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Early menopause and other gynecologic risk indicators for chronic fatigue syndrome in women

Roumiana S. Boneva, MD, PhD, **Jin-Mann S. Lin, PhD**, and **Elizabeth R. Unger, PhD, MD**

Centers for Disease Control and Prevention, Atlanta, GA

Abstract

Objective—This study aims to examine whether gynecologic conditions are associated with chronic fatigue syndrome (CFS).

Methods—This study includes a subset of 157 women from a population-based case-control study in Georgia, United States, conducted in 2004-2009. Gynecologic history was collected using a self-administered questionnaire. Crude odds ratios (ORs) with 95% CIs and ORs adjusted for body mass index and other covariates, where relevant, were estimated for gynecologic conditions between 84 CFS cases and 73 healthy controls.

Results—Cases and controls were of similar age. Women with CFS reported significantly more gynecologic conditions and surgical operations than controls: menopause status (61.9% vs 37.0%; OR, 2.37; 95% CI, 1.21-4.66), earlier mean age at menopause onset (37.6 vs 48.6 y; adjusted OR, 1.22; 95% CI, 1.09-1.36), excessive menstrual bleeding (73.8% vs 42.5%; adjusted OR, 3.33; 95% CI, 1.66-6.70), bleeding between periods (48.8% vs 23.3%; adjusted OR, 3.31; 95% CI, 1.60-6.86), endometriosis (29.8% vs 12.3%; adjusted OR, 3.67; 95% CI, 1.53-8.84), use of noncontraceptive hormonal preparations (57.1% vs 26.0%; adjusted OR, 2.95; 95% CI, 1.36-6.38), nonmenstrual pelvic pain (26.2% vs 2.7%; adjusted OR, 11.98; 95% CI, 2.57-55.81), and gynecologic surgical operation (65.5% vs 31.5%; adjusted OR, 3.33; 95% CI, 1.66-6.67), especially hysterectomy (54.8% vs 19.2%; adjusted OR, 3.23; 95% CI, 1.46-7.17). Hysterectomy and oophorectomy occurred at a significantly younger mean age in the CFS group than in controls and occurred before CFS onset in 71% of women with records of date of surgical operation and date of CFS onset.

Conclusions—Menstrual abnormalities, endometriosis, pelvic pain, hysterectomy, and early/surgical menopause are all associated with CFS. Clinicians should be aware of the association between common gynecologic problems and CFS in women. Further work is warranted to determine whether these conditions contribute to the development and/or perpetuation of CFS in some women.

Address correspondence to: Roumiana S. Boneva, MD, PhD, Centers for Disease Control and Prevention, Mailstop A-30, 1600 Clifton Rd, Atlanta, GA 30333. rboneva@cdc.gov.

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Keywords

Chronic fatigue syndrome; Hysterectomy; Menopause; Endometriosis; Menstrual abnormalities; Pelvic pain

Chronic fatigue syndrome (CFS) is a debilitating and complex illness affecting more than 1 million US adults and accounting for sizable economic costs to the individual, healthcare system, and society as a whole. [1-5] CFS is characterized by profound fatigue that is accompanied by symptoms affecting multiple body systems, including, most characteristically, postexertional malaise, unrefreshing sleep, problems with memory and concentration, and pain. [1] The fatigue in CFS is not relieved by rest; medical or psychiatric conditions that could explain the fatigue and symptoms have been ruled out or fully managed.[1] The cause of CFS remains unknown. CFS affects women two to four times more frequently than men, with the highest prevalence found in women in their middle to late 40s.[3-6] Although CFS is more common in women, only few studies have examined sex-specific risk factors for CFS. A case-control study with a population-based sample of women with CFS (n = 22) identified hysterectomy as a risk factor for CFS.[7] Another case-control study of women with CFS (n = 150) from a tertiary referral center found endometriosis, ovarian cysts, polycystic ovaries, uterine fibroids, menstrual abnormalities, and galactorrhea to be risk factors for CFS.[8] Furthermore, Harlow et al[8] and Studd and Panay[9] hypothesized that a deficiency or imbalance in endogenous sex hormones may be a risk factor for CFS in some women. We recently reported that endometriosis, irregular periods, a history of gynecologic surgical operation, and pelvic pain unrelated to menstruation were all significantly associated with CFS in a population-based sample from Wichita, KS.[10] Using the conceptual framework that irregular periods, bleeding between periods, menopause, and oophorectomy could be indicators of gonadal hormone deficiency, we examined the association between gynecologic conditions and CFS in this study to replicate previous findings and to explore additional risk indicators.

METHODS

Data were obtained from the follow-up phase (T_1) of a two-wave population-based longitudinal study of CFS and fatiguing illness in Georgia, United States, conducted between 2004 and 2009.[6] Sampling methodology and study participants have been described in detail elsewhere[6] and are briefly summarized later and in the flow chart (Fig. 1). The study was approved by the Institutional Review Boards of the Centers for Disease Control and Prevention and Abt Associates. All participants gave written informed consent.

Recruitment of participants

The baseline study (T_0) took place in 2004-2005 and has been described in detail previously.[6] In brief, the baseline study included a random-digit-dialing household screening interview to identify household residents aged 18 to 59 years from 14 Georgia counties, including metropolitan, urban, and rural areas. This enumerated 19,807 individuals screened (residing in 10,873 households reached of 11,247 working eligible residential numbers; ie, 96% participation rate).[6] The screening interview was followed by individual computer-

assisted telephone interview (CATI) to identify: (i) participants who met the interview criteria for CFS-like illness (CFS-like group); (ii) participants who were well (control group); or (iii) participants who had been unwell for a long time (an intermediate group with some case-defining CFS symptoms [eg, cognition problems, unrefreshing sleep, or pain] with or without fatigue). Controls were identified to match CFS-like cases on age (within 3 y), sex, race/ethnicity, and geographic area. All CFS-like cases, their matched controls, and a similar number of participants randomly selected from the intermediate group were invited for baseline (T_0) clinical evaluation; 783 completed it (Fig. 1). The clinical evaluation (performed by physicians, trained psychologists, and nurses) included medical history, physical examination, laboratory tests, psychiatric evaluation, and a battery of instruments to measure symptoms, functionality, and impairment. The data collected during the clinical evaluation were used by a panel of physicians and other researchers to identify comorbid and/or exclusionary medical and psychiatric conditions and to classify clinical participants into study groups. Participants were classified into the following groups: (i) CFS cases, according to the 1994 case definition based on standardized/operationalized criteria for fatigue, function, and symptoms; (ii) nonfatigued well controls; (iii) an intermediate group with insufficient number of symptoms and/or fatigue to meet full CFS case definition criteria (ISF); or (iv) persons with exclusionary medical or psychiatric conditions.[1,6,11]

The follow-up study (T_1) was conducted during 2007-2009. All persons who had been to the clinic at baseline and did not have permanent exclusionary conditions (n = 681 eligible) were invited for a follow-up telephone interview and a follow-up clinical evaluation. Additional baseline CATI participants (with no exclusions identified in the baseline detailed telephone interview) were contacted for a second telephone interview. Those whose interview findings qualified them as new CFS-like cases or as well controls were also invited for a clinical evaluation (Fig. 1). A total of 919 participants were eligible and invited for T_1 clinical evaluation; 751 completed it (ie, 82% participation rate). Of these 751 participants, 560 were women (Fig. 1, flow chart). Of these 560 women, 188 were found to have medical or psychiatric conditions exclusionary for CFS and were not considered for final classification. Final ascertainment classified participants as follows: 84 CFS cases, 73 consistently well controls, 186 women with insufficient number of symptoms and/or fatigue to meet full CFS case definition criteria (ISF group), and 29 women who did not consistently meet criteria for nonfatigued well controls. Of the 84 women in the CFS group, 70 women were seen at both T_0 and T_1 clinics, and 14 CFS cases were only seen at T_1. (Of the women seen at both times, 44 women fully met CFS case definition criteria both times, 12 women were in the ISF group at T_0 and converted into CFS cases at T_1, and 14 women who met CFS criteria at T_0 were ill at T_1 without sufficient symptoms or fatigue to fully meet CFS criteria [ISF].) The control group (n = 73) consisted of 44 women who were consistently classified as well controls at T_0 and T_1 clinical evaluations and 29 well controls who were clinically evaluated only at T_1 (who were also consistently well at both T_0 and T_1 detailed telephone interviews). This analysis only concerned 157 women: 84 CFS cases and 73 nonfatigued well controls (see shaded boxes at the bottom row of flow chart; Fig. 1). The gynecologic history questionnaire was administered only during the second wave before T_1 clinical evaluation. Although the source study was designed to have “CFS-like” cases and “well” controls matched on detailed telephone interviews (CATI), case-control matching

was broken owing to reclassification and/or diagnosis of exclusionary conditions (CFS ruled out) at clinical evaluation. Common reasons for exclusion of participants after the clinical evaluation included the following: not meeting sufficient number of criteria for CFS or for control and/or having hypothyroidism, anemia, or other exclusionary medical or psychiatric conditions.[1,6]

Measurements

Demographic information was collected during telephone interviews and further confirmed at the clinic. Height and weight were collected at the clinic as part of physical examination. Body mass index (BMI) was calculated as follows: BMI = weight/height^2 (kg/m^2).

The gynecologic history questionnaire was an adaptation of the Reproductive History Questionnaire/Menstruation-Menopause History developed by the National Cancer Institute Division of Cancer Epidemiology and Genetics.[12] The gynecologic history questionnaire was mailed to participants before their scheduled T_1 clinic visit, allowing them to complete the questionnaire at home and to consult their medical records (the study itself did not include chart review). During the clinic visit, the questionnaire was reviewed by clinic staff for completeness and accuracy. The gynecologic history questionnaire included the following: age at menarche; regularity of menstrual cycles; duration and heaviness of bleeding in a typical menstrual period; excessive menstrual bleeding; bleeding between periods; missed periods (defined as periods missed for reasons other than pregnancy, breast-feeding, or menopause); pelvic pain unrelated to menstrual periods during the last 6 months; diagnosis of endometriosis; age at menopause; and use of hormones to treat irregular periods, menopausal symptoms, or bone loss. The questionnaire included a definition of menopause ("Menopause is when your periods stop for at least a year [NOT because of pregnancy or breast-feeding]"), which preceded questions about menopause. We assessed menopause status and age at menopause by responses to the questions, "Are you currently menopausal?" and "How old were you when your periods stopped because of menopause?" We also collected data on gynecologic surgical operations (yes or no) and number of surgical operations. Women were further asked, "Have you ever had any surgery/operation involving removal (either partial or total) of one or both of your ovaries, uterus (womb), or tubes?" They were asked, "For each surgery, please indicate the month and year of the surgery, what was removed during the surgery, and the reason for the surgery." Self-reporting of hysterectomy and bilateral oophorectomy has been shown to have a high positive predictive value (PPV; 97% and 100%, respectively), whereas self-reported unilateral oophorectomy has a PPV of 73%, with 19% of reported unilateral oophorectomies being actually bilateral.[13] For each gynecologic surgical operation that included removal of the uterus, ovary, tube, or cyst, women were asked to select applicable answers from these possibilities: "total uterus, part of the uterus; two ovaries, one ovary; two tubes, one tube; other surgical operation [specify]." We collected no additional details on what was involved in the partial removal of the uterus. Women who reported hysterectomy (without bilateral oophorectomy) were classified as menopausal if they answered "yes" to the question, "Are you currently menopausal?" For each woman with CFS who underwent a major gynecologic surgical operation (ie, with removal of the entire uterus and removal of ovaries), we derived a new variable—the time interval between the date of that surgical operation and the date of

fatigue onset (derived from the Centers for Disease Control and Prevention Symptom Inventory). We calculated the mean interval between surgical operation and subsequent fatigue onset. The gynecologic questionnaire did not contain information on physical activity, alcohol use, or tobacco use.

Statistical analyses

Group means (SEM) were calculated for continuous variables. For categorical variables, we compared differences in proportions between the CFS group and the control group using χ^2 test or Fisher's exact test, as appropriate. To estimate the association of CFS with gynecologic conditions, we calculated crude and adjusted odds ratios (ORs) for CFS (with 95% CIs) using unconditional logistic regression.

We also calculated adjusted ORs that included BMI as a possible confounder because BMI has been shown to be significantly associated with both CFS and gynecologic conditions (menopause and hysterectomy).[14,15] Besides the main effects, we also included an interaction term of each gynecologic variable and BMI in the models. In addition to BMI, the ORs for hysterectomy, excessive bleeding, and pelvic pain were also adjusted for endometriosis because it can be associated with these conditions. Statistical significance was set at an α of 0.05. P values were based on two-sided tests. We used SAS version 9.2 software.

RESULTS

Overall demographic characteristics of the CFS and control groups are presented in Table 1. Women from the CFS and control groups did not differ significantly in age, race/ethnicity, or residential area (Table 1). The CFS group was less educated, had a higher proportion of women who were previously married, and had a lower proportion of women who were never married. There was no significant difference in overall household income between the groups; however, a higher proportion of the CFS group belonged to the lowest-income category (<US$30,000) compared with controls ($P = 0.047$; data not shown in Table 1). The CFS group had significantly higher BMI than controls. Of the 55 women in the CFS group who had data on type of illness onset, most (76.4%) reported gradual onset of their fatigue (data statistics not shown in Table 1). Among women with CFS, the mean (SEM) duration of fatigue/exhaustion was 10.1 (0.7) years.

Gynecologic variables

Mean age at menarche was the same for CFS cases and controls (12 y; Table 2). The CFS group had a longer mean (SEM) duration of menstrual flow (5.7 [0.2] vs 4.8 [0.2] d for controls). A significantly higher proportion of women in the CFS group reported excessive bleeding during periods (73.8% vs 42.5% in controls), bleeding between periods (48.8% vs 23.3%), and missing periods (38.1% vs 21.9%), with OR ranging between 2.16 and 3.33 (Table 2).

Significantly more women with CFS than controls reported having been diagnosed as having endometriosis (29.8% vs 12.3%; OR, 3.01; 95% CI, 1.30-6.98; Table 2). Pelvic or lower abdominal pain unrelated to menstrual period was significantly more common in women

with CFS (26.2% vs 2.7% in controls; OR, 12.60; 95% CI, 2.85-55.73), and adjusting for endometriosis did not significantly alter this association (Table 2).

Although women in the two groups were of similar mean age, a significantly higher proportion of women in the CFS group reported being menopausal (61.9% vs 37.0% in controls). In the subset of postmenopausal women (52 with CFS and 27 controls), those with CFS reported a significantly younger mean (SEM) age at menopause (38.5 [1.3] y) compared with controls (48.6 [0.9] y; Tables 2 and 3). Hysterectomy was experienced by 78.8% (ie, 41 of 52) of postmenopausal women with CFS compared with 37% (ie, 10 of 27) of controls ($P < 0.001$; Table 3). Natural menopause occurred 2 years earlier in the CFS group compared with the control group (mean [SEM], 48.6 [1.7] vs 50.6 [0.5] y, $P = 0.25$). Hysterectomy was experienced by women with CFS at a significantly younger mean (SEM) age (about a decade earlier) compared with controls (35.8 [1.2] vs 45.2 [1.8] y, respectively).

Major gynecologic surgical operations

At least one gynecologic surgical operation was reported by 65.5% of women with CFS versus 31.5% of controls (OR, 4.12; 95% CI, 2.11-8.04; Table 2). Hysterectomy was the most common surgical operation (54.8% of women with CFS vs 19.2% of controls). As shown in Table 2, most women who reported a hysterectomy also reported removal of ovaries and tubes. Stratified analysis by type of hysterectomy (alone, with bilateral oophorectomy, or with unilateral oophorectomy) is presented in Table 2. CFS was significantly associated with any hysterectomy (OR, 5.10; 95% CI, 2.47-10.52), total hysterectomy alone (OR, 5.12; 95% CI, 1.54-17.05), hysterectomy with bilateral oophorectomy (OR, 3.38; 95% CI, 1.25-9.16), or hysterectomy with unilateral oophorectomy (OR, 7.09; 95% CI, 1.44-34.88). Early surgical menopause (at or before age 45 y) occurred in 61.5% of postmenopausal women with CFS compared with 33.3% of postmenopausal controls (OR, 3.20; 95% CI, 1.21-8.49; $P = 0.02$; Table 3). Overall, mean age at time of surgical operation was younger in women with CFS than in controls, respectively: 35.8 (1.2) versus 45.2 (1.8) for any hysterectomy; 37.7 (2.7) vs 45.3 (2.5) for hysterectomy with bilateral oophorectomy; and 34.1 (1.4) vs 44.0 (3.6) for hysterectomy with ovarian preservation (Tables 2 and 3).

After adjustment for BMI, all gynecologic factors remained statistically significantly associated with CFS (Table 2). There were no statistically significant interactions between gynecologic variables and BMI. When total hysterectomy, age at menopause, and BMI were included in the model, only age at menopause remained statistically significantly associated with CFS (OR,1.22; 95% CI, 1.09-1.36; $P < 0.001$; overall model fitting, 0.96; $c = 0.84$).

Conditions leading to surgical operation (reasons for surgical operation)

We compared the proportions of the most common reasons for removal of the uterus and ovaries in the two groups in two ways. First, in a stratified analysis, we broke down the variable “gynecologic surgical operation” (Table 2) into several subgroups based on “reason for surgical operation.” CFS was strongly associated with both bleeding (OR,10.38; 95% CI, 2.33-94.22) and uterine fibroids (OR, 3.45; 95% CI, 1.01-15.01) as reason for gynecologic surgical operation (data not shown). Second, we used a conservative estimate by including in

the denominator only women who reported gynecologic surgical operations (Table 4). Bleeding (as reason for surgical operation) remained significantly associated with CFS (OR, 5.81; 95% CI,1.01-59.12). Neither of the other examined reasons—endometriosis, uterine fibroids, ovarian cysts, or precancerous cervical lesions—differed significantly between cases and controls.

Relationship between time of surgical operation and CFS onset

Of the 51 women who reported hysterectomy and/or bilateral oophorectomy and/or removal of both tubes, 42 had information on both date of surgical operation and date of onset of unusual fatigue. Of these 42 women, 30 (71.4%) had surgical operation before the onset of illness by a mean (SEM) of 9.1 (1.4) years (range, 0-21 y; median, 10.5 y). When we limited the analysis of hysterectomy to only 30 cases in which hysterectomy occurred before the onset of fatigue, the magnitude of the association of CFS with hysterectomy was reduced (OR, 1.56; 95% CI, 0.74-3.22; $P = 0.24$).

Use of noncontraceptive hormone therapy

Women with CFS were significantly more likely to have ever been prescribed hormonal preparations to treat irregular periods, menopausal symptoms, or bone loss: overall, 57.1% of the CFS group versus 26.0% of controls (OR, 3.79; 95% CI, 1.92-7.47), after adjustment for menopause status (OR, 2.95; 95% CI, 1.36-6.38). Interestingly, among the 14 women in the CFS group who were CFS cases at T_0 and classified in the ISF group at T_1, 35.7% reported currently using hormone therapy. Inversely, of the 12 women who were classified in the ISF group at T_0 and became CFS cases at T_1, only 16.7% (two women) were currently using hormones.

DISCUSSION

Our study supports previously identified associations of CFS with gynecologic conditions: endometriosis,[8,10,16] menstrual abnormalities,[8] gynecologic surgical operation (particularly hysterectomy),[7,10,17] and pelvic pain unrelated to menstruation.[10] In addition, our study found that CFS was associated with early hysterectomy/menopause and use of noncontraceptive hormonal preparations. The gynecologic conditions associated with CFS and the possible links between them are summarized in Figure 2. As shown in Figure 2, we suspect that aberrations in female sex hormones may contribute to these associations; however, because of cross-sectional data, our findings do not demonstrate causality.

In our study, women with CFS were four times more likely than controls to have had a hysterectomy. Most importantly, hysterectomy was performed at a significantly younger mean age in CFS cases than in controls. Our finding that only age at menopause remained significantly associated with CFS in the multivariate model (covariates: hysterectomy, BMI, and age at menopause) suggests that the risk for CFS increases with earlier reduction/depletion of endogenous sex hormones. Indeed, premenopausal hysterectomy (even with ovarian preservation) precipitates ovarian failure, with documented reduction of estrogen and progesterone levels[18] and elevation of follicle-stimulating hormone (FSH) levels.[19] The reported early menopause (mostly postsurgical) in the CFS group (mean, 38.5 y; ie, 10 y

earlier than controls) bolsters our previous (not statistically significant) observation in a sample from a population-based case-control study in Wichita, KS.[10] Before this study, a significant association of CFS and early menopause has not been reported. However, in fibromyalgia, which shares many symptoms with CFS, early menopause (<45 y) was reported by 38% of women in one study.[20] In another study, 48% of women with fibromyalgia had a hysterectomy. Hysterectomy preceded fibromyalgia diagnosis in 90.7% of cases who had both conditions.[21] Similarly, in our study, hysterectomy and oophorectomy preceded fatigue onset in 71% of women with available data on both. Although associations between hysterectomy and severity of illness have not been studied in women with CFS, in fibromyalgia, women who have had hysterectomy have lower physical function and greater severity of pain, fatigue, stiffness, and depression than those who have not had hysterectomy.[22] In our study, CFS was also associated with menstrual irregularities and excessive bleeding conditions, which often may have hormonal reasons.[23] Disturbed menstrual cycle function (including hyperprolactinemia and hyperandrogenism) in women with CFS has been suggested by Harlow et al[8] but has barely been explored. A small study reported sex hormone deficiency in women with CFS and improvement in 80% with use of cyclic estrogen/progestogen.[9] Reduced levels of ovarian sex hormones in early hysterectomy/early ovarian failure can have considerable nonreproductive consequences because sex hormones are involved in a variety of nonreproductive bodily functions (see later discussion). The significantly higher use of noncontraceptive female hormones in our CFS group may be explained by earlier menopause and/or other sex hormone abnormalities requiring additional hormonal support. Although the numbers were quite small to draw any conclusions, the proportion of current hormone use was twice as high (35.7%) in the subgroup that converted from CFS to ISF (ie, improved) between T_0 and T_1 compared with the subgroup that converted from ISF to CFS (current hormone use, 16.7%).

Of the gynecologic conditions examined in this study, the strongest association was found between CFS and pelvic pain unrelated to menstruation (with pelvic pain being least reported by controls [2.7%]). Possible increased pain sensitivity may underlie this association.[24] Increased pain sensitivity may exist in several overlapping pain conditions (CFS, fibromyalgia, endometriosis, irritable bowel syndrome, and interstitial cystitis), with women often having more than one condition.[17] Both estrogen and progesterone modulate pain in the nociceptive pathways in the spinal cord and at the central level (via interaction with the serotonin system).[25-27] Similar to our findings, women with interstitial cystitis/painful bladder syndrome have reported higher use of noncontraceptive female hormones,[28] suggesting coexisting hormonal problems. Both estrogen and progesterone have numerous nonreproductive functions[29-39]: they are neuroprotective[29-31]; they influence sleep,[32] cognition,[33,34] and immune responses/inflammation[35-37]; they support muscle, joint, and bone health[38]; and they modulate pain sensitivity[39]—all of which are present in the symptom domains of CFS. A detailed discussion of the various nongynecologic effects of female hormones is beyond the purpose of this study. Notably, however, both physical and mental stressors, which have been implicated in the pathogenesis of CFS, can compromise sex hormone production via the hypothalamopituitary axis.

Although our sample size (N = 157) was not large, the study's strengths include its population-based design (with sample identified from random-digit-dialing telephone

screening interviews covering 19,807 residents in Georgia),[6] detailed gynecologic history, and extensive clinical workup to correctly define cases and controls and to rule out conditions other than CFS that could explain the symptoms. Limitations of our study include self-reported (not chart-abstracted) conditions, potential selection bias (from nonparticipation), inability to adjust for tobacco and alcohol use, and possible recall bias. However, completing the questionnaire at home allowed participants to consult their medical records, which potentially reduced recall bias. Furthermore, validation studies of self-reported hysterectomy and bilateral oophorectomy have shown high PPVs (97% and 100%, respectively) with moderate specificity (ie, under-reporting of bilateral oophorectomy).[13] Our study sample was population-based and was identified using the 1994 case definition; therefore, it may not be representative of women with CFS seen in tertiary clinical practice. The findings may also not be generalizable to all women with CFS because most cases in our study had gradual CFS onset. In our study, some women who have had hysterectomy (alone or with unilateral oophorectomy) were possibly misclassified as menopausal if their hysterectomy occurred before biological menopause. Therefore, in women who have had hysterectomy with ovarian preservation, age at menopause was probably an underestimate. However, even if we disregard age at menopause for the abovementioned reason and examine only mean age at hysterectomy as a risk factor, the CFS group had a significantly younger age at hysterectomy (mean, 8-10 y earlier than the control group; Table 2), and early hysterectomy (at <45 y) was significantly more common in the CFS group. Although ovarian function will probably continue after removal of the uterus with ovarian preservation (ie, hysterectomy alone or with unilateral oophorectomy), prospective cohort studies with FSH measurement show that ovarian function declines more rapidly and that menopause occurs earlier compared with same-age women who have not had hysterectomy.[19,40,41] For example, premenopausal women who have had hysterectomy with ovarian preservation reach menopause (confirmed by FSH levels >40 IU), on average, 3.7 years earlier than similar-age women who have not had hysterectomy. Furthermore, among women who have had hysterectomy, those who have had unilateral oophorectomy reached menopause 4.4 years earlier than women with both ovaries preserved.[40]

CONCLUSIONS

CFS in women is associated with self-reported menstrual abnormalities, endometriosis, pelvic pain unrelated to menstruation, early age at hysterectomy/surgical menopause, and other gynecologic conditions and surgical operations. It should be emphasized, however, that our findings do not demonstrate causality. These findings could be used for further hypothesis generation for future studies. Nevertheless, the significantly higher prevalence of various gynecologic conditions in women with CFS warrants clinicians' attention on tailoring these women's medical care. Gynecologists need to be aware that women who have had early hysterectomy and/or other gynecologic conditions discussed here may be at risk for CFS. Therefore, gynecologists need to assess these women periodically for symptoms suggestive of CFS (such as persisting/relapsing problems with memory and concentration, sleep problems, muscle and joint pain without swelling or redness, persistent or relapsing fatigue that reduces previous levels of functioning, headaches of new onset or severity, postexertional malaise [ie, worsening of symptoms after mental or physical exertion], and

other symptoms; for a detailed list of symptoms and differential diagnosis, see Fukuda et al[1]). When CFS is suspected, supportive care and appropriate clinical referrals are needed. Similarly, physicians seeing women with CFS need to carefully evaluate their gynecologic history for risk factors associated with CFS and work with gynecologists for further management of identified gynecologic problems. The exact reasons for the reported associations cannot be determined from this study; future studies need to examine whether any of the associations reported here may be pathophysiologically related to the onset or perpetuation of CFS in some women. Further work may be warranted to determine whether aberrations in endogenous sex hormones contribute to the pathogenesis and/or perpetuation of CFS in a subset of women with this illness.

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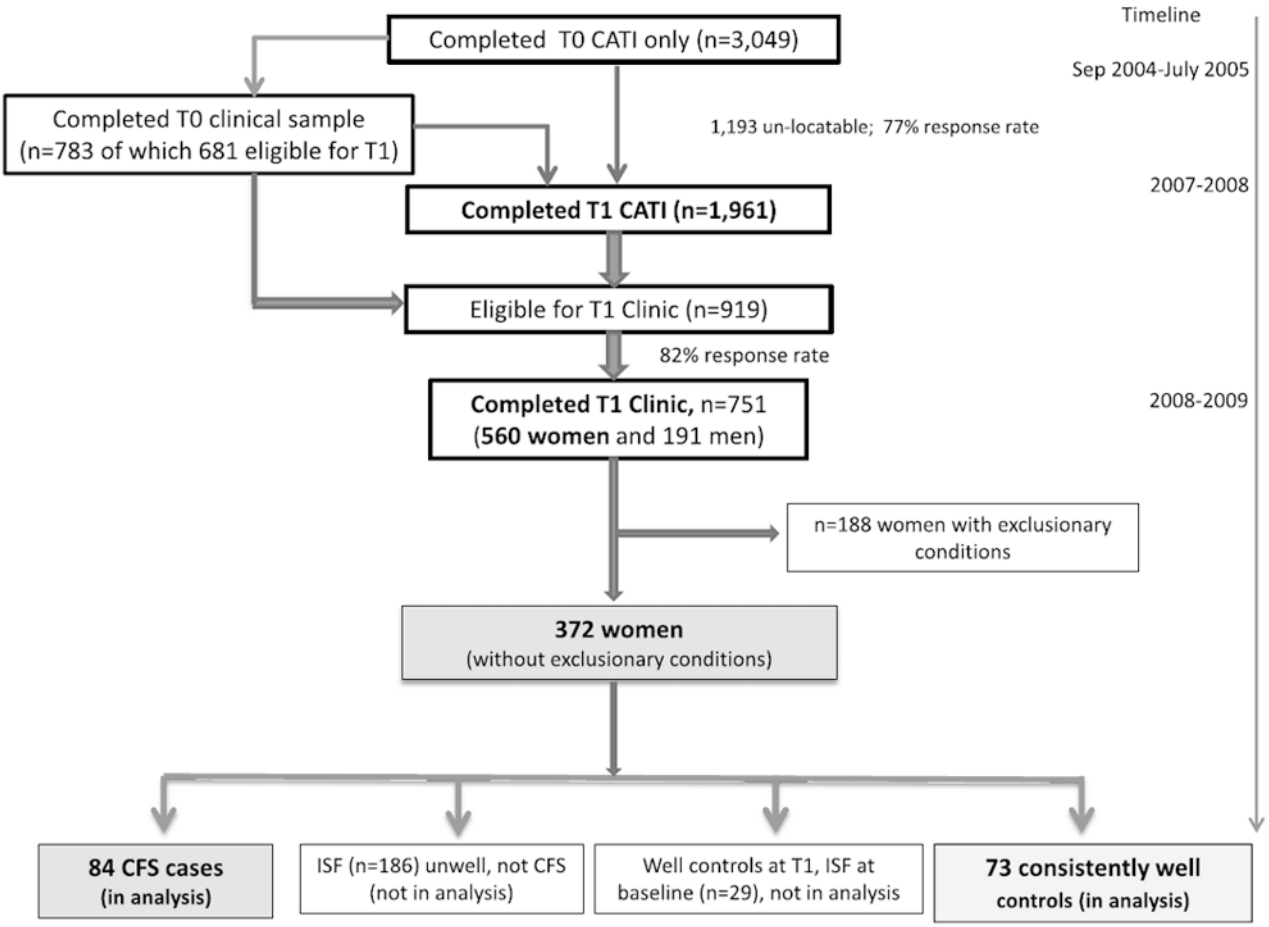

FIG. 1.

Flow chart of the baseline (T_0) and follow-up (T_1) study of fatiguing illness in Georgia showing recruitment of chronic fatigue syndrome (CFS) cases and controls. CATI, computer-assisted telephone interview; ISF, insufficient number of symptoms and/or fatigue to meet full CFS case definition criteria.

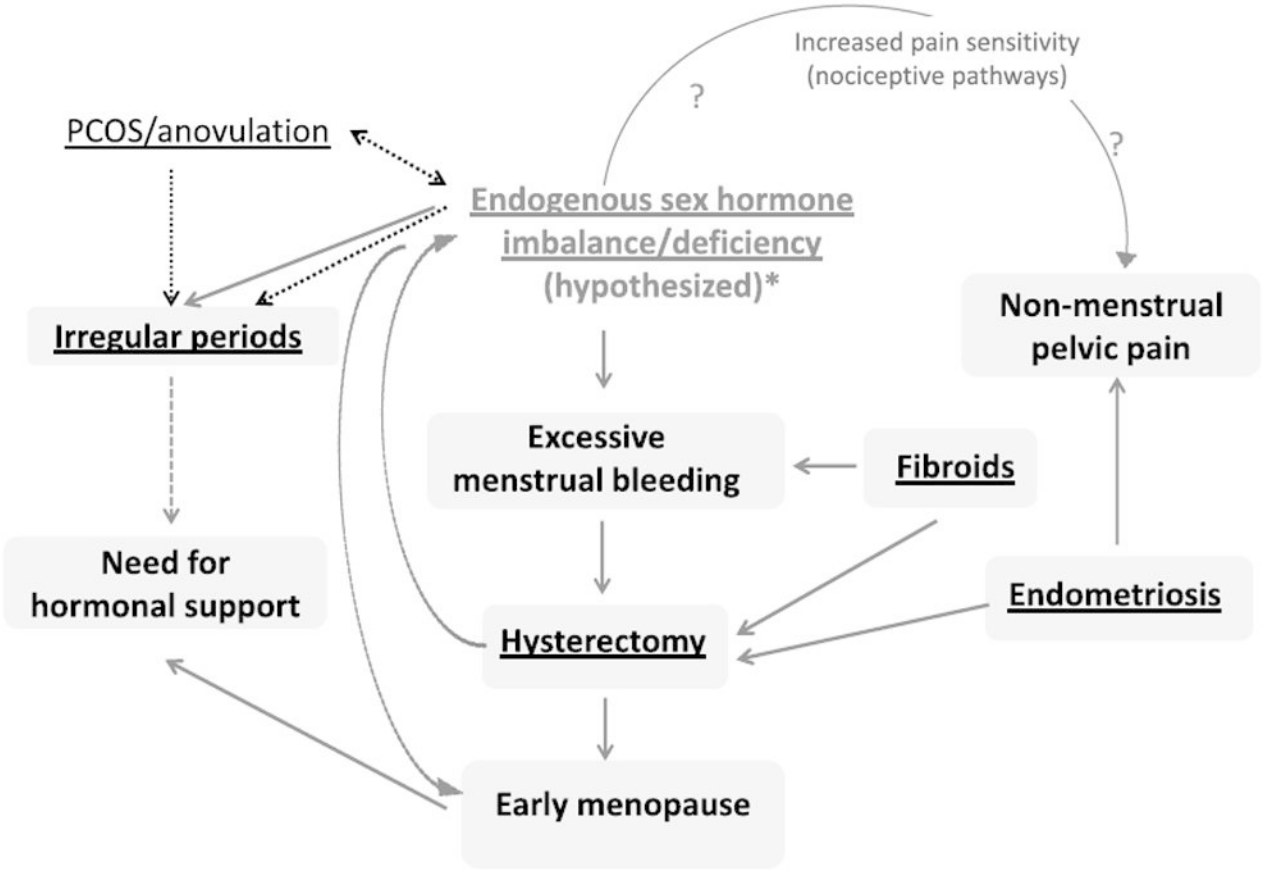

FIG. 2.

Schema of possible links between various gynecologic conditions found to be associated with chronic fatigue syndrome (in this and other studies). This conceptual model warrants further investigation. Boxed text, findings from this study; underlined text and dotted black lines, findings/hypothesis from other studies. *Reported by Studd and Panay[9]; hypothesized by Harlow et al,[8] by Boneva et al,[10] and in the current study. PCOS, polycystic ovary syndrome.

TABLE 1

Demographic characteristics of the CFS and control groups

Variable	CFS (n = 84)	Control (n = 73)	*P*
Age, mean (SEM), y[a]	48.3 (1.0)	46.5 (1.2)	0.24
Body mass index, mean (SEM), kg/m^2	28.8 (0.6)	25.3 (0.6)	0.0002
Race[a]			0.26
Black	14 (16.7)	12 (16.4)	
White	67 (79.8)	61 (83.6)	
Other	3 (3.5)	0 (0)	
Geographic stratum[a]			0.34
Urban	27 (32.1)	21 (28.8)	
Rural	46 (54.8)	36 (49.3)	
Metropolitan	11 (13.1)	16 (21.9)	
Household income			0.10
Missing data	6 (7.1)	2 (2.7)	
<US$30,000	18 (21.4)	7 (9.6)	
US$30,000-60,000	24 (28.6)	27 (37.0)	
>US$60,000	36 (42.9)	37 (50.7)	
Education			0.024
Less than high school	3 (3.6)	1 (1.4)	
High school	19 (22.6)	9 (12.3)	
≤3 y of college	32 (38.1)	19 (26.0)	
≥4 y of college	29 (34.5)	44 (60.3)	
No data	1 (1.2)	0 (0)	
Marital status			0.038
Married	55 (65.5)	49 (67.1)	
Divorced, widowed, or separated	25 (29.8)	12 (16.4)	
Never married	4 (4.8)	11 (15.1)	
No data	0 (0)	1 (1.4)	

Data are presented as n (%), unless otherwise specified.

CFS, chronic fatigue syndrome.

[a]Variable on which controls were matched to CFS-like cases based on detailed telephone interview before clinical evaluation.

TABLE 2

Gynecologic variables and their association with CFS: CFS study, Georgia, United States

Variable	CFS (n = 84)	Control (n = 73)	OR (95% CI)	*P*	BMI-adjusted OR (95% CI)	Adjusted *P*
Age at menarche, mean (SEM), y	12.6 (0.2)	12.8 (0.2)	NA	0.34	NA	
Duration of menstrual cycle, mean (SEM), d[a]	5.7 (0.2)	4.8 (0.2)	1.37 (1.11-1.68)	0.002	1.39 (1.12-1.72)	0.003
Excessive menstrual bleeding	62 (73.8)	31 (42.5)	3.82 (1.95-7.48)	<0.0001	3.33 (1.66-6.70)[b]	0.0007
			3.25 (1.62-6.54)[b]			
			3.42 (1.71-6.83)[b,c]	0.0005[b,c]		
Bleeding between periods	41 (48.8)	17 (23.3)	3.14 (1.57-6.27)	0.001	3.31 (1.60-6.86)[b]	0.001
			2.73 (1.35-5.55)[b]			
Missing periods	32 (38.1)	16 (21.9)	2.19 (1.08-4.45)	0.028	2.16 (1.03-4.54)	0.04
Endometriosis	25 (29.8)	9 (12.3)	3.01 (1.3-6.98)	0.007	3.67 (1.53-8.84)	0.004
Lower abdominal/pelvic pain unrelated to menstrual periods	22 (26.2)	2 (2.7)	12.60 (2.85-55.73)	<0.0001[d]	12.29 (2.72-55.46)[d]	0.0001[d]
			11.42 (2.56-51.05)[b]	0.0001[b,d]	11.98 (2.57-55.81)[b,d]	0.0003[b,d]
Currently menopausal	52 (61.9)	27 (37.0)	2.77 (1.38-5.59)	0.0018	2.37 (1.21-4.66)	0.012
Age at menopause onset, mean (SEM), y	38.5 (1.3)	48.6 (0.9)	1.21 (1.10-1.32)	<0.001	1.21 (1.10-1.32)	<0.0001
					1.22 (1.09-1.36)[c]	0.0006[e]
Gynecologic surgical operation (to remove partial or total uterus, one or two ovaries, one or two tubes, or cysts)	55 (65.5)	23 (31.5)	4.12 (2.11-8.04)	<0.0001	3.33 (1.66-6.67)	<0.001
No gynecologic surgical operation	29 (34.5)	50 (68.5)	Referent		Referent	
Removal of the uterus (hysterectomy)	46 (54.8)	14 (19.2)	5.10 (2.47-10.52)	0.0001	4.16 (1.97-8.79)	<0.001
			4.40 (2.07-9.37)[b]	0.0001[b]	3.23 (1.46-7.17)[b]	0.004[b]
Total uterus[e]	37 (44.1)	13 (17.8)	3.63 (1.74-7.60)	0.0004	2.92 (1.36-6.28)	0.006
Part of uterus[e]	9 (10.7)	1 (1.4)	8.64 (1.07-69.93)[d]	0.02[d]	8.63 (1.01-73.95)[d]	0.049[d]
Total hysterectomy alone[e,f]	13 (15.5)	4 (5.5)	5.12 (1.54 17.05)	0.008	3.70 (1.05-12.97)	0.004
			4.93 (1.47-16.51)[b]	0.010[b]	3.50 (0.995-12.34)[b]	
Hysterectomy with bilateral oophorectomy[e]	15 (17.9)	7 (9.6)	3.38 (1.25-9.16)	0.017	2.79 (1.00-7.76)	0.049
Hysterectomy with unilateral oophorectomy[e]	9 (10.7)	2 (2.7)	7.09 (1.44-34.88)[d]	0.016[d]	5.99 (1.07-62.38)[d]	0.039[d]
No hysterectomy or surgical operation to remove tubes or ovaries	33 (39.3)	52 (71.2)	Referent		Referent	

Variable	CFS (n = 84)	Control (n = 73)	OR (95% CI)	*P*	BMI-adjusted OR (95% CI)	Adjusted *P*
Unilateral oophorectomy alone[g]	1 (1.2%)	3 (4.1)	Not done	Not done	Not done	Not done
Other with oophorectomy[h]	1 (1.2%)	1 (1.4)	Not done	Not done	Not done	Not done
Age at hysterectomy with bilateral oophorectomy, mean (SEM) [range]	37.7 (2.7) [23-54]	45.3 (2.5) [39-57]	Not done	0.09	Not done	
Age at hysterectomy with ovarian preservation (ie, unilateral or no oophorectomy), mean (SEM) [range]	34.1 (1.4) [21-45]	44 (3.6) [37-49]	Not done	0.015	Not done	

CFS, chronic fatigue syndrome; OR, odds ratio; BMI, body mass index; NA, not applicable.

[a]Excludes one woman with CFS who reported a flow duration of 30 to 60 days.

[b]Adjusted for endometriosis.

[c]The model includes also hysterectomy.

[d]Fisher's exact test.

[d]Row represents a subset of all hysterectomies.

[f]Two CFS cases and two controls reported also tubal surgical operation.

[g]Reason for oophorectomy: benign tumor or cyst in three controls and pain in the CFS case.

[h]The CFS case had her two ovaries removed at different times and reported preceding partial removal of the uterus attributable to positive findings on Papanicolaou test; the control reported one surgical operation with "partial" removal of the uterus for "excessive bleeding" and subsequent bilateral oophorectomy in a second surgical operation. These two participants were not included in the analyses for hysterectomy with unilateral or bilateral oophorectomy.

TABLE 3

Risk indicators for CFS in postmenopausal women

Postmenopausal women only	CFS (n = 52)	Control (n = 27)	OR (95% CI)	*P*
Age at menopause onset (all), mean (SEM), y	38.5 (1.3)	48.6 (0.9)	NA	<0.001
Time since menopause, mean (SEM), y	13.5 (1.3)	7.2 (0.9)	NA	0.002
Age at natural menopause, mean (SEM), y	48.6 (1.7) [n = 11]	50.6 (0.5) [n = 17]	NA	0.25
Hysterectomy, n (%)[a]	41 (78.8)	10 (37.0)	6.34 (2.27-17.68)	<0.001
Age at hysterectomy, mean (SEM), y	35.8 (1.2)	45.2 (1.8)	NA	<0.05
Early surgical menopause (aged ≤45 y), n (%)	32/52 (61.5)	9/27 (33.3)	3.20 (1.21-8.49)	0.02

CFS, chronic fatigue syndrome; OR, odds ratio; NA, not applicable.

[a]The numbers differ from those in Table 2 because not all women with reported hysterectomy considered themselves postmenopausal.

TABLE 4

Comparison of the CFS and control groups by reason for gynecologic surgical operation involving removal of the uterus and/or ovaries/tubes

Reason for surgical operation involving removal of the uterus and/or ovaries/tubes	Among women with surgical operations only			
	CFS (n = 37)	Controls (n = 13)	OR (95% CI)	*P*
Endometriosis	7 (18.9)	3 (23.1)	0.78 (0.14-5.57)	0.75[a]
Uterine fibroids	12 (32.4)	3 (23.1)	1.60 (0.32-10.61)	0.53[a]
Bleeding	19 (51.4)	2 (15.4)	5.81 (1.01-59.12)	0.02[a]
Ovarian cysts	11 (29.7)	3 (30.8)	1.41 (0.32-6.14)	0.73[a]
Abnormal Papanicolaou test findings or precancerous cervical lesions	3 (8.1)	1 (7.7)	1.06 (0.08-60.16)	0.96[a]

Data are presented as n (%).

CFS, chronic fatigue syndrome; OR, odds ratio.

[a]Fisher's exact test.