SHORT COMMUNICATION

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Posttraumatic stress disorder and development of premenstrual syndrome in a longitudinal cohort of women

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Abstract
We examined the association between posttraumatic stress disorder (+PTSD) symptoms and incident premenstrual syndrome (PMS) in a longitudinal study with 14 years follow-up of 2924 women aged 27–44. Compared to women with no trauma exposure, women with trauma/PTSD were at significantly increased risk of PMS (p-trend < .001): 1) trauma/no PTSD odds ratio (OR) = 1.31 [95% confidence interval (CI) 1.05–1.63], 2) 1–3 PTSD symptoms OR = 1.71 [95% CI = 1.33–2.20], 3) 4–5 PTSD symptoms OR = 2.90 [95% CI = 2.07–4.05], and 4) 6–7 PTSD symptoms OR = 3.42 [95% CI = 2.18–5.36].

Keywords Trauma · Posttraumatic disorder · Premenstrual syndrome

Introduction

Premenstrual syndrome (PMS) is a disorder with recurring physical and emotional symptoms during the late luteal phase of the menstrual cycle, which causes substantial impairment. Premenstrual syndrome affects about 8–20% of ovulating women (Chocano-Bedoya et al. 2013). The exact cause is unknown, but factors associated with increased risk of PMS include cigarette smoking, obesity, micronutrient deficiency, and a family history of PMS.

Emerging evidence suggests exposure to traumatic events, such as sexual assault, and posttraumatic stress disorder (PTSD) also may increase risk of PMS. PTSD is a common and debilitating mental disorder that may occur following a traumatic event and is associated with numerous adverse health outcomes in women. The lifetime prevalence of PTSD among US women is 12.8% (Kilpatrick et al. 2013). Longitudinal (Bertone-Johnson et al. 2014) and cross-sectional (Golding et al. 2000; Pilver et al. 2011; Takeda et al. 2013) epidemiologic studies have

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observed an association between traumatic event exposure and/or PTSD and higher risk of developing PMS.

We examined whether PTSD was associated with increased risk of incident PMS in a sub-sample of women ($N = 2924$) from the Nurses' Health Study II (NHS II) cohort.

Methods

Study population

The Nurses' Health Study II started in 1989 including 116,429 registered US female nurses and is still an on-going prospective study. Following the baseline survey in 1989, participants were mailed questionnaires biennially and updated medical history, dietary factors, and health-related behaviors in NHS II. The study protocol was approved by the Institutional Review Board at Brigham and Women's Hospital. Informed consent was obtained from all individual participants included in the study.

Incident PMS was ascertained in a sub-study of the NHS II, as described previously (Bertone-Johnson et al. 2014). Incident PMS cases were 4108 premenopausal women who reported a new PMS diagnosis between 1991 and 2005. Controls were 3248 randomly selected premenopausal women who did not report PMS between 1991 and 2005. To ensure information from cases and controls was provided for comparable time periods, we assigned a "reference year," which was same as the year of PMS diagnosis for cases. For controls, it was randomly assigned between 1991 and 2005. We excluded women with history of cancer, endometriosis, infertility, hysterectomy, or higher irregular menstrual cycles prior to the reference year in both cases and controls.

Selected women were mailed a questionnaire based on the Calendar of Premenstrual Experiences (Mortola et al. 1990), a list of questions to measure premenstrual syndrome severity. Completed questionnaires were received from 87% of the cases and 95% of the controls. Of women reporting PMS, 1257 (35%) met established criteria for moderate-to-severe PMS and were classified as cases (Bertone-Johnson et al. 2007). Of women not reporting PMS, 2463 (80%) confirmed experiencing few symptoms of minimal impact and were included as controls. Women meeting neither case nor control criteria were excluded from further analysis. We previously reported on the validity of our classification (Bertone-Johnson et al. 2007).

Assessment of trauma, PTSD, and other covariates

The assessment of trauma and PTSD has been described in detail (Koenen et al. 2009). In 2008, trauma exposure was assessed via the Brief Trauma Questionnaire (Schnurr et al. 2005). The symptoms of PTSD were assessed via the seven-item short screening scale for DSM-IV PTSD in reference to the worst (or only) traumatic event (Breslau et al. 1999). The age of onset of PTSD was defined as the year that the worst (or only) traumatic event occurred. As this study was conducted in a case-control design nested within a cohort study, we assigned PTSD cases based on 1991 PTSD status.

Childhood physical and emotional abuse was assessed in 2001 with the five questions from the physical and emotional abuse subscale of Childhood Trauma Questionnaire (CTQ) (Fink et al. 1995). The total CTQ score was calculated by summing responses to these five items. Childhood sexual abuse was assessed with four questions that queried unwanted, forced, or coerced sexual contact by older child or adult and was coded as none, mild, moderate, or severe (Roberts et al. 2013).

Age at cohort entry, age at menarche, race/ethnicity, and body mass index (BMI) at age 18 were assessed in 1989. Parity, oral contraceptive use, and smoking were queried at baseline and updated every 2 years. Antidepressant use was queried in 1993, 1997, 1999, 2001, 2003, 2005 and parent's education was asked in 2005. In 1991, 1997, and 2007, physical activity was measured. Using a validated semi-quantitative food frequency questionnaire, nutrient intake was measured in 1991, 1995, 1999, and 2003. The development of the diet questionnaire in NHS II is described elsewhere (Hu et al. 2016) (Full questionnaire can be found: http://www.nurseshealthstudy.org/participants/questionnaires). Using the residual method, intake of B vitamins, vitamin D, potassium, and calcium, was estimated adjusting for total energy intake.

The final sample included women who completed the 2001 and 2008 questionnaires: 857 PMS cases and 2067 controls.

Statistical analysis

Using logistic regression, we estimated odds ratios for PMS across five categories of PTSD. Model 1 was adjusted for age and parental education, as a proxy for early life environment. Model 2 was additionally adjusted for BMI, cigarette smoking, and alcohol use at reference year. Model 3 was additionally adjusted for use of oral contraceptive, antidepressant use, and dietary factors as potential mediators. Model 4 was adjusted for childhood trauma. All statistical analyses were conducted with SAS 9.4.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its latest amendments or comparable ethical standards.

Table 1 Age-standardized characteristics by PMS at baseline (1991)

	Cases (N = 857)	Controls (N = 2067)	p value
Age in 1991*, mean (SD)	33.9 (4.2)	34.4 (3.9)	< 0.001
Age at menarche, mean (SD)	12.4 (1.4)	12.5 (1.4)	0.05
Body mass index (kg/m^2) at age 18, mean (SD)	21.4 (3.1)	21.1 (3.1)	0.04
Body mass index (kg/m^2), 1991, mean (SD)	24.4 (4.9)	23.7 (4.6)	0.0001
Parity at 1991, mean (SD)	1.9 (0.7)	2.0 (0.7)	0.22
Total Activity, Mets/Week, mean (SD)	20.0 (21.7)	21.1 (24.6)	0.23
Alcohol intake, gm, mean (SD)	3.1 (5.8)	3.2 (5.9)	0.62
Tubal ligation, %	15.1	16.4	0.40
Current smokers, %	12.4	7	< 0.001
Ever smokers, %	38.3	24.2	< 0.001
Current OC users, %	12	10.7	0.33
Ever OC users, %	85	77.8	< 0.001
Duration of OC use in months, 1991, mean (SD)	47.2 (45.2)	41.5 (44.1)	< 0.001
Antidepressant use(1993), %	11.2	4.5	< 0.001
History of depression diagnosis(1993), %	14.4	6.1	< 0.001
Parental education			
College or greater, %	23.7	27.9	0.03
Race/ethnicity			
White, %	95.8	95	0.38
Others, %	4.2	5	

Values are standardized to the age distribution of the study population

* Value is not age-adjusted

Results

Table 1 shows age-standardized baseline characteristics of 857 PMS cases and 2067 controls. Cases were slightly younger, had higher BMI, and were less physically active. Cases had higher prevalence of smoking, oral contraceptive use, and antidepressants use than controls.

Table 2 presents the association between PTSD and subsequent PMS using logistic regression. In all models, a dose-response pattern was observed, with increasing likelihood of PMS related to the number of PTSD symptoms (p-trend < 0.001 for all models). Compared to those with no trauma exposure, women with 6–7 PTSD symptoms had an OR of a 3.42 [95%CI 2.18–5.36] in models adjusted for lifestyle

Table 2 Association between posttraumatic stress disorder and subsequent risk of PMS, NHS2, 1991–2005 (N = 2924)

	No trauma	Trauma-exposed				p-trend
		No PTSD	PTSD 1–3 Sx	PTSD 4–5 Sx	PTSD 6–7 Sx	
Case-control ratio	197:722	305:797	192:381	102:116	61:51	
Age-adj. OR (95% CI)	1.00	1.40 (1.13–1.72)	1.91 (1.50–2.42)	3.38 (2.46–4.65)	4.71 (3.11–7.16)	< 0.001
Model 1 OR (95% CI)	1.00	1.39 (1.13–1.72)	1.89 (1.49–2.41)	3.43 (2.50–4.72)	4.80 (3.16–7.29)	< 0.001
Model 2 OR (95% CI)	1.00	1.32 (1.06–1.63)	1.76 (1.38–2.24)	3.19 (2.31–4.40)	4.06 (2.65–6.24)	< 0.001
Model 3 OR (95% CI)	1.00	1.31 (1.05–1.63)	1.71 (1.33–2.20)	2.90 (2.07–4.05)	3.42 (2.18–5.36)	< 0.001
Model 4 OR (95% CI)	1.00	1.24 (0.99–1.54)	1.48 (1.14–1.91)	2.41 (1.70–3.40)	2.74 (1.72–4.36)	< 0.001

Model 1. Adjusted for age, parental education

Model 2. Additionally adjusted for BMI, smoking, and alcohol use at reference year

Model 3. Additionally adjusted for oral contraceptive use, antidepressant use, and dietary factors (dietary riboflavin, vitamin B6, potassium, calcium, and vitamin D intake in quintiles) at reference year

Abbreviations: Sx symptoms, PMS premenstrual syndrome, NHS2 Nurse's Health Study 2, OR odds ratio, CI confidence interval

factors, diet, and medication use; in models further adjusting for childhood trauma, the OR was 2.74 [95%CI 1.72–4.36] for women with 6–7 PTSD symptoms.

Discussion

PTSD was positively associated with PMS in a dose-response pattern, even after accounting for multiple potential confounders. The increased risk of PMS associated with PTSD was large; women with more than four PTSD symptoms showed greater than three times the odds of developing PMS compared to women with no trauma.

Our findings were consistent with a cross-sectional work (Pilver et al. 2011) that found increased ORs of PMS in women with PTSD. Our results differed from Perkonigg et al. (Perkonigg et al. 2004), the only other longitudinal study on this subject, which showed no statistically significant association between PTSD and PMS among women aged 14 to 24 years. This, in part, could be due to the relatively low power in their study, which had only approximately 370 premenstrual dysphoric disorder cases, whereas our study included approximately 857 PMS cases. Their study also included women with narrower age range than our study; it is possible that they may not have captured the full incidence of late-onset PMS.

Our study was nested within a large, ongoing prospective cohort of 116,688 civilian women, which enabled us to observe the association between PTSD and PMS. We selected women who met strict criteria for moderate to severe PMS, and identified controls with few PMS symptoms with no personal impact. We also categorized trauma/PTSD groups according to the number of PTSD symptoms, enabling a dose-response assessment of symptom prevalence with PMS risk. However, limitations should be noted. Women retrospectively reported PMS symptoms, which could have resulted in underreporting of symptom severity, misclassifying women with PMS symptoms into the control group, and attenuating the association between PTSD and PMS. In addition, it is possible that experience of PMS may have affected recollection of past trauma or abuse. However, Bertone-Johnson et al. (Bertone-Johnson et al. 2014) found that results were similar with or without restricting PMS cases to those diagnosed after the report of childhood abuse. Furthermore, our cohort, which was composed of women already aged 27–44 years at baseline, may have failed to include the most prevalent PMS population, as younger women report PMS frequently. Finally, since this study was conducted in nurses only, the findings might not generalize to the general population.

Conclusions

We found a significant positive dose-response relationship between PTSD and PMS. After controlling for other risk factors and childhood trauma, the effect remained substantial. This study provides evidence that the effects of PTSD may extend to the menstrual cycle and suggests a need for further study. Also, training on the relation among trauma, PTSD, and PMS may be useful for gynecologists training so as to assist them in making appropriate referrals for treatment.

Role of the funder/sponsor The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Author's contributions Dr. Jung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design and concept: Jung, Chocano, Koenen.

Acquisition, analysis, or interpretation of data: Jung, Roberts, Koenen.

Drafting of the manuscript: Jung.

Critical revision of the manuscript for important intellectual content: Jung, Roberts, Whitcomb, Missmer, Manson, Hankinson, Bertone-Johnson, Koenen.

Statistical analysis: Jung, Roberts.

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Study supervision: Koenen.

Compliance with ethical standards

Conflict of interest disclosures The authors declare that they have no conflict of interest.

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