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Absence of Circadian Rhythms of Preterm Premature Rupture of Membranes and Preterm Placental Abruption

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Abstract

Purpose—Data regarding circadian rhythm in the onset of spontaneous preterm premature rupture of membranes (PROM) and placental abruption (PA) cases are conflicting. We modeled the time of onset of preterm PROM and PA cases and examined if the circadian profiles varied based on the gestational age at delivery.

Methods—We used parametric and nonparametric methods, including trigonometric regression in the framework of generalized linear models, to test the presence of circadian rhythms in the time of onset of preterm PROM and PA cases, among 395 women who delivered a singleton between 2009 and 2010 in Lima, Peru.

Results—We found a diurnal circadian pattern, with a morning peak at 07h:32' (95%CI:05h:46' – 09h:18') among moderate preterm PROM cases (P-value<0.001), and some evidence of a diurnal circadian periodicity among PA cases in term infants (P-value=0.067). However, we did not find evidence of circadian rhythms in the time of onset of extremely or very preterm PROM (P-value=0.259) and preterm PA (P-value=0.224).

Conclusions—The circadian rhythms of the time of onset of preterm PROM and PA cases varied based on gestational weeks at delivery. While circadian rhythms were presented among moderate preterm PROM and term PA cases, there was no evidence of circadian rhythms among preterm PA and very or extremely preterm PROM cases, underlying other mechanisms associated with the time of onset.

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Keywords

Circadian rhythm; preterm birth; preterm premature rupture of membranes; placental abruption

INTRODUCTION

Biological periodicities occur based on a periodicity (rhythm) in a spectrum of frequencies ranging from milliseconds to years. The most common of these rhythms are those with periodicity close to 24 hours, namely the circadian rhythm. A circadian rhythm is any biological process that displays an endogenous oscillation of about 24 hours [1, 2].

The onset of labor is influenced by both maternal and fetal hypothalamic-pituitary-adrenal axes (HPA) that regulates cortisol release into periphery in a circadian and stress-related homeostasis. During normal pregnancy, cortisol in maternal circulation undergoes diurnal variation with an early morning peak, and minor peaks after meals. Cortisol reaches its lowest level approximately 3 to 5 hours after the onset of sleep [3-5]. Circulating diurnal levels of cortisol during pregnancy are likely related to the onset of deliveries [6], although evidence for the role of this mechanism in complicated pregnancies, such as in very or extremely preterm premature rupture of membranes (PROM) and placental abruption (PA), is vastly limited [7]. A circadian pattern has been described for the time of onset of spontaneous preterm deliveries [8]. However, little has been done to assess the extent to which, if at all, preterm PROM and PA cases present an identifiable circadian pattern [9, 10].

Spontaneous preterm PROM accounts for one-third of preterm births. Preterm PROM and PA have been regarded as part of a syndrome resulting from multiple pathophysiological pathways including infection or inflammation, vascular disease, trauma and uterine overdistension [11]. PA is seen in 4 to 12% of pregnancies diagnosed with preterm PROM, mostly prior to 28 gestation weeks [12-14].

We modeled the time of onset of preterm PROM and abruption cases by gestation weeks and examined if the circadian profiles for preterm PROM and PA varied based on the gestational age at delivery.

MATERIAL AND METHODS

Study Population and Data Collection

Data were drawn from women who delivered singleton infants at three hospitals in Lima, Peru, between January 2009 and July 2010. This study was approved by the institutional review boards from the participating hospitals in Lima, Peru and the Swedish Medical Center, in Seattle, US (IRB-4450). All personal identifiers were stripped from the study materials before conduct of the present study.

A total of 232 preterm PROM (gestational age 21 to <37 completed weeks) and 163 abruption (gestational age 21 to 42 completed weeks) cases were identified by daily monitoring of all new deliveries at the postpartum departments of the three hospitals.

Women that delivered as a result of obstetrical intervention (e.g., labor induction or a planned cesarean), or for whom the chorioamniotic membranes were artificially ruptured were excluded from the study.

From maternal medical records, a certified nurse midwife abstracted detailed information about gestational age and the time of onset of preterm PROM and PA cases. Gestational age was based on the date of the last menstrual period and confirmed by an ultrasound examination during prenatal visits before 20 weeks of gestation [15]. From records with a diagnosis of spontaneous preterm PROM (<37 weeks), the time of onset was defined as women self-reported starting time of leaking or gushing of fluid from the vagina, and confirmed by medical exploration at the time of the admission or only by medical records if the event happened during hospitalization. The time of the onset of abruption was defined as women's self-reported starting of profuse external bleeding accompanied by uterine tenderness or hypertonia plus intense back pain, confirmed by medical anamnesis at the moment of the admission.

Statistical Methods

First, we aggregated the number of preterm PROM and PA cases over a 60-minute epoch within a 24-hour period. Then we described the distribution of the time of spontaneous preterm PROM and abruption onset using the number of cases and percentages by hours and the four segments of the day. To compare the relative change in the number of events per segment of the day (morning: 07h:00' – 12h:00'; afternoon: 13h:00' –18h:00'; evening/night: 19h:00' – 24h:00'; and night: 01h:00' – 06h:00') , we estimated the prevalence ratios of the segment with the night segment as the reference. The estimated prevalence ratios and their respective 95% confidence intervals (CI) were derived using univariate generalized linear models under the assumption of a Poisson distribution, logarithmic link and scaled error standards to account for over-dispersion.

We then used a nonparametric descriptive approach to locally explore the probability density function of the observed data using the Epanechnikov kernel function with an optimal smoothing parameter [16]. We also developed an observational Fourier analysis to identify the presence of periodicity among preterm PROM and PA cases over a 24-hour period using a periodogram. The periodogram is a scatterplot of the sinusoidal amplitude (ordinate) versus the frequency (w , $\in [0; 0.5]$) of the natural log (the log truncates the graph at ± 6) of the values of the sinusoidal decomposition (discrete Fourier transformation). A strong sinusoidal signal for some frequency is represented with a peak in the periodogram at that frequency [17].

We categorized the gestational age at delivery into extremely or very preterm (<32 weeks) and moderate preterm (32 to <37 weeks) for preterm PROM cases and into preterm (<37 weeks) and term (37 weeks) for PA cases [18]. Afterwards, to model the time of onset of preterm PROM and PA, we used a non-linear trigonometric regression approach, modeling time in a circular scale [19]. We fitted four generalized trigonometric models with scaled standard errors of the regression coefficients to account for over-dispersion, family Poisson and link log. We fitted one model for each of the categories of gestation weeks of preterm PROM (very or extremely preterm and moderate preterm) and PA cases (term and preterm).

For all models we used the numbers of hourly onset as a dependent variable and sine and cosine functions (harmonic terms) as independent predictors of the number of cases. We computed the harmonic terms using the time (t) measured in a discrete 24 hours scale [19, 20]. We then transformed the resulting estimated harmonic terms to identify the time-phase shift and amplitude [20, 21]. We used the delta method to compute the standard errors of the estimated time-phase shift resulting from the nonlinearity of the transformed sine and cosine parameters for those models with a significant circadian pattern [22].

We used a k-fold cross validation strategy to compare the root mean squared error of different trigonometric models (with two, four, and six and harmonic terms) and decided the number of harmonic terms to include in the model. We also developed a piecewise cubic spline with six knots fixed at 04h:00', 08h:00', 12h:00', 16h:00', 20h:00' and 24h:00' hours and we used the Akaike Information Criteria (AIC) to compare models goodness of fit. Finally, based on the descriptive analysis, the cross validation strategy and the AIC, we decided to present the trigonometric model with four harmonic terms to allow a bimodal periodicity. We then used the estimated sinusoidal amplitude from this model to parametrically test the presence of a significant circadian pattern, assumed to be sinusoidal in shape and stationary in time [20] (more details about the derivation of the amplitude, phase, and circadian test, could be found in the appendix).

Finally, we replicated our analysis by applying the trigonometric models to data from the National Collaborative Perinatal Project (NCPP). Briefly, the NCPP is a prospective pregnancy cohort study that included 53,391 women enrolled from 12 academic centers in the US between 1959 and 1966 [23, 24]. For these replication analyses, we restricted data to 2,262 spontaneous singleton preterm PROM cases and 394 PA cases with complete information regarding the time of onset. All analyses were completed using Stata v.13.1 (StataCorp, College Station, Texas, USA).

RESULTS

Spontaneous preterm PROM onsets

The observed number of hourly spontaneous preterm PROM onsets showed a clear peak during the morning between 06h:00' and 10h:00' (40% of the cases) but this number falls during the afternoon and then another minor peak of cases appeared between 20:00' and 22h:00' (13% of the cases) (Table 1).

The onsets of moderate preterm PROM cases showed the highest frequency during the morning (36.4%) and the lowest frequency during the evening/night (14.9%). The morning showed two times higher frequency in the number of onsets compared with the evening/night (PR= 2.44, 95%CI 1.47, 4.14) (Table 2).

The onsets of extremely-very preterm cases showed the highest frequency during the morning (33.3%) and the lowest frequency during the afternoon (20.5%). The morning showed 1.4 times higher frequency in the number of onsets compared with the evening/night (PR= 1.44 95%CI 0.79, 2.68) (Table 2).

The local smoothed distribution and the periodogram of the observed number of preterm cases over 24 hours suggested the presence of regular periodicity compatible with a distinct circadian pattern. (Figure S1A, S1C).

Figure 1 shows the observed and fitted trigonometric distributions of the time of onset of preterm PROM cases. Assuming a sinusoidal circadian pattern, we identified a phase shift in a 24 hours period (modeled peak corresponding to the highest frequency of onsets over time and the crest time of the trigonometric curve fitted to the data) at 07h:53' (95% CI: 05:46' – 09:18') for moderate PROM cases. The sinusoidal circadian test was strongly significant (P-value <0.001) for moderate preterm PROM cases indicating a clear sinusoidal circadian pattern (Figure 1A). However, the observed data did not support the evidence of a circadian rhythm in the time of onset of extremely or very preterm PROM cases (P-value= 0.259) (Figure 1B).

Placental abruption onsets

The observed number of hourly placental abruption onsets also showed a peak during the morning between 05h:00' and 10h:00' (35% of the cases) and then another minor peak of cases appeared between 19:00' and 22h:00' (19% of the cases) (Table 1).

The onsets of term PA cases showed the highest frequency during the night (28.6%) and the lowest frequency during the afternoon (20.8%). The morning showed 1.2 times higher frequency in the number of onsets compared with the evening/night (PR= 1.22, 95%CI 0.65, 2.31) (Table 2).

The onsets of preterm PA cases showed the highest frequency during the morning (36.0%) and the lowest frequency during the afternoon (17.4%). The morning showed 1.5 times higher frequency in the number of onsets compared with the evening/night (PR= 1.48, 95%CI 0.85, 2.06) (Table 2).

The local smoothed distribution and the periodogram of the observed number of PA cases over 24 hours suggested the presence of regular periodicity compatible with a circadian pattern (Figure S1B, S1D).

Figure 2 shows the observed and fitted trigonometric distributions of the time of onset of placental abruption cases. Assuming a sinusoidal circadian pattern, we identified a phase shift in a 24 hours period at 04h:40' (95% CI: 03:53' – 06:48') for term PA cases. The sinusoidal circadian test was of borderline statistical significance (P-value= 0.067) for placental abruption cases at term (37 weeks), suggesting a sinusoidal circadian pattern (Figure 2A). However, the observed data did not support the evidence of a circadian rhythm in the time of onset of preterm PA cases (P-value= 0.224) (Figure 2B).

Replication Analysis

The replication analysis showed a significant circadian pattern for moderate preterm PROM (Figure S2A) and term PA cases (Figure S2C). We identified a phase shift in a 24 hours period at 02h:50' (95% CI: 02:38' – 03:20') for moderate PROM cases (Figure S2A) and at 02h:37' (95% CI: 02:32' – 03:13') for term PA cases (Figure S2C). For extremely or very

preterm PROM (Figure S2B) and preterm PA (Figure S2D) the replication did not support the evidence of a circadian rhythm in the time of onset of the cases (Supplementary Figure S2).

DISCUSSION

Main findings

We found a significant circadian pattern in the timing of onset of preterm PROM cases and evidence of a possible circadian pattern among cases of PA at term. This pattern is characterized by a diurnal cycle with a distinct morning peak between 05:46' and 09:18' for moderate preterm PROM cases and, between 03:53' and 06:48', for term PA cases, and a minor increase in the number of onsets approximately at 20:00' during the evening for both groups respectively. However, we did not find evidence of a circadian pattern among cases of very or extremely preterm PROM and preterm PA.

Strengths and Limitations

To the best of our knowledge, our study is the first to model the time of onset of preterm PROM and PA cases using trigonometric functions and time modeled as a circular scale. This robust methodological approach to model periodicity supports the validity of the absence of circadian rhythms driven by fetal immaturity.

Despite these findings, our data must be interpreted with some caution. First, measurement error based in maternal self-reports starting signs and symptoms of placental abruption and PROM is likely. We consider that our case definition, provided in the study protocol to identify cases through medical records, was accurate for major cases associated with obvious signs of preterm PROM and abruption. However, our abruption case definition ensures high specificity with some compromise in sensitivity, especially for mild cases. Regarding cases of severe abruption, the diagnosis generally is obvious. As a result, we have to limit the interpretation of our results to severe cases of preterm PROM and abruption.

Second, even if the sinusoidal circadian test used to statistically prove the presence of a circadian rhythm is sufficiently powered with samples sizes greater than 50 units, the power is dependent on the size of the estimated sinusoidal amplitude [19, 25]. We entertain the possibility that our findings may have been limited in terms of power when modeling cases by gestation weeks among abruption cases. However, the replication analysis confirmed the circadian periodicity among term PA cases. Given the low prevalence of PA, ranging between 3 and 12 cases per 1000 births [26], our study is to the best of our knowledge the first analysis identifying circadian rhythms among cases of PA.

Earlier evidence based on data from the NCPP also revealed a circadian pattern among spontaneous preterm PROM cases with a phase shift at 03h:00' [9]. Using the original NCPP data in our replication analysis, we also found a phase shift at 02h:50' for moderate preterm PROM cases whereas in our main analysis the phase shift for moderate preterm PROM cases was estimated at 07h:53'. This difference in the modeled phase shift did not affect the main finding regarding the presence of a circadian rhythm. However, previous

evidence established the time of the onset of spontaneous preterm deliveries with and without PROM ranging between 03h:00' and 07h:00'. [8-10, 27]

Finally, even if there is previous evidence regarding circadian rhythms of the time of onset of PROM in other geographical areas and periods that support our findings, the evidence is limited and the methods used to identify the circadian rhythms were not the most appropriate. In contrast, our statistical approach, modeling time in a circular scale and testing parametrically the presence of a circadian pattern, vastly support the internal validity of our findings. However, more evidence is needed, using the appropriate methodology with different populations and geographic areas, to externally validate these observations.

Interpretation

The diurnal circadian pattern for spontaneous preterm PROM found in our study, is consistent with other studies, and may be explained by a biological mechanism (HPA-axis) related to the triggering or initiation of parturition in term and moderate preterm pregnancies [6, 8, 9, 27-28]. The findings of a previous study modeling the time of onset of spontaneous PROM, showed a circadian pattern for moderate preterm but not for extremely preterm (<28 weeks gestation) cases, supporting the evidence of our results [27]. The investigators of that study hypothesized that for extremely preterm deliveries the onset of PROM may result from a pathological rather than a physiological process and the absence of a circadian pattern could be explained by the immaturity of the HPA-axis [27]. In addition, we did not find evidence of a circadian pattern among preterm PA cases. However, among term cases, the sinusoidal circadian test suggested some evidence of a circadian pattern being of borderline statistical significance.

Therefore, early preterm delivery associated with HPA-axis immaturity, and pathological rather than biological mechanisms, such as infections, may explain the absence of a circadian pattern among preterm PROM and PA cases. This observation provides room to speculate why tocolytic agents fail to arrest labor in some cases. While management with tocolytics is generally contraindicated in the setting of impending abruptions, their use may be less effective at very early gestational ages of PROM [29].

Furthermore, recent evidence showed that there was a significant increased risk of chorioamnionitis in women with preterm PROM who received treatment with tocolytics without significant benefits to the infant [29]. More evidence is needed in order to clarify the extent to which the increased risk of chorioamnionitis among preterm PROM cases treated with tocolytics is due to the treatment, a preexisting infection (responsible of the PROM), or the interaction of both conditions.

The fetal HPA-axis, which normally mediates the diurnal variation in uterine contractility [30], may account for the absence of circadian rhythms in extremely preterm deliveries. Uterine contractions have been studied using mobile tocodynamometer and data-storing units that document the hourly number of contractions that occur prior to labor, from 24 weeks and onwards [30, 31]. A strong diurnal variation to non-labor uterine contractions increased with advanced gestation and contraction frequency reached a maximum rate in the early morning hours [31]. Oxytocin is known to have a diurnal rhythm that demonstrates a

peak of activity at midnight [31, 32]. Therefore, early preterm delivery is likely to circumvent the physiological mechanism of the onset of labor and normal rupture of membranes responsible for a circadian rhythm [8, 9, 27].

CONCLUSIONS

In summary, we have demonstrated a circadian pattern among moderate preterm PROM and term PA cases. However, there was no evidence of circadian rhythms among preterm PA and very or extremely preterm PROM cases. This absence of circadian pattern underlies other pathological mechanisms associated with the time of the onset of preterm PROM and PA rather than a normal biological circadian rhythm. Increased understanding of circadian rhythms in pregnancy and parturition may yield important insights towards an understanding of the pathophysiologic mechanisms leading to spontaneous preterm PROM and PA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Models specification was:

$$g(Y_t) = c \cos(w_t) + s \sin(w_t), \quad t=1, \dots, 24$$

$$g(\cdot) = \text{link} = \log(\text{number of cases}); \quad \text{family: Poisson}$$

where the frequency of the time was converted to a circular scale:

$$w_t = 2\pi \left(\frac{\text{hours}_t - 0.5}{24} \right) k, \quad k = \text{Number of cycles per day}$$

where the amplitude (A) was defined as:

$$A = \sqrt{c^2 + s^2}, \quad (A \geq 0)$$

and the phase (P) in time scale was:

$$P = 24 \left(\frac{\arctan\left(\frac{s}{c}\right)}{2\pi} \right) + 1$$

The circadian test statistic used was:

$$Z=n\bar{A}^2, \quad \bar{A}=\sqrt{\bar{C}^2+\bar{S}^2}$$

The p-value for the null hypothesis that (average amplitude) = 0 was computed as the exponent of (-Z) [17, 22].

List of abbreviations

AIC	akaike information criteria
CI	confidence intervals
HPA	hypothalamic-pituitary-adrenal axes
NCPP	national collaborative perinatal project
PA	placental abruption
PROM	premature rupture of membranes

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Highlights

- Data regarding circadian rhythm in the onset of spontaneous preterm PROM and PA cases are conflicting.
- This study shows that the time of onset of spontaneous moderate preterm PROM and term PA cases is characterized by a diurnal circadian pattern. However, the time of onset of very preterm PROM and PA cases seem to be characterized by an absence of a circadian pattern associated with fetal immaturity.
- Increased understanding of circadian rhythms in pregnancy and parturition may yield important insights towards an understanding of the pathophysiologic processes and mechanisms leading to spontaneous preterm PROM and PA.

Figure 1.
Modeled time of the onset of preterm PROM cases by gestation weeks in Lima, Peru, 2009-2010 (moderate preterm PROM from 32 to <37 weeks, n=154 and very-extremely preterm PROM, <32 weeks, n=78)

Figure 2.
Modeled time of the onset of placental abruption cases by gestation weeks in Lima, Peru,
2009-2010 (37 to 42 weeks, n=77 and <37 weeks, n=86)

Table 1

Counts of preterm PROM and placental abruption onsets by hour per day, in Lima, Peru, 2009-2010 (Preterm PROM, n=232 and Placental Abruption, n= 163)

	Preterm PROM (n=232)	PA (n=163)
Time in 24h	%	%
01h:00' - 01h:59'	4.3	3.1
02h:00' - 02h:59'	2.6	8.6
03h:00' - 03h:59'	4.7	2.5
04h:00' - 04h:59'	0.0	0.6
05h:00' - 05h:59'	6.5	3.1
06h:00' - 06h:59'	11.2	7.4
07h:00' - 07h:59'	6.0	6.8
08h:00' - 08h:59'	7.3	8.0
09h:00' - 09h:59'	3.9	6.1
10h:00' - 10h:59'	11.6	3.1
11h:00' - 11h:59'	3.0	4.3
12h:00' - 12h:59'	3.5	3.7
13h:00' - 13h:59'	1.7	3.1
14h:00' - 14h:59'	3.0	2.5
15h:00' - 15h:59'	2.2	6.1
16h:00' - 16h:59'	3.5	3.1
17h:00' - 17h:59'	3.5	1.8
18h:00' - 18h:59'	3.9	2.5
19h:00' - 19h:59'	0.9	5.5
20h:00' - 20h:59'	5.6	3.7
21h:00' - 21h:59'	2.2	4.9
22h:00' - 22h:59'	5.2	4.9
23h:00' - 23h:59'	2.6	3.1
00h:00' - 00h:59'	1.3	1.8

Table 2

Distribution of preterm PROM and placental abruption onset by segment of the day and gestation weeks, in Lima, Peru, 2009-2010 (Preterm PROM, n=232 and Placental Abruption, n= 163)

Segments of the day	Preterm Premature Rupture of Membranes (n= 232)				Placental Abruption (n=163)			
	Moderate Preterm (32 to <37 weeks, n=154)		Extremely-very Preterm (<32 weeks, n=78)		Term (37 to 42 weeks, n=77)		Preterm (<37 weeks, n= 86)	
	n(%)	PR* (95%CI)	n(%)	PR(95%CI)	n(%)	PR(95%CI)	n(%)	PR(95%CI)
Night								
01h:00' to 06h:00'	50(32.5)	2.18(1.33, 3.62)	18(23.1)	1.00(0.51, 1.92)	22(28.6)	1.22(0.65, 2.31)	19(22.1)	0.91(0.48, 1.69)
Morning								
07h:00' to 12:00'	56(36.4)	2.44(1.47, 4.14)	26(33.3)	1.44(0.79, 2.68)	21(27.3)	1.16(0.61, 2.22)	31(36.0)	1.48(0.85, 2.06)
Afternoon								
13h:00' to 18h:00'	25(16.2)	1.08(0.61, 1.93)	16(20.5)	0.88(0.44, 1.76)	16(20.8)	0.88(0.45, 1.75)	15(17.4)	0.71(0.36, 1.39)
Evening/night								
19h:00' to 24h:00'	23(14.9)	Ref.	18(23.1)	Ref.	18(23.3)	Ref.	21(24.4)	Ref.

* PR: Prevalence Ratio