

RESEARCH REPORT

Longitudinal study of the inception of perimenopause in relation to lifetime history of sexual or physical violence

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Study objective: To investigate of the extent to which violence over the life course accelerates the onset of perimenopause, as measured by menstrual changes.

Design: Prospective cohort study.

Setting: Boston, Massachusetts.

Participants: 603 premenopausal women aged 36–45 years at baseline who completed a cross sectional survey on childhood and adult violence history.

Main outcome measure: Time to perimenopause, defined as time in months from baseline interview to a woman's report of (1) an absolute change of at least seven days in menstrual cycle length from baseline or subjective report of menstrual irregularity; (2) a change in menstrual flow amount or duration; or (3) cessation of periods for at least three months, whichever came first.

Main results: Experience of abuse was associated with delayed onset of menstrual changes indicative of onset of perimenopause. Women reporting childhood or adolescent abuse entered perimenopause about 35% slower than women who reported no abuse (IRR_{adj} = 0.65, 95% CI 0.45 to 0.95) after adjusting for age, age at menarche, ever live birth, ability to maintain living standard, smoking, BMI, and depression. There was a similar association among women who reported first abuse during adulthood (IRR_{adj} = 0.72, 95% CI 0.28 to 1.80). These findings persisted when the cohort was restricted to non-depressed women (childhood/adolescent IRR_{adj} = 0.57, 95% CI 0.36 to 0.90; adulthood IRR_{adj} = 0.63, 95% CI 0.23 to 1.77).

Conclusions: This study is the first longitudinal analysis of the timing of perimenopause to show an association with a history of physical or sexual abuse. Further study of the relation between violence and reproductive aging is needed.

Violence has long been recognised to cause long term psychological effects,¹ however recent research has found that somatic effects, independent of injury, occur many years after the experience of trauma, possibly involving neuroendocrine pathways.^{2–6} For example, a study correlating childhood abuse and household dysfunction found that people who reported four or more traumas were more likely to have been diagnosed with ischaemic heart disease, cancer, stroke, and diabetes than those with no history of trauma.³ Similarly, women with a history of psychological violence who had not been physically or sexually abused had more health problems—including ulcers, arthritis, migraines, and chronic pain—than women who had never experienced psychological violence.⁴

One mechanism linking experiences of violence with poorer health is dysregulation of the body's stress responses, particularly the hypothalamic-pituitary-adrenal (HPA) axis function.^{7–8} A number of studies have observed chronic HPA axis activation in association with childhood sexual abuse.^{9–12} For example, Heim reported that women with a history of childhood sexual or physical abuse exhibited more than sixfold greater response to stress than age matched women with no history of abuse.¹²

While studies have examined the effects of socioeconomic position,^{13–15} race/ethnicity¹⁴ and racism on age of menopause,¹⁶ to our knowledge, only our previous cross sectional study¹⁷ has investigated the extent to which violence affects ovarian function. This study found that physical and sexual violence was associated with higher levels of follicle stimulating hormone (FSH) and lower levels of oestradiol—potentially indicating earlier ages of menopause. In this

investigation, we extend these analyses to examine longitudinal changes in menstrual cycle characteristics. Specifically, does the rate of onset of perimenopausal changes differ among women who reported experiences of violence during childhood/adolescence or adulthood compared with women who reported no violence?

METHODS

Study population

This study was based on a cohort of women participating in the Harvard study of moods and cycles (HSMC), a longitudinal study investigating the relation between ovarian function and depression among premenopausal women. Between 1995 and 1997, 976 women in the Boston area were enrolled from a population based, random sample of 6222 women 36–44 years of age (see Harlow 1999¹⁸ and 2003¹⁹ for details). The survey of interpersonal relationships (SIPR) was mailed to 907 members of the longitudinal cohort in March 1999. A second questionnaire was mailed to 344 non-respondents five to eight weeks later. The response rate was 81%, with 732 surveys completed among the 907 women who received them.

To be eligible for the study, women had to be premenopausal at the baseline interview and have completed the SIPR (n = 732). Women were excluded if they: (1) were taking oral contraceptives (OCs), hormone replacement therapy, or

Abbreviations: HSMC, Harvard study of moods and cycles; SIPR, survey of interpersonal relationships; OC, oral contraceptive; BMI, body mass index; CESD, Center for Epidemiology study of depression; IRR, incidence rate ratios; HPA, hypothalamic-pituitary-adrenal; FSH, follicle stimulating hormone

fertility medication ($n = 60$); and/or (2) reported irregular cycles throughout their lifetime or current irregularity ($n = 72$). In all, 129 women were excluded, leaving 603 women in the final sample. Women in the HSMC were interviewed biannually for three years; assessments collected detailed information on menstrual cycle characteristics, general health and reproductive events, such as pregnancy, breast feeding, and hormone use.

Assessment of perimenopausal changes

The conceptual outcome was time from baseline interview to menstrual changes indicative of perimenopause, the two to eight year period (mean 3.8 years²⁰) when the biological and clinical features commence until the first year of menopause.²¹ There is significant debate about which changes are the best indicators perimenopause. The study of women's health across the nation²² and the Massachusetts women's health study^{23, 24} defined perimenopause as onset of menstrual cycle irregularity and/or periods of amenorrhea lasting at least three months. Alternatively, the Seattle midlife women's health study defined perimenopause as any change in flow amount, flow duration, cycle length, menstrual cycle irregularity, or amenorrhea.²⁵ The primary definition of perimenopause used in this study was modelled after that

used by the Seattle study. Perimenopause was time from the baseline interview to first occurrence of any of the following events: (1) pronounced change in amount of menstrual flow amount (≥ 2 flow categories) or duration (≥ 2 days), (2) change in menstrual cycle length (≥ 7 days), or (3) period of amenorrhea lasting at least three months. Furthermore, to evaluate whether our choice of perimenopause influenced findings, we also created a second definition—time to menstrual cycle irregularity or amenorrhea lasting for three months or longer.

Women who became pregnant, had a hysterectomy, or started using hormones (hormone replacement therapy, OCs, or fertility treatment) were censored at that follow up interval. Women without any indication of perimenopause were censored at the end of the observation period. While we sought to follow up women for 36 months, there was some drop out. Never abused women had a mean follow up time of 30.0 months, while women first abused in childhood/adolescence and during adulthood, had mean follow up times of 30.5 and 28.7 months, respectively.

Assessment of lifetime exposure to violence

The conceptual exposure was experience or fear of physical or sexual abuse over the life course, which was defined as:

Table 1 Characteristics of 603 women aged 36 to 45 years by first experience or fear of physical or sexual harm

	Childhood or adolescence ($n = 324$)	Adulthood ($n = 27$)	Never harmed ($n = 252$)
Age at baseline (mean (SD))	40.3 (2.4)	41.0 (2.6)	40.3 (2.5)
Race/ethnicity*			
White, non-Hispanic	310 (96)	26 (96)	241 (96)
Other	13 (4)	1 (4)	11 (4)
Education			
High school/some college	92 (28)	5 (19)	50 (20)
Bachelors degree	115 (35)	9 (33)	71 (28)
Graduate degree	117 (36)	13 (48)	131 (52)
Duration able to maintain standard of living if current income lost*			
Less than 2 months	73 (23)	4 (15)	21 (8)
2 months to 1 year	127 (39)	12 (44)	106 (42)
More than 1 year	81 (25)	9 (33)	96 (38)
Don't know	41 (13)	2 (7)	29 (12)
Material deprivation during childhood	69 (21)	4 (15)	26 (10)
Ever had a live birth	212 (65)	17 (63)	165 (65)
Number of pregnancies			
None	73 (23)	6 (22)	65 (26)
One or two	46 (14)	4 (15)	36 (14)
Three or four	128 (40)	13 (48)	107 (42)
Five or more	77 (24)	4 (15)	44 (17)
Age of menarche			
≤ 11 years	54 (17)	2 (7)	34 (13)
12 to 13 years	197 (61)	19 (70)	150 (60)
≥ 14 years	73 (23)	6 (22)	68 (27)
Duration of OC use			
Never	82 (25)	7 (26)	75 (30)
1 to 5 years	155 (48)	12 (44)	107 (42)
6 to 10 years	32 (10)	4 (15)	39 (15)
11 or more years	20 (6)	2 (7)	13 (5)
Not known	35 (11)	2 (7)	18 (7)
Cigarette use at baseline			
Never smoked	161 (50)	17 (63)	154 (61)
Past smoker	40 (12)	2 (7)	20 (8)
Current smoker	123 (38)	8 (30)	78 (31)
Body mass index (kg/m^2)			
< 20	45 (14)	1 (4)	40 (16)
20–24.9	165 (51)	21 (78)	139 (55)
25–29.9	73 (23)	3 (11)	51 (20)
≥ 30	41 (13)	2 (7)	22 (9)
Depressive symptoms at baseline	147 (45)	5 (19)	41 (16)

*Does not total 100% because of missing data. Data shown as number (percentages) unless otherwise stated.

Table 2 Crude incidence rates of perimenopause and adjusted incidence rate ratios by first experience or fear of physical or sexual abuse

	Number	Woman years (w-y)	Perimenopause defined by menstrual cycle length, flow, duration, and amenorrhea				Perimenopause defined by menstrual cycle irregularity and amenorrhea			
			Number of cases	Crude IR (cases per 1000 w-y)	Age adjusted IRR (95%CI)	Fully adjusted IRR (95% CI)	Number of cases	Crude IR (cases per 1000 w-y)	Age adjusted IRR (95%CI)	Fully adjusted IRR (95% CI)
Among the entire cohort (n = 603)										
Childhood or adolescence	324	823	59	72	0.71 (0.50 to 1.02)	0.65 (0.45 to 0.95)*	59	72	0.71 (0.50 to 1.04)	0.74 (0.50 to 1.08)*
Adulthood	27	65	5	77	0.78 (0.31 to 1.94)	0.72 (0.28 to 1.80)*	5	77	0.44 (0.14 to 1.41)	0.43 (0.13 to 1.38)*
Never abused	252	630	60	95	–	–	60	95	–	–
Among non-depressed women (n = 410)										
Childhood or adolescence	177	449	31	69	0.62 (0.40 to 0.97)	0.57 (0.36 to 0.90)†	31	69	0.64 (0.40 to 1.02)	0.69 (0.43 to 1.11)†
Adulthood	22	53	4	75	0.66 (0.24 to 1.83)	0.63 (0.23 to 1.77)†	4	75	0.35 (0.08 to 1.43)	0.33 (0.08 to 1.39)†
Never abused	211	531	54	102	–	–	54	102	–	–

*Adjusted for age, age at menarche, ever live birth, ability to maintain living standard, smoking, BMI, and depression. †Adjusted for age, age at menarche, ever live birth, ability to maintain living standard, smoking, and BMI.

childhood (≤ 11 years), adolescence (12–18 years), and adulthood (≥ 19 years). Because of similarities, the childhood and adolescent categories were collapsed for these analyses. We classified by stage of first experience or fear because under the hypothesised biological mechanism early life experiences could have a different effect than those experienced in adulthood. For example, women abused during both childhood and adulthood were categorised as “childhood”. Operationally, experiences and fears of abuse were defined from responses to the SIPR, a self administered questionnaire modified, in part, from the conflict tactics scale²⁶ and the abuse assessment screen.²⁷ Questions asked about lifetime exposure to feared and actual physical and sexual harm. Exposure to sexual harm was any experience or fear of: (1) being forced to be sexual against one’s will; (2) sexual assault; as well as more than a few times being exposed to someone’s genitals. Exposure to physical harm was defined as more than a few times when any of the following were experienced or feared: (1) pushed, grabbed or shoved; (2) had something thrown at her that could or did injure; (3) hit with something that hurt her body; (4) choked, burned or hurt with hot water; (5) spanked; and (6) physically attacked in some other way; as well as witnessing any of these committed on a household member. A final criterion for physical harm was a single experience or fear that they or someone they loved would be killed. Concerned that this definition could overestimate abuse exposure, we created two more stringent definitions that include only acts most likely to be interpreted as traumatic. The first defined abuse as exposure to any sexual harm as described above, but limited the experience of certain physical harm items (hit with something that hurt body; choked, burned or hurt with hot water; attacked in some other way) that occurred “more than a few times”. The second stringent definition further limits this subset of more severe exposures to only events that were experienced, not feared.

Data analysis

Time to perimenopause was measured as time from baseline to experience of a perimenopausal event or censoring. The effect parameter estimated was the incidence rate ratio calculated from a proportional hazards regression model. All analyses were adjusted for age to account for natural increases in the rate of perimenopause as women age. We

considered as potential confounders: highest level of education (\leq Bachelor’s degree, graduate school), current economic wellbeing (ability to maintain standard of living if no income for two months or longer), material deprivation in childhood (not enough money for food or lodging; borrow money for medical expenses; not enough money to make ends meet; or received public assistance), cigarette use (never/current/past), body mass index (BMI; <20 , 20–24.9, 25–29.9, ≥ 30 kg/m²), ever had live birth (yes/no), number of pregnancies (0, 1–2, 3–4, 5+), always irregular menstrual cycles at baseline (yes/no), OC use duration (never, 1–5, 6–10, 11+ years), and age of menarche (≤ 11 , 12–13 or ≥ 14 years). We considered the following in identification of confounders: biological plausibility; prior published evidence; and 10% change in estimate of the main effect upon addition to the model. Finally, we evaluated effect modification by depression (Center for Epidemiology study of depression (CESD) score >23) using methods described by Rothman.²⁸ All analyses were conducted using SAS v8.02 (SAS Institute, Cary, NC, 1999). Research was approved by the human

Key points

- Violence, especially early in life, may affect age of perimenopause via stress response dysregulation.
- Other studies have examined the effects of socioeconomic position, race/ethnicity and racism on age of menopause, but this is the first investigation into whether violent experiences affect ovarian aging and onset of perimenopause.
- In a prospective cohort study we found lower rates of perimenopause inception among women with histories of childhood or adolescent violence. This finding persisted when limiting the sample to women who were not depressed at the time of the baseline interview.
- Given that age of natural menopause is an important determinant of women’s post-menopausal health, it is important to understand the role of stressful life experiences on onset of menopause.

subjects committees at each of the collaborating centres (Brigham and Women's Hospital, Brown University and Harvard School of Public Health).

RESULTS

About 58% of the women in this study reported the experience or fear of physical or sexual harm at some point in their lifetimes. Of the 324 women who reported first abuse during childhood/adolescence, 40% reported physical harm only, 22% reported sexual harm only, and 38% reported both physical and sexual harm. Similarly, among the 27 women who reported first abuse during adulthood, this distribution was 26%, 63%, and 11%, respectively.

Abused women were less likely to have attended graduate school, less likely to be able to maintain their current standard of living for more than two months without their income, and more likely to have experienced material deprivation during childhood than never abused women (table 1). While there were no systematic differences in nulliparity, gravidity, menarche, or OC use, 13% of women first abused during childhood/adolescence had a BMI over 30 kg/m² compared with 7% of women first abused in adulthood and 9% of never abused women. Similarly, women first abused in childhood/adolescence were more likely to be current or past smokers. Finally, 16% of never abused women reported depressive symptoms (CESD>23) at the baseline interview compared with 19% of women first abused in adulthood and 45% of women first abused in childhood/adolescence as reported in previous analyses of this cohort.^{19 29}

Table 2 presents a summary of number of perimenopausal events during the follow up period as well as crude incidence rates and adjusted incidence rate ratios (IRR) for the time to onset of perimenopause by age at first experience of abuse (childhood/adolescence or adulthood). During the follow up period 124 of 603 women experienced some change in menstrual cycle regularity, length, or flow, or amenorrhea lasting at least three months. The crude incidence of perimenopause was 95 cases per 1000 woman years for never abused women and 72 and 77 for women first abused in childhood/adolescence or adulthood. After adjusting for age, menarche, nulliparity, ability to maintain standard of living as well as smoking and BMI, there was evidence that women abused in childhood/adolescence (IRR_{adj} = 0.65, 95%CI 0.45 to 0.95) entered perimenopause at slower rates than never abused women. We also estimated the effect of the two more stringent definitions on the association of childhood/adolescent abuse and the estimates were essentially unchanged (IRR_{adj} = 0.65, 95%CI 0.44 to 0.96 and IRR_{adj} = 0.63, 95%CI 0.40 to 0.96, respectively). Finally, although limited by the small number of observed events, there was a similar association among women who reported first abuse during adulthood (IRR_{adj} = 0.72, 95%CI 0.28 to 1.80).

Furthermore, we evaluated whether the presence of depression at baseline modified the association between abuse and timing of perimenopause (table 2). Although the associations between childhood/adolescent abuse and perimenopause timing were consistent with the main analyses, there was also evidence that depression attenuated this effect. Lastly, we evaluated whether an alternative definition of perimenopause based on menstrual cycle irregularity and amenorrhea changed these findings (table 2). The association among those first abused in adulthood was more extreme using the alternative, but the small number of events observed limits interpretation. Among those first abused during childhood/adolescence the association was attenuated, but the conclusion was not changed.

DISCUSSION

In contrast with our original hypothesis, supported by our previous cross sectional analyses,¹⁷ which posited that women with histories of abuse would experience onset of perimenopause at higher rates, and thus earlier ages, than never abused women, we found that women who were abused during childhood/adolescence or adulthood showed signs of menstrual cycle change indicative of onset of perimenopause at slower rates compared with never abused women. These discrepant findings are either the result of bias in estimates of effect (in one or both studies), or the originally hypothesised biological mechanism is incorrect.

The original hypothesis was that HPA axis dysregulation stimulated gonadotropin production leading to more frequent ovulation that contributed to depletion of the follicle pool and earlier menopause. Specifically, stressful experiences start secretion of glucocorticoids that affect ovarian function³⁰ via the hypothalamus. The hypothalamus regulates menstrual function by secreting gonadotropin releasing hormone in pulses, which stimulates the periodic release of both FSH and luteinising hormone from the pituitary gland. FSH is necessary for follicular maturation, while luteinising hormone stimulates oestradiol secretion by the maturing follicle and helps to maintain the corpus luteum.³¹ As the reserve of follicles capable of developing a functioning corpus luteum decreases, evidence of perimenopause is observed by menstrual cycle changes.

However, our results could be consistent with an alternative biological mechanism; possibly involving underactivity of the HPA axis,^{32 33} leading to fewer ovulatory cycles and reduced follicle depletion. According to Heim³⁴ and Gunnar,³⁵ underactivity of the HPA axis may be more common than previously understood, especially among people exposed to long term stress. While atresia is the predominate mechanism through which the follicle pool is depleted,³⁶ lifetime number of ovulatory cycles may play a modest part in menopause timing.^{37 38} Studies have found that high parity, longer menstrual cycles, and long term OC use, all indicative of fewer ovulatory cycles, were associated later menopause.^{14 23 38-46} For example, Meschia found that nulliparous women had a mean age of menopause of 50.0 years, while women with five or more live births had a mean age of 50.9 years.³⁹ These studies, taken together, provide evidence that fewer ovulatory cycles may contribute to small delays in the onset of menopause.

There are several possible sources of bias that should be considered. One is, if the women who were not included in this study were systematically different than those included. To investigate this we examined whether: (1) the 171 women who did not return the SIPR differed from the women who did, and (2) the 73 women who dropped out early in the study before distribution of the SIPR differed from those who did not.

Firstly, we considered whether women who responded to the SIPR were more likely to have later ages at perimenopause and violence histories than women who did not complete the SIPR. Indeed, responders did have later onset of menstrual changes, but it is unlikely given similarities in rates of depression and smoking that the non-responders were more likely to have violence histories. Furthermore, the high response rate (81%) decreases the likelihood that non-response bias could explain the findings.

Secondly, we compared women who dropped out early in the study (n = 73) with those in these analyses. Despite similarities in age and gravidity, the early drop outs had higher rates of depression, past smoking, and mean BMI, earlier menarche, and were slightly more likely to have never used OCs. Given the strong correlation of depression, smoking, and BMI with abuse, it is possible that women with abuse histories were more likely to drop out. These data,

combined with evidence that women with abuse histories may be less willing to enrol in research studies, leaves us unable to rule out this alternative explanation for these findings.

Another possible source of error is recall bias. That is, did women with menstrual changes have differential recall of abuse experiences? It is possible that women with violence histories were less likely to report menstrual changes. However, all women in these analyses were unaware of the hypothesis and had completed multiple follow up batteries by the time of the distribution of the SIPR. Exposure to abuse may have also been over-reported non-differentially with respect to menstrual changes⁴⁷; however, the comparability of our estimates of abuse with those in other studies do not support this.^{48, 49}

We also examined whether misclassification of our exposure variable could have affected our results by using the two restricted definitions of exposure to first abuse in childhood/adolescence compared with the never exposed women. We considered whether experiences with multiple levels of severity (for example, pushing could range from a mild confrontation to a more violent assault) or the inclusion of feared violence could be causing us to classify mildly and severely exposed women as exposed. The first definition eliminated exposures that could have multiple levels severity while the second definition excluded these as well as limiting exposure to actual experience of events, not just fear. When using the more restricted definitions, the confidence intervals were less precise, yet the direction of the effect remained the same and the magnitude changed little.

There are a number of reasons that may explain the difference in this study with a similar cross sectional analysis from the same cohort. To begin, the cross sectional analysis examined the association of abuse with level of FSH and oestradiol—hormones known to increase in lability as menopause approaches^{50, 51}—while this study used a menstrual cycle based definition. In addition, the methodological change of adjusting for, rather than stratifying by, age—could have contributed to the divergent findings between this analysis and the cross sectional.¹⁷ While the change in analytical approach of age is the result of sample size concerns, the transition to a menstrual cycle based definition similar to that used in other studies,^{22–25} may represent an improvement over the individual hormone and centile based approach applied in the cross sectional analysis. In fact, the Stages of Reproductive Aging Workshop Executive Summary stated that the variability of oestradiol limits its usefulness for reproductive staging and FSH, while useful for determinations of later reproductive stages cannot differentiate among them (that is, late reproductive stage from early perimenopause).⁵²

Age at natural menopause is an important determinant of women's post-menopausal health. While the association of age at menopause with increased risk of cardiovascular disease is currently an issue under debate,^{53–55} delayed menopause may have important health consequences including increased risk of breast cancer,^{56, 57} while early menopause is believed to be associated with osteoporosis,⁵⁸ certain cancers^{59, 60} as well as cognitive function.^{61, 62} This study is the first of its kind to show an association of violence with lower rates of perimenopause onset. The conflicting results between the cross sectional¹⁷ and this longitudinal analysis from this cohort, especially in light of the importance of age of menopause as indicator of postmenopausal health, indicate that further study is needed on this topic.

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