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Impact on pregnancy outcomes of exposure to military stress during the first or second trimester as compared with the third trimester

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Abstract

Objective: To compare pregnancy outcomes after exposure to military stress in different trimesters of pregnancy.

Methods: A retrospective study of medical records of deliveries in the Wolfson (WMC) and Barzilai (BMC) medical centers in Israel between July 2014 and April 2015. All parturients were exposed to military stress for 51 days during pregnancy. Pregnancy outcomes were compared between those exposed to military stress in the first or second trimester, and those exposed in the third trimester. Outcomes were also compared between WMC (a new-onset military stress exposure area) and BMC (a chronic military stress exposure area).

Results: At WMC, women exposed in the first or second trimester (n=2657) had a higher rate of preterm delivery (<37 weeks) as compared with those exposed in the third trimester (n=2037; 214 [8.1%] vs 121 [5.9%]; *P*=0.005). At BMC, women exposed in the first or second trimester (n=2208) had a tendency toward lower rates of diabetes mellitus (*P*=0.055) and macrosomia [103 (4.7%) vs 84 (6.3%); *P*=0.037], as compared with those exposed in the third trimester (n=1337).

Conclusion: Exposure to military stress during pregnancy had different impacts on pregnancy outcomes, depending on the time of exposure and whether continuous exposure to stress occurred.

KEYWORDS

Chronic stress exposure; Diabetes; Hypertensive disorder; Macrosomia; Military stress exposure; Pregnancy outcome; Preterm labor

1 | INTRODUCTION

Maternal stress during pregnancy has been associated with adverse pregnancy and delivery outcomes, including preterm birth, low birthweight, and pre-eclampsia.[1–5] The activation of the hypothalamic–pituitary–adrenal (HPA) axis, as a response to stress, is the mechanism which best explains this association; The HPA axis activation results in an increased secretion of cortisol and catecholamines, and as a consequence blood pressure and glucose levels rise, and continuous oxidative stress is caused.[3] In addition, increased cortisol level is a normal physiologic change during pregnancy, that peaks before delivery. Therefore, stress exposure during pregnancy may elevate blood cortisol levels prematurely and increase the secretion of catecholamine, which are known to have a role in the development of preterm delivery.[6]

The association between military conflicts and pregnancy outcome has been investigated: prenatal stress during the 1999 bombing in Belgrade and the armed conflict of 2011 in Libya was associated in higher rates of caesarean deliveries (CDs), low-birth-weight, and preterm births.[2,7] Wainstock et al.[4] also demonstrated that Israeli women who were residing close to the Gaza strip and were constantly exposed to rocket attack during pregnancy had a higher rate of preterm delivery. By contrast, Mor-Yosef et al.[8] found no difference in gestational age at delivery or frequency of preterm delivery in an Israeli population during the Gulf War in 1991.

It is possible that the stage of pregnancy when women are exposed to stress and anxiety might affect pregnancy outcomes differently. The military operation “Protective Edge” was launched by Israel in July 2014[9] and ended after 51 days. During this time period, Israeli citizens were subjected to massive rocket attacks almost on a daily basis. During those attacks, sudden-stressful sirens were heard, warning people to find a cover within a few seconds. During the conflict over 4600 sirens were sounded, with about 90 sirens per day, on average. Many civilians suffered from a continuous anxiety and had abrupt stress attacks, even with the absence of a physical hit.

The aim of the present study was therefore to investigate the outcomes of pregnant women exposed to the stress of this military operation. The primary aim was to compare outcomes between exposure during the first or second trimester and exposure during the third trimester. A secondary aim was to compare outcomes between a medical center in an area exposed for the first time to such military stress (Wolfson Medical Center [WMC], Holon) and a medical center in an area that has been exposed to such sirens and military stress since 2001, with an escalation during the Protective Edge military operation (Barzilai Medical Center [BMC], Ashkelon).

2 | MATERIALS AND METHODS

The present retrospective, population-based study reviewed pregnancy outcomes for all women who were exposed to the stress of the Protective Edge military operation and delivered at WMC, Tel Aviv, Israel, or BMC, Ashkelon, Israel, between July 7, 2014, and April, 30, 2015. The study was approved by the local institutional review boards of both medical centers. Because the study was retrospective and based on data retrieval, informed consent was not needed. Due to the sensitivity of the data retrieved, the data were encoded for analysis.

The WMC medical center is located 70 km from the Gaza strip. For the present analysis, this region was defined as a new-onset stress area (“new-onset stress exposure” group). The BMC medical center is located in the city of Ashkelon, 15 kilometers from the Gaza strip. This region was defined as a chronic stress area (“chronic stress exposure” group) and was affected by massive bombing and missile attacks, dozens of times every day.

The following data were collected from the computerized medical files of the medical centers: maternal demographic and characteristics including body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), medical background, delivery outcomes, pregnancy complications, and neonatal outcomes. Early and late preterm delivery was defined as delivery before 34 and 37 complete weeks of gestation, respectively; multiparity was defined as 5 or more births. Hypertensive disorders included eclampsia, pre-eclampsia, and chronic and gestational hypertension, and were diagnosed in accordance with the recommendations of the American College of Obstetrics and Gynecology.[10] A woman was considered to have diabetes mellitus (DM) if she had a diagnosis of type 1 or type 2 diabetes in her medical record. Gestational diabetes mellitus (GDM) was diagnosed by an oral glucose challenge test at 24–28 gestational weeks.

Pregnancy outcomes were compared between women who were exposed to the military operation during the first or second trimester (defined as <24 gestational weeks) and those who were exposed during the third trimester (24–42 gestational weeks) at each medical center.

If the 51-day exposure period straddled the second and third trimesters, women were considered as part of the first group. Outcomes were also compared between the two medical centers.

Data were analyzed by SPSS version 23 (IBM, Armonk, NT, USA). Continuous data were compared by the student *t* test, and categoric data by χ^2 or Fisher exact test, as appropriate. Multivariate logistic regression was performed to adjust for potential confounders. A *P* value of less than 0.05 was considered statistically significant.

3 | RESULTS

In the new-onset stress area (WMC), 4694 women were pregnant during the Protective Edge operation: 2657 were exposed during the first or second trimester (n=2657), and 2037 were exposed during the third trimester (Table 1). There were no differences between the two groups in the frequency of maternal hypertensive disorders, DM, GDM, or cesarean delivery. Women who were exposed to the military stress during the first or second trimester were younger (30.4 ± 5.8 years vs 30.0 ± 6.7 years, *P*=0.012), with a higher rate of nulliparity (879 [33.8%] vs 654 [32.1%], *P*=0.023). Late preterm delivery (<37 weeks) was more common for women exposed to stress during the first or second trimester than for those exposed to stress during the third trimester (214 [8.1%] vs 121 [5.9%], *P*=0.005). In multivariate regression, exposure to stress during the first or second trimester was associated with preterm delivery after adjustment for maternal age and nulliparity (adjusted odds ratio, 1.36; 95% confidence interval, 1.08–1.71, *P*=0.009). The frequency of early preterm delivery (<34 weeks) was similar in the two groups.

In the chronic stress area (BMC), 3545 women were pregnant during the Protective Edge operation: 2208 were exposed to stress during the first or second trimester, and 1337 were exposed to stress during the third trimester (Table 2). There were no differences between the two groups in maternal age or the frequency of maternal hypertensive disorders, GDM, preterm delivery, or cesarean delivery. Women exposed to the military stress during the first or second trimester had a lower frequency of neonates who were macrosomic (birthweight >4000 g) as compared with those exposed during the third trimester (103 [4.7%] vs 84 [6.3%],

TABLE 1 Pregnancy characteristics and outcomes in the new-onset stress area by trimester of exposure.[a]

Characteristics/outcomes	1st or 2nd trimester exposure (n=2657)	3rd trimester exposure (n=2037)	*P* value
Pregnancy characteristic			
Maternal age, y	30.4 ± 5.8	30.0 ± 6.7	0.012
Maternal age >35 y	460 (17.3)	336 (16.5)	0.456
BMI	23.4 ± 4.1	23.6 ± 5.1	0.136
Nulliparity	879 (33.8)	654 (32.1)	0.023
Multiparity (≥5)	122 (4.6)	88 (4.3)	0.721
Multiple gestation	117 (4.4)	86 (4.2)	0.828
Hypertensive disorders[b]	96 (3.6)	73 (3.6)	0.954
DM	156 (5.9)	124 (6.1)	0.328
GDM	56 (2.1)	31 (1.5)	0.102
Pregnancy outcome			
Cesarean delivery	545 (20.5)	432 (21.2)	0.562
Mean GA, d	274 ± 16	275 ± 13	0.037
Delivery <37 wk	214 (8.1)	121 (5.9)	0.005
Delivery <34 wk	57 (2.1)	6 (1.8)	0.352
Mean birthweight, g	3213 ± 546	3229 ± 533	0.320
Birthweight >4000 g	131 (4.9)	113 (5.5)	0.345
Birthweight <2000 g	63 (2.4)	48 (2.4)	0.972

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DM, pre-gestational diabetes mellitus; GA, gestational age; GDM, gestational diabetes mellitus.
[a]Values are given as mean ± SD or number (percentage).
[b]Hypertensive disorders include chronic hypertension, gestational hypertension, and pre-eclampsia.

P=0.037). There was a trend toward a higher rate of DM among women exposed to stress during their third trimester, as compared with those exposed during the first or second trimester (72 [5.4%] vs 88 [4.0%], *P*=0.055).

Pregnancy characteristics and outcomes were compared between the new onset stress exposure group (n=4694) and the chronic stress exposure group (n=3545) (Table 3). As compared with the chronic stress exposure group, women in the new-onset stress exposure group had lower BMI (23.4 ± 4.5 vs 30.4 ± 2.9, *P* < 0.001) and delivered slightly earlier (274 ± 2 days vs 275 ± 2 days, *P*=0.030).

4 | DISCUSSION

The present study had three main findings. First, among the women with acute exposure to military stress, the frequency of preterm delivery before 37 gestational weeks (but not that before 34 weeks) was higher for those exposed during the first or second trimester. Second, DM and macrosomia were more common among chronic stress-exposed mothers when the repeated stressors occurred during the third trimester. Third, maternal BMI was higher among mothers in the chronic stress exposure area than among those in the new-onset exposure area.

The associations among obstetric implications of armed conflict have been studied previously.[2,4,7] For example, Bodalal et al.[7] compared data from deliveries during the armed conflict in Libya in 2011 to data from deliveries that preceded it, reporting a higher frequency of cesarean delivery, preterm delivery, and low birthweight (<2500 g). Maric et al.[2] studied outcomes among pregnant women exposed to bombing in Serbia in 1999, finding lower birthweight (by 86 g) and a lower rate of cesarean deliveries among exposed women, but no difference in the frequency of preterm delivery or other complications between exposed and unexposed groups.[2] Wainstock et al.[4] also compared Israeli pregnant women between a city that was subjected to constant rocket attacks and one that was not exposed to such attacks, reporting higher rates of preterm delivery and low birthweight among mothers from the exposed city.

The present findings imply that the type of stress and the stage when a pregnant woman is exposed to stress might affect her and her fetus differently. Palmeiro-Silva et al.[11] found that male newborns who were exposed to stress during the second trimer had a shorter gestation, whereas female newborns showed no such association, suggesting that the risk of a shorter pregnancy varies by fetal gender. Preterm delivery in cases of maternal stress exposure might be due to the effects of the increased production of corticotrophin-releasing hormone, adrenocorticotrophic hormone, and cortisol,[12] which are all stress hormones associated with the timing of delivery.[6,13] Moreover, maternal anxiety and stress may also evoke immediate changes in uterine blood flow via uterine artery vasoconstriction, fetal heart rate, and fetal movements, and

TABLE 2 Pregnancy characteristic and outcomes in the chronic stress area by trimester of exposure.[a]

Characteristics/outcomes	1st or 2nd trimester exposure (n=2208)	3rd trimester exposure (n=1337)	*P* value
Pregnancy characteristics			
Maternal age, y	30.0 ± 5.1	29.9 ± 5.2	0.435
Maternal age >35 y	341 (15.4)	204 (15.2)	0.923
BMI	30.4 ± 1.8	30.3 ± 2.4	0.158
Nulliparity	734 (33.2)	440 (32.8)	0.854
Multiparity (≥5)	99 (4.5)	89 (6.6)	0.149
Multiple gestation	42 (1.9)	38 (2.8)	0.061
Hypertensive disorders[b]	123 (5.6)	63 (4.7)	0.262
DM	88 (4.0)	72 (5.4)	0.055
GDM	43 (1.9)	32 (2.4)	0.399
Pregnancy outcomes			
Cesarean delivery	473 (21.4)	274 (20.5)	0.516
Mean GA, d	275.5 ± 13.6	275.6 ± 14.0	0.864
Delivery <37 wk	154 (7)	97 (7.3)	0.752
Delivery <34 wk	51 (2.3)	30 (2.2)	0.889
Mean birthweight, g	3233 ± 534	3230 ± 536	0.848
Birthweight >4000 g	103 (4.7)	84 (6.3)	0.037
Birthweight <2000 g	57 (2.6)	28 (2.1)	0.355

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DM, pre-gestational diabetes mellitus; GA, gestational age; GDM, gestational diabetes mellitus.
[a]Values are given as mean ± SD or number (percentage).
[b]Hypertensive disorders include chronic hypertension, gestational hypertension, and pre-eclampsia.

thereby induce long-term changes in fetal growth, metabolism, behavior, and cognition. Potential factors from the stressed mother that might affect the fetus include not only cortisol, but also catecholamines, reactive oxygen species, cytokines, serotonin/tryptophan, and maternal microbiota. Thus, the autonomic nervous system is also involved in these processes.[14,15]

The current study also found that BMI was higher among women in the chronic stress exposure area than among those in the new-onset stress expose area (*P* < 0.001). This finding supports previous observations that chronic stress and post-traumatic stress disorders are associated with increased BMI and eating disorders.[16] In addition, in the chronic stress exposure area, there was a maternal trend toward DM when the repeated stressors occurred during the third trimester (*P*=0.055). This tendency was associated with a higher rate of macrosomia among this population. Notably, along the same line, Wang et al.[17] found that women exposed to prenatal earthquake stress in the mid-to-late period of pregnancy had significantly shorter leukocyte telomere length, a factor related to age-related diseases such as

TABLE 3 Pregnancy characteristics and outcomes by stress area.[a]

Characteristic	New-onset stress area (n=4694)	Chronic stress area (n=3545)	*P* value
Pregnancy characteristics			
Maternal age, y	30.2 ± 6.2	30.02 ± 5.1	0.159
Maternal age >35 y	796 (16.9)	545 (15.4)	0.053
BMI	23.4 ± 4.5	30.4 ± 2.9	<0.001
Nulliparity	1551 (33.0)	1174 (33.1)	0.397
Multiparity (≥5)	210 (4.5)	188 (5.3)	0.069
Pregnancy outcomes			
Cesarean delivery	976 (20.9)	747 (21.1)	0.848
Mean GA, d	274 ± 2	275 ± 2	0.030
Mean birthweight, g	3228 ± 524	3233 ± 534	0.733

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); GA, gestational age.
[a]Values are given as mean ± SD or number (percentage) unless stated otherwise.

cancer and early mortality, as compared with women exposed in the early period of pregnancy.

Exposure to stress during pregnancy has future implications for parenthood as well as for the child's development and behavior. Huizink et al.[18] demonstrated that anxiety during pregnancy predicts higher levels of parenting stress after delivery. In addition, the child's future brain development and function is subject to, among other factors, maternal mental conditions during pregnancy through effects on intracellular signaling pathways.[19] As a result, both prenatal and early-life parental stress exposure might synergistically or separately challenge a child's normal development.[20] Indeed, children who were prenatally exposed to increased maternal anxiety were found to have a twofold increase in behavioral problems.[19] Moreover, maternal stress during pregnancy was found to account for 17% of the variance in childhood cognitive abilities.[21]

The present study has some strengths. To our knowledge, it is the first to include two populations of pregnant women with different extents of stress exposure: namely, new onset stress exposure; and chronic stress exposure with an escalation in exposure during the military operation. Outcomes were compared between first- or second-trimester exposure and third-trimester exposure within the same population delivering at the same birth center, thereby eliminating possible demographic confounders. Although it is not possible to generalize the present findings, the results might also hold true for other cohorts.

The study also has limitations. First, due to its retrospective nature, data on previous obstetric complications such as preterm delivery were not available. Second, because pediatric follow-up, especially for mental health services, is registered separately, long-term neonatal outcomes including developmental and behavioral characteristics were not available. Moreover, the present analysis was conducted after the last women who were exposed gave birth, and it was not designed to measure or quantify the exposure to stress (e.g., by valid questionnaires or laboratory exams) among women at either medical center. At present, however, there is no established method to objectively measure stress exposure during pregnancy. In some cases, questionnaires or interviews have been used to quantify the women's perceived level of stress, whereas in others the level of stress has been defined by the extent of exposure, with no evaluation of subjective stress levels.[22–25]

In conclusion, the present study found that exposure to military-induced mental stress during pregnancy for a period of almost 2 months has different impacts on pregnancy outcome depending on the trimester of pregnancy when exposure occurred, and on whether the stress was new onset or prolonged chronic stress. Further studies are needed to elucidate the biologic mechanisms that underlie trimester-specific exposure to stress, and the impact of exposure on maternal and neonatal health later in life.

AUTHOR CONTRIBUTIONS

OG, LG, and MK contributed to study design, data acquisition, and manuscript writing. YM contributed to data analysis and interpretation, and manuscript revision. SL contributed to data acquisition and manuscript writing. AN contributed to study design and data acquisition. EA contributed to study design, data analysis, and manuscript revision. JB contributed to study design and conception, and manuscript writing and revision.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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