Hormones and Sexuality: Effect of Estrogen and Progestogen

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This study was planned to determine the effects of estrogen and progestogen on female sexual behavior. Forty-nine women who had undergone hysterectomy and bilateral salpingo-oophorectomy took part in a double-blind placebo-controlled cross-over study. Over a 12-month period each woman received 3 months each of ethinyl estradiol, 50 μg per day; levonorgestrel, 250 μg per day; combination of these 2 substances (Nordiol); and a placebo. Significant differences between medications were found in sexual desire, enjoyment, and orgasmic frequency. The most beneficial effects occurred during medication with ethinyl estradiol. There were no differences observed in the effect of hormones or placebo on coital rate or on the analogue rating scales scored daily. The validity of this scale in the present study is questionable.

Sexuality in the female is acknowledged to be the end result of a complex interaction of biologic, sociocultural, and psychologic factors.[1] The last 2 factors are claimed to play an increasingly prominent role in the sexual behavior of primates, especially the human. The role of hormones in determining human female sexual behavior has been the subject of much controversy. In contrast, the sexual behavior of other mammals has been shown to vary consistently with the phases of the reproductive cycle.[2,3] In monkeys, estrogen activates sexual interaction, whereas progesterone has an inhibitory effect. In addition to influencing female receptivity and initiative, both estrogen and progesterone affect male response via a pheromonal pathway.[4]

Studies of human female sexuality report conflicting findings. Different investigators, using different samples and methods, report peaks of sexual desire and activity at virtually every phase of the menstrual cycle.[5] Contradictory results of prospective studies may be in part explained by the various methods used to assign behavior to menstrual cycle phases.[5] Few studies identified menstrual cycle phases on the basis of hormone assays or attempted to correlate behavioral and hormonal events.[6] Varying results may also reflect the type of sexual behavior studied—whether initiated by female, male, or both.[7] There was also little attempt made to control for the influence of the subject's or the investigator's expectations on the behavior observed, despite the considerable evidence to indicate that subject's expectations can substantially influence behavioral findings in research.[8]

Studies of oral contraceptives have also produced conflicting findings.[9] Adverse effects may reflect psychologic or pharmacologic aspects of contraceptive pill taking. Attempts have been made to differentiate these using placebo-controlled double-blind studies. Two such studies[10,11] using cross-over designs demonstrated inhibitory effects of oral contraceptives on sexual behavior, whereas a study[12] that used comparison groups found no difference between the contraceptive pill and placebo.

Epidemiologic studies[13,14] of the effects of depletion of estrogen and progesterone at the menopause suggest an associated decline in female sexual interest, capacity for orgasm, and coital frequency. Few double-blind studies of hormone therapy have measured the effects of hormones on sexual response. Campbell[15] found a significant decrease in vaginal dryness with estrogen compared with placebo but no change in masturbation, orgasm, frequency of coitus, or coital satisfaction. In constrast, Fedor-Freybergh[16] found a significant beneficial effect of estrogen on libido, sexual activity, satisfaction, experience of pleasure, sexual fantasies, and capacity for orgasm.

The conflicting findings reported make it difficult to reach any conclusions about the effects of estrogen or progesterone on the sexual behavior of the human fe-

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male. An experimental model used extensively in the investigation of animal sexual behavior studied the effects of the administration of estrogen and progesterone to castrated animals. Many of the studies that have used this model were reviewed by Davidsen.[17] The present authors chose this model to investigate the behavioral effects of an estrogen and a progestogen in oophorectomized human females. Bilateral oophorectomy ensured that all women were in a similar and definable state of ovarian hormonal deficiency. The individual and combined effects of estrogen and progestogen could then be evaluated.

Previous reports have detailed some of the findings of this double-blind placebo-controlled cross-over study. After the study women rated their preferences[18]: ethinyl estradiol was most preferred, then the combination of ethinyl estradiol and norgestrel, norgestrel, and placebo was last. All hormonal compounds were found to be more effective than the placebo in alleviating hot flushes.[19] The frequency of headache[20] was found to be related to a fall in the estrogen content of the medication. The estrogen and progestogen studied were also found to have pharmacologic effects on mood.[21] The most beneficial influence was observed with ethinyl estradiol. Increasing the progestogen:estrogen balance had an adverse influence on mood. Lowest mood scores were obtained in months when placebo was taken.

This report concerns the effect of hormones on sexual behavior.

Patients and Methods

The sample consisted of 49 women who had undergone both hysterectomy and bilateral oophorectomy for benign disorders. Absence of the uterus provided the additional advantage for the present study of preventing abnormal bleeding due to the use of unopposed estrogens or progestogens or hyperplastic changes of the endometrium.

A preliminary study[22] demonstrated that many women experience deterioration of sexual relationships as a result of this operation and that psychosexual dysfunction other than dyspareunia may not be responsive to hormone therapy. Only women who had stable satisfying heterosexual relationships with a coital frequency of at least twice per month were accepted for the present study. Only 1 woman in the present study had more than 1 current sexual relationship. She agreed to rate her sexual response with her regular partner (her husband) during the study.

Women with a past or present history of hypertension, thromboembolic disorder, coronary artery disease, diabetes, impaired hepatic function, and neoplasia were excluded from the study, as were women currently taking any medication with a known influence on mood or sexual function.

The women were requested not to use hormones during the 2 weeks before the start of the trial. After initial assessment they were randomly allocated to 1 of 4 medication groups: ethinyl estradiol, 50 μg per day; levonorgestrel, 250 μg per day; combination of the above hormones (Nordiol, Wyeth); and placebo. When the study commenced the combination of ethinyl estradiol 50 μg and levonorgestrel 250 μg was the most frequently prescribed oral contraceptive in Australia. All drugs were supplied as identical tablets (Wyeth). Double-blind cross-over methodology was used so that each woman received each drug for 3 months. If a woman was unable to tolerate the side effects in the hormone-free or drug phases of the study, she was given the next drug in the sequence. Drug-taking was continuous, and there was no drug-free period between the various medications. Women were assessed initially and monthly by 1 investigator (LD). Daily subjective assessments were also recorded by the women. The types of assessments are summarized in Table 1.[23-29]

Various methods were used to detect changes in sexual behavior. During the monthly interview, information was sought about any changes in sexual desire, sexual enjoyment, or vaginal lubrication. The verbal reports were rated by the interviewer on an ordinal scale. Orgasmic and coital frequency for the month were also reported by the women at this interview and a written analogue rating scale of sexual response was completed. This scale[27] consisted of 15 questions, each

Table 1. Type and Frequency of Assessment

Type of assessment	Frequency
Semistructured interview	Initially, monthly
Psychologic rating scales	
Eysenck personality inventory[23]	Initially
Hamilton rating for depression[24]	Initially, monthly
Analogue rating scales	
Depression[25]	Initially, daily, monthly
Anxiety[26]	Initially, daily, monthly
Sexual response[27]	Initially, daily, monthly
Physiologic	
Examination	Initially
Weight	Initially, monthly
Blood pressure	Initially, monthly
Hormones (plasma radioimmunoassay)	
Estradiol, testosterone, follicle-stimulating hormone, luteinizing hormone[28]	Initially only
Ethinyl estradiol, levonorgestrel[29]	Monthly, 2, 8 and 26 hours after tablet ingestion

preceding a 100-mm line. The questions covered various aspects of sexuality such as sexual activities (sexual dreams, fantasy, response to music, literature, masturbation); foreplay (kissing, breast and genital stimulation); and arousal, enjoyment, and initiation of sexual intercourse. Women completing the scale were told to regard each end of the line as representing the greatest extreme of their feelings and the middle as the middle of their feelings. Questions were to be answered with regard to sexual function in the previous month. In addition each woman was asked to record daily the occurrence of sexual intercourse and to rate her enjoyment of sexual intercourse on an analogue scale (100-mm line).

Results

Sample Profile

The mean age of the 49 women was 46.2 years, with a standard deviation of 8.92 years. Time since oophorectomy varied from 6 months to 27 years, with a median of 2 years. Most of the women had 1 child, but parity ranged from 0 to 7. Most (78%) had not completed secondary school. Twenty-four women were housewives. Most of the employed women worked as secretaries or saleswomen.

Twenty-six women (53%) had received no previous psychiatric treatment. Psychotropic drugs had been prescribed in the past by the general medical practitioner for another 16 women (33%). The remaining 7 (14%) had been treated by a psychiatrist. Six of these 7 had been treated by a psychiatrist for depression, and the other woman had been treated for anxiety. The Eysenck Personality Inventory[22] recorded the 49 women as having a mean neuroticism score of 12.8, with a standard deviation of 4.99. This did not differ significantly from the normal values cited.[23]

A total of 13 women ceased the study without receiving all 4 treatment regimens. The reasons for withdrawal have been reported in detail previously.[18] Seven of the women cited psychologic symptoms such as depression, irritability, fatigue, and anxiety. Other reasons included hospitalization, moving to another city, and terminal illness of the partner. There were no significant differences in the type of drug taken at the time the women withdrew from the study. A further 12 women requested a change of drugs because of intolerable side effects, mainly hot flushes. Significantly more women requested a change of medication because of intolerable hot flushes while taking placebo (χ^2 16.3, 3 degrees of freedom; $P < .001$). When possible, data from women in this latter group were included in the analysis of results.

Verbal Self-Reports

Interview reports of sexual desire, sexual enjoyment, and amount of spontaneous vaginal lubrication with coitus were recorded on an ordinal scale. Drugs were ranked and Figures 1 to 3 were drawn as histograms from the rankings. Increasing sexual desire, enjoyment, and vaginal lubrication are shown as increasing ranks. Wilcoxon's matched pairs signed-rank test was used to test for differences between drugs.

After the first month, no statistically significant findings ($P < .05$) were evident.

After the second month, there was a significant difference between the estrogen-containing compounds and the non–estrogen-containing compounds for both sexual desire and enjoyment. The difference between norgestrel and the estrogen-containing drugs was highly significant ($P < .01$) for sexual enjoyment. There was also significantly more vaginal lubrication reported after 2 months of ethinyl estradiol therapy than after 2 months of placebo.

After the third month, ethinyl estradiol was associated with significantly more sexual enjoyment ($P < .05$) and desire ($P < .01$) than placebo.

An interesting trend, although it is not statistically significant, was that during months 1 and 2, sexual enjoyment was lower with norgestrel alone than with placebo (Figure 2).

Analogue Rating Scales of Sexual Response

A Friedman 2-way analysis of variance found no significant differences between drugs on any of the analogue scales administered monthly or daily.

A correlation of the analogue scales administered monthly found that correlation coefficients increased markedly in the first 3 months of the study, so that most scales became highly correlated by the end of the third month.

Frequency of Orgasm

The frequency of orgasm was reported at monthly interviews. An analysis of variance was used to test for drug effects on orgasmic frequency. This method of analysis allowed a statistical determination of the separate effects of medication, patient differences, and the interaction between specific medication and individual patients to be evaluated. Statistically significant effects are noted in Table 2. The results indicate that there was a significant difference between the various drugs on the frequency of orgasm. The highest number of orgasms occurred with ethinyl estradiol, then Nordiol, then norgestrel, and the lowest number during placebo therapy. There was also a highly significant dif-

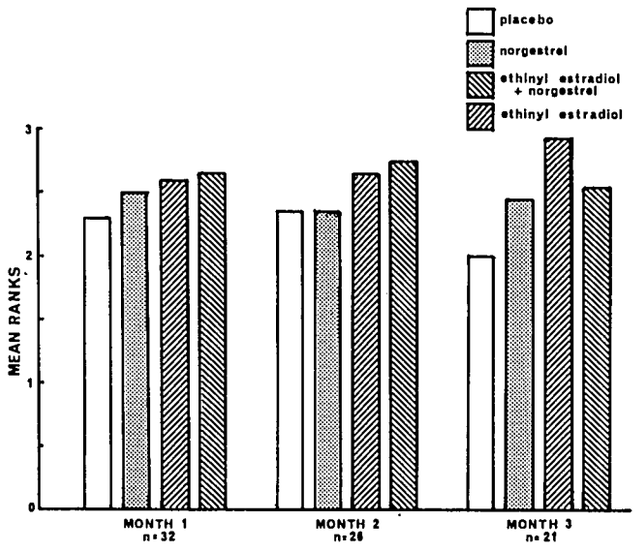

Figure 1. Hormone therapy and sexual desire.

ference between individual patients in the frequency of orgasms experienced and a highly significant patient–drug interaction, indicating that some women responded to different drugs in different ways.

Orgasmic Frequency and Hot Flush Relief

The hormones studied were known to have differential effects on hot flushes, which were quite debilitating in some women.

An analysis of covariance was carried out to determine the proportion of the variance in orgasmic frequency that could be explained by the effect of hormones on hot flushes. The results detailed in Table 3 demonstrate that the frequency of hot flushes also had a statistically significant effect on orgasmic frequency. As the magnitude of the effect of drugs on orgasmic frequency was uninfluenced by including hot flush frequency as a covariate (compare F for drugs in Table 2 with those in Table 3), the drugs appear not to affect orgasmic frequency by alleviation of hot flushes alone.

Frequency of Coitus

The frequency of coitus was reported at monthly interviews. The occurrence of coitus was also noted on daily calendars. The Spearman correlation coefficient of daily and monthly reports of coitus was 0.76 ($P < .001$). An analysis of variance was carried out on both daily and monthly reports of coital frequency. This showed no significant effects of the drugs administered on the frequency of intercourse. There were

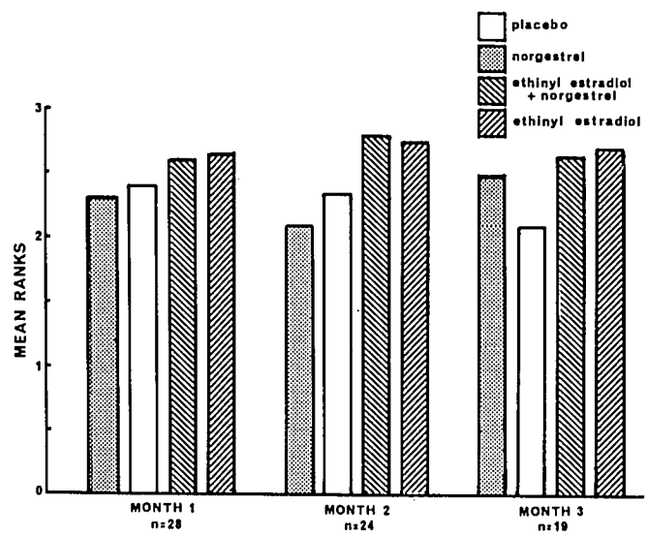

Figure 2. Hormone therapy and sexual enjoyment.

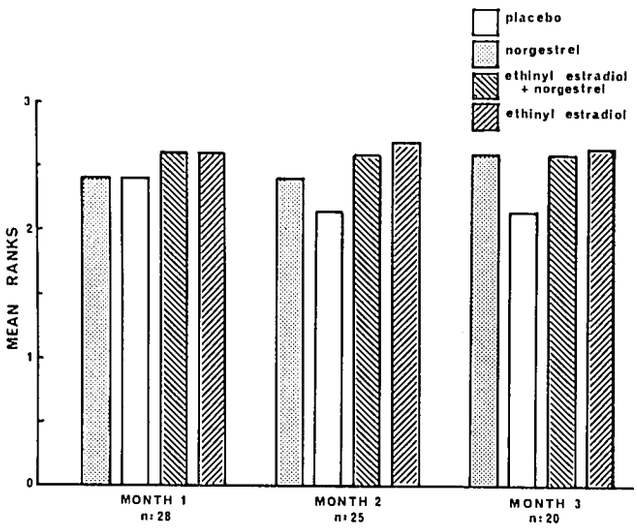

Figure 3. Hormone therapy and lubrication.

highly significant differences between patients and patient–drug interactions ($P < .001$) with both daily and monthly reports of coital frequency.

Relationship Between Mood and Sexual Interest

A previous study[12] had postulated a relationship between mood, sexual desire, and hormonal contraception. Monthly assessments of various aspects of effect were correlated with the verbal report of sexual desire using the Spearman nonparametric correlation. The results shown in Table 4 list the correlation coefficients obtained at the initial visit and after 3, 6, 9, and 12 months of therapy. The highest correlation coefficients were obtained between general feelings of well-being and sexual desire.

Discussion

The major findings of the present study were that ethinyl estradiol had beneficial effects on female sexual desire, enjoyment, vaginal lubrication, and orgasmic frequency, whereas norgestrel appears to be inhibitory. These results provide some evidence of similar effects of hormones in the human female to those found in experiments with castrated primates. The estrogen–progestogen combination studied was less inhibitory than the progestogen (norgestrel) given alone, but not as beneficial for sexual response as the estrogen alone. This suggests that the effect of any particular oral contraceptive will probably reflect the balance of these hormones. The more estrogenic pills would be expected to have a more favorable effect on sexual response.

The highly significant patient–drug interaction for orgasmic and coital frequency suggests, as would be expected, that there were other factors influencing sexual response. It was of interest that hormones had a significant effect on orgasmic frequency but not on coital frequency. Coital frequency is perhaps more likely to be influenced by the partner's wishes, whereas orgasmic frequency is likely to reflect internal

Table 2. Analysis of Variance of Orgasmic Frequency ($N = 28$)

Source	*df*	MS	*F*
Patients	27	358.95	38.60†
Drugs	3	30.75	3.31*
Interaction (patients × drug)	81	22.08	2.37†
Residual	218	9.30	
Patients	27	359.02	26.01†
Therapy months	2	20.57	1.49
Interaction (patients × months)	54	8.72	0.63
Residual	246	13.80	

* $P < .05$.
† $P < .001$.
df = degrees of freedom; MS = mean square; *F* = variance ratio; *P* = probability.

Table 3. Analysis of Covariance of Hot Flush Frequency and Orgasmic Frequency ($N = 28$)

Covariate	*df*	MS	*F*
Hot flush frequency	1	41.03	4.42*
Main effects			
Drugs	3	32.51	3.50*
Patients	27	353.68	38.09†
Interaction			
Drugs × patients	81	22.09	2.38†
Residual	217	9.28	

* $P < .05$.
† $P < .001$.
df = degrees of freedom; MS = mean square; *F* = variance ratio; *P* = probability.

Table 4. Spearman Rank Correlation Coefficients of Affect and Sexual Desire

Time of evaluation	Verbal reports				Hamilton rating
	Mood	Irritability	Anxiety	Feelings of well-being	
Initial visit	0.26	0.40	0.22	0.38	0.30
3 months	0.06	0.25	0.07	0.61	0.19
6 months	0.30	0.60	0.47	0.76	0.48
9 months	0.09	0.10	0.25	0.69	0.31
12 months	0.10	0.05	0.27	0.89	0.37

factors more strongly. These findings highlight the importance of distinguishing female from male response when studying sexual behavior. This seemingly obvious distinction has received little attention in previous studies of the effects of hormones on sexuality. Adams and co-workers[7] recently demonstrated the usefulness of such approaches in their study of sexual behavior during the menstrual cycle. Their findings of an ovulatory peak for female-initiated behavior, and its suppression in women using oral contraceptives, are in agreement with the results of the present study.

The analysis of covariance demonstrated that orgasmic frequency was not substantially changed by allowing for the influence of hormones on hot flushes. This finding suggests a direct influence of hormones on certain aspects of sexuality.

Studies of the oral contraceptive pill had suggested that changes in sexual desire were secondary to the effects of the pill on mood. The findings of the present study suggest that general feelings of well-being correlate more closely with sexual desire than does mood. Whether the significant association between general feelings of well-being and sexual desire reflects any cause or effect is not immediately clear.

Several other issues of methodologic importance were highlighted by this study. The analyses of variance showed highly significant differences between patients. These differences were also evident when the effects of drugs on hot flushes and mood were analyzed. The large interpatient variability suggests that in studies of the effects of hormones it is highly desirable to use a cross-over design. This may explain why studies such as that of Cullberg,[12] which utilized comparison groups, reported no effect of estrogens on sexual behavior. In cross-over designs, larger numbers of women than in the present study may be necessary to overcome patient variability. This perhaps may be reflected in the marginal significance obtained in analyses of verbal reports, although another factor was the difficulty involved in quantitating sexual behavior. The major problem with cross-over designs is that there may be a carry-over effect into subsequent months of therapy. Previous debate[30] suggests that a minimum period of 3 months is necessary to overcome any carry-over effect of estrogen or progestogen. Monthly results were analyzed separately to indicate any carry-over effects. These were not evident with regard to the effects of hormones on sexual behavior but were clearly demonstrated for headaches.[20] It may have been desirable to have a drug-free period between medications. It did not seem justifiable to have lengthened the present trial, as it was realized that it would be difficult enough to keep women participating for the 12 months planned.

Analogue scales used in this study showed no significant effect of drugs. This could reflect various factors. The Spearman correlation showed that it appeared to take 3 months for correlation coefficients to stabilize, indicating either a practice effect or that some time was necessary to integrate self-perception adequately on these scales. This may mean that analogue scales recorded in the first 3 months of the study were not valid. This scale was validated on a group of patients who presented for therapy of sexual problems. Changes with therapy were possibly larger than the variations that might be expected during hormone therapy of a group of women who claimed no sexual problems. These scales may not have been appropriate for the measurement of sexual behavior in the present study or in similar investigations. This may perhaps explain why Campbell,[15] who also utilized analogue scales, found few effects of estrogen on sexual behavior.

Conclusion

There is now increasing evidence that the sex steroid hormones estrogen and progestogen do have behavioral effects in the human female. In the present study estrogen was found to stimulate sexual desire, enjoyment, vaginal lubrication, and orgasm as measured by verbal reports and records of orgasm. When progestogen was added to estrogen or given alone, a less beneficial effect was observed. These findings have

implications for women both with regard to variations in endogenous hormones and for the many women receiving exogenous hormones.

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