.3	2.2 ± 1.1	3.2 ± 1.4	3.5 ± 1.9	<0.001 <sup>a</sup>
Age of mother (y)	26.7 ± 6.2	30.0 ± 5.8	32 ± 5.9	28 ± 5	23 ± 0	<0.001 <sup>a</sup>
AMA, age > 35	1110 (12.9)	199 (17.3)	33 (31.7)	0	0	<0.001 <sup>b</sup>
Race						<0.001 <sup>b</sup>
White	6300 (73.8)	902 (78.9)	98 (94.2)	9 (100)	6 (100)	
Black	1628 (19)	189 (16.5)	6 (5.8)	0	0	
Hispanic	361 (4.2)	30 (2.6)	0	0	0	
Other	253 (3)	24 (2)	0	0	0	
Tobacco use	1925 (22.6)	176 (15.3)	4 (4)	5 (55.6)	0	<0.001 <sup>b</sup>
No PNC	299 (4.1)	16 (1.9)	0	0	0	0.006 <sup>b</sup>
ART	55 (1.2)	77 (13.3)	33 (47.8)	4 (50)	0	<0.001 <sup>b</sup>
Prior PTB	481 (5.7)	46 (4.2)	11 (10.9)	0	0	0.037 <sup>b</sup>
CHTN	156 (1.8)	38 (3.4)	8 (7.7)	0	0	<0.001 <sup>b</sup>
GHTN	350 (4.2)	70 (6.3)	6 (5.8)	0	0	0.016 <sup>b</sup>
Pregest DM	114 (1.32)	16 (1.39)	0	0	0	0.009 <sup>b</sup>
GDM	428 (5)	91 (7.9)	18 (17.3)	0	0	<0.001 <sup>b</sup>
Cerclage	102 (1.19)	23 (2)	15 (14.4)	0	0	<0.001 <sup>b</sup>
Tocolysis	409 (4.8)	102 (8.9)	19 (18.3)	0	0	<0.001 <sup>b</sup>

Continuous variables are expressed as mean ± standard deviation. Binary variables are expressed as number (percent). AMA, advanced maternal age; ART, artificial reproductive technology; CHTN, chronic hypertension; GDM, gestational diabetes mellitus; GHTN, gestational hypertension; PNC, prenatal care; Pregest DM, pregestational diabetes mellitus; PROM, premature rupture of membranes; PTB, preterm birth.

<sup>a</sup>Analysis of variance t test.

<sup>b</sup>Chi-square test.

(19.6%), and higher-order multiples (100%) compared with singleton pregnancies (3.1%;  $p < 0.001$ ). Multifetal gestations complicated by PROM were more likely to occur in women who were of advanced maternal age (>35 years), Caucasian, recipients of artificial reproductive technology, diagnosed with chronic hypertension and gestational diabetes, and those who underwent interventions such as cerclage and tocolysis (► **Table 2**).

PROM occurred more frequently in multifetal gestations and at earlier gestational ages. In singleton pregnancies, the rate of PROM increased with earlier gestational age at birth. Compared with the frequency of PROM at term (1.8%), PROM affected 10.5% of late preterm singletons (34 to 37 weeks) (adjusted odds ratio [adjOR] 5.4, 95% CI 5.1 to 5.7), 18.2% born at 28 to 34 weeks (adjOR 10.8, 95% CI 10 to 11.7), and 27.1% of extreme preterm singleton births <28 weeks (adjOR 18.8, 95% CI 16.5 to 21.4). Similarly, the rate and risk of PROM increased with degree of prematurity in twins. The rate of PROM increased in twins from 2% at term to 35.7% at less than 28 weeks of gestation (adjOR 39.6, 95% CI 27.8 to 56.5). The rate of PROM was particularly high in quadruplets and higher-order multifetal gestations born at extremely preterm gestational ages, 50% and 100%, respectively (► **Table 3**).

The relative proportion of preterm births <37 weeks complicated by PROM increased with gestational plurality: PROM contributed to 13.2% of all preterm births <37 weeks

in singletons, 16.8% in twins, 20.0% in triplets, 19.6% in quadruplets, and 100% in higher-order multiples ( $p < 0.001$ ). ► **Figure 1** demonstrates the relative proportion of PROM in preterm births by plurality and gestational age. The relative proportion of PROM in preterm births increased with earlier gestational age at birth. At late preterm gestational ages, 34 to 37 weeks, PROM contributed to 10.2% of singleton births, 11% of twins, 12.2% of triplets, and 10% of quadruplets ( $p = 0.516$ ). At 28 to 34 weeks, PROM contributed to 17.8% of singleton, 24.3% of twin, 23.1% triplets, and 14.3% of quadruplet births ( $p < 0.001$ ). And at extremely preterm gestational ages, the proportion of preterm births attributable to PROM was 26.5% for singleton births, 34.6% for twins, 26.9% for triplets, 50% for quadruplets, and 100% of higher-order multifetal gestations ( $p < 0.001$ ).

## Discussion

In this study, we found that preterm birth complicated by PROM occurred with increasing frequency in multifetal gestations compared with singletons. PROM became a more frequent contributor to preterm birth in multiples as the plurality of the gestation increased. Likewise, we found that PROM occurred with increasing frequency at the earliest gestational ages in higher-order multifetal gestations, less than 28 weeks, when outcomes are most compromised.

**Table 3** Risk of PROM by Gestational Age, Stratified by Plurality

	Singleton <sup>a</sup>	Twin	Triplet	Quad	Higher Order	p Value
PROM, n (%)	8607	1150	104	9	6	
37–42 wk <sup>a</sup>	4373 (1.8%)	73 (2%)	3 (11.5%)	0	0	0.001
OR	1.0	1.0	1.0	1.0		
34–37 wk	2441 (10.5%)	461 (11.2%)	23 (12.2%)	1.0 (10%)	0	0.52
adjOR <sup>c</sup>	5.4 (5.1, 5.7)	6.0 (4.5, 8.0)	1.8 (0.5, 6.6)	<sup>b</sup>		
28–34 wk	1272 (18.2%)	454 (24.8%)	57 (23.5%)	4 (14.3%)	0	<0.001
adjOR <sup>c</sup>	10.8 (10, 11.7)	19.1 (14.2, 25.6)	2.2 (0.6, 7.9)	<sup>b</sup>	<sup>b</sup>	
<28 wk	521 (27.1%)	162 (35.7%)	21 (28.4%)	4 (50%)	6 (100%)	<0.001
adjOR <sup>c</sup>	18.8 (16.5, 21.4)	39.6 (27.8, 56.5)	7.3 (1.8, 29.0)	<sup>b</sup>	<sup>b</sup>	
p value	<0.001	<0.001	0.03	0.08	N/A	

Total n for this population is 291,782. N/A, not applicable; PROM, premature rupture of membranes.

<sup>a</sup>Singleton gestation and PROM at term (37–42 wk) were the reference groups used for comparison.

<sup>b</sup>Unable to calculate due to zero observations in reference group.

<sup>c</sup>Covariates in the regression model include: parity, no prenatal care, race, prior preterm birth, gestational hypertension.

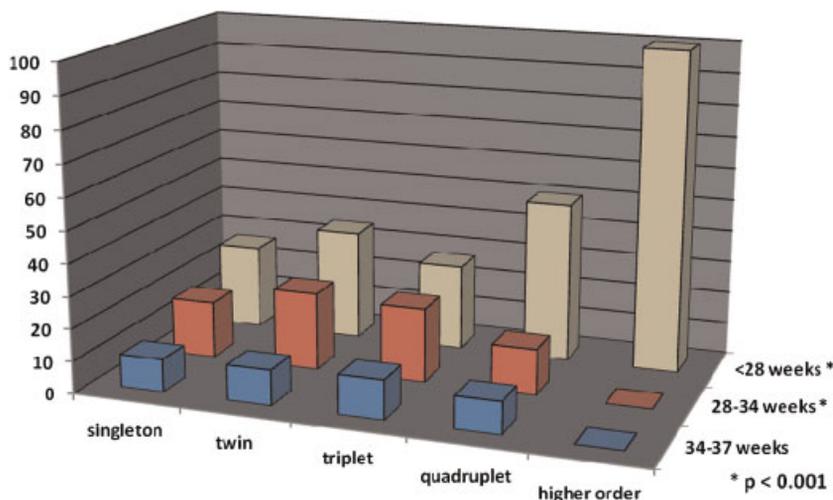
The complications associated with the birth of a preterm baby, especially a neonate delivered after PROM, include but are not limited to respiratory distress syndrome, intraventricular hemorrhage, neonatal sepsis, pulmonary hypoplasia, and restrictive deformation. In fact, Chen et al found that infants born following PROM had the highest risk of neonatal death compared with births attributed to the other subtypes of prematurity.<sup>10</sup>

The complex pathophysiological mechanisms leading to preterm PROM are not completely understood, but it is widely accepted that underlying infection and inflammation disproportionately affect cases of PROM, which may in part explain poorer neonatal outcomes for these births.<sup>11</sup> Ascending uterine infection can lead to fetal infection, which may further lead to a fetal inflammatory response syndrome that is not only linked to preterm labor but also fetal morbidity

such as periventricular leukomalacia, cerebral palsy, and chronic lung disease.<sup>3</sup>

A population-based study similar to ours examined data from the Perinatal Information System database in Montevideo, Uruguay, where 885,338 pregnancies were studied and of which, 15,484 were multifetal gestations.<sup>12</sup> Their study differed in that they found no increased risk of PROM in multiple gestations when compared with singleton pregnancies.<sup>12</sup> However, the authors did not categorize multifetal gestations by order of plurality, instead classifying all pregnancies with two or more fetuses as “multiple gestation.”

Ananth et al performed a retrospective cohort study of twin live births delivered in the United States by reviewing U.S. twin natality files between 1989 and 2000. They noted an increase in medically indicated preterm births in black and white populations in the United States within the

**Figure 1** Relative contribution of premature rupture of membranes to preterm birth by plurality and gestational age.

aforementioned time period.<sup>13</sup> However, preterm births attributed to PROM remained the same in the white population and decreased in the black population in the study period. Our study differs from Ananth et al's study in that we examined the frequency of PROM in higher-order multiples greater than twins and calculated the relative risk of birth at a preterm gestational age due to PROM in each category of multifetal gestation and included all racial/ethnic groups.

This was a population-based analysis with a large sample size and hence had sufficient power to detect small differences in the relative frequency of PROM by increasing plurality of gestation, its relative proportional contribution to preterm birth, and its occurrence by gestational age. Unlike prior studies that examined a variety of maternal and perinatal outcomes in multiple births, this study focused solely on PROM and its effect on preterm birth by plurality of gestation and stratified the risks by gestational age. The other strengths of the data source used for this study include diversity and a representation of the different strata of society and physician practices that allowed for generalization.

This study demonstrated that PROM is a frequent contributor to preterm birth in singletons as well as multifetal gestations. Ours is the first study we are aware of that quantified the risk of PROM by plurality of gestation and by gestational age and its proportional contribution to preterm birth, compared with preterm birth with intact membranes. It also demonstrated that PROM affects multifetal gestations more commonly than singletons with its highest frequency occurring in higher-order multiples and at the earliest gestational ages when the outcomes are the poorest.

The limitations of this study include a low number of higher order (>4) multiple gestations in the study and the inability to differentiate between spontaneous versus indicated preterm birth. In large medical databases such as this, the validity of data depends on the validity of information in the medical record and the ability of coding personnel to extract relevant patient data.<sup>14</sup>

Another drawback of analyzing information from vital statistics data is missing information. This limitation can be minimized by posing questions that do not require the use of variables with significant missing values or the use of statistical techniques to account for the absent information.<sup>14</sup> This study avoided some of the published biases in that we chose exposure and outcomes that had minimal missing data (gestational age and plurality). We also had rates of demographic characteristics similar to reported norms and minimal missing data for variables identified. Undercoding or misclassification of specific diagnoses is common in vital statistics data. For example, a recent study from the Ohio Perinatal Quality Collaborative compared medical indications for labor induction between chart abstracted data and medical information gathered from Ohio birth certificates.<sup>15</sup> The authors found that lack of a documented medical indication was 11 times more frequent in birth certificate data compared with data found in the patient record. This is likely due to lack of documentation of a medical indication in the birth certificate, when in fact one does exist. Similarly, we found the rate of PROM contributing to preterm birth in this study to

be 10 to 15%, which is considerably lower than previously published reports attributing one-third of preterm births to PROM.<sup>16,17</sup> This likely reflects the underreporting of PROM across all gestational subtypes in the birth certificate database in Ohio. Although we do not suspect that PROM was differentially misclassified by plurality or gestational age, if it was more frequently undercoded in singletons or later gestational ages, this could result in an overestimate in our comparisons of relative proportional differences and risks among groups. Additionally, the possibility of residual confounding by unaccounted environmental and behavioral risk factors in the study also cannot be excluded with complete certainty.

It is also interesting to note that the previously mentioned and oft-quoted studies quantifying the contribution of PROM to preterm birth were performed in 1987 and 1991, respectively, and there has been a lack of recent data reflecting the contribution of PROM to preterm birth.

## Conclusion

Multifetal gestations had a higher frequency of preterm birth complicated by PROM in this study. This occurred more frequently in higher-order multiples and at extremely premature gestational ages. This study provides additional information to support the important role that PROM plays in preterm birth especially in multifetal gestations and helpful evidence in counseling of this high-risk category of obstetric patients.

## Note

"The relative contribution of PROM to preterm birth in multifetal compared with singleton gestations: A population-based study" was presented at the 77th Annual Meeting of the Central Association of Obstetricians and Gynecologists, October 27 to 30, 2010, Las Vegas, Nevada.

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