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Acute Associations between Outdoor Temperature and Premature Rupture of Membranes

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Abstract

Background—Extreme ambient temperatures have been linked to preterm birth. Preterm premature rupture of membranes is a common precursor to preterm birth but is rarely studied in relation to temperature.

Methods—We linked 15 381 singleton pregnancies with premature rupture of membranes from a nationwide US obstetrics cohort (2002–2008) to local temperature. Case–crossover analyses compared daily temperature during the week preceding delivery and the day of delivery to two control periods, before and after the case period. Conditional logistic regression models calculated the odds ratio (OR) and 95% confidence intervals (CI) of preterm and term premature rupture of membranes for a 1°C increase in temperature during the warm (May–September) and cold (October–April) season separately after adjusting for humidity, barometric pressure, ozone and particulate matter.

Results—During the warm season, 1°C increase during the week before delivery was associated with a 5% (95% CI: 3–6%) increased preterm premature rupture of membranes risk, and a 4% (95% CI: 3–5%) increased term premature rupture of membranes risk. During the cold season, 1°C increase was associated with a 2% decreased risk for both preterm (95% CI: 1–3%) and term premature rupture of membranes (95% CI: 1–3%). The day-specific associations for the week before delivery were similar, but somewhat stronger for days closer to delivery.

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Conflicts of interest

The authors have declared no actual or potential conflict of interest.

Data availability

The data of this study are currently not publicly available. A data use agreement is required and can be obtained from the corresponding author.

Conclusions—Relatively small ambient temperature changes were associated with the risk of both preterm and term premature of membranes. Given the adverse consequences of premature rupture of membranes and concerns over global climate change, these findings merit further investigation.

Keywords

temperature; climate change; rupture of membranes; preterm birth; PROM; PPRM

Background

Premature rupture of membranes is the rupture of the fetal membranes without the onset of labor. Premature rupture of membranes after 37 weeks of gestation (generally considered term) occurs in approximately 8%–10% of pregnancies.¹ Although shown to be associated with increased risk of some adverse outcomes including neonatal sepsis, maternal chorioamnionitis, and endometritis, term premature rupture of membranes is considered a relatively pathologically benign pregnancy complication resulting from the natural weakening of the fetal membranes towards the end of pregnancy.² Women who present with term premature rupture of membranes typically have labor induced without serious consequences. On the other hand, preterm premature rupture of membranes—defined as premature rupture of membranes prior to 37 weeks of gestation—is more serious and complicates about one in three preterm births.³ Preterm premature rupture of membranes is associated with increased risk of serious complications for both mothers^{4,5} and infants,^{1,6,7} both during the perinatal window and later in life. As a leading identifiable cause of preterm delivery, it accounts for 18%–20% of perinatal deaths in the US¹, and many subsequent health sequelae including developmental complications.⁷

The exact cause of premature rupture of membranes is not well understood, but underlying infection, inflammation, and oxidative stress may play a pivotal role.^{3,8} In fact, prenatal exposures to environmental hazards (e.g., air pollution and smoking) have been linked to both term and preterm premature rupture of membranes potentially through these pathways.^{9–11} However, the potential associations of other ubiquitous ambient environmental exposures such as outdoor temperature with term and preterm premature rupture of membranes have rarely been explored. This is an important research gap given the world-wide concerns related to the expected increase in the magnitude and frequency of extreme weather events associated with climate change,^{12,13} and the deleterious consequences of premature rupture of membranes, and preterm premature rupture of membranes in particular¹.

Previous research suggests that similar to other environmental hazards, extreme ambient temperature may affect health through long- and short-term systemic inflammatory and oxidative stress responses.^{14–17} Both high and low ambient temperatures have been associated with preterm delivery, possibly with preterm premature rupture of membranes as a precursor, but many studies were unable to distinguish between spontaneous and indicated preterm birth, making it difficult to assess whether there is a true relationship.^{18–20} Given preterm premature rupture of membranes is a proximal cause of many preterm births,

determining the association between extreme ambient temperature and the risk of preterm premature rupture of membranes will help clarify this relationship. To date, we are aware of only one study that examined the potential influence of meteorological factors on the risk of preterm premature rupture of membranes, which was conducted in the Negev, a semi-arid area in the south of Israel. High temperature and humidity appeared to increase the risk of preterm premature rupture of membranes as did desert heat waves in this population of primarily rural women, including semi-nomadic Bedouins.²¹ No prior studies have examined this association in urban areas with a temperate climate. Our objective was to examine the acute associations between ambient temperature and the risk of premature rupture of membranes (both preterm and term) in a nationwide, contemporary US obstetric cohort. To control for time-invariant confounding, we used a case–crossover design with each premature rupture of membranes case serving as her own control, where the ambient temperature over a hazard window (week before delivery) was compared to that during control periods before and after the event.²²

Methods

Data and participants

The Air Quality and Reproductive Health study linked participants from the Consortium on Safe Labor (CSL) to local meteorological measures. CSL was an observational cohort study comprising 228 438 deliveries 23 weeks of gestation across 12 US clinical centers (15 non-overlapping hospital referral regions) from 2002 to 2008 (Figure 1). Maternal demographics; medical history; labor and delivery, obstetric, and neonatal outcomes were abstracted from electronic medical records and/or discharge summaries. A more detailed description of the CSL study design and its data validation methods have been previously published.²³ The study had been approved by Institutional Review Boards from all participating clinical centers. Informed consent was not required because the study was based on anonymous data. Initially eligible for this analysis were 15 588 singleton pregnancies with reported premature rupture of membranes at any gestational age (7.0% of the 223 385 singleton pregnancies in the original cohort). Women who had two deliveries with premature rupture of membranes during the study period (n=207) were included only for their first pregnancy, leaving 15 381 pregnancies in the final analysis.

Exposure assessment

Daily ambient meteorologic factors were obtained for each woman using the Weather Research and Forecasting (WRF) models. WRF modeling method and validation have been published elsewhere.^{24,25} Briefly, WRF is a state-of-the-art weather prediction system, designed and used by many leading research, governmental, and academic entities for atmospheric research and forecasting. WRF outputs hourly temperature for 12×12km² grids across the US. Since the CSL was anonymous, we did not have detailed residential addresses to perform spatial interpolation. Instead, we used the 15 non-overlapping hospital referral regions (range 415–312,644 km²) as a proxy for residence and local mobility associated with commuting for work and other daily activities. In other words, each woman's exposure was assigned as the average daily temperature in the grids that fell within her hospital referral region (Figure 1) over specific periods of interest (i.e., case and control periods).

Since our main objective was to investigate acute associations of temperature with premature rupture of membranes we calculated average daily temperature over a hazard period: the week preceding delivery, day of delivery (lag 0), and each of the seven days before delivery (lag1–lag7), and compared exposures during this hazard period to two alternate control periods for the same women using a case–crossover analysis.²² We selected the week preceding delivery as the hazard period since literature on acute health effect of ambient temperature on other delivery outcomes shows meaningful associations within this time window.^{26,27} To minimize time trend bias, we used the symmetric bidirectional method to select two control periods: the second week after delivery and the week two full gestational weeks before delivery.²⁸ Post-event control period may not seem intuitive because the person is considered no longer at risk after the event. However, studies have shown that the bidirectional control selection method is preferred over the unidirectional method (i.e., selecting control periods only before the event), which is sensitive to time-trend bias.^{28,29}

Outcome and covariate assessment

All outcomes were determined based on electronic delivery records, and supplemented with International Classification of Diseases Version 9 (ICD-9) codes from discharge summaries. Premature rupture of membranes was defined as rupture of membranes before the onset of labor at any gestational age. Preterm premature rupture of membranes was defined as premature rupture of membranes before 37 weeks of gestation, and term premature rupture of membranes was defined as premature rupture of membranes occurring at or after 37 weeks of gestation. Given recent evidence on the associations between air pollution and premature rupture of membranes in our data¹¹, we also assessed ozone and particulate matter with diameter <2.5 microns (PM_{2.5}) during the same exposure windows as previously described for temperature. Air pollution exposures were estimated using modified Community Multiscale Air Quality (CMAQ) models. Briefly, these models predict air pollution levels at any given time/space using inputs from multiple sources including local emission from the National Emission Inventory, local weather from the WRF, population density, and photochemical properties of the pollutants. Outputs for these pollutants were also corrected for measurement error between modeled and observed levels at local air monitors using inverse distance weighting.²⁴ In addition, we included humidity and barometric pressure predicted from the WRF model as a covariate as both of these parameters may be associated with temperature and potentially affect premature rupture of membrane risk.^{21,30}

Statistical analysis

We used a case–crossover analysis to investigate acute effects of temperature during the week preceding delivery (daily temperature at lag0–lag7 and weekly average). This design allows us to control for both measured and unmeasured time-invariant confounding by comparing a hazard period to alternative control periods, where each woman served as her own control. The control periods were selected to reflect the background exposure levels for the same woman, and since control periods were relatively close to delivery, temperature levels were not likely affected by seasonal variation. In this analysis, we tested whether the women with premature rupture of membranes were experiencing temperatures higher than usual during the hazard periods holding everything else about their delivery and time-

invariant characteristics constant. We estimated the odds ratio (OR) and 95% CI for each 1°C (2.8 °F) increase in temperature using conditional logistic regression adjusting for relative humidity, barometric pressure, and exposures to PM_{2.5} and ozone during the same lag. We analyzed temperature as a continuous exposure for two reasons. First, we expect the temperature differences between the case and control periods to be small (since they were only a few weeks apart). Categorization of temperature would result in many subjects having the same exposure category in the case and control periods; these subjects would contribute no information to estimating the conditional logistic regression. Second, our exploratory analyses did not suggest any quadratic temperature effect, so a nonlinear relationship was unlikely. We also chose the unconstrained lag model because of the linear nature of the relationship and a hypothesized short lag.³¹ We stratified our analyses by season of delivery (warm: May–September, cold: October–April) to further minimize seasonal confounding, and by premature rupture of membranes status (preterm and term). To ensure consistency, we repeated our analysis excluding site 5, the largest geographic area with potentially the most imprecise exposure estimates.

Sensitivity analyses

In addition to the main analyses, we also repeated our analyses restricting the cold season to November–February, and warm season to May–August to ensure robustness of our findings. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

Results

Of the 15 381 singleton pregnancies with premature rupture of membranes, 5032 (33%) were preterm and 10 349 (67%) were term (Table). More participants delivered during the cold season compared to the warm season. Among all women with premature rupture of membranes, most were White, had a male infant, and had private insurance (Table). The proportion of unmarried women was higher among term compared to preterm premature rupture of membranes. In addition, the proportions of women who smoked or consumed alcohol during pregnancy or had gestational complications were higher in the preterm compared to the term premature rupture of membranes group (Table). eTables 1 and 2 describe the temperature distributions and their correlations during the week before delivery by season of delivery, respectively.

Figures 2 and 3 illustrate the acute associations between ambient temperature during the week before delivery and the odds of premature rupture of membranes during the cold and warm season, respectively. Effect estimates can be found in eTable 3. In the cold season, each 1°C increase in average temperature during the week preceding delivery was associated with about a 2% decrease in risk for both preterm (aOR_{lag0–7}: 0.98, 95% CI: 0.97–0.99) and term premature rupture of membranes (aOR_{lag0–7}: 0.98, 95% CI: 0.97–0.99). The associations for the day of delivery and each of the 7 days before delivery (lags 0 to lag 7) were similar (Figure 2, eTable 3). In the warm season, we found a 4–5% increase in risk of premature rupture of membranes for each 1°C increase in temperature during the week before delivery (preterm premature rupture of membranes aOR_{lag0–7}: 1.05, 95% CI: 1.03, 1.06; term premature rupture of membranes aOR_{lag0–7}: 1.04, 95% CI: 1.03–1.05) as shown

in Figure 2 and eTable 3. The associations for the day of delivery and each of the 7 days before delivery in the warm season were also generally consistent during the days closer to delivery but associations were less significant on lag day 6 and null on day 7, especially for preterm premature rupture of membranes. Additional analyses excluding site 5 (Intermountain Health) showed consistent results (eTable 4).

When restricting cold season to November–February and warm season to May–August, the results remained consistent with evidence of stronger associations during these time windows when temperatures are typically more extreme (eTable 5). For example, a 1°C increase in temperature during the day of delivery was associated with 4% decrease ($OR_{lag0}: 0.96$, 95% CI: 0.95–0.97) in preterm premature rupture of membranes risk during the newly defined cold season while the main analyses showed a 1% decreased risk. Similarly, 1°C increase in temperature on the day of delivery was associated with an 8% ($OR_{lag0}: 1.08$, 95% CI: 1.06–1.10) increase in risk of preterm premature rupture of membranes in the newly defined warm season whereas main analyses showed 4% decreased risk.

Discussion

In this large nationwide case–crossover analysis of women with premature rupture of membranes, we found consistent evidence suggesting short-term increase in the risk of both term and preterm premature rupture of membranes associated with higher temperature during the warm season and lower temperature during the cold season. These findings suggest short-term adverse effects of both high and low ambient temperatures on the risk of premature rupture of membranes. To our knowledge, this is the first study to investigate the acute, potentially triggering effects of ambient temperature on premature rupture of membranes. One prior study reported associations between preterm premature rupture of membranes and temperature, including desert heat waves, during 1999²¹. This is the first study in a temperate region of the globe and the first to examine differences in absolute temperature over a short timeframe. Our case–crossover analysis finds that the week prior to a delivery complicated by premature rupture of membranes is likely to have a higher temperature in the warm season and a lower temperature in the cold season. These findings are also consistent with multiple studies on the acute associations between ambient temperature and preterm birth, a direct consequence of most cases of preterm premature rupture of membranes^{18,27,32–34}. Many existing studies on temperature and preterm birth do not distinguish between spontaneous and indicated preterm birth and none address the spontaneous premature rupture of membranes cases separately from spontaneous labor. Our results suggest that there is a relatively strong association of acute temperature with risk of premature rupture of membranes over a small range of temperature change. If our findings are replicated it also suggests that previously observed temperature effects on preterm birth may be partially mediated through preterm premature rupture of membranes, which is a precursor of about one third of all preterm births³. In addition, our results also showed associations of a similar magnitude with term premature rupture of membranes, which further suggests that there may be a relationship between temperature and premature rupture of membranes that is independent of gestational age. These observations are also consistent with studies suggesting that temperature is also a trigger for labor among term births^{32,34}.

Our findings are biologically plausible although the mechanisms underlying the associations between ambient temperatures and premature rupture of membranes remain unclear. Programmed cell death, activation of catabolic enzymes, maternal inflection, and/or mechanical forces can trigger rupturing of the membranes.³⁵ With proper thermoregulation, the human body is able to regulate small environmental changes in temperature but it is possible that high and low ambient temperatures exacerbate these natural processes, leading to preterm premature rupture of membranes. For example, a small body of evidence suggests that the increase in oxidative stress and inflammatory markers following acute exposures to high or low ambient temperatures may play an important role³⁵. Specifically, both animal and human studies have shown that acute exposures to high and low temperatures are associated with oxidative stress and systemic inflammation^{17,36–39}. These mechanisms are more evident in the cardiovascular literature, but there is evidence that they may also contribute to the risk of term and preterm premature rupture of members³⁵. The fact that we found stronger associations for days closer to delivery is also consistent with findings on temperature effect on cardiovascular biomarkers. For example, a study among type 2 diabetic patients in China found increased levels of inflammatory, coagulation, and vasoconstriction markers as soon as 3 hours after exposure to cold temperature and these effects lasted up to about 72 hours post exposure. This further supports the notion of a similar mechanism between premature rupture of members and cardiovascular system effects.

Although the magnitude of associations (for 1°C increase in temperature) observed in our study are modest, they have important implications especially in the context of climate change and the ubiquitous nature of exposure to ambient temperature. Global warming is expected to lead to more frequent and more severe extreme temperature events⁴⁰. During the last few decades, ambient temperature in the US has risen more than 2 °F (>1 °C) and is expected to increase⁴¹. In this study, the 5% increase in risk of preterm premature rupture of membranes associated with 1°C increase in temperature during the week prior to delivery is equivalent to approximately 16 excess cases of preterm premature rupture of membranes per 1000 preterm births in the US (calculated based on a rate of preterm premature rupture of membranes of 33% among preterm births) during the warm season.⁴² This number is also expected to increase as the temperature distribution shifts to the right. In the US, the rate of preterm birth was ~11% during the study period,⁴³ based on about 1.8 million births taken place in the warm season each year, we might expect approximately 3200 excess cases of preterm birth due to temperature-related preterm premature rupture of membranes. Our findings are also particularly relevant for other parts of the world where both temperature extremes and preterm births are more prevalent.

While higher temperature was found to be associated with increased risk in the warm season, it was associated with lower risk during the cold season. It is important to note here that although climate change is expected to increase the mean temperature, it is also associated with increased temperature variance resulting in extreme temperatures on both ends. Therefore, while we expect more frequent and intense heat events during the warm season, cold temperature is still expected to occur during the cold season and is still an important health concern in the context of global warming.⁴⁴

There are some limitations to consider in the interpretation of the current findings. First, due to the anonymous nature of the data, we did not have access to maternal residential address for detailed interpolation of exposure, and had to use referral hospital regions as a proxy for residence. While this may account for local mobility, it may be a source of error in exposure assessment. Specifically, average exposure across a hospital referral region as a proxy for residential exposure may not be representative of true exposure and may have smoothed smaller local extremes. This likely decreased exposure variability and biased our results towards the null. Meanwhile, it is reassuring that excluding the largest geographic region did not change the results. We note that in this study women are their own controls, so their long-term trend in local mobility likely had minimal influence on the results. On the other hand, we had no information on short-term change in other time-varying activities (within a month), which could potentially affect our findings. For example, if a woman relocates between our case and control periods (i.e., the week before or after delivery) to a region with different exposures, then this may have caused exposure misclassification and biased our results. However, we expect this to be a rare occurrence given our exposure windows are close to time of delivery. In addition, we had no detailed information on the exact time of the occurrence of premature rupture of membranes, which required us to use time of delivery as a proxy. However, since the American College of Obstetricians and Gynecology's Practice Bulletin's recommends labor induction at the time of term premature rupture of membranes presentation to minimize the risk of choriomanionitis^{2,45}, it is a reasonable assumption that there is not a long delay between premature rupture of membranes and delivery. Our use of the weekly average comparison may also help alleviate this issue. We also did not have refined information on time lapse (i.e., the time between membrane rupture and onset of labor), and relied on clinical diagnosis of premature rupture of membranes which was recorded in the medical records as any rupture of membranes before the onset of labor. However, the case–crossover design can mitigate this concern as women served as their controls.

This is the first large study with rich clinical data to examine the association between ambient temperature and risk of premature rupture of membranes. The case–crossover design allows us to control for both measured and unmeasured time-invariant confounders. The symmetric bidirectional control selection method, coupled with the stratification by delivery season helped minimize time trend bias. We were also able to control for other environmental pollutants, barometric pressure, and humidity to ensure our results are not confounded by other ambient environmental factors. Studying a region with temperature, we were able to show that even small changes in temperature within a relative short but critical period of time were associated with risk of premature rupture of membranes.

Conclusion

In this nationwide case–crossover analysis of US women affected by any premature rupture of membranes, we found a pattern of association consistently suggestive of increased risk following acute exposures to cold temperature during the cold season or hot temperature during the warm season. Given the adverse health sequelae associated with preterm premature rupture of membranes, the change in population-level maternal risk factors (e.g., increasing prevalence of maternal obesity, advanced maternal age, and gestational

complications), and the increasing trend in global temperature, these findings merit further investigation. Meanwhile, awareness of the potential adverse effects of extreme ambient temperature on delivery outcomes for pregnant women is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study sites.

Figure 2.

Acute associations between ambient temperature during the week prior to delivery and premature rupture of membranes during the cold season (October–April). Models were adjusted for humidity, barometric pressure, ozone, and particulate matter with aerodynamic diameter <2.5 microns during the same lag. ORs are for 1 degree Celsius (2.8 °F) increase in temperature. The y-axis is on the logarithmic scale.

Figure 3.

Acute associations between ambient temperature during the week prior to delivery and premature rupture of membranes during the warm season (May–September). Models were adjusted for humidity, barometric pressure, ozone, and particulate matter with aerodynamic diameter <2.5 microns during the same lag. ORs are for 1 degree Celsius (2.8 °F) increase in temperature. The y-axis is on the logarithmic scale.

Table

Characteristics of study participants who had singleton pregnancies complicated by premature rupture of membranes (N=15 381)

Characteristics	PPROM 5032 (33)		Term PROM 10 349 (67)	
	n	%	n	%
Race/ethnicity				
Non-Hispanic White	2127	42	5153	50
Non-Hispanic Black	1587	32	2173	21
Hispanic	819	16	1635	16
Asian/Pacific Islander	168	3	672	7
Other	121	2	229	2
Unknown	210	4	487	5
Maternal age				
<20	552	11	946	9
20–24	1218	24	2406	23
25–29	1161	23	2609	25
30–34	1145	23	2472	24
35	948	19	1903	18
Unknown	8	0	13	0
Infant sex				
Female	2298	46	5072	49
Male	2709	54	5267	51
Unknown	25	1	10	0
Marital status				
Married	2461	49	3806	37
Not married	2395	48	6080	59
Unknown	176	4	463	5
Parity				
0	2265	45	5745	56
1	2767	55	4604	45
Pre-pregnancy BMI				
<18.5	177	4	329	3
18.5–24.9	1468	29	3507	34
25–29.9	650	13	1429	14
30	587	12	1071	10
Unknown	2150	43	4013	39
Smoking during pregnancy	582	12	626	6
Alcohol use during pregnancy	121	2	119	1
Hypertensive disorders of pregnancy	184	4	324	3
Gestational diabetes	368	7	486	5
Insurance type				
Private	2565	51	6232	60

Characteristics	PPROM 5032 (33)		Term PROM 10 349 (67)	
	n	%	n	%
Public	1920	38	2532	25
Other	83	2	146	1
Unknown	464	9	1439	14
Season of delivery				
Cold	2697	54	5695	55
Warm	2335	46	4654	45

Abbreviations: PROM premature rupture of membrane; PPRM preterm premature rupture of membrane; BMI body mass index.