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CLINICAL ARTICLE

Exposure to life-threatening stressful situations and the risk of preterm birth and low birth weight

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ABSTRACT

Objective: To evaluate the association between exposure to life-threatening rocket attacks and the risks of preterm birth (PTB) and low birth weight (LBW). *Methods:* The present retrospective cohort study compared the outcomes of 1851 births by women exposed to rocket attacks and 2979 births by unexposed women. The timing, frequency, and intensity of exposure were calculated for each trimester and for the entire pregnancy period. Demographic and medical data were abstracted from the patients' records. *Results:* The rates of PTB and LBW were higher among exposed than unexposed women (PTB: 9.1% versus 6.8%, $P = 0.004$; LBW: 7.6% versus 5.8%, $P = 0.02$). The rate of infants who were small for gestational age did not differ between the groups. After controlling for potential confounders, the risks for PTB and LBW remained significantly higher in the exposed group (PTB: adjusted odds ratio 1.3 [95% confidence interval, 1.1–1.7]; LBW: adjusted odds ratio 1.3 [95% confidence interval, 1.03–1.7]). There was no linear association between the intensity of exposure and the risk of PTB or LBW. *Conclusion:* Maternal exposure to intermittent but repeated life-threatening rocket attacks for a prolonged period might be associated with increased risks of PTB and LBW.

1. Introduction

The incidence of preterm birth (PTB), defined as delivery before completion of 37 weeks of pregnancy and usually associated with low birth weight (LBW), has been rising in all high-income countries [1]. It is the leading cause of infant mortality in these countries and a prime contributor to infant and child morbidity, resulting in a major burden on healthcare systems [2].

Although genetic, behavioral, and social factors are known to increase the risk for PTB [3], its etiology remains unclear. The relationship between prenatal maternal stress and PTB has been extensively researched [4–6], but the evidence is inconclusive. Further, stress has been shown to adversely affect pregnancy through unhealthy behaviors, such as smoking and inadequate prenatal care [7]. However, not all studies have confirmed that stress has a negative impact on pregnancy outcomes [8,9], and some have even found the opposite affect [6,10]. In addition, the data are inconsistent with regard to the period of pregnancy when stress exposure is most likely to affect pregnancy outcome.

The unfortunate situation in southern Israel presents an opportunity to study this association. The southern Israeli town of Sderot (population of approximately 20 000) has been a constant target of rocket-firing from the Gaza Strip (4 km away) since 2001. These rocket attacks are preceded by a warning alarm, informing residents to seek shelter. The alarms are loud, sudden, and stress-inducing because they are sounded only a few seconds before rockets hit the town. Between April 2001 and December 2008, over 1000 alarms were sounded around the town [11]. Numerous rockets fell and exploded, causing damage to property and human lives [11].

The aim of the present study was to evaluate the association between exposure to stress during pregnancy (as measured by the number of rocket-attack alarms) and the risks of PTB and LBW.

2. Materials and methods

The present retrospective cohort study was carried out at Barzilai Medical Center, the single regional hospital in the area surrounding the Gaza strip, located in the city of Ashkelon. Barzilai is the closest medical center to Sderot (20 km north), and approximately 75% of Sderot's parturients deliver there. The remaining deliveries are carried out in other medical centers, which provide similar services including operating rooms and neonatal intensive care units. Women residing in Sderot who delivered between January 1, 2002 (that is, women who conceived after April 15, 2001, when rocket attacks on the town began, and who were therefore exposed throughout pregnancy), and December 27, 2008 (the date a military conflict began and a wide area of southern

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Israel became intensively exposed to rocket attacks), comprised the "exposed" group. Women residing in the town of Kiryat Gat who delivered during the same period at Barzilai Medical Center comprised the "unexposed" group. Kiryat Gat, which—at the time of the study—was outside the range of rocket attacks, was chosen for comparison because it had a similar socioeconomic profile to Sderot [12], and is located the same distance (20 km east) from Barzilai Medical Center. To further test the hypothesis that exposure to rocket attacks may be associated with adverse birth outcomes, we compared birth outcomes in the 2 towns between January 1, 2000, and April 14, 2001, when neither town was exposed to rocket attacks, to establish a historical reference. The study was approved by the Institutional Review Board of Barzilai Medical Center. Informed consent was not required.

In Israel, routine prenatal care is covered by universal national health insurance and almost all Jewish women in Israel seek prenatal care. The standard of prenatal care includes an early pregnancy ultrasound scan for confirmation of pregnancy and pregnancy dating, an ultrasound scan of fetal systems in the second trimester, and a glucose tolerance test.

Hospital admission records of all women from Sderot and Kiryat Gat who delivered at Barzilai Medical Center between January 1, 2000, and December 27, 2008, were identified during the year 2009. Medical and demographic information of all parturients with a singleton pregnancy, including parity, maternal age, country of birth, and pregnancy complications and outcomes, was collected. Identifying characteristics were coded and all data were analyzed anonymously.

The pregnancy duration was determined by early ultrasound or the date of the last menstrual cycle. Preterm birth was defined as delivery before 37 completed weeks. Low birth weight was defined as a birth weight of less than 2500 g, and small for gestational age (SGA) as a birth weight below the 5th percentile for the pregnancy duration at birth, according to the WHO growth tables [13].

Information about the dates when rocket-attack warning alarms were sounded in Sderot during the study period was obtained from local authorities. For each pregnancy, the mean number of alarms per week from conception until delivery and during each trimester was calculated. The intensity of exposure was classified by quintiles and was determined separately for each trimester and for the total pregnancy period.

The data were coded and analyzed using SPSS version 17.0 (IBM, Armonk, NY, USA). WinPepi (Brixton Health, London, UK) was used for the power calculation. Univariable comparisons were made using the *t*, Mann–Whitney *U*, and χ^2 tests as appropriate. The incidences of PTB and LBW in the exposed and unexposed groups were compared using odds ratios (OR) with 2-sided 95% confidence intervals (CI). $P < 0.05$ was considered statistically significant.

Multivariable logistic regression models were created using generalized estimating equations, in which pregnancies occurring in the same woman were entered as a cluster. The models were evaluated using receiver operating characteristic analysis and the final models were chosen by the highest concordance, or *c*, statistic score. The models were used to evaluate the association of stress exposure with PTB or LBW, with adjustment for all risk factors that were hypothesized to be related to these outcomes or found to be potential confounders in the study population.

Exposure variables used in the univariable and multivariable analyses included town of residence (dichotomous variable) and intensity of exposure during each trimester (continuous variable).

3. Results

The study included 4830 births (2979 in the unexposed group and 1851 in the exposed group) by 3676 women (2275 unexposed and 1401 exposed). The number of weekly alarms in the exposed group ranged from 0 to 71, with a mean of 2.16 ± 2.71 and a median of 0 during all weeks of pregnancy.

There were 2128 women who delivered more than once during the study period, none of whom had moved from one town to the other changing their exposure status. Most women in the study population were 21–35 years old, married, and born in Israel, had a high school diploma, and had conceived spontaneously (Table 1). Compared with the exposed group, a larger proportion of women in the unexposed group was older than 35 years, was born in Israel, and had less than 12 years of education. The rate of women in the exposed group with more than 12 years of education remained steady throughout the period of exposure: 32.2% (76/236 women) in 2002, 33.6% (90/268 women) in 2004, 29.9% (61/204 women) in 2006, and 34.3% (86/251 women) in 2008. The exposed and unexposed groups were similar in terms of other characteristics, pregnancy complications, and cesarean delivery rates (Table 1).

In the total study population, the mean pregnancy duration was 275.6 ± 13.2 days and the mean birth weight was 3227 ± 503 grams. The rate of LBW was 6.5%, that of PTB was 7.7%, and that of SGA was 3.1% (Table 2). The pregnancy duration was shorter (mean 0.9 days) among exposed than among unexposed women ($P = 0.02$). There were no significant differences between the groups' mean birth weights or SGA rates.

The rates of PTB and LBW were higher among exposed women than among unexposed women (PTB: 9.1% versus 6.8%, $P = 0.004$; LBW: 7.6% versus 5.8%, $P = 0.018$) (Table 2). Among women with a PTB (according to medical records), the primary reason for hospital admission—induced labor versus spontaneous labor (preterm premature rupture of the membranes or uterine contractions)—did not differ significantly between the groups.

In the multivariable analysis controlling for maternal age, origin, parity, gestational diabetes mellitus, and pregnancy-induced hypertension, stress exposure remained a risk factor for both PTB and LBW (Table 3). Maternal age and parity were both entered into the multivariable model because the correlation between these 2 parameters was not high (Spearman $r = 0.414$, $P < 0.001$). The level of education and the rate of compliance with the recommended standard of prenatal care were removed from the final model because they were no longer statistically significant.

A separate multivariable model was created for primiparous women only, to control for a history of PTB (model not presented). The rate of PTB was 10.9% (52/478) among exposed primiparas and 7.5% (57/760) among unexposed primiparas. After controlling for maternal age and pregnancy-induced hypertension, the risk for PTB was higher among exposed than unexposed women (adjusted OR 1.51 [95% CI, 1.01–2.26]; $P = 0.04$).

Another multivariable model was created for women with spontaneous PTB following preterm premature rupture of the membranes or contractions. Overall, 94/1324 (7.1%) women in the exposed group and 123/2238 (5.5%) women in the unexposed group had a spontaneous PTB. After controlling for maternal age and pregnancy-induced hypertension, the association between stress exposure and PTB was not significant (adjusted OR 1.3 [95% CI, 0.9–1.7]; $P = 0.1$).

The intensity of exposure (during the entire pregnancy and during each trimester) was not linearly associated with the risk of PTB or LBW.

During the period preceding the onset of rocket attacks (before April 15, 2001), the PTB rates were similar between the 2 towns (Table 4). After the onset of the attacks, the PTB rate increased in Sderot (from 7.2% to 9.1%), whereas it decreased in Kiryat Gat (from 7.3% to 6.8%). A similar pattern was observed for the rate of newborns with LBW (increase from 5.8% to 7.6% in Sderot and decrease from 7.5% to 5.8%). In multivariable generalized estimating equation models controlling for possible confounders, the differences in the rates of LBW and PTB between the 2 time periods were not significant in either group (Table 4).

4. Discussion

The objective of the present population-based retrospective cohort study was to test the hypothesis that exposure to life-threatening stress