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ORIGINAL RESEARCH REPORT

Fetal sex modifies effects of prenatal stress exposure and adverse birth outcomes

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Abstract

Prenatal maternal stress is associated with pregnancy complications, poor fetal development and poor birth outcomes. Fetal sex has also been shown to affect the course of pregnancy and its outcomes. The aim of this study was to evaluate whether fetal sex modifies the association between continuous exposure to life-threatening rocket attack alarms and adverse pregnancy outcomes. A retrospective cohort study was conducted in which the exposed group was comprised of 1846 women exposed to rocket-attack alarms before and during pregnancy. The unexposed group, with similar sociodemographic characteristics, delivered during the same period of time at the same medical center, but resided out of rocket-attack range. Multivariable models for each gender separately, controlling for possible confounders, evaluated the risk associated with exposure for preterm births (PTB), low birthweight (LBW), small for gestational age and small head circumference (HC). In both univariable and multivariable analyses exposure status was a significant risk factor in female fetuses only: PTB (adj. OR = 1.43; 1.04–1.96), LBW (adj. OR = 1.41; 1.02–1.95) and HC < 31 cm (adj. OR = 1.78; 1.11–2.88). In addition, regarding all adverse outcomes, the male-to-female ratio was higher in the exposed group than in the unexposed group. The findings support the hypothesis that male and female fetuses respond differentially to chronic maternal stress.

Keywords

Chronic stress, cohort study, fetal growth, low birthweight, preterm birth, secondary sex ratio

History

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Introduction

Prenatal maternal stress has been associated with pregnancy complications, poor fetal development and poor birth outcomes (Copper et al., 1996; Hobel, 2004; Maric et al., 2010; Rondo et al., 2003; Wainstock et al., 2014). Several mechanisms are proposed to explain this association (Hobel et al., 2008). A primary physiological response to stress is activation of the hypothalamic–pituitary axis (HPA), which leads to secretion of cortisol. Cortisol levels increase gradually during pregnancy, reaching a peak before delivery. Chronic stress may exhaust the HPA axis, causing elevation of blood cortisol levels that in turn may lead to preterm labor (Hobel et al., 1999, 2008). The release of catecholamines as a response to stress may also induce contractions leading to early labor (Copper et al., 1996; Hobel et al., 2008). Another possible mechanism is the effect of stress on the immune system. Stress is correlated with immune system biomarkers, which may explain medical conditions presenting during stressful periods (Glaser et al., 1999). Stress during pregnancy has been found associated with chorioamnionitis, pre-eclampsia, premature rupture of the membranes and preterm delivery (Da Costa et al., 1998; Hobel et al., 2008). Other indirect mechanisms may be involved in the association of stress with adverse pregnancy outcomes, such as the negative effect that stress may have on other lifestyle variables, i.e. smoking, diet etc.

While the demonstrated effect of maternal stress on the risk of adverse birth outcomes may be small (Littleton et al., 2010), some of these, such as preterm birth (PTB) and low birthweight (LBW) are known risk factors for infant short- and long-term mortality and morbidity, posing a major concern for public health (Copper et al., 1996).

Fetal growth, size and risk for adverse pregnancy outcomes have been shown to vary between sexes (Engel et al., 2008; Khalil & Alzahra, 2013; Melamed et al., 2013). Female fetuses grow considerably slower than do male fetuses (e.g. second trimester head circumference (HC) is smaller in female than in male fetuses) (Melamed et al., 2013). Regarding intra-uterine growth retardation (IUGR), the evidence is inconsistent; while one study had shown it is more prevalent in females fetuses (Engel et al., 2008), another study reported the opposite (Clifton, 2010). Higher rates of pre-eclampsia have been reported among mothers of females as compared to male fetuses (Shiozaki et al., 2011), while

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gestational diabetes mellitus (GDM), PTB and stillbirths have been reported to be more frequent in male gestations (Aibar et al., 2012; Chien et al., 2011; Di Renzo et al., 2007; Engel et al., 2008; Khalil & Alzahra, 2013; Shiozaki et al., 2011). Fetal immune system activation (Howerton & Bale, 2012) and higher levels of androgen have been found in pre-eclamptic versus normotensive mothers in both human and animal studies (Sathishkumar et al., 2012; Sharifzadeh et al., 2012). These findings suggest that maternal response to variety of exposures might interact with fetal sex hormones, the immune system and the placenta.

Male-to-female ratio at birth, defined as secondary sex ratio (SSR), is usually greater than 1.0, and has been shown to vary with exposure to stressful conditions experienced by pregnant women either pre-conception or during pregnancy. Under circumstances including terror attacks, earthquakes, periods of economic insecurity and unemployment, a decreased SSR has been observed (Catalano et al., 2005, 2006; Hansen et al., 1999; Navara, 2010; Obel et al., 2007). It is suggested that female fetuses adapt to poor intrauterine environment by decreasing growth rate, while fetal male response may be less adaptive, and may be expressed as IUGR stillbirth or early pregnancy loss, often referred to as the ''male culling effect'' (Clifton, 2010; Torche & Kleinhaus, 2012). The differential effects associated with fetal sex may suggest different placental function, since the placenta originates in fetal cells, which are sex-specific. These differences include placental gene expression, immune functions and response to cortisol (Clifton, 2010; Navara, 2010). The latter may explain the different coping strategies under circumstances of adverse uterine environment, resulting in the differing sex ratio, as suggested by Chason et al. (2012).

Since 2001, the Israeli southern city of Sderot (population ~20,000) has been constantly exposed to rocket attacks from the Gaza Strip (distance 4 km), creating extremely stressful conditions. These rocket attacks are preceded by warning alarms, informing residents to seek shelter. The alarms are loud, sudden and stress-inducing, as they are sounded only a few seconds before the rocket hit the town and residents have 15 s to run for cover. In previous studies, higher risk of miscarriages, LBW and PTB were found among women living in Sderot compared to a town not exposed to rocket attacks (Wainstock et al., 2013b, 2014). This situation has, unfortunately, provided the opportunity to further investigate the effect of prolonged stress on pregnancy outcomes, as well as the differential effect on fetuses of each sex.

The aim of the current study is to test the hypothesis that continuous exposure to life-threatening stress differentially affects pregnancy outcomes of male and female fetuses.

Methods

A retrospective cohort study was conducted in which the exposed group was comprised of women who resided in Sderot, and the unexposed group was comprised of women living in Kiryat Gat, a city of the same socioeconomic rank as Sderot (2008 Census data) (The Israeli Bureau of Statistics, 2008) at which rockets were not aimed. Women in both groups delivered in Barzilai Medical Center, the main tertiary medical center serving the residents of both cities. According to the 1995 National Health Insurance Law, all Israeli citizens have universal health insurance, covering prenatal care and childbirth. All deliveries in Israel are in tertiary level hospitals. Further information regarding the study population and comparison between background characteristics of the study groups is described elsewhere (Wainstock et al., 2013a,b).

Hospital records of Sderot and Kiryat Gat parturients were abstracted for data regarding pregnancy, birth and neonatal outcomes. Since the rocket attacks began on 15 April 2001, the study included deliveries from January 2002, so that the exposed group would have been exposed throughout the pregnancy. The study ended on 27 December 2008, when the unexposed group also became exposed and could no longer serve for comparison. Exposure status was determined by address, as noted in the hospital records. Address is routinely verified by the hospital before discharge, to enable further communication with the mother, e.g. for reporting abnormal newborn screening.

Statistical analysis

Univariate comparison between the two groups was performed, and included sociodemographic and medical characteristics, including: maternal age and origin; gestational diabetes (GDM); pregnancy induced hypertension (PIH); other background health problems; poor obstetric history and outcome measures, including: PTB, LBW, small-for-gestational-age (SGA) and HC reduction. Mean and standard deviations are reported for variables with normal distribution. General estimating equation (GEE) multivariate logistic regression models were used separately for each sex to assess the risk of adverse birth outcomes associated with stress exposure, as defined according to place of residence. These models adjusted for women with multiple deliveries during the study period. The final models included variables that reached statistical significance of $p < 0.1$ at the univariable level, thus were considered potential confounders.

The outcome variables were defined as follows: PTB < 37 weeks of gestation; LBW < 2500 g; and SGA, birthweight <5th and <10th percentile for gestational week and sex, according to the World Health Organization tables (WHO Growth Tables). Since measurements of HC in the data source were reported in 0.5 cm increments (e.g. 30.0 cm; 30.5 cm etc.) and not as continuous values as used in the WHO charts, it was not possible to use WHO definitions of reduced HC. WHO cutoff points for below the 5th percentile are <32.4 cm and <31.9 cm for males and females, respectively, and the 1st percentile is defined as <31.5 cm and <31.1 cm for males and females, respectively). Therefore the dichotomous variable ''reduced HC'', was defined in two ways: HC < 31 cm and as HC < 30 cm, for both sexes.

In SSR analysis, only PTB and LBW were analyzed both as dichotomous variables and by sub-categories, to assess whether the SSR declines as the outcomes are more extreme (≥37, 34–35 + 6, 32–33 + 6 or below 32 gestational weeks; ≥2500 g, 1500–2499 g, 1000–1499 g or ≤999 g, regarding PTB and LBW, respectively).

Data about the pre-exposure period (the year 2000) was collected to gain additional historic perspective; the risk for

adverse pregnancy outcome in female and male pregnancies was compared between the time periods.

Pregnancy complications were recorded as noted in the medical record. The study was approved by the Barzilai Medical Center IRB (# 40/2009).

Results

The study population included 4830 births (1851 in the exposed group and 2979 in the unexposed group) by 3676 women (1401 in the exposed group and 2275 in the unexposed group). Data on offspring sex was missing for 17 women, thus their deliveries were not included in the analysis.

As can be seen in Table 1, most women in the study population were 21–35 years old (mean: 29.2, SD: 5.6), married, born in Israel, had a high school diploma and had conceived spontaneously. For nearly half of the women, the pregnancy was their second or third, and for one-fifth it was their fourth or more. SSR was 0.987 in the exposed group and 1.066 in the unexposed group. As compared to the exposed group, women in the unexposed group were significantly older (mean: 29.49, SD: 5.7, versus mean: 28.69, SD: 5.6, $p = 0.002$), more women in the unexposed group were over 35 years old, born in Israel and with fewer than 12 years of education. The groups were similar in other socio-demographic characteristics, rates of pregnancy complications and cesarean sections.

The mean birthweight (g) was: 3211.0, SD: 508 and 3230.6, SD: 496 in exposed and unexposed, respectively, ($p = 0.18$), mean gestational age at delivery (days) was 275.0, SD: 13.2 and 275.9, SD:13.3 in exposed and unexposed, respectively, ($p = 0.02$) and the mean HC (cm) was 34.1, SD: 1.6 and 34.1, SD: 1.6 in exposed and unexposed, respectively ($p = 0.2$). Rates of LBW and PTB were higher in the exposed compared to the unexposed group (PTB: 9.1% versus 6.8%, $p = 0.004$; LBW: 7.6% versus 5.8%, $p = 0.016$), and these differences remained significant after adjusting for possible confounders in multivariable logistic models. There were no differences in SGA or IUGR rates between the groups (Wainstock et al., 2014).

Among males, the rate of LBW was 6.7% versus 5.6% in exposed versus unexposed groups (OR = 1.20; 95%

Table 1. Demographic and obstetric characteristics of the study population by exposure status.

	Total $N = 4813$ *N* (%)	Exposed $n = 1846$ *N* (%)	Unexposed $n = 2967$ *N* (%)	X^2	*p* Value
Offspring sex				1.69	0.19
Males	2448 (50.9)	917 (49.7)	1531 (51.6)		
Females	2365 (49.1)	929 (50.3)	1436 (48.4)		
M/F ratio (95% Cl)	1.035 (0.978; 1.095)	0.987 (0.901; 1.081)	1.066 (0.992; 1.146)		
Maternal age group				11.5	0.003
≤20	203 (4.2)	90 (4.9)	113 (3.8)		
21–35	3878 (80.6)	1512 (81.9)	2366 (79.7)		
>35	732 (15.2)	244 (13.2)	488 (16.4)		
Marital status[a]				0.47	0.92
Married	4377 (91.0)	1678 (90.9)	2699 (91.0)		
Single	64 (1.3)	25 (1.4)	39 (1.3)		
Divorced	363 (7.5)	139 (7.5)	224 (7.6)		
Widow	8 (0.2)	4 (0.2)	4 (0.1)		
Country of birth				4.66	0.032
Israel	3043 (63.8)	1132 (61.3)	1911 (64.4)		
Other	1770 (36.8)	714 (38.7)	1056 (35.6)		
Years of education[a]				16.96	<0.001
<12 years	643 (14.5)	235 (13.6)	408 (15.0)		
12	2493 (56.2)	921 (53.5)	1572 (57.9)		
>12 years	1302 (29.3)	566 (32.9)	736 (27.1)		
Mode of conception				1.35	0.22
Assisted reproductive technology	127 (2.6)	55 (3.0)	72 (2.4)		
Spontaneous	4686 (97.4)	1791 (97.0)	2895 (97.6)		
Parity[a]				3.52	0.17
1	1463 (30.4)	582 (31.6)	881 (29.7)		
2–3	2346 (48.8)	902 (48.9)	1444 (48.8)		
>4	996 (20.7)	359 (19.5)	637 (21.5)		
Gravidity[a]				0.07	0.90
1	1229(25.5)	474 (25.7)	755 (25.5)		
2–3	2097 (43.6)	800 (43.4)	1297 (43.7)		
>4	1485 (30.9)	571 (30.9)	914 (30.8)		
Background health problems[a,b]	271 (5.6)	104 (5.6)	167 (5.6)	0.001	1.0
Bad obstetric history (among parity ≥ 2)[b]	51 (1.1)	19 (1.0)	32 (1.1)	0.26	0.87
Gestational diabetes mellitus	341 (7.1)	143 (7.7)	198 (6.7)	1.99	0.16
Pregnancy-induced hypertension	294 (6.1)	113 (6.1)	181 (6.1)	0.001	0.99
Cesarean section	819 (17.0)	316 (17.1)	503 (17.0)	0.75	0.85

Bad obstetric history: history of intrauterine fetal death. Data is presented as numbers and percentages for categorical variables, and as ratio and confidence interval for M/F ratio.

[a]Missing information: parity ($n = 2$), family status ($n = 1$), gravidity ($n = 8$), mode of delivery ($n = 3$), years of education: 605(10%). Background health problems: 1212 (20.1%).

[b]Background health problems, including: asthma, skin, connective tissue, heart, psychiatric or neurological conditions.

Table 2. Multivariable logistic models (GEE) for PTB and LBW in males and females.

	PTB				LBW			
	Females		Males		Females		Males	
Variables	Adjusted OR; 95% CI	*p*	Adjusted OR; 95% CI	*p*	Adjusted OR; 95% CI	*p*	Adjusted OR; 95% CI	*p*
Exposure status								
Unexposed	1		1		1		1	
Exposed	1.43; 1.04–1.96	0.029	1.30; 0.97–1.78	0.083	1.41; 1.02–1.95	0.039	1.27; 0.87–1.73	0.24
Maternal age at delivery								
≤20	0.99; 0.48–2.03	0.98	1.56; 0.81–2.97	0.18	1.23; 0.64–2.37	0.53	2.02; 1.06–3.84	0.03
21–35	1		1		1		1	
>35	0.73; 0.44–1.23	0.24	1.23; 0.80–1.89	0.34	0.86; 0.51–1.45	0.57	1.22; 0.73–2.04	0.46
Origin								
Israel	1		1		1		1	
Other	0.81; 0.58–1.12	0.19	0.80; 0.59–1.08	0.14	0.71; 0.50–0.98	0.044	0.91; 0.64–1.30	0.60
Parity								
1	1		1		1		1	
2–3	0.58; 0.41–0.84	0.004	1.05; 0.74–1.50	0.78	0.46; 0.31–0.66	<0.001	0.77; 0.52–1.13	0.18
≥4	0.89; 0.56–1.43	0.65	0.78; 0.48–1.28	0.30	0.82; 0.51–1.31	0.41	0.61; 0.353–1.07	0.08
Marital status								
Married	1		1		1		1	
Unmarried	1.31; 0.80–2.12	0.28	1.10; 0.66–1.81	0.72	1.42; 0.88–2.29	0.15	1.22; 0.71–2.09	0.48
Gestational diabetes mellitus	1.76; 1.03–3.00	0.041	1.67; 1.04–2.66	0.032	1.00; 0.52–1.92	0.99	0.76; 0.38–1.53	0.44
Pregnancy induced hypertension	2.02; 1.21–3.37	0.007	2.88; 1.86–4.46	<0.001	2.07; 1.23–3.46	0.006	2.12; 1.24–3.61	0.006

Table 3. Multivariable logistic model (GEE) for small HC in males and females.

	HC < 30				HC < 31			
	Females		Males		Females		Males	
Variables	Adjusted OR; 95% CI	*p*	Adjusted OR; 95% CI	*p*	Adjusted OR; 95% CI	*p*	Adjusted OR; 95% CI	*p*
Exposure status								
Unexposed	1		1		1		1	
Exposed	2.22; 0.96–5.10	0.058	0.44; 1.54–1.24	0.12	1.78; 1.11–2.88	0.018	0.80; 0.42–1.51	0.49
Origin								
Israel	1		1		1		1	
Other	1.51; 0.63–3.60	0.35	0.41; 0.16–1.04	0.062	0.82; 0.50–1.32	0.41	0.62; 0.34–1.15	0.13
Gestation week	0.43; 0.37–0.51	<0.001	0.40; 0.34–0.48	<0.001	0.50; 0.45–0.56	<0.001	0.45; 0.39–0.51	<0.001
Gestational diabetes mellitus*	0.24; 0.04–1.47	0.12	0.50; 0.08–3.04	0.46	0.71; 0.29–1.72	0.45	0.95; 0.34–2.61	0.92

*Results remained similar after removing GDM from the models.

CI = 0.85–1.68). The rates of PTB were 9.3% versus 7.4% in exposed versus unexposed (OR = 1.27; 95% CI = 0.95–1.70). The rates of HC < 31 cm were 2.5% versus 3.2% in exposed versus unexposed (OR = 0.78; 95% CI = 0.47–1.29), and the rates of HC < 30 cm were 1.1% versus 2.2% in exposed versus unexposed (OR = 0.52; 95% CI = 0.25–1.02).

Among females, the rates of LBW were 8.5% versus 6.1% in exposed versus unexposed (OR = 1.44; 95% CI = 1.05–1.98) and the rates of PTB were 8.9% versus 6.1% in exposed versus unexposed (OR = 1.50; 95% CI = 1.10–2.05). The rates of HC < 31 cm were 5.3% versus 3.0% in exposed versus unexposed (OR = 1.85; 95% CI = 1.21–2.82), and the rates of HC < 30 cm were 2.2% versus 1.1% in exposed versus unexposed (OR = 1.96; 95% CI = 1.01–3.80). In both males and females, there were no differences between the exposed and unexposed groups in the subcategories of LBW, PTB and SGA.

GEE multivariable logistic models assessing the effect of exposure on PTB and LBW (Table 2), and HC < 30 cm and HC < 31 cm (Table 3) were analyzed separately for females and males. Exposure status was a significant risk factor for LBW, PTB and HC < 31 cm in female but not in male-fetus pregnancies.

Multivariable logistic models were created for SGA of < 5th and <10th percentiles (not shown). Exposure status was not a significant risk factor for either sex.

For all adverse pregnancy outcomes, there was a higher representation of females in the exposed group as compared to the unexposed group, thus SSR was consistently lower in the exposed group than in the unexposed group (Figures 1–4, by outcomes). For example, among LBW, SSR were 0.77 and 0.99 in exposed and unexposed groups, respectively. Although findings were statistically insignificant, the differences in SSR were greater between exposed and unexposed groups at the extremes of adverse birth outcomes (BW < 1000, GA < 32 weeks and HC < 30 cm) in which SSR was <1 in the exposed group, and >1 in the unexposed group.

Data from the pre-exposure period (the year 2000) were analyzed to assess differences between the study groups by fetal sex. In both male ($n = 527$) and female ($n = 618$) groups, there were no differences in rates of LBW, PTB and reduced HC between the two towns. For instance, among males the PTB rates were 7.6% versus 7.0% in the subsequently exposed group versus the unexposed group, respectively ($p = 0.78$).

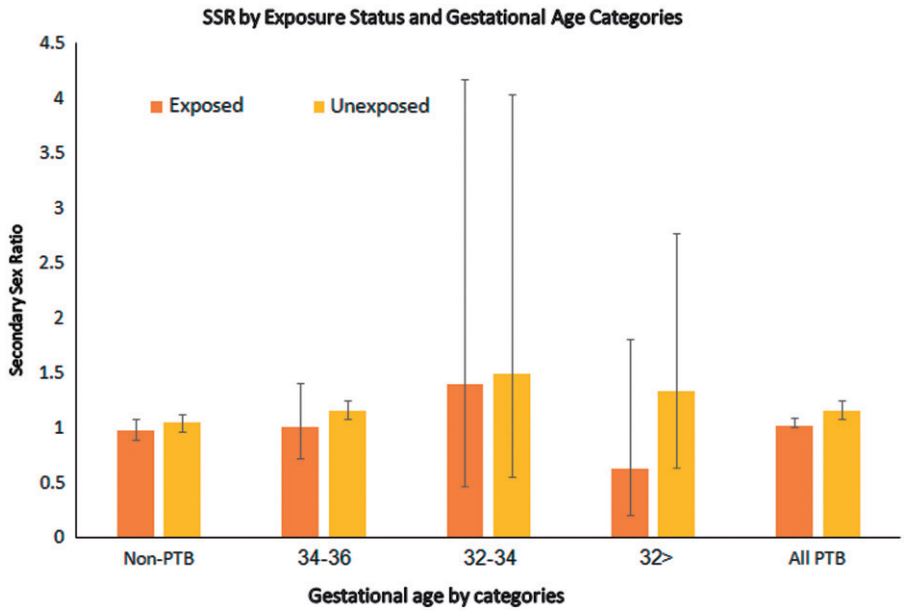

Figure 1. Secondary sex ratio by gestational age categories, in the exposed and unexposed groups.

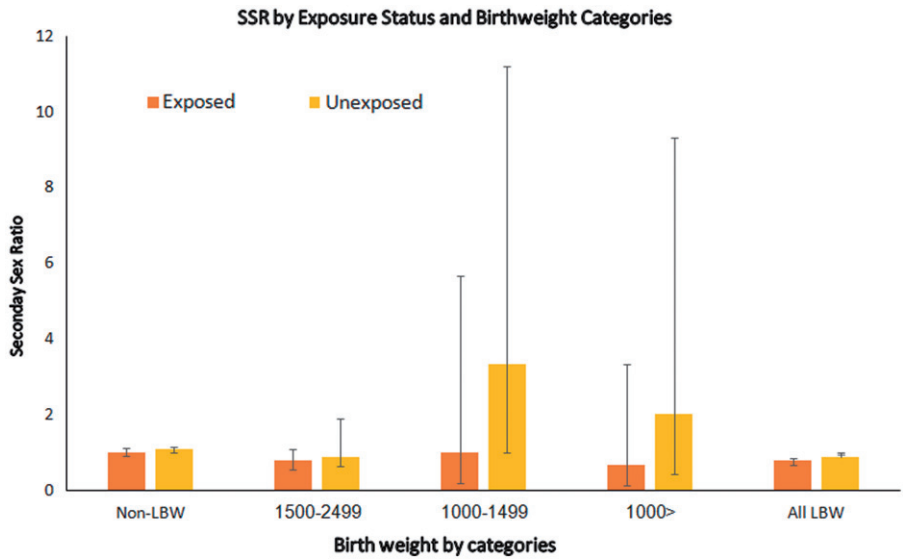

Figure 2. Secondary sex ratio by birthweight categories, in the exposed and unexposed groups.

Figure 3. Secondary sex ratio by small for gestational age status, in the exposed and unexposed groups.

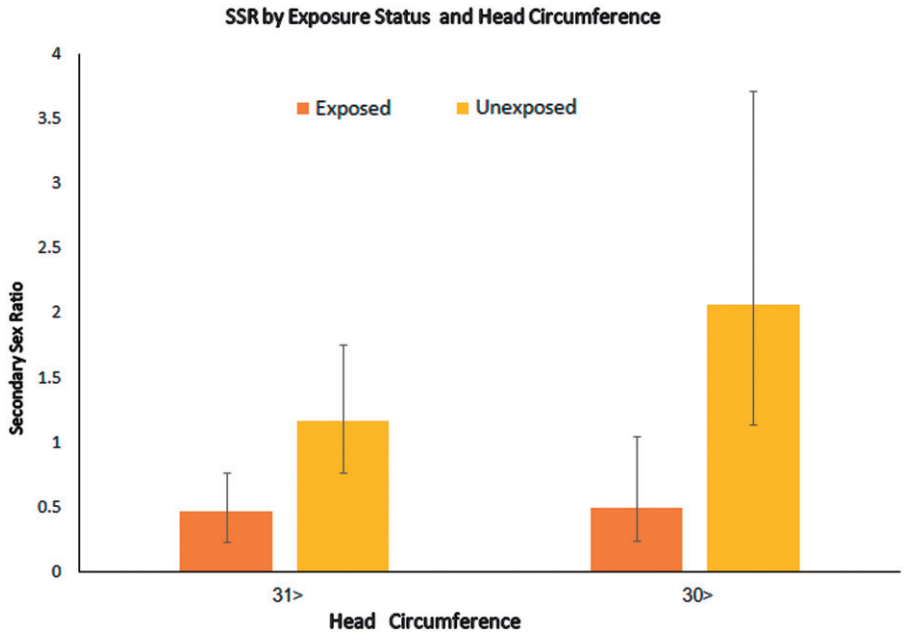

Figure 4. Secondary sex ratio by head circumference, in the exposed and unexposed groups.

Discussion

The aim of this population-based retrospective cohort study was to evaluate differential response of fetal sex to chronic intense maternal prenatal stress. An increased risk for PTB and LBW in the exposed group compared to the unexposed group has been reported previously (Wainstock et al., 2014). The current findings suggest that female fetuses survive through early gestation stressors, but respond to stress by PTB and LBW. While there were fewer male pregnancies resulting in PTB and LBW among the exposed group, it is possible that those pregnancies were culled, resulting in a low SSR for all adverse outcomes in the exposed group, i.e. fewer males than females were born in the exposed group compared to the unexposed group. The differences in SSR were most striking between exposed and unexposed groups at the extremes of adverse birth outcomes.

The decrease in SSR might suggest that the male placenta responds to stress by means of a different mechanism than does the female placenta, possibly involved in higher rates of fetal loss in male- compared to female-fetus pregnancies, as suggested by Catalano et al. (2009). In an earlier study, Catalano et al. (2006) noted two possible mechanisms involved in the reduced SSR in populations exposed to stress: reduced conception of males due to lower sperm motility associated with stress, leading to reduced sex ratio at conception or increased rates of spontaneous abortion or stillbirths of vulnerable male fetuses. The latter mechanism is supported by their findings following the 9/11 terror attack in New York.

Timing of delivery is determined by placental maturation, a process associated with cortisol levels, which are elevated in response to stress. It is suggested that this may be involved in the PTB mechanism (Glynn et al., 2001). Female and male placentas may respond differently to stress (Belfort et al., 2010; Clifton, 2010). Several studies support the hypothesis that female placentas may be more sensitive and reactive to chronic maternal stress, while male placentas may be more sensitive to acute stress (Murphy et al., 2003; Stark et al., 2009). This could also explain the current findings of different adverse pregnancy outcome rates between the sexes in response to prenatal stress. For instance, Ghidini & Salafia (2005) have shown increased inflammatory placental lesions in male versus female preterm deliveries. Higher risk for retained placenta and fetal loss in male-fetus pregnancies are reported in other studies as well (Catalano et al., 2006; Torche & Kleinhaus, 2012; Belfort et al., 2010).

The differential effect of stress on male and female pregnancies is further supported by the comparison with pre-exposure data (from the year 2000). During this period, before the residents of Sderot (the exposed city) became exposed, there were no sex-specific differences in PTB and LBW rates between the two cities. Aside from exposure status there were no other major differences between the cities during the two time periods, supporting the hypothesis that as a result of stress experienced by pregnant women in the exposed town, female-fetus pregnancies were at higher risk for the assessed adverse outcomes than were male-fetus pregnancies.

Some stressors induce their effect only at certain window of vulnerability, and in pregnancy critical periods of stress exposure have been found in several studies (Class et al., 2011; Glynn et al., 2001). Unlike some studies dealing with more acute stress, with an exact timing, in our study most exposed participants had been exposed to rocket attacks during the entire pregnancy, and had experiences a stress of a chronic nature. It was not relevant in this setting to study exact window of exposure which maybe most harmful.

In a meta-analysis of research on the relationship between psychosocial stress and pregnancy outcomes, Littleton et al. (2010) concluded that the strongest evidence was for an effect of stress on neonatal weight and LBW risk, and for the effect of highly stressful life events rather than minor stressors. Although the type of exposure in the current study was not evaluated in their meta-analysis, our results support their conclusion. The current findings are also in agreement with Torche & Kleinhaus (2012), who investigated the effect prenatal stress caused by a Chilean earthquake on pregnancy

outcomes. Their findings indicate that female fetuses whose mothers were exposed to the earthquake during the second and third months of gestation were more likely to be born prematurely at LBW and with low HC, compared to unexposed female fetuses, while male fetuses were not similarly affected.

Many other conditions associated with prenatal exposures are known to exhibit sex differences, including affective disorders, attention deficit-hyperactivity disorder, depression, anxiety, schizophrenia and autism (Dunn et al., 2011; Weinstock, 2007). It is likely that sex-specific responses to fetal antecedents contribute to these differences (Bogoch et al., 2007; Weinstock, 2007, 2011).

Some limitations of the study need to be addressed. First, stress exposure was not directly ascertained, but determined by place of residence. However, address is routinely verified when mothers are discharged from the hospital following delivery. Further, background characteristics of the study population, such as nutrition and pregnancy weight gain, which may influence pregnancy outcomes, were unaccounted for since the analysis was based only on information from medical records. To address these issues, we conducted a pilot study that included a sample of the current study participants (Wainstock et al., 2013b). In the pilot study, participants were asked about their BMI, health behaviors and level of stress during pregnancy. In addition to verifying place of residence, the findings confirmed that the level of stress was higher among the exposed group and that the two study groups were similar in BMI and health behaviors. Although this was a population-based study, the sample size was not large enough to detect significant differences in SSR between the study groups. Nevertheless, the sex ratios of both study groups are similar to those reported in other studies (Catalano et al., 2006). A previous study of this population has shown that spontaneous abortions were associated with stress exposure (Wainstock et al., 2013a,b). From that analysis, it is not possible to directly assess the ''culling hypothesis'' since there was no information regarding fetal sex in cases of spontaneous abortion or stillbirths. However, the current findings seem to be consistent with the theory of culling the most vulnerable male fetuses, while the surviving males might be more resilient to maternal stress. Females on the other hand may have survived, but with higher rates of PTB, LBW and small HC.

Conclusions

The results of this study support the hypothesis that male- and female-fetus pregnancies respond differently to prenatal stress: fewer males were delivered, possibly due to culling, and more females survived, but were at higher risk for PTB, LBW and reduced HC.

Declaration of interest

The authors report no conflicts of interest.

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