Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 12, pp. 1351-1359
DOI: 10.1097/GME.0000000000000929

Lifelong estradiol exposure and risk of depressive symptoms during the transition to menopause and postmenopause

Wendy K. Marsh, MD, MSc,[1] Joyce T. Bromberger, PhD,[2] Sybil L. Crawford, PhD,[3] Katherine Leung, MS,[4] Howard M. Kravitz, DO, MPH,[5] John F. Randolph, MD,[6] Hadine Joffe, MD, MSc,[7] and Claudio N. Soares, MD, PhD, FRCPC, MBA[8]

Abstract

Objective: Depression risk increases during the menopausal transition (MT) and initial postmenopausal years—both times of significant fluctuations of estrogen. Research to date provides limited support for the hypothesis that estrogen fluctuations play a role in the greater susceptibility to midlife depression. Importantly, not all women report depressive symptoms during the MT, and recent reports suggest that duration of exposure to estradiol throughout the adult years may also play a role in vulnerability to depression. This study examines patterns of estrogen exposure during the reproductive years and risk of depression during the MT and early postmenopausal years.

Methods: A longitudinal, US community-based, multiethnic study of menopause. Data were collected at baseline and annually for 10 years, and included 1,306 regularly menstruating premenopausal women, aged 42 to 52 years at study entry. The main outcome was incidence of high level of depressive symptoms, Center for Epidemiological Studies Depression Scale (CES-D) score at least 16, in the MT and initial postmenopausal years, independent of premenopausal depression symptoms. Risk factors examined were duration of estrogen exposure (menarche to MT), duration of hormonal birth control use, pregnancies, and lactation.

Results: In a multivariate adjusted model, longer duration of estrogen exposure from menarche to MT onset was significantly associated with a reduced risk of depression (CES-D $\geq$16) during the MT and 10 years or less postmenopause (odds ratio 0.85, 95% confidence interval 0.78-0.92). Longer duration of birth control use was associated with a decreased risk of CES-D at least 16 (odds ratio 0.90, 95% confidence interval 0.83-0.98), but number of pregnancies or breastfeeding was not.

Conclusions: Patterns of reproductive lifetime exposure to estrogen are associated with risk of high depressive symptoms during the MT and initial postmenopausal years; longer exposure to estrogen seemed protective.

Key Words: Depression – Estrogens – Menopause.

The menopausal transition (MT),[1-4] and early postmenopausal[5-7] years confer an increased risk of major depression and depressive symptoms. These years around the final menstrual period (FMP) are characterized by fluctuating and unpredictable reproductive hormone concentrations, particularly estrogens.[8] Estradiol, the principal estrogen, modulates the synthesis, availability, and metabolism of serotonin,[9] a key neurotransmitter in depression. Thus, reproductive hormones are often considered to be involved in the susceptibility to depression, especially during periods of alterations in ovarian function such as postpartum and the MT. Nonetheless, given that fluctuations of estradiol

Received December 23, 2016; revised and accepted April 3, 2017.

From the [1]Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA; [2]Departments of Epidemiology and Psychiatry, University of Pittsburgh, Pittsburgh, PA; [3]Division of Preventive and Behavioral Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, MA; [4]Department of Obstetrics and Gynecology, University of Massachusetts Medical School, Worcester, MA; [5]Department of Psychiatry and Department of Preventive Medicine, Rush University Medical Center, Chicago, IL; [6]Depart-Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI; [7]Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and [8]Department of Psychiatry, Queen's University School of Medicine, Kingston, Ontario, Canada.

Author contributions: S.L.C., PhD, and K.L., MS, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding/support: Funding was received from The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, and U01AG012495). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH. Supplemental funding obtained from The National Institute of Mental Health is also gratefully acknowledged.

Financial disclosure/conflicts of interest: First Author's time was covered on a KL2RR031981 Clinical Research Scholar Award. H.J. received research grants from Merck, Cephalon/Teva. Advisory/consulting: Noven, Merck, Mitsubishi Tanabe. Dr Joffe's R01 (R01MH082922) provided as the support for her time on this study. W.K.M., J.T.B., S.L.C., K.L., H.M.K., J.F.R., and C.N.S. report no conflicts of interest.

Address correspondence to: Wendy K. Marsh, MD, MSc, Department of Psychiatry, University of Massachusetts Medical School, 55 Lake Avenue North, Ste3-301, Worcester, MA 01605. E-mail: marshw@ummhc.org

during the MT are universal, it is unclear why only some women experience an onset of depressive symptoms during the transition. Furthermore, research to date provides limited support for the hypothesis that wide fluctuations in estrogen levels may render women susceptible to depression. Importantly, recent reports also suggest that, perhaps, duration of exposure to estradiol throughout the adult years may contribute to a greater vulnerability to depression[2,10] Herein, we examine the relationship between duration of estrogen exposure during the premenopausal years, from menarche to MT onset, accounting for reproductive events associated with estrogen changes as potential risk factors for the occurrence of depression during the MT and initial postmenopausal years.

Estradiol is the predominant estrogen during reproductive years both in absolute levels and estrogenic activity. During the MT and early postmenopause ($\leq$6 years after FMP),[11] there is marked variability in estradiol levels that ultimately end in a significant decline.[8,12,13] In epidemiologic studies,[2] including the Study of Women's Health Across the Nation (SWAN),[6] absolute estradiol levels were not associated with concurrent levels of depressive symptoms (ie, high Center for Epidemiological Studies Depression Scale [CES-D]) scores during the MT. In contrast, some studies show that wider within-patient variations in sex hormones measured over time are associated with high CES-D scores[2,14] and administration of exogenous estradiol to depressed[15-17] women has improved mood during the MT.

The notion that hormone fluctuations, but not absolute estradiol levels, are related to depression in the MT and that use of exogenous estrogen might mitigate depressive symptoms during this period has been the cornerstone of the ''window of vulnerability'' theory. This theory proposes that the onset or worsening of mood symptoms in perimenopausal women results from the dynamic hormonal process associated with a significant fluctuation in peripheral concentrations of estradiol.[18,19] Indeed, increased variability of estradiol has been associated with high CES-D in the MT,[2] and withdrawal of exogenous estradiol in postmenopausal women who experienced depression during the MT resulted in onset of depressive symptoms.[20]

The medical literature has begun to examine the association of estrogen exposure in the reproductive years and the development of hormonally related conditions, such as breast cancer, cognitive decline, and bone fracture, during the MT. For example, fewer full-term pregnanies[21,22] and later menopause[23] have been associated with increased risk of breast cancer; nulliparity, and late menopause, with decreased risk of cognitive decline,[24] and more years of menstruation[25] and lactation,[26] but not parity,[26] were associated with lower postmenopausal fracture incidence. These data suggest that greater estrogen exposure could be related to both positive and negative outcomes later in life.

In relation to depression, a meta-ananlysis of 14 studies found that longer exposure to endogenous estrogens, expressed as older age at menopause (defined as FMP) and a longer reproductive period, was associated with a lower risk of reported depression in later postmenopausal life.[10] Similar findings were reported in prior studies that examined adult hormone-related factors and their relationship with risk for later life depression.[14] Specifically, later menopause age, longer duration of reproductive years, and longer OC use (>10 years) were associated with decreased odds of depression during postmenopause,[14,27] whereas parity and age at menarche were not associated with any postmenopausal depression.[14]

This study investigates lifelong estrogen exposure—duration over the reproductive years—and whether it is associated with risk of depression onset in the MT itself. We examine the association of patterns of estrogen exposure during the reproductive years and risk of depression during the MT and up to 10 years postmenopause. We hypothesize that longer duration of estradiol exposure from the menarche to MT, taking into account other reproductive factors, will have a lasting influence and be associated with decreased risk for the emergence of depressive symptoms during the MT.

To address the hypotheses, we utilize data regularly collected over 10 years from women aged 42 to 52 at study entry, who are participants in SWAN—a large multisite study of menopause and aging. In addition to duration of years between menarche and MT, we evaluate several other adult hormone-related factors as potential contributors to estrogen exposure and thus to MT depression risk. Specifically, we looked at the impact of oral contraception use on hormone millieu, perhaps contributing to greater mood stablility in women and reducing the risk of depression,[28] during the MT. A greater number of pregnancies, which are characterized by high levels of estrogens, could also have an impact on depression during the MT. Conversely, lactation, which lowers estrogen levels, could potentially increase risk of depression during the MT.

METHODS

Participants

The SWAN is a longitudinal, multiethnic, multisite, community-based study of menopause among initially pre and early MT/perimenopausal women.[29] Women were recruited from 1995 to 1997. Eligibility criteria included being 42 to 52 years old, having an intact uterus and at least one ovary, not being pregnant or lactating, and in the previous three months both having at least one menstrual period and not using exongenous hormone therapy (HT). Of the 16,065 screened, 3,302 eligible women (50.7% of those eligible) enrolled in the longitudinal cohort. Each of seven sites recruited white women and women from one specified minority group (African American women in Pittsburgh, Pennsylvania; Boston, Massachusetts; Detroit, Michigan; and Chicago, Illinois; Japanese women in Los Angeles, California; Chinese women in the region of Oakland, California; and Hispanic women in Newark, New Jersey). The institutional review boards at all sites approved the study protocol and all women gave their informed consent.

Participants were premenopausal at baseline and provided data at one or more MT or postmenopausal annual follow-ups

over 10 years. We excluded 1,964 women whose onset of MT/perimenopause was not observed because they were already in early MT at baseline (n = 1,540) or were using HT or had a hysterectomy and/or bilateral oophorectomy or had missed visit(s) before the first MT/postmenopausal visit without HT use (n = 424 women); 17 women due to an atypically older age (≥60 years) at the first MT visit or age at menarche was not recorded or was atypical (<7 or >21 years); and 15 women with no MT/postmenopausal visits. The final analytic sample totaled 1,306 women, including 15, who passed directly from premenopause to postmenopause. Overall study retention at the tenth annual visit was 78%.

Procedures

The SWAN participants were assessed at study entry (baseline) and annually with a standardized protocol including self-administered and interviewer-administered questionnaires about health, lifestyle, and psychosocial factors, and a fasting blood sample for hormone measurements. At baseline, information about past medical, pregnancy, and menstrual cycles factors were obtained.

Measures

Depressive symptoms

Depressive symptoms were assessed with the CES-D,[30] which has been validated and reliable in diverse ethnic populations.[31-33] Primary analyses used a score of at least 16 to identify potential clinical depression[34]; a score of above 22, which has been used in SWAN, was also examined as a more stringent assessment of depression.[6]

Menopause status

At each visit, menopause status was defined based on menstrual bleeding patterns in the previous 12 months in the absence of HT, and was categorized according to classifications similar to those recommended by the World Health Organization (WHO, 1996)[35,36]: premenopausal (no change in regularity of menstrual period); MT/perimenopausal (change in regularity to occurrence of at least one menstruation in previous 12 months); postmenopausal (no menstruation for ≥12 months not due to medical reasons).[8,36]

Reproductive history variables

The following reproductive time invariant variables were self-reported at baseline.[37] The number and outcomes of pregnancies (''*How many times have you been pregnant? Please include miscarriages, stillbirths, tubal pregnancies, abortions, and livebirths''*). Only pregnancies continuing beyond the first trimester (ie, live and still birth) were counted as estradiol levels increase markedly in the second trimester to about 100 times over nonpregnant levels.[38] The number of pregnancies per woman was truncated at four or more as there were few women with more. History of lactation (''*If you breastfed, for how long did you breastfeed?'')* was collected for each live birth pregnancy, truncating the months of breastfeeding per live birth at 6 months and then summing the months for each pregnancy. Infants typically begin to eat solids and reduce frequency and duration of breastfeeding by or around 6 months. Prolactin inhibition of gonadotropins during lactation suppresses ovulation, and estradiol levels are typically low for the first 6 months of lactation.[39] OC use (''*Have you ever taken oral birth control pills, if yes, for how long?''*) was categorized as 0, less than 1 year; 1, less than 3 years, 3 to 5 years, and more than 5 years. OC potency varies by estrogen formulation taken[39]; however, distinguishing among the multiple formulations was beyond the scope of SWAN. Nevertheless, estradiol levels are more stable and tend to be higher in OC users than in women who are naturally cycling. Age of menarche (''*How old were you when your periods or menstrual cycles started?'')* was recorded in years. Age at onset of the MT was defined as age at the first annual SWAN visit that was beyond premenopause. This was early MT for most participants. Consistent with previous SWAN analyses,[40] the date of the transition from premenopause to perimenopause or postmenopause was interpolated as the midpoint between the two consecutive visits. Duration of estrogen exposure was calculated as the age at MT onset minus age at menarche.

Covariates

Variables obtained at baseline include age, race/ethnicity, education, employment (work at any job in the past 2 weeks), marital status, site, height, weight, including body mass index (BMI), physical activity, smoking (current vs not), mother's age at menopause, and history of use of antidepressants, barbiturates, sleeping pills, and tranquilizers before entering SWAN. Depression during a premenopausal SWAN visit was defined as a CES-D score of at least 16 and treated as a time invariant variable in analyses of depression during her MT and initial postmenopausal years.

Time-varying variables assessed at annual visits include self-reported medication use for ''nerves or depression'' at least twice per week in the month before interview. Vasomotor symptoms (VMS) were coded as frequency of hot flashes, cold sweats, or night sweats in the previous 2 weeks. Psychosocial variables included social support, the sum of four items from the Medical Outcomes Study Social Support Survey,[41] weight (by 1-kg increments), and number of upsetting life events since previous study visit.

Statistical analysis

Baseline characteristics were compared between women ever and never observed to have elevated depressive symptoms (at both the CES-D ≥16 and >22 levels) during the MT or up to 10 years postmenopause, using chi-square testing for categorical variables and Wilcoxon rank-sum test for continuous variables.

The association between the interval between menarche and the MT with risk of experiencing a high depressive symptoms (CES-D ≥16 and >22) during the MT, was estimated using random-effects binomial logistic regression.[42] Estimated associations were presented in terms of odds ratios (ORs), exponentiating model coefficients.

Unadjusted associations of covariates with incident CES-D at least 16 were estimated in bivariate analysis of each predictor singly. Adjusted associations were estimated from a multivariate model that included duration from menarche to MT, baseline age, ethnicity, education, site, any premenopausal depression, ever-use of antidepressants at baseline, concurrent menopause status (early MT, late MT, early postmenopause, and late postmenopause), and concurrent (time-varying) antidepressant use. Prevalence of CES-D at least 16 during the MT, from early transition through early postmenopause (6 years post-FMP) was compared with late postmenopause (>6 yrs/p FMP)[36]. This cut-off was chosen to compare a time of notable variability and unpredictability in reproductive hormones, that is, up to 6 years after the FMP in contrast to the hormonal stability in later postmenopause.[10] Presence or absence of CES-D at least 16 at a premenopausal visit was included as a covariate.

Additional candidate predictors were reproductive variables (number of months breastfeeding, number of pregnancies, and OC duration), and also VMS symptom frequency, life events, baseline height/weight/change in weight, smoker, and social support. Backward selection with a cut-off of P 0.20 or less was used for these predictors. Predictors with nonlinear associations with the outcome were categorized. Participants' data were censored at initiation of HT and at hysterectomy and/or bilateral oophorectomy. Observations in which the participant was breastfeeding or pregnant, or with missing data for the outcome and/or predictors were omitted.

To assess whether the contribution of the duration between menarche and the MT onset of depression risk in the MT/postmenopause varied by menopause status at the time depression was observed, we tested the interaction between duration of menarche to MT and concurrent menopause status. To examine the contributions of both determinants of the interval between menarche and the MT, we repeated analyses, omitting the interval as a predictor and substituting age at menarche and age at the first MT or postmenopausal visit as separate predictors. We also calculated the Pearson's correlation time from menarche to MT onset with menarche age and age at onset of MT.

Statistical significance was set at P less than 0.05; all analyses used SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Participant characteristics

Women were observed for a mean of 5.4 (SD = 3.5) visits during the MT/postmenopause. The number of years from menarche to onset of MT (age at start of MT minus age at menarche) was normally distributed with a mean of 35.6 ± SD 3.2 years (range 24.4-48.9 years). Time from menarche to MT onset was negatively associated with menarche age (Pearson's correlation coefficient = −0.46, $P < 0.001$) and positively associated with age at onset of MT (Pearson's correlation coefficient = 0.86, $P < 0.001$).

Table 1 summarizes baseline characteristics of the study sample. Women reporting depression (CES-D ≥16) during MT or up to 10 years postmenopause, compared with those who did not, were more likely to have a premenopausal history of depression, less education, be prior users of antidepressants, be Hispanic, and smoke at baseline.

Univariate/unadjusted associations with risk of depression in MT or postmenopause

In unadjusted analyses (Table 2), a longer interval between menarche and MT onset was protective against risk for high depressive symptoms (CES-D ≥16) in MT/postmenopause. Each additional year between menarche and MT onset was associated with a 5% lower odds of depression (OR 0.95, 95% CI 0.92-0.98). The interval from menarche to MT onset continued to be significantly associated with depression in the unadjusted model even when using a more stringent CES-D cut-off score (CES-D >22). Results for prevalent depression (CES-D ≥16) during MT/postmenopause were consistent. Older age at MT onset, but not age of menarche, was associated with lower risk of subsequent high depressive symptoms. Risk for depression also varied by menopausal stage. Compared with early MT, late MT had a greater odds and early + late (all) postmenopause had lower odds of depression.

Associations of other hormone-related factors with the risk of CES-D at least 16 during MT/postmenopause varied. Longer duration of OC use and fewer days with VMS were protective against the emergence of depressive symptoms, whereas number of pregnancies and duration of breastfeeding were not significantly associated with incidence of MT/postmenopausal depression. None of the other hormone-related factors—number or pregnancies, duration of lactation, or OC use—was statistically significantly associated with CES-D above 22.

Other nonhormonal factors were associated with lower risk of depressive symptoms in the MT/postmenopause, including being Chinese (vs White), reporting fewer negative life events, and having higher social support. Greater risk for depressive symptoms during MT/postmenopause was found among those of Hispanic ethnicity compared with Whites, those with a history of premenopausal depression, baseline antidepressant use, and smokers. Baseline age and weight change adjusted for height were not significantly associated with MT/postmenopausal depression.

When age at menarche and age at MT were substituted for interval between menarche and MT, the former was not significantly associated with incidence of CES-D depression ($P = 0.262$), but age at MT was negatively related (OR 0.94, 95% CI 0.91-0.97, $P < 0.001$).

Multivariable analyses

In a multivariate model (Table 3) adjusted for variables associated with risk of high depressive symptoms during the MT/postmenopause, the interval between menarche and MT onset remained significantly protective against a risk of MT/postmenopausal depression, with each additional year interval conferring a 15% decreased odds of depression (OR 0.85,

TABLE 1. *Baseline characteristics*

	Total (N = 1,306)		Menopausal transition and early + late postmenopausal CES-D depression symptoms				
			Never has MT or early + late postmenopausal depression (n = 800)		Has MT or early + late postmenopausal depression (n = 506)		
	Mean	SD	Mean	SD	Mean	SD	*P*
Baseline age, yrs	46.0	2.5	46.1	2.6	45.8	2.5	0.114
BMI	27.3	6.7	26.8	6.5	27.9	7.2	0.005
Age at onset of menopausal transition	48.2	2.8	48.5	2.8	47.7	2.6	<0.001
Baseline total physical activity score	7.8	1.8	7.9	1.8	7.6	1.7	0.007
	N	Col %	n	Col %	n	Col %	
Menarche age							0.298
10 and under	87	6.7%	49	6.1%	38	7.5%	
11	204	15.6%	132	16.5%	72	14.2%	
12	335	25.6%	193	24.1%	142	28.1%	
13	393	30.1%	242	30.2%	151	29.8%	
14	146	11.2%	94	11.7%	52	10.3%	
15	65	5.0%	46	5.8%	19	3.7%	
16+	76	5.8%	44	5.5%	32	6.3%	
Depression (CES-D ≥16) during premenopause SWAN visit							
No	966	74.5%	686	86.3%	280	55.8%	<0.001
Yes	331	25.5%	109	13.7%	222	44.2%	
Ever used antidepressants, barbiturates, sleeping pills, or tranquilizers at baseline							
No	1,137	87.3%	736	92.1%	401	79.7%	<0.001
Yes	165	12.7%	63	7.9%	102	20.3%	
Ethnicity							0.006
African American	306	23.4%	195	24.4%	111	21.9%	
White	601	46.0%	377	47.1%	224	44.3%	
Chinese	137	10.5%	92	11.5%	45	8.9%	
Hispanic	111	8.5%	53	6.6%	58	11.5%	
Japanese	151	11.6%	83	10.4%	68	13.4%	
Education							0.004
<High school or high school	284	21.9%	156	19.6%	128	25.5%	
>High school	381	29.4%	224	28.1%	157	31.3%	
College or post college	633	48.8%	416	52.3%	217	43.2%	
Smoking status							
No	1,139	87.8%	709	89.3%	430	85.5%	0.041
Yes	158	12.2%	85	10.7%	73	14.5%	
Baseline employment							
No	238	18.3%	137	17.1%	101	20.0%	0.408
Yes	1,066	81.7%	662	82.9%	404	80.0%	
Baseline marital status							
Never married	172	13.3%	99	12.5%	73	14.7%	0.077
Currently married/partnered	893	69.1%	567	71.4%	326	65.5%	
Previously married	227	17.6%	128	16.1%	99	19.9%	
Age biological mother stopped menstruating							
<40	74	5.7%	50	6.3%	24	4.7%	0.296
40-44	98	7.5%	65	8.1%	33	6.5%	
45-49	168	12.9%	108	13.5%	60	11.9%	
50-54	325	24.9%	192	24.0%	133	26.3%	
55+	156	11.9%	86	10.8%	70	13.8%	
Unknown/missing	485	37.1%	299	37.4%	186	36.8%	

BMI, body mass index; CES-D, center for epidemiological studies depression scale; MT, menopausal transition; MT, menopausal transition; SD, standard deviation; SWAN, study of women's health across the nation.

95% CI 0.78-0.92). Similar to the CES-D at least 16 model, using a CES-D above 22 cut-off resulted in the risk of depression onset during MT/postmenopause, which significantly decreased by 17% (OR 0.83, 95% Wald CI 0.85-0.92, $P < 0.001$, N = 1,306) for each additional year between menarche and MT onset. Education, site, menopause status, baseline or change in weight, and smoking status were not associated with depression at CES-D above 22. The adjusted OR for CES-D at least 16 during the MT compared with late post menopause was not statistically significant.

DISCUSSION

In this study, a longer duration of estrogen exposure from menarche to the onset of MT was protective against the incidence of high depressive symptoms (CES-D score ≥16 and CES-D >22) through 10 years of follow-up that included

TABLE 2. *Risk of depression onset during the menopausal transition and early postmenopause (unadjusted associations, N = 5,695)*

Variable	Odds ratio	95% Wald confidence limits		*P*	Overall *P*
Duration of Menarche to MT (1-yr increase)	0.95	0.92	0.98	<0.001	
Age at MT (1-yr increase)	0.94	0.90	0.97	<0.001	
Menopause status[a]					0.031
Late MT vs early MT	1.20	0.81	1.78	0.051	
Early postmenopause vs early MT	0.66	0.48	0.90	0.018	
Late postmenopause vs early MT	0.79	0.53	1.17	0.424	
Birth control time (1-yr increase)	0.93	0.87	0.99	0.024	
VMS[b]					<0.001
1-5 vs 0 d	1.78	1.44	2.20	0.095	
6+ vs 0 d	2.25	1.75	2.89	<0.001	
Number of pregnancies					
1 vs 0	1.36	0.98	1.87	0.132	0.233
2 vs 0	1.14	0.87	1.51	0.855	
3 vs 0	1.03	0.75	1.41	0.234	
4+ vs 0	1.32	0.94	1.85	0.252	
Breastfeeding duration, yrs					
0.083-0.34 vs 0	1.01	0.77	1.34	0.629	0.952
>0.34-<0.75 vs 0	0.96	0.72	1.28	0.997	
0.75-1.0 vs 0	0.93	0.71	1.22	0.787	
>1 vs 0	0.90	0.67	1.21	0.587	
Age of menarche, yrs					0.272
<11 vs 12	1.15	0.78	1.69	0.166	
11 vs 12	0.81	0.60	1.09	0.266	
13 vs 12	0.95	0.75	1.21	0.761	
14 vs 12	0.85	0.61	1.20	0.569	
15 vs 12	0.65	0.39	1.07	0.092	
16+ vs 12	1.17	0.78	1.77	0.163	
Any premenopause depression					
Depressed (≥16) vs not depressed (<16)	4.72	3.87	5.75	<0.001	<0.001
Current antidepressant use[b]					
Yes vs no	3.16	2.48	4.03	<0.001	<0.001
Ever use antidepressants at baseline					
Yes vs no	2.83	2.21	3.62	<0.001	<0.001
Stressful life events[b]					<0.001
1 vs 0	2.43	1.89	3.14	0.634	
2+ vs 0	5.30	4.25	6.62	<0.001	
Social support score (1-unit increase)[b]	0.85	0.82	0.87	<0.001	
Baseline age (1-yr increase)	0.97	0.93	1.01	0.098	
Ethnicity					<0.001
African American vs White	0.98	0.77	1.24	0.132	
Chinese vs White	0.74	0.53	1.03	0.001	
Hispanic vs White	2.23	1.61	3.09	<0.001	
Japanese vs White	1.13	0.84	1.50	0.996	
Education					
>High school vs <HS or HS	0.85	0.66	1.09	0.492	<0.001
College or grad school vs <HS or HS	0.63	0.50	0.79	<0.001	
Baseline height (1-cm increase? Or is it meters?)	0.99	0.98	1.01	0.375	
Baseline weight (1-kg increase?)	1.01	1.00	1.01	0.006	
Weight change[b] (1-kg increase?)	0.99	0.97	1.00	0.132	
Concurrent smoking status					
Yes vs no	1.51	1.15	1.99	0.003	0.003
16+ vs 12	1.17	0.78	1.77	0.163	

Each row (or set of rows for categorical variables) represents one regression model with CES-D ≥16 as the outcome.
Cell N will vary due to missing data.
FMP, final menstrual period; HS, high school; MT, menopausal transition; VMS, vasomotor symptoms.
[a]Menopause status definitions. Early postmenopause: no menstrual period within the past 12 months up to 2 years since FMP. Late postmenopause: more than 24 months since FMP.
[b]Indicates time varying.

the MT and initial 10 postmenopausal years. For each additional year of estrogen exposure (time between menarche and menopause onset), the odds of experiencing depression (CES-D ≥16) during the MT, and postmenopause decreased by 15% (17% for CES-D>22), independent of relevant demographic, psychosocial, behavioral, and health factors including VMS. The age at MT onset was the more relevant variable (vs age of menarche) for predicting incident depression during the MT/postmenopause; this is consistent with MT onset having a stronger association with the duration of the interval between the two variables because there is less variability in age at menarche than at age at onset of MT. Contrary to our hypothesis, reproductive events including pregnancy (which increases estradiol levels) or lactation (which lowers estradiol production) were not significantly associated with risk of depression during MT/postmenopause.

TABLE 3. *Risk of depression onset during the menopausal transition early and late postmenopause (adjusted associations, N = 4,631)*

Variable	Odds ratio	95% Wald confidence limits		Pr > χ^2	Overall *P*
Menarche to MT duration (1-yr increase)	0.85	0.78	0.92	<0.001	
Menstrual status					
Late perimenopause vs early perimenopause	1.15	0.70	1.90	0.190	0.333
Early postmenopause vs early perimenopause	0.75	0.50	1.12	0.239	
Late postmenopause vs early perimenopause	0.74	0.44	1.25	0.317	
Birth control time	0.90	0.83	0.98	0.014	
VMS[a]					<0.001
1-5 vs 0 d	1.62	1.25	2.09	0.374	
6+ vs 0 d	2.11	1.54	2.87	0.001	
Age of menarche, yrs					0.001
<11 vs 12	0.93	0.55	1.57	0.123	
11 vs 12	0.90	0.62	1.31	0.043	
13 vs 12	0.78	0.58	1.05	0.073	
14 vs 12	0.72	0.46	1.13	0.445	
15 vs 12	0.21	0.10	0.42	<0.001	
16+ vs 12	0.41	0.21	0.80	0.115	
Any pre-menopause depression during SWAN					
Depressed (16 ≤ CES-D) vs not depressed (CES-D<16)	3.82	2.95	4.95	<0.001	
Current antidepressant use[a]					
Yes vs no	1.70	1.21	2.39	0.002	
Ever used antidepressants, barbiturates, sleeping pills, or tranquilizers at baseline					
Yes vs no	1.73	1.23	2.44	0.002	
Life events[a]					<0.001
1 vs 0	2.44	1.82	3.27	0.511	
2+ vs 0	5.01	3.82	6.55	<0.001	
Social support score[a] (1-unit increase)	0.85	0.82	0.88	<0.001	
Baseline age (1-yr increase)	1.18	1.08	1.28	<0.001	
Ethnicity					0.003
African American vs White	0.67	0.48	0.93	<0.001	
Chinese vs White	1.06	0.60	1.90	0.204	
Hispanic vs White	5.67	1.19	26.96	0.039	
Japanese vs White	2.02	1.16	3.53	0.302	
Education					
>High school vs <HS or HS	0.89	0.64	1.23	0.977	0.341
College or grad school vs <HS or HS	0.79	0.57	1.09	0.163	
Baseline height (1-cm increase)	1.00	0.98	1.02	0.889	
Baseline weight (1-kg increase)	1.00	0.99	1.01	0.738	
Weight change (1-kg increase)	0.98	0.96	1.00	0.028	
Concurrent smoker vs nonsmoker	1.15	0.80	1.64	0.451	

Results are also adjusted for site.
CES-D, center for epidemiological studies depression scale; FMP, final menstrual period; HS, high school; MT, menopausal transition; SWAN, study of women's health across the nation; VMS, vasomotor symptoms.
[a]Indicates time varying.

However, longer duration of OC use, resulting in extended exposure to higher levels of estrogen and decreased exposure to natural and endogenous hormone fluctuations (as most OCS mitigate the exposure to cyclic changes in the hormone milieu), was protective against risk of depressive symptoms during MT and beyond. We found independent predictors of depression in midlife women to be similar to those previously reported, including VMS, ethnicity, stressful life events, prior depression, less education, use of antidepressants,[6] and weight change.[6,43] Social support reduced depression risk.[44]

Estradiol modulates the activity of many systems implicated in the pathogenesis of depression: regulation of neurotransmitter synthesis and metabolism, hypothalamic pituitary adrenal axis activation, neuroplasticity (including regulation of brain-derived neurotrophic factor), epigenesis, and immune system activation.[45] Our results suggest that the longer exposure to menstrually regulated estradiol variations, and also relatively steady oral contraceptive hormonal levels during the reproductive years could translate into a lasting effect on the modulation (synthesis, availability) of monoamines, such as serotonin, that are known to affect mood. Polymorphisms in genes related to estrogen synthesis and metabolism have been associated with higher risk for depressive symptoms,[46] and disturbances in the hormonal milieu due to gene-related changes in estrogen synthesis and/or metabolism may be related to depression due to downstream effects on dysregulated monoamines.[18]

These indicate a possible genetic mechanism behind the risk of menopausal depression association with lifelong estradiol exposure. Another genetic explanation could include the FMR1 gene and its role in the development of neurodegenerative disorders; this gene has been associated both with risk of depression and early age of menopause.[47] Consistent with this finding are the results from The Harvard Study of Moods and Cycles that reported major depression was associated with early decline in ovarian function.[48] They

also found that several factors associated with early menopause could also be associated with depression and thus could be considered confounders.[49] For example, smoking is more prevalent in people suffering from depression[50] and is also associated with an earlier onset of menopause.[51,52] Likewise, obesity is associated with depression,[53] and with a greater rate of anovulatory than ovulatory cycles in women undergoing the MT.[54,55] This study adjusted for both smoking and BMI and our results remained significant.

History of depression has often,[49] but not always,[56] been associated with risk of early MT, possibly by disrupting hypothalamic pituitary ovarian function.[57,58] We previously found that a history of major depressive disorder was associated with risk for depression during the MT.[59] Although this study did not have full diagnostic criteria on major depressive episode history, it did adjust for history of antidepressant use, which is a reasonable indicator of past depressive episodes. Additionally, variables associated with current stress such as upsetting life events (increased stress) and social support (decreased stress) were adjusted for. Finally, this study also adjusted for high depressive symptoms experienced by women in SWAN in their late reproductive years, but before entering the MT. Our findings of a longer duration of reproductive life being associated with a lower risk of depression during the MT remained significant through all above adjustments.

OCs have been associated with a later age at menopause,[60] and later age at MT onset has been found to be associated with a shorter MT.[61] If a shorter MT duration is itself associated with lower risk of depression during the MT and first years postmenopause, then this might help explain why age at MT onset, but not age at menarche, is related to incident depression found here.

Limitations of this study include the use of depressive symptoms, rather than categorical diagnosis of clinical depression. History of reproductive variables was assessed by self-report and retrospective recall, which is subject to recall biases or other inaccuracies. Given the data point of longest OC exposure was only above 5 years, this might underestimate the reduced risk of depression associated with OC use. Whereas the use of first perimenopausal visit as an indicator of MT onset is a soft indicator (as it is difficult to pinpoint the actual start of the MT), this increased variability would bias the estimated associations towards the null, and thus lead to a potential underestimation of the association of duration of estrogen exposure with menopausal depression.

Noteworthy strengths include a large sample with data on reproductive history, up to 10 years of prospective annual follow-up data on onset of the menopausal transition, and adjustment for multiple relevant risk factors for depression, many of which are time-varying.

CONCLUSIONS

The relative contribution of estrogen to the risk of developing depression during MT and postmenopause has long been debated. The current study provides important new evidence that reproductive events and estrogen exposure might be setting the stage premenopausally for the risk of clinically significant depressive symptoms during the MT and beyond. Differences in duration of estradiol exposure and moderators of the patterns of exposure during the reproductive years may inform future research on disentangling the inter-relationships between depressive symptoms and hormone dynamics, and aid in identifying women who are at increased risk of depression during the MT. They warrant futher investigation on the putative mechanistic factors. If further corroborated, these findings may also have implications for the extent to which variations in reproductive hormone exposure during reproductive years might subsequently alter the risk for depression later in life.

Acknowledgment: We thank the study staff at each site and all the women who participated in SWAN.

REFERENCES

1. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry* 2006;63:385-390.
2. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006;63:375-382.
3. Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry* 2004;161:2238-2244.
4. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry* 2004;61:62-70.
5. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). *J Affect Disord* 2007;103:267-272.
6. Bromberger JT, Schott LL, Kravitz HM, et al. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: results from the Study of Women's Health Across the Nation (SWAN). *Arch Gen Psychiatry* 2010;67:598-607.
7. Maartens LW, Knottnerus JA, Pop VJ, et al. Menopausal transition and increased depressive symptomatology: a community based prospective study. *Maturitas* 2002;42:195-200.
8. Burger HG, Dudley EC, Hopper JL, et al. Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. *J Clin Endocrinol Metab* 1999;84:4025-4030.
9. Lokuge S, Frey BN, Foster JA, Soares CN, Steiner M. Depression in women: windows of vulnerability and new insights into the link between estrogen and serotonin. *J Clin Psychiatry* 2011;72:e1563-e1569.
10. Georgakis MK, Thomopoulos TP, Diamantaras AA, et al. Association of age at menopause and duration of reproductive period with depression after menopause: a systematic review and meta-analysis. *JAMA Psychiatry* 2016;73:139-149.
11. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause* 2012;19:387-395.
12. Metcalf MG. The approach of menopause: a New Zealand study. *N Z Med J* 1988;101:103-106.
13. Metcalf MG, Donald RA, Livsey JH. Pituitary-ovarian function before, during and after the menopause: a longitudinal study. *Clin Endocrinol (Oxf)* 1982;17:489-494.
14. Ryan J, Carrière I, Scali J, Ritchie K, Ancelin ML. Lifetime hormonal factors may predict late-life depression in women. *Int Psychogeriatr* 2008;20:1203-1218.
15. Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2001;58:529-534.

16. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 2000;183:414-420.
17. Rasgon NL, Altshuler LL, Fairbanks LA, et al. Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *J Clin Psychiatry* 2002;63(Suppl 7):45-48.
18. Schmidt PJ, Roca CA, Bloch M, et al. The perimenopause and affective disorders. *Semin Reprod Endocrinol* 1997;15:91-100.
19. Soares CN. Mood disorders in midlife women: understanding the critical window and its clinical implications. *Menopause* 2014;21: 198-206.
20. Schmidt PJ, Ben Dor R, Martinez PE, et al. Effects of estradiol withdrawal on mood in women with past perimenopausal depression: a randomized clinical trial. *JAMA Psychiatry* 2015;72:714-726.
21. Kalache A, Maguire A, Thompson SG. Age at last full-term pregnancy and risk of breast cancer. *Lancet* 1993;341:33-36.
22. Ramon JM, Escriba JM, Casas I, et al. Age at first full-term pregnancy, lactation and parity and risk of breast cancer: a case-control study in Spain. *Eur J Epidemiol* 1996;12:449-453.
23. Trichopoulos D, MacMahon B, Cole P. Menopause and breast cancer risk. *J Natl Cancer Inst* 1972;48:605-613.
24. McLay RN, Maki PM, Lyketsos CG. Nulliparity and late menopause are associated with decreased cognitive decline. *J Neuropsychiatry Clin Neurosci* 2003;15:161-167.
25. Nguyen TV, Jones G, Sambrook PN, White CP, Kelly PJ, Eisman JA. Effects of estrogen exposure and reproductive factors on bone mineral density and osteoporotic fractures. *J Clin Endocrinol Metab* 1995;80: 2709-2714.
26. Bjornerem A, Ahmed LA, Jørgensen L, Størmer J, Joakimsen RM. Breastfeeding protects against hip fracture in postmenopausal women: the Tromso study. *J Bone Miner Res* 2011;26:2843-2850.
27. Jung SJA, Shin D. Kang, menarche age, menopause age and other reproductive factors in association with post-menopausal onset depression: Results from Health Examinees Study (HEXA). *J Affect Disord* 2015;187:127-135.
28. Joffe H, Petrillo LF, Viguera AC, et al. Treatment of premenstrual worsening of depression with adjunctive oral contraceptive pills: a preliminary report. *J Clin Psychiatry* 2007;68:1954-1962.
29. Sowers MF, Crawford SL, Sternfeld B, et al. SWAN: a multicenter, multiethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey J, Marcus R, eds. *Menopause: Biology and Pathobiology*. San Diego: Academic Press; 2000. pp. 175-188.
30. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385-401.
31. Guarnaccia PJR, Angel JL. Worobey: the factor structure of the CES-D in the Hispanic Health and Nutrition Examination Survey: the influences of ethnicity, gender and language. *Soc Sci Med* 1989;29:85-94.
32. Jones-Webb RJLR. Snowden: symptoms of depression among blacks and whites. *Am J Public Health* 1993;83:240-244.
33. Ying YW. Depressive symptomatology among Chinese-Americans as measured by the CES-D. *J Clin Psychol* 1988;44:739-746.
34. Boyd JH, Weissman MM, Thompson WD, Myers JK. Screening for depression in a community sample. Understanding the discrepancies between depression symptom and diagnostic scales. *Arch Gen Psychiatry* 1982;39:1195-1200.
35. WHO. Research on the menopause in the 1990s: report of a WHO Scientific Group. *WHO Technical Report Series*. Geneva, Switzerland: World Health Organization; 1996.
36. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop +10 addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012;97: 1159-1168.
37. Gold EB, Eskenazi B, Lasley BL, et al. Epidemiologic methods for prospective assessment of menstrual cycle and reproductive characteristics in female semiconductor workers. *Am J Ind Med* 1995;28:783-797.
38. Speroff LGR, Kase NG. The endocrinology of pregnancy. *Clinical Gynecologic Endocrinology and Infertility*. Maryland: Williams & Wilkins; 1994;251-289.
39. Fritz M, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*, 8th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.
40. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab* 2008;93:861-868.
41. Sherbourne CD, Stewart AL. The MOS social support survey. *Soc Sci Med* 1991;32:705-714.
42. Molenberghs G, Verbeke G. *Models for Discrete Longitudinal Data*. New York: Springer Science+Business Media, Inc.; 2005.
43. Frey BN, Lord C, Soares CN. Depression during menopausal transition: a review of treatment strategies and pathophysiological correlates. *Menopause Int* 2008;14:123-128.
44. Acog Committee on Practice Bulletins–Obstetrics. ACOG Practice bulletin: clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol* 2008;111:1001-1020.
45. Rubinow DR, Schmidt PJ, Craft CD. Gonadal steroids and mood disorders. In: Charney D, ed. et al. *Neurobiology of Mental Illness*. New York, NY: Oxford University Press; 2013. pp. 483-495.
46. Kravitz HM, Janssen I, Lotrich FE, Kado DM, Bromberger JT. Sex steroid hormone gene polymorphisms and depressive symptoms in women at midlife. *Am J Med* 2006;119(9 Suppl 1):S87-S93.
47. Kenna HA, Tartter M, Hall SS, et al. High rates of comorbid depressive and anxiety disorders among women with premutation of the FMR1 gene. *Am J Med Genet B Neuropsychiatr Genet* 2013;162B:872-878.
48. Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. *Arch Gen Psychiatry* 2003;60:29-36.
49. Harlow BLLB. Signorello, Factors associated with early menopause. *Maturitas* 2000;35:3-9.
50. Matcham F, Carroll A, Chung N, et al. Smoking and common mental disorders in patients with chronic conditions: an analysis of data collected via a web-based screening system. *Gen Hosp Psychiatry* 2017;45:12-18.
51. Midgette AS, Baron JA. Cigarette smoking and the risk of natural menopause. *Epidemiology* 1990;1:474-480.
52. McKinlay SM, Bifano NL, McKinlay JB. Smoking and age at menopause in women. *Ann Intern Med* 1985;103:350-356.
53. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Res* 2010;178:230-235.
54. Santoro N, Crawford SL, Lasley WL, et al. Factors related to declining luteal function in women during the menopausal transition. *J Clin Endocrinol Metab* 2008;93:1711-1721.
55. Beser E, Aydemir V, Bozkaya H. Body mass index and age at natural menopause. *Gynecol Obstet Invest* 1994;37:40-42.
56. Li J, Eriksson M, Czene K, Hall P, Rodriguez-Wallberg KA. Common diseases as determinants of menopausal age. *Hum Reprod* 2016;31:2856-2864.
57. Young EA, Altemus M. Puberty, ovarian steroids, and stress. *Ann N Y Acad Sci* 2004;1021:124-133.
58. Young EA, Altemus M, Lopez JF, et al. HPA axis activation in major depression and response to fluoxetine: a pilot study. *Psychoneuroendocrinology* 2004;29:1198-1204.
59. Bromberger JT, Kravitz HM, Matthews K, Youk A, Brown C, Feng W. Predictors of first lifetime episodes of major depression in midlife women. *Psychol Med* 2009;39:55-64.
60. Gold EB, Crawford SL, Avis NE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am J Epidemiol* 2013;178:70-83.
61. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas* 1992;14:103-115.