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Effects of Reproductive History on Symptoms of Menopause: A Brief Report

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Abstract

Objective—To examine the relationship between reproductive history and menopausal symptoms among urban women.

Methods—A cohort study of women aged 35–47 recruited in Philadelphia, PA. Two hundred and ninety one pre-menopausal women meeting study eligibility criteria and contributing reproductive health history and infertility information completed assessments of occurrence and severity of several menopausal symptoms over a 14 year period. Reproductive history included the number of pregnancies, live births, preterm deliveries and miscarriages. Trying to get pregnant for more than one year was used as an assessment of infertility. The occurrence of severe hot flashes, vaginal dryness and decreased libido were evaluated.

Results—Women scoring positive on the infertility index were significantly more likely to report severe decreased libido (OR=1.86, 95% CI: 1.05–3.31) and over twice as likely to report severe vaginal dryness (OR=2.79, 95% CI: 1.19–6.94) in multivariable models. None of the other reproductive health indices were related to report of severe hot flashes, vaginal dryness or decreased libido. The race-specific models continued to find a significant, increased risk of severe vaginal dryness (OR=2.79, 95% CI: 1.22–6.36) and decreased libido (OR=1.87, 95% CI: 1.04–3.34) among white women scoring positive on the infertility index; however the relationship did not remain significant among African-American women.

Conclusions—Severe vaginal dryness and decreased libido are common and important considerations of the menopausal transition and the experience of infertility problems may influence the report of severe vaginal dryness and decreased libido particularly among white women.

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Keywords

infertility; vaginal dryness; decreased libido; menopausal symptoms; reproductive history

Introduction

The menopausal transition is often characterized by a variety of symptoms including hot flashes, night sweats, vaginal dryness, decreased libido, sleep disturbances and mood changes.^{1–3} Approximately 85% of women report experiencing at least one menopausal symptom⁴ with vasomotor symptoms such as hot flashes being especially prevalent^{1,5} and sexual health-related variables including vaginal dryness and decreased libido being associated with reduced quality of life.^{6–8}

A woman's experience of menopausal symptoms is affected by a myriad of factors including demographic (age, race, ethnicity), psychological (stress, anxiety), health behaviors (smoking status, physical activity) and health status (body mass index) variables.^{7,9} Fertility levels and reproductive history have also been implicated by a small number of studies as affecting the onset of menopause or prevalence of menopausal symptoms. Specifically, data from one longitudinal study examining the relationship between number of retrieved oocytes at the first in vitro fertilization attempt and age of menopause, showed that women with lower levels of fertility (i.e. low number of retrieved oocytes at a first in vitro fertilization stimulation) were more than 10-times more likely to become postmenopausal at an early age than women with higher levels of fertility.¹⁰ In another study, nulligravida women (women with no pregnancies or births) and nulliparous women (women with one or more pregnancies but no live births) were half as likely to report hot flashes as parous women (women with one or more live births). Nulligravida women also reported less vaginal dryness than parous women.¹¹

A greater understanding of the relationship between reproductive history and the experience of menopausal symptoms could help inform the dialogue about symptom expectations and management between health providers and their pre-menopausal patients.¹ The goal of the current study was to examine the relationship between indices of reproductive history, including infertility, and the severity of hot flashes, vaginal dryness and decreased libido.

Material and Methods

Data Collection

This prospective cohort study enrolled a population-based sample of 436 women, identified through random digit dialing, which were living in the City of Philadelphia from 1996–1997. To ensure a racially diverse study population, eligible women were stratified by race (African American or white). Eligible women were between the ages of 35 and 47 years, reported menstrual cycles in the normal range (22 to 35 days) for the previous 3 months, and had at least one intact ovary. Exclusion criteria included any serious illness that might compromise ovarian or hormonal function (i.e. diabetes, liver disease, breast or endometrial cancer); current use of exogenous hormones or psychotropic drugs; self-reported chronic alcohol or drug abuse within the past year; or current pregnancy, lactation, or intention to become pregnant. The goal of this assessment was to determine the role of reproductive factors on the risk of onset of severe menopausal symptoms; thus, premenopausal women were enrolled at baseline and followed for up to 14 years for the incidence of severe menopausal symptoms. The Institutional Review Board of the University of Pennsylvania approved the study and all women provided written informed consent.

At enrollment, eligible women consented to participate in a long-term women's health study with no specific emphasis on the examination of menopause. Project data were collected at approximately 9 month intervals for the first 5 years of the study and approximately annually during the subsequent 9 years over the entire 14-year period. At each assessment period, an extensive structured questionnaire was administered by trained research interviewers who collected information on demographics, menstrual cycle characteristics, type and severity of menopausal symptoms, physical activity, menstrual and obstetric history, general health status, medication use (including hormone replacement therapy), and substance use. In addition, participants completed a set of standard self-reported questions including the Center for Epidemiological Studies' Depression Scale (CES-D),¹² the Zung Anxiety Scale,¹³ and the Perceived Stress Scale.¹⁴

At the 11-year assessment period, additional detailed reproductive history questions were added to the annual questionnaire which collected information on the particular reproductive history indices of interest in this study (i.e. gravidity, parity, history of preterm delivery, history of premature rupture of the membranes, number of prior stillbirth, miscarriage or ectopic pregnancies). History of infertility was collected in the initial baseline questionnaire. Whether captured at baseline or during the year 11 interview, each of the reproductive indices of interest was collected retrospectively for events occurring during the reproductive years. It is important to note that the vast majority of women, over 90% had complete information for all of the reproductive indices of interest. For this study, 291 participants who were followed for up to 14 years and had reproductive history data were included.

Study Measures

As described, each woman was asked a series of questions concerning her reproductive history. The question which assessed history of infertility; "Did you ever try to get pregnant for over one year without being able to?" was used to create the infertility index. Women responding yes to this question were classified as positive for a history of infertility and women reporting no to this question were classified as negative for infertility. In addition, women were asked questions concerning past obstetrical and reproductive history including; the number of pregnancies (gravity), the number of live births (parity), the experience of a preterm delivery (delivery prior to 37 completed weeks gestation), the experience of premature rupture of the membranes, and the number of pregnancies which ended in a stillbirth, miscarriage or ectopic pregnancy. Each question was used to create separate reproductive history indices. We were most interested in examining the role of infertility and reported menopausal symptoms.

Using the Penn Menopausal Symptoms List (MSL), adopted and validated from the Kupperman Menopausal Index, we collected information on the frequency and severity of menopausal.¹⁵ The symptoms were rated by the participants for their presence and severity in the past month. At each assessment period, severity was assessed as mild, moderate or severe. For this study, we were most interested in examining the initial occurrence of severe of hot flashes, severe vaginal dryness or severe decreased libido since these are the menopausal symptoms frequently reported by peri-menopausal women and linked to similar hormonal changes experienced during the reproductive years and menopausal transition.

At each assessment period, the Zung Anxiety Scale was used to measure anxiety in the past week. The questionnaire included 20 items that were sensitive to the frequency of affective and somatic anxiety symptoms¹³. Participants rated each item from 1 (none or a little of the time) to 4 (most or all of the time), and the ratings were summed for a total anxiety score. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D).¹² Stress was measured using the Cohen's Perceived Stress Scale which measures the degree to which situations in the past month are appraised as stressful¹⁴. Since

these psychometric profiles were correlated with each other, we chose to include the assessment of anxiety in multivariate models since anxiety has been consistently linked to reported menopausal symptoms in our prior analyses and in other studies of menopausal symptoms.² Smoking status and body mass index (BMI) were also collected at each assessment period.

Menopausal status at each assessment period was constructed using data from the menstrual dates concurrent with each study interview plus the dates of the two previous menstrual periods recorded at each of the two interview visits, the self-reported number of menstrual periods between assessment periods, and cycle length and number of days of bleeding. The definitions of menopausal stage were from the consensus statement on a staging system for reproductive aging in women (Stages of Reproductive Aging Workshop).¹⁷ We previously demonstrated that these Stages of Reproductive Aging Workshop stages were significantly associated with reproductive hormone levels and differentiated the earliest stages in the menopausal transition in this cohort.^{16,18} At each assessment period, each participant was assigned to one of the following five menopause categories based on the available information: Premenopausal defined as having regular menstrual cycles in the 22–35 day range; Late premenopausal defined as within-participant change in cycle length ≥ 7 days, in either direction, for one cycle compared to the participant's baseline at enrollment in the cohort; Early transitional defined as within participant change in cycle length ≥ 7 days, in either direction, for at least 2 cycles compared to the participant's baseline at enrollment in the cohort; Late transitional defined as 3–11 months of amenorrhea; or Postmenopausal defined as ≥ 12 months amenorrhea without a hysterectomy.¹⁶ At each assessment period, we measured and adjusted for menopausal status to understand the independent contribution of each of the indices of reproductive history and the report of severe menopausal symptoms.

Statistical Analysis

To examine the relationship between indices of prior reproductive history (yes/no) or the infertility index (positive/negative) predicting severe menopausal symptom (hot flashes, vaginal dryness and decreased libido) over the 14 year period, separate generalized linear regression models were developed (SAS PROC GEMOD)⁴⁰. Individual logistic regression models for binary data were used to estimate the association of the reproductive history described above on the occurrence of severe hot flashes (yes/no), severe decreased libido (yes/no), or severe vaginal dryness (yes/no). Each menopausal symptom was modeled separately for each reproductive factor and included only women reporting the relevant events. To recognize the other factors which may contribute to severe menopausal symptoms among this cohort, all multivariable models included age, menopausal stage, race, cigarette use, anxiety scores, BMI and a race-reproductive history interaction term.

The occurrence of the menopausal symptom of interest was identified and classified during the assessment period when the symptom was first reported as severe. Given the repeated measures inherent in this cohort study, variance estimates for the Wald statistics of the true regression coefficients were adjusted for the repeated observations from each participant using Generalized Estimates Equations approach.¹⁹ All available data for each participant at each assessment period were included in the repeated measures models, and women were censored at the point of first report of severe vaginal dryness, decreased libido or hot flashes. The final selection of covariates included in the models was guided by whether the variables remained statistically significant at $p < 0.05$ and whether inclusion modified other significant associations in the model by 15% or more (25). Menopausal status (five groups, described above), race (white vs. African American), smoking (yes/no), age (continuous), anxiety (continuous) and BMI (normal, overweight, obese) were included as covariates in final multivariable models. Assessment periods where a woman reported exogenous hormone use

were censored. In addition, the exposures of interest (i.e. history of infertility, number of prior pregnancies, number of prior live births, and prior pregnancy outcomes) were retrospectively reported events occurring during the reproductive years and did not change over the 14 follow-up period; however, the other covariates included in the models (i.e. smoking, age, anxiety, BMI) may change and the repeated measures analysis recognized and accounted for this potential change over time.

To explore potential effect modification by race, race-reproductive health interaction terms were added to multivariable models and separate multivariable analyses were conducted for African American and white women to examine the role of reproductive history indices on menopausal symptoms among these racial groups. All analyses were performed using the SAS statistical package, Version 9.1 (SAS Institute Inc, Cary, NC).

Results

Descriptive Information

The average age at baseline was 42 years old (± 3.5), 53% were African American, 58% reported more than a high school education, 35% smoked cigarettes at enrollment and 35% reported a baseline BMI greater than 30. The average anxiety score at baseline was 35 ± 8.1 (mean/std deviation). By design, all of the women were pre-menopausal at enrollment and fourteen years after enrollment, 55% of the women were classified as post-menopausal with an additional 15% classified in the late transitional phase. During the fourteen year follow-up period, 73% of women reported at least one episode of severe hot flashes and at the point of first report of severe hot flashes 30% of women were classified in the post-menopausal or late transition phase. Sixty-two percent of women reported at least one episode of severe decreased libido during the follow-up period and 33% of these women were classified as post-menopausal or in the late transition phase at initial report. In addition, during the 14 year follow-up period, 39% of women reported at least one episode of severe vaginal dryness with 28% of these women classified as post-menopausal or in the late transition phase of menopausal at the point of first.

Eleven percent of women in this cohort reported no pregnancies; among women with a prior pregnancy, 83% of these women reported at least one prior live birth (parous), over one-half of parous women reported three or more live births, 22% of women reported at least one prior preterm birth, 11% of women reported at least one episode of premature rupture of membranes, 8% women reported two or more miscarriages, and 28% of women reported at least one induced abortion. Twenty percent scored positive on the infertility index.

Reproductive History and Menopausal Symptoms

As shown in Table 1, women scoring positive on the infertility index (women unable to conceive after one year of trying to get pregnant) were significantly more likely to report severe decreased libido (OR=1.86, 95% CI: 1.05–3.31; n=46 infertile women reporting decreased libido vs. n=59 infertile women without decreased libido) and over twice as likely to report severe vaginal dryness (OR=2.79, 95% CI: 1.19–6.94; n=27 infertile women reporting decreased vaginal dryness vs. n=59 infertile women without vaginal dryness) in the multivariable models. Women with no prior pregnancies were significantly less likely to report severe decreased libido (OR=0.38, 95% CI: 0.16–0.91; n=14 women with no pregnancies reporting decreased libido vs. n=31 women with no pregnancies without decreased libido) and were less likely to report severe vaginal dryness (OR=0.36, 95% CI: 0.12–1.08; n=6 women with no pregnancies reporting vaginal dryness vs. n=32 women with no pregnancies reporting vaginal dryness) compared to women with at least one prior pregnancy in the multivariable models. These models included age, menopausal stage, race,

cigarette use, anxiety scores, BMI and the race interaction term. None of the other reproductive health indices were related to report of severe vaginal dryness or decreased libido (Table 1). In addition, none of the reproductive health indices, including the infertility index, were related to the report of severe hot flashes among this cohort of urban women. For example, women scoring positive on the infertility index and women with no prior pregnancies were similar in their report of severe hot flashes (aOR=0.97, 95% CI: 0.54 – 1.74; aOR=0.90, 95% CI: 0.43 – 1.92 respectively).

Race-specific Models

The race-specific models continued to find a significant, increased risk of severe vaginal dryness (OR=2.79, 95% CI: 1.22–6.36) and decreased libido (OR=1.87, 95% CI: 1.04–3.34) among white women scoring positive on the infertility index; however the relationship between infertility and menopausal symptoms did not remain significant among African-American women (Table 2). In these race specific models, none of the other reproductive health indices, including women with no prior pregnancies, continued to be related to menopausal symptom reports (Table 2).

Discussion

Data from the current study show that among a cohort of community dwelling women approaching and completing the transition to menopause, decreased libido and severe vaginal dryness were prevalent menopausal symptoms and these symptoms did not necessarily occur primarily among the group of women reaching menopause. In fact, we found the majority of severe vaginal dryness and decreased libido among women in the premenopausal (25% and 38%, respectively) and late premenopausal (18% and 20%, respectively) stages. We also found that women who reported fertility problems were almost twice as likely to report severe decreased libido and almost three times more likely to report severe vaginal dryness compared to women not reporting infertility problems. We should note that the prevalence of the reported reproductive factors (parity, infertility and gravidity) were very similar and convergent with those reported for the general population.^{20–22} Others have linked a history of infertility with the experience of menopause. De Boer et al reported that women experiencing infertility reported menopause at an earlier age; our data suggest a relationship between infertility and a higher occurrence of decreased libido and severe vaginal dryness, particularly among white women.¹⁰

We found the effect of infertility on the experience of decreased libido and increased vaginal dryness was significant for white but not African-American women. Prior studies have clearly demonstrated racial differences in reproductive stages. For example, African American girls tend to initiate puberty up to 1-year earlier than white girls²³ and African American women tend to respond more poorly (lower successful live birth rates) to fertility treatments.²⁴ In addition, during menopause African American women are significantly more likely to experience vasomotor dysfunction,^{25–27} vaginal dryness^{28,29} and pain during sex compared to white women.³⁰ Most notably, racial and ethnic disparities in the etiology of infertility have been described. For example, decreased ovarian reserve and ovarian function occur more frequently among white women and infertility due to tubal blockage or fibroids occur more frequently among African American women.³¹ Biologic and sociocultural factors have been suggested to explain the racial disparity in infertility rates and include the higher prevalence of chlamydial exposure, differences in access to primary and specialty care, and reduced health care utilization rates among African American compared to white women.^{32–33} In addition, African American women commonly present with longer duration of infertility compared to white women, and have a lower success rate following in vitro fertilization compared to white women.³⁴ These factors related to the racially-specific etiology of infertility may also explain the observed decreased in libido and

increased vaginal dryness, symptoms also driven by hormonal factors, among white but not African American women with a history of infertility. Future studies are needed to elucidate the racial differences in cultural, social and physiological mechanisms linking a woman's etiology and experience of infertility during the reproductive years and menopause symptomatology.

Other studies have found that decreased libido and interest in sex has been implicated in the menopausal transition,² with recent data suggesting that this relationship is independent of vaginal dryness.³ The occurrence of vaginal dryness has also been associated with the menopausal transition,^{7,35} particularly among women with multiple pregnancies compared to women with no pregnancies.¹¹ In contrast, we found that women with no prior pregnancies were less likely to report severe decreased libido and severe vaginal dryness compared to women with at least one pregnancy although this relationship did not remain when we examined racial differences and accounted for other factors which may also contribute to menopausal symptoms, most importantly BMI and smoking. We did not collect information on a woman's choice to not get pregnant which may be vastly different from the group of women reporting infertility.

It is important to note that we did not find an association between any of the reproductive history indices, including the infertility index, and severity of hot flashes. Our finding that prior infertility was related to a woman's report of decreased libido and increased vaginal dryness but not the occurrence of hot flashes is a point of interest. A recent longitudinal study conducted by Hess and Colleagues (2008) reported that nulligravida and nulliparous women were half as likely to report hot flashes and half as likely to report vaginal dryness compared to multigravida women¹¹. In this study, we did not find a role of parity in severe hot flashes however inherent differences between the two studies may help with interpreting these inconsistencies particularly given the different study populations, and menopausal symptom measures used. These methodological differences underscore the importance of recognizing that menopausal symptom perception and interpretation occur in a broader social and cultural context and that symptom assessment and reporting formats can differ between studies. Nevertheless, our findings converge with Hess and Colleagues' argument that parity and alterations of estrogen, testosterone and sex hormone-binding globulin may be implicated in the relationship between reproductive history and vaginal dryness.¹¹

Several limitations exist which need to be mentioned. First, our assessment of decreased libido was captured using the question: 'Please tell me if you have experienced a decreased libido or interest in sex in the past month.' A decrease in libido was defined as an affirmative answer to this question. We recognize that other measures of hypoactive sexual desire disorder or decreased libido have been developed which may capture more fully the various aspects of sexual function such as assessments of sexual arousal, lubrication, orgasm, satisfaction and pain/discomfort.³⁷ However, we have used this classification of decreased libido in other studies and found decreased libido to be related to prior vaginal dryness, prior depression and predictive of fluctuations in testosterone during the menopausal transition.³⁸ Second, data from the current study should be interpreted with consideration since the sample was drawn from an urban setting and the results may have limited generalizability to non-urban women. Third, many of the reported confidence intervals are wide given the limited sample size and multiple comparisons were conducted which need to be recognized when interpreting the results. Fourth, we argue that the experience of infertility during the reproductive years may be a marker for premature ovarian failure.³⁶ However, it should be noted that infertility itself may be a risk factor for sexual dysfunction. Millheiser et al reported that following a diagnosis of infertility, women were at higher risk for reporting sexual dysfunction compared to a control group of women without infertility and patients with infertility reported significantly lower scores in the desire and arousal

domains and lower frequency of intercourse and masturbation³⁹. Finally, data on fertility and menopausal symptomology was based on self-report, although this approach has been successfully used in the context of other community based studies when access to medical records was not possible.^{27,29}

Conclusion

This study suggests an association between infertility and severity of menopausal symptomology (vaginal dryness and decreased libido) which is particularly specific to white women. Together, these data both support and extend our current understanding of the individual reproductive health factors that may contribute to a woman's experience of menopausal symptomology. The current data add to a growing literature suggesting that consideration of a woman's reproductive history is a valid tool for practitioners to consider when counseling their pre-menopausal patients about menopause and the incidence and severity of symptoms they can expect.

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Table 1**Reproductive Indices and Menopausal Symptoms**

Reproductive Indices	Severe Decreased Libido aOR and 95% CI	Severe Vaginal Dryness aOR and 95% CI
Women with no prior pregnancies	0.38 (0.16 – 0.91)	0.36 (0.12 – 1.08)
Women with at least one prior pregnancy	1.0	1.0
Women with three plus pregnancies	1.33 (0.78 – 2.26)	0.56 (0.28 – 1.15)
Women with no prior pregnancies	1.0	1.0
Women with no prior live births	0.37 (0.19 – 1.74)	0.63 (0.16 – 2.51)
Women with at least one prior live birth	1.0	1.0
Women with at least one prior preterm birth	0.91 (0.51 – 1.61)	0.89 (0.51 – 1.59)
Women with at least one prior live birth without a prior preterm birth	1.0	1.0
Women with two or more miscarriages	1.06 (1.04 – 1.08)	0.49 (0.14 – 1.75)
Women with at least one prior pregnancy but no prior miscarriages	1.0	1.0
Women with a Positive Infertility Index	1.86 (1.05 – 3.31)	2.79 (1.19 – 6.94)
Women with a Negative Infertility Index	1.0	1.0

Each GEE model adjusted for age, menopausal stage, race, cigarette use, anxiety, BMI and race/reproductive indices interaction term.

Table 2

Racial Differences by Selected Reproductive Indices

Reproductive Indices	Severe Decreased Libido aOR and 95% CI	Severe Vaginal Dryness aOR and 95% CI
African American Women		
Women with no prior pregnancies	0.85 (0.19 – 3.73)	0.73 (0.12 – 4.45)
Women with at least one prior pregnancy	1.0	1.0
Women with a Positive Infertility Index	0.59 (0.33 – 1.04)	0.56 (0.26 – 1.32)
Women with a Negative Infertility Index	1.0	1.0
White Women		
Women with no prior pregnancies	0.43 (0.17 – 1.07)	0.38 (0.11 – 1.33)
Women with at least one prior pregnancy	1.0	1.0
Women with a Positive Infertility Index	1.87 (1.04 – 3.34)	2.79 (1.22 – 6.36)
Women with a Negative Infertility Index	1.0	1.0

Each GEE model adjusted for age, menopausal stage, cigarette use, anxiety, and BMI