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Changes in sexual behavior as a function of plasma sex steroid levels in post-menopausal women

Barbara B. Sherwin

*Department of Psychology, McGill University, and Department of Obstetrics and Gynecology,
Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, Canada.*

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Eight women who had been maintained on a combined estrogen-androgen drug since hysterectomy and bilateral oophorectomy 2 yr previously were investigated for changes in sexual behavior during the course of 1 treatment cycle. Following intramuscular injection of both sex steroids, plasma estradiol levels were within the normal range of young, cycling women but plasma testosterone exceeded the upper limit of normal female values. Sexual motivational behaviors (desire, fantasies and arousal) covaried with plasma steroid levels. Rates of coitus and orgasm, however, were unrelated to the changing levels of circulating hormones. A differential effect of the sex steroids on various aspects of sexual functioning was thus confirmed.

Introduction

Decreases in various aspects of sexual functioning in pre-menopausal women subsequent to total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) have been well documented [1–3] but poorly explained. However, controversy concerning the role of hormonal influences has been somewhat clarified in recent years. From an etiological point of view, it now seems unlikely that the significant decline in estrogen levels induced by ovarian ablation is implicated in these behavioral changes. Although some hormone replacement therapy studies have found beneficial effects of estrogen on libido compared to placebo [1,4], most report no effect of exogenous estrogen on sexual behavior [5,6]. Moreover, this occurs despite the fact that atrophic vaginitis and dyspareunia are reliably alleviated by this sex steroid [9]. Consistent with these findings in post-menopausal women are results of investigations on the covariation of plasma estrogen levels and sexual behavior in young, healthy women [8,9]. These have also failed to demonstrate a psychoendocrine relationship.

Of apparently greater relevance to sexual functioning in this population is the finding that circulating levels of testosterone also decrease significantly following bilateral removal of the ovaries in pre-menopausal women [10]. Early anecdotal

Correspondence to: Dr. B. Sherwin, McGill University, Department of Psychology, 1205 Dr. Penfield Avenue, Montreal, P.Q., Canada, H3A 1B1

reports found an increase in libido in post-menopausal women following administration of exogenous androgens [11] and radical decreases consequent to oophorectomy and adrenalectomy in uncontrolled investigations of women being treated for metastatic breast cancer [12]. More recently, studies of surgically post-menopausal women demonstrated that parenteral administration of androgen, either alone or in combination with estrogen, increased motivational aspects of sexual behavior (such as desire and arousal) compared to estrogen alone or placebo [13]. Androgen-containing drugs also induced lower depression scores [14], lower somatic symptom scores and enhanced well-being in these same women [15].

The strikingly beneficial therapeutic efficacy of a combined estrogen-androgen drug in surgically post-menopausal women stimulated further investigation of its effects. The goal of the present study was to determine whether changes in sexual behavior occurred across one treatment phase concomitant with variations in circulating hormone levels while a standard dosage of the drug was being metabolized.

Materials and methods

Subjects

Eight women who had undergone TAH and BSO for benign disease 2–3 yr previously participated in this study. All subjects had been receiving 1 ml of an estrogen-androgen combined drug intramuscularly approximately every 28 days since surgery. Other selection criteria required that patients be free of acute or chronic disease, that they were not taking any other medication, and that they had no history of psychiatric disease for which treatment had been sought and/or obtained. Finally, it was necessary that they be married or in a stable heterosexual relationship for at least 3 yr and that their partners be in a state of good general health. The first 8 women to attend a university hospital Menopause Clinic who met these selection criteria were recruited into the study. All subjects signed an information and consent form approved by an ethics committee.

Procedure

At the time of their recruitment into the study, subjects were asked to delay their next hormone injection for as long as possible, to a maximum of 8 weeks. The women themselves were the judge of when symptoms were sufficiently distressing to require treatment before the 2-mth baseline period had elapsed. At such time, a blood sample was taken followed by administration of a hormone injection. Blood was sampled again on post-injection days 1, 2, 8, 15, 30, and 42.

Drugs

One ml of an estrogen-androgen combined drug (Climacteron, Merck Frosst, Montreal, Canada) was administered intramuscularly once after the baseline mea-

TABLE I

ESTROGEN-ANDROGEN COMBINED DRUG (CLIMACTERON)

Contents	mg/ml
Testosterone enanthate benzilic acid hydrozone	150.0
Estradiol dienanthate	7.5
Estradiol benzoate	1.0

tures were obtained. This is the recommended dosage for the treatment of post-menopausal symptoms, and the same dose that subjects had been receiving monthly for the 2 yr prior to this investigation. The hormonal composition of this drug appears in Table I.

Plasma hormone levels

Fifteen ml of blood was collected by venipuncture between 8:00 and 9:00 a.m. at the 8 test times. The blood was immediately centrifuged and the plasma stored at -20°C until the conclusion of the study. Plasma estradiol was measured in duplicate by radioimmunoassay using an antibody raised to estradiol (17 β -succinyl-BSA) after extraction into ethyl ether; charcoal was used as the adsorbent [16]. The limit of the assay sensitivity was 5 pg/ml. Serum testosterone levels were measured using the immuno-testosterone ^{125}I -extraction method [17]. The lower level of sensitivity of the testosterone- ^{125}I Assay in female serum was 0.1 ng/ml. All samples from each subject were measured twice in the same assay at the conclusion of the study.

Marital Adjustment Scale (MAS)

This test was administered prior to subjects' recruitment into the study, to eliminate the possibility that extreme marital disharmony may have confounded any effect of drug on sexual behavior. It is a 15-item inventory that requires the subject to rate various aspects of married life, and has been shown to have good reliability and validity [18].

Daily Menopausal Rating Scale (DMRS)

Various aspects of sexual functioning were monitored daily by means of the DMRS. This psychometric instrument was devised and tested in a previous study, in which it was found to be a reliable and sensitive index of drug effects [19]. Two parameters of sexual behavior are measured by means of bipolar, interval rating scales that have a range of 0-7. The poles of each scale have a verbal description of the behavior in question. Subjects were instructed to circle the number that best represented the intensity of sexual desire and sexual arousal they had experienced during the previous 24 h period. The other parameters of sexual behavior monitored daily, namely the number of sexual thoughts or fantasies, the number of specific

sexual encounters with the partner and the number of times orgasm was achieved, required discrete, numerical responses on the DMRS.

In the attempt to distinguish between the components of sexual behavior, three behaviors—sexual desire, sexual fantasy and sexual arousal—were defined as being indicative of a subject's sexual motivation, i.e., the predisposition to seek out or to generate sexual stimuli. A second classification included frequency of coitus and orgasm, behaviors that may be more concerned with physiological response. At the beginning of each month, subjects were given 30 stamped addressed envelopes and were instructed to fill in and mail a questionnaire daily. Thus, there were 95 recording days per subject per measure and 760 patient-days in the entire study.

Results

Subject characteristics

The 8 women in the study had a mean age of 48.1 yr. Each had undergone TAH and BSO approximately 2.7 yr previously for the treatment of benign uterine fibroids. All subjects had been receiving monthly injections of 1 ml of the estrogen-androgen combined drug for at least 1.8 yr prior to initiation of this investigation and they were all in good general health. Subjects attained a mean score of 119.4 on the MAS (range 106–135) indicating that they all had satisfactory marital relationships.

At the outset of the study, subjects were able to delay their monthly injection for a mean of 54.8 days (range was 52–58 days). It is this period of time therefore, that defines the baseline measure.

Estradiol and testosterone levels

An analysis of variance (ANOVA) for repeated measures was carried out on each of the variables. In each case where the ANOVA found a significant interaction effect, Tukey post-hoc tests were performed between the means to determine at which test times the changes had occurred.

Changes in sex steroid levels appear in Table II. The ANOVA on plasma estradiol levels revealed a significant interaction effect ($P < 0.001$). Estradiol levels were higher on days 1 and 2 post-injection compared to all other test days ($P < 0.01$). Moreover, by day 8, estradiol levels had declined to 32% of the peak value recorded on day 1. The time course of this decrease indicated that the half-life of the estradiol dosage administered was approximately 6 days.

Analysis of plasma testosterone levels also showed an interaction effect ($P < 0.03$) such that mean values on day 2 were higher than at preinjection baseline and than days 30 and 42 ($P < 0.05$). Apart from the significant, albeit modest peak on day 2, plasma testosterone levels remained fairly stable throughout the course of the study.

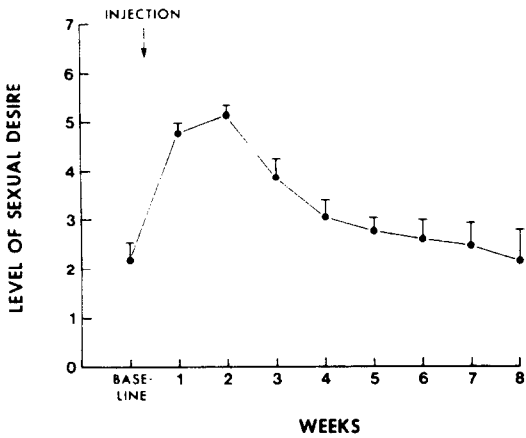


Fig. 1. Mean level of sexual desire

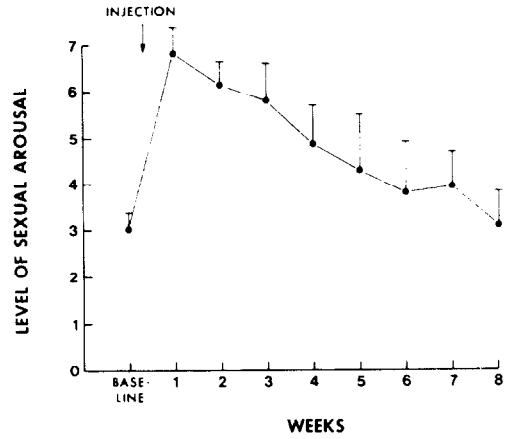


Fig. 2. Mean level of sexual arousal

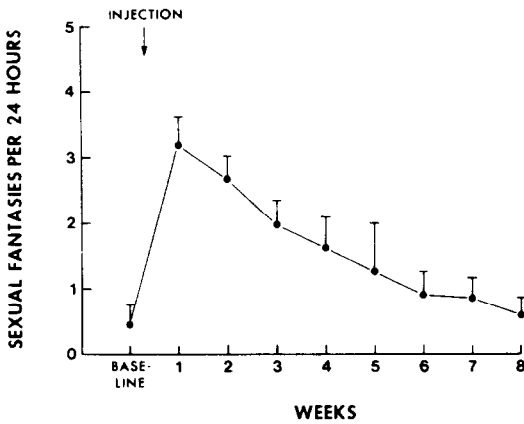


Fig. 3. Mean number of sexual fantasies

TABLE II
PLASMA ESTRADIOL AND TESTOSTERONE LEVELS

	Estradiol pg/ml $\pm$ SEM	Testosterone ng/ml $\pm$ SEM
Baseline (day 55)	80.1 $\pm$ 8.2	1.22 $\pm$.11
Day 1	342.5 $\pm$ 14.8 **	1.80 $\pm$.12
Day 2	265.7 $\pm$ 18.5 **	1.93 $\pm$.12 *
Day 8	94.3 $\pm$ 7.2	1.64 $\pm$.07
Day 15	78.5 $\pm$ 4.7	1.44 $\pm$.09
Day 24	80.2 $\pm$ 3.4	1.31 $\pm$.10
Day 30	74.0 $\pm$ 6.8	1.20 $\pm$.13
Day 42	78.3 $\pm$ 7.8	1.19 $\pm$.16

* Significantly higher than all other test times ($P < 0.05$)

** Significantly higher than all other test times ($P < 0.01$)

Sexual behavior

The ANOVAs of mean weekly scores on sexual desire (Fig. 1), sexual arousal (Fig. 2), and number of sexual fantasies (Fig. 3), each found a significant interaction effect ($P < 0.001$). On each of the 3 variables, scores were higher during weeks 1 and 2 post-injection compared to baseline and weeks 4, 5, 6, 7 and 8 ($P < .01$). Analysis of the data on frequency of coitus and orgasm however, showed that there were no significant changes in these behaviors between various points throughout the study.

Discussion

The dose of estrogen administered in this study induced peak plasma estrogen levels of 324 ± 84 pg/ml one day after injection that fell to 94 ± 23 pg/ml by day 8. The estimated half-life of 6 days is consistent with that found following administration of a different estrogen depot preparation [20]. Furthermore, plasma estradiol levels induced by the combined drug we used were within the range of normally fluctuating menstrual cycle values [21] throughout the study.

Inasmuch as mean circulating testosterone levels have been estimated to range from 0.2–0.6 ng/ml in ovulating women [22], levels in these women who received a combined drug were higher, at least in absolute terms. Furthermore, testosterone levels were sustained for a considerable period of time (55 days in this study). Consistent with these findings are results of investigations of subcutaneous pellet implants of estradiol and testosterone in post-menopausal women that showed plasma testosterone levels still exceeded the upper limit of the normal female range after 5 mth [23–24]. Our data indicate that testosterone administered intramuscularly also results in a very slow rate of metabolism of this steroid. However, apart from one patient who developed mild facial hirsutism, there were no virilizing side-effects observed or reported.

Overall, results of this study showed that changes in sexual motivation in surgically post-menopausal women receiving hormone replacement therapy covary with circulating steroid levels as the drug is metabolized. Previous findings of the association between sex steroid levels and certain aspects of sexual behavior [13] are thus confirmed. It is acknowledged that the design of this pilot study does not permit discrimination between the effects of the 2 sex hormones. A larger investigation incorporating the appropriate control groups is currently in progress. An earlier controlled study, however, demonstrated clearly that exogenous testosterone, but not estradiol, enhanced sexual functioning in surgically post-menopausal women [13].

Two recent investigations of subcutaneous pellet implants of both sex hormones on sexual behavior provide additional supportive evidence for these findings. The effect on symptoms was assessed of pellets containing estradiol 50 mg and testosterone 100 mg [23]. A single questionnaire item that compared 'loss of libido' (undefined) before and after implant therapy was administered at the beginning of the study. Whereas loss of libido was a presenting symptom in over 80% of these post-menopausal patients, implant therapy with both sex steroids was reported to

have produced 'a complete cure' in two-thirds. A second investigation tested symptom response monthly for 6 mth following implantation of pellets containing testosterone 100 mg and estradiol 40 mg [24]. These post-menopausal women were preselected on the basis of their loss of libido, which had not been ameliorated by oral estrogen therapy. Baseline testing required that patients rate various aspects of their sexual functioning relative to their recall of their experience in their 20s. Significant improvements were documented for absent or reduced libido, absent or reduced enjoyment of sex, absence of climax and failure to initiate sex. It is interesting that 43% of the women still reported absent or reduced libido after 3 mth, the time when the testosterone effect was maximal. It is also noteworthy that, in these 2 implant studies as well as in the present study, symptoms worsened as a function of increasing time since hormone administration even though plasma estradiol levels were still in the mid-follicular range and plasma testosterone values were at or above the upper limit of normal for females. The consistency in these data strongly suggests that it is the change in circulating levels of the sex steroids and not the absolute levels that is critical in influencing symptom severity.

Our failure to find differences in coital or orgasmic frequency with testosterone administration may conceivably have been due to partner variables that were not investigated in this study. It is also possible however, that testosterone affects only motivational aspects of sexual behavior and not frequency or response. This hypothesis is consistent with our own previous findings [13], with evidence of differential response of sexual behaviors to the mid-cycle rise in testosterone in young women [25], and with the differential effect of androgen on aspects of sexual behavior in hypogonadal men [26]. Results of all these studies are in agreement that the major impact of androgen in both men and women is on sexual motivation and not on frequency or response aspects of sexuality. Additional rigorous research efforts are needed to further substantiate the apparent specificity of this hormone-behavior relationship.

With respect to future research in this area, several general points are worthy of mention. Two methodological issues have frequently marred efforts to investigate changes in sexual behavior associated with hormone administration. The first problem involves the common failure to define the term 'libido'. While most researchers would now readily agree that human sexuality is not a unitary concept, 'libido' has remained as a descriptor. The use of vague, encompassing terms to measure sexual behaviors does not allow for uncovering the potential specificity of hormone-behavior relationships. Also, general, undefined terms require individual subjects to interpret them, so that the validity of such data is seriously compromised. A second major problem concerns retrospective and one-shot monitoring of sexual behaviors. The premenstrual syndrome literature serves to point out the unreliability of retrospective data [27]. One-shot sampling, particularly with the use of psychometric tests of unknown reliability, is itself a serious source of unreliability. Future research efforts, designed to further elucidate the role of hormones in sexual behavior, ought therefore to incorporate precise operational definitions of the various parameters of sexual functioning and prospective, multiple sampling of the behaviors under investigation.

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