Length of rupture of membranes in the setting of premature rupture of membranes at term and infectious maternal morbidity

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OBJECTIVE: This study was undertaken to define the time thresholds of increased risk for infectious maternal morbidities with relationship to length of ruptured membranes at term.

STUDY DESIGN: We designed a retrospective cohort study of all women with premature rupture of membranes beyond 37 weeks' gestation at a single institution. Dichotomized time thresholds of length of ruptured membranes before delivery were examined in 2-hour increments using bivariate and multivariable analyses to assess the rates of chorioamnionitis and endomyometritis.

RESULTS: Among the 3841 women meeting inclusion criteria, increased rates of chorioamnionitis and endomyometritis were noted at time thresholds of 12 hours (adjusted odds ratio 2.3 [95% confidence interval, 1.2-4.4]) and 16 hours (adjusted odds ratio 2.5 [95% confidence interval, 1.1-5.6]), respectively.

CONCLUSION: We found that when length of time of ruptured membranes before delivery is examined via dichotomized time thresholds, the risks of chorioamnionitis and endomyometritis are significantly increased at 12 hours and 16 hours, respectively. These time thresholds derived from dichotomized time analyses should be considered during risk-based counseling and labor management in the setting of term premature rupture of membranes.

Key words: chorioamnionitis, endomyometritis, postpartum hemorrhage, premature rupture of membranes, term premature rupture of membranes

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Premature (prelabor) rupture of membranes (PROM) affects 8-10% of pregnancies at term.[1] Although some physicians advocate for immediate induction of labor in this setting, citing various studies that have demonstrated increased risks of adverse maternal and neonatal morbidity with increased lengths of time from rupture of membranes,[2,3] others opt for expectant management based on reported associations between increased rates of cesarean section and immediate labor induction in the setting of term PROM[4,5] as well as consideration of the preferences of some patients to avoid labor induction or the use of pharmacologic agents. Among those who opt for expectant management, various time thresholds, most commonly 18 hours duration of ruptured membranes,[6] have been used to define prolonged rupture of membranes, after which time antibiotics are administered for prophylaxis against neonatal group B streptococcus (GBS) sepsis by using a risk-based protocol. Thus, the management of pregnancies complicated by PROM at term remains controversial.

Although it is well-established that the risk of infectious morbidity increases with increasing length of time of ruptured membranes,[7] previous studies have compared various arbitrary serial time intervals of ruptured membranes such as 0-6 hours, 6-12 hours, 12-18 hours, and so forth, to one another or to a single comparison group (eg, < 12 hours) to determine associated risks.[8,9] However, this methodology may not accurately reflect the a priori risk of developing infectious morbidity related to duration of membrane rupture until delivery. When examining obstetric outcomes, the use of appropriately defined denominators as well as making relevant clinical comparisons is paramount. This statistical issue of appropriate denominator has been examined previously.[10] In the setting of diagnosing preeclampsia, whether to use the denominator of "pregnancies delivered" or "ongoing pregnancies" changes the clinical finding. Similarly, when examining time interval as a predictor of obstetric outcomes, the groups compared may change the clinical implications derived from the analysis.

When a woman presents with term PROM, it is not possible to predict how long membranes will be ruptured before delivery. Ultimately, the time at which she delivers, and thus the total amount of time that membranes are ruptured, will in retrospect be categorizable into delivery before or after a certain threshold of time (eg, before or after 18 hours of ruptured membranes). Accordingly, from a methodologic standpoint, comparisons should then be made between all those women who deliver before a certain time threshold

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TABLE 1
Bivariate analysis of length of time of ruptured membranes and maternal outcomes

Time threshold of ruptured membranes (h)[a]	Chorioamnionitis rates before vs after various time thresholds	Endomyometritis rates before vs after various time thresholds	Postpartum hemorrhage rates before vs after various time thresholds
8	2.4% vs. 11.1%[b]	0.0% vs. 3.2%	7.2% vs. 21.8%[b]
10	1.9% vs. 11.4%[b]	1.0% vs. 3.2%	9.8% vs. 22.2%[b]
12	2.7% vs. 11.8%[b]	1.3% vs. 3.3%[b]	11.1% vs. 22.6%[b]
14	2.2% vs. 12.4%[b]	1.0% vs. 3.4%[b]	12.7% vs. 23.0%[b]
16	3.6% vs. 12.8%[b]	1.0% vs. 3.6%[b]	13.8% vs. 23.5%[b]
18	4.0% vs. 13.4%[b]	1.3% vs. 3.7%[b]	14.5% vs. 24.0%[b]

[a] Length of time of ruptured membranes from 0 h through specific time threshold.

[b] $P < .05$.

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and all those who deliver after that time threshold. Thus, in counseling patients, it is most accurate to make comparisons using dichotomized time thresholds rather than serial time intervals. In particular, this type of data categorization is relevant in counseling women because we know that we can hasten delivery of women with term PROM by the use of augmentation of labor.[3]

The goal of this study was to define the thresholds of increased risk for maternal infectious morbidities, specifically, chorioamnionitis and endomyometritis, in pregnancies with PROM at term by using dichotomized time thresholds.

Materials and Methods

After institutional review board approval from the Committee on Human Research at the University of California, San Francisco (UCSF) was obtained, a retrospective cohort study was conducted. We included all women who had PROM diagnosed at 37 weeks' gestation and beyond with singleton, cephalic gestations delivering at UCSF from 1981-2001. Exclusion criteria included multiple gestations, transport patients, placenta previa, and breech presentation.

The primary outcomes were chorioamnionitis and endomyometritis. In addition, because chorioamnionitis is commonly associated with postpartum hemorrhage,[11,12] we included this as a secondary outcome. The diagnoses of chorioamnionitis and endomyometritis were made clinically and diagnoses were abstracted from patient records. Chorioamnionitis was defined by temperature of 100.4°F or greater that occurred during labor, accompanied by 1 or more of the following: uterine tenderness, fetal tachycardia, or purulent amniotic fluid. Similarly, endomyometritis was defined by maternal temperature higher than 100.4°F that occurred in the postpartum period along with uterine tenderness, leukocytosis with left shift, or foul lochia. Postpartum hemorrhage was defined as the clinicians' estimated blood loss (EBL) of greater than 500 mL in the setting of a vaginal birth and greater than 1000 mL in the setting of a cesarean delivery. Information on potential confounding factors was also abstracted from an existing perinatal research database including: maternal age, race/ethnicity, parity, gestational age, insurance status, educational level, epidural use, labor induction, and mode of delivery.

The primary predictor, length of time of rupture of membranes until delivery, was examined before and after various dichotomized time thresholds by using 2-hour time increments as a predictor of the 3 outcomes, chorioamnionitis, endomyometritis, and postpartum hemorrhage. For example, women delivering with a total duration of ruptured membranes of 6 hours or less were compared with all those delivering with duration of ruptured membranes greater than 6 hours. Similar comparisons were made for 8-, 10-, and 12-hour or more time thresholds to determine the threshold at which rates of each of the outcomes of interest achieved statistical significance ($P < .05$).

Bivariate analyses of the predictor variable, various time thresholds of total time of membrane rupture until delivery, were performed for the dependent variables of chorioamnionitis, postpartum endomyometritis, and postpartum hemorrhage. To compare the dichotomous comparisons with the more traditional analyses of time and infectious morbidity, length of rupture of membranes was also categorized into 6-hour intervals to identify the group(s) at highest risk of infectious morbidity. Multivariable logistic regression was performed to examine total time of membrane rupture until delivery as a predictor for these same outcomes while controlling for maternal ethnicity, age, parity, education level, insurance status, gestational age, epidural usage, induction of labor, and mode of delivery. The data were analyzed by using STATA 9 (STATA Corporation, College Station, TX). All categorical variables were compared using χ^2 test. P values less than .05 were considered statistically significant.

Results

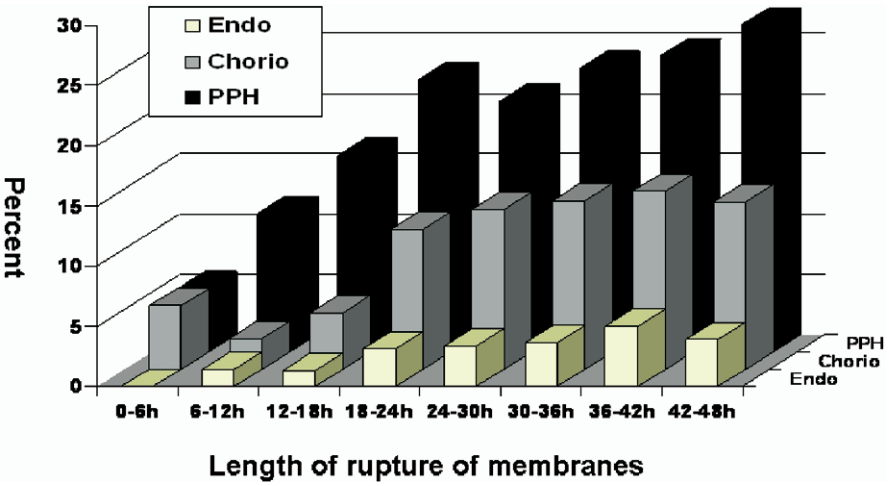
During the study period, there were 3841 women who met the inclusion criteria. In bivariate analyses (Table 1), rates of chorioamnionitis were noted to differ significantly when data were dichotomized to length of rupture of membranes less than 8 hours vs greater than 8

hours (2.4% vs 11.1%, $P = .01$). Similar differences in rates of chorioamnionitis were noted when data were dichotomized and analyzed by using 10-, 12-, 14-, 16-, and 18-hour thresholds ($P < .001$). Rates of endomyometritis began varying significantly when comparing length of rupture of membranes less than 12 hours vs greater than 12 hours (1.3% vs 3.3%, $P = .04$). Similar to chorioamnionitis, significant differences in rates of endomyometritis were noted for all subsequent 2-hour time thresholds examined ($P < .001$). Rates of postpartum hemorrhage began differing significantly at a time threshold of less than 8 hours vs greater than 8 hours (7.2% vs 21.8%, $P = .001$), and these differences persisted for all subsequent 2-hour time thresholds examined ($P < .001$).

Figure 1 shows the puerperal infection and postpartum hemorrhage rates by time of ruptured membranes. Rates of all 3 outcomes were noted to increase with increasing time of ruptured membranes before delivery. The overall incidence of chorioamnionitis and endomyometritis in the study group was 10.9% and 3.1%, respectively, and the overall incidence of postpartum hemorrhage was 21.5%. When each period was compared with the prior period, chorioamnionitis and endomyometritis were not significantly increased until beyond the 18-hour threshold, whereas postpartum hemorrhage increased at the 12-hour mark.

In the multivariable model (Table 2), examining various dichotomized time thresholds of total length of ruptured membranes as a predictor for puerperal infection and postpartum hemorrhage, we found that rates of chorioamnionitis differed significantly at a time threshold of greater than 12 hours vs less than 12 hours of ruptured membranes (odds ratio [OR] 2.3, 95% confidence interval [CI], 1.2-4.4), and this finding continued for all subsequent 2-hour increment thresholds examined. Rates of endomyometritis varied significantly when comparing length of rupture of membranes greater than 16 hours vs less than 16 hours (OR 2.5 [95% CI, 1.1-5.6]). Finally, multivariable analyses also showed that rates of postpartum hemorrhage differed significantly when comparing length of membrane rupture greater than 8 hours vs less than 8 hours (OR 2.8 [95% CI, 1.1-7.2]). In this model, we controlled for maternal parity, age, ethnicity, insurance status, gestational age, epidural usage, induction of labor, and mode of delivery.

FIGURE
Length of ruptured membranes and maternal outcomes



Length of time from rupture of membranes to delivery is categorized into 6-hour groups and rates of chorioamnionitis, endomyometritis, and postpartum hemorrhage are plotted on the y-axis.

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TABLE 2
Multivariable analysis of length of time of ruptured membranes and maternal outcomes[a]

Time threshold of ruptured membranes(h)[b]	Chorioamnionitis OR [95% CI]	Endomyometritis OR [95% CI]	Postpartum hemorrhage OR [95% CI]
8	2.2 [0.5-9.1]	N/A	2.8 [1.1-7.2][c]
10	2.6 [0.9-7.2]	1.6 [0.4-7.0]	1.7 [1.0-2.8][c]
12	2.3 [1.2-4.4][c]	1.3 [0.5-3.4]	1.6 [1.1-2.3][c]
14	3.2 [1.8-5.7][c]	2.3 [0.9-6.0]	1.4 [1.1-1.9][c]
16	2.4 [1.6-3.7][c]	2.5 [1.1-5.6][c]	1.4 [1.1-1.8][c]
18	2.5 [1.8-3.6][c]	1.9 [1.0-3.5][c]	1.3 [1.0-1.6][c]

[a] Controlling for maternal parity, age, ethnicity, insurance status, gestational age, epidural usage, induction of labor, and mode of delivery.

[b] Length of time of ruptured membranes from 0 h through specific time threshold.

[c] $P < .05$.

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Comment

Increasing duration of ruptured membranes in the setting of term PROM is associated with increased infectious morbidity. This has been previously demonstrated in multiple studies.[1-3,7-9] However, a priori consideration of the length of time of ruptured membranes until delivery, when examined by dichotomizing time intervals and comparing all the women delivering before that threshold with all those delivering after that time as performed in this study, finds such morbidity increasing sooner than previously demonstrated[8,9] at 12,

16, and 8 hours for chorioamnionitis, endomyometritis, and postpartum hemorrhage, respectively. These thresholds are also earlier than when the current data were analyzed using categorized serial time groups (eg, 0-6, 6-12, and 12-18 hours) compared with each other, revealing thresholds of 18 hours, 18 hours, and 12 hours, for chorioamnionitis, endomyometritis, and postpartum hemorrhage, respectively.

In the current article, the determination of a statistically significant difference in outcome rates is based on what the authors believe to be relevant and appropriate comparison groups. That is, all women delivering with a total membrane rupture time of less than a particular period (eg, 0-18 hours) are compared with the remaining women who delivered with a total membrane rupture time of greater than that period (in this example, 18 hours and beyond). Because, a priori, one cannot know whether a particular patient will deliver in one future time category or another, dichotomized time thresholds seem more clinically relevant when counseling women regarding risks related to duration of ruptured membranes.

These findings are particularly important to consider when deciding how to manage term PROM. From the large, prospective randomized controlled trial by Hannah et al,[3] the median time from membrane rupture to delivery was 33.3 hours for women managed expectantly and 17.2 hours for those who underwent immediate oxytocin induction. By using our chorioamnionitis rates and these times, immediate use of oxytocin would lead to a 50% reduction in the rate of chorioamnionitis in our population from approximately 10% down to 5%. Thus, one would need to augment 20 women to prevent 1 case of chorioamnionitis. Our findings thus support immediate labor induction to reduce maternal infectious morbidity. Some clinicians have extended the studies of increased neonatal infectious morbidity at 18 hours of rupture of membranes[13] to manage PROM at term expectantly for 18 hours postrupture before initiating augmentation or induction of labor. However, our data suggest that such a practice may lead to belated efforts to minimize infectious morbidity.

The large, prospective study by Hannah et al[3] was the largest study conducted on the management issues related to term PROM. However, it was not powered to find a difference in some of the neonatal outcomes examined. Our work could potentially assist in the design of such a study in several ways. First, because duration of ruptured membranes is associated with infectious morbidity, stratified randomization and analysis by duration of ruptured membranes should be considered. Second, because of the risk stratification by length of time since rupture of membranes, the prospective power analysis could potentially be modified to better characterize the theoretical sample size to identify a difference in neonatal outcomes.

We found that the risk for postpartum hemorrhage increased with increasing time of ruptured membranes and that this increase paralleled that of puerperal infection. This association between postpartum hemorrhage and infection has been previously described,[11,12] and it has been postulated that chorioamnionitis may have a deleterious effect on uterine function that may in turn result in uterine atony and increased blood loss. It is interesting that the threshold for postpartum hemorrhage is lower than that for chorioamnionitis, possibly because of the effect of subclinical infection that occurs before a frank diagnosis of chorioamnionitis.

There are several potential limitations of our study. Because of the retrospective nature of the study, only association, rather than causation, can be drawn from the findings. In addition, the diagnoses of chorioamnionitis and endomyometritis were based on the judgment of the clinician providing care rather than objective, culture-proven infections. However, we believe that our findings are still generalizable, given that amniotic fluid culture is not performed routinely at the study institution or most other institutions, and diagnosis of these infections is typically made clinically. During the study period, antibiotic prophylaxis for GBS was administered predominantly on the basis of a risk-based protocol. In patients at term, antibiotic prophylaxis primarily occurred in patients with prolonged rupture of membranes. Of note, in the last few years of the study, most of the clinicians had switched to a culture-based protocol, which has lead to an increase in the administration of antibiotics for GBS. If anything, this increase in antibiotic usage would have led to an overall decrease in maternal infection rates and would have in turn decreased the strength of our findings. Moreover, because term PROM has not been shown to be related to GBS colonization,[14,15] this should not bias the results.

In summary, we found that when length of time of ruptured membranes before delivery is examined via dichotomized time thresholds as opposed to serial time intervals, the risks of chorioamnionitis, endomyometritis, and postpartum hemorrhage are significantly increased at time thresholds of 12, 16, and 8 hours, respectively. These findings were robust to examination with multivariable techniques controlling for confounding. With regard to chorioamnionitis, our finding of a 12-hour threshold is earlier than the 18-hour threshold commonly utilized by clinicians to define prolonged rupture of membranes.[6,13,16] From a research standpoint, we suggest that consideration be given to the methodology used to define critical thresholds of risk when interpreting data that is examining risks associated with increasing time. Furthermore, these significant time thresholds should be considered when providing patients with risk-based counseling and to guide labor management in the setting of term PROM. ■

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