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Mood and Behavioural Changes with Progestational Agents

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Steroid hormones may produce a wide variety of psychiatric syndromes (1), (2), and the progestational steroids are no exception. We were alerted to this by the occurrence of an acute schizophrenic psychosis following the withdrawal of 30 mg. Enovid (Enavid) daily, which was being used to control endometriosis (3). The patient's psychotic symptoms showed remission with drug replacement and relapse on placebo.

Following this, we requested doctors in the region to refer women suspected of having psychological effects related to taking progestational agents. We utilized a screening procedure consisting of an open-ended clinical interview to evaluate response to these drugs. We collected data on sexual habits, reaction to menses, pregnancy and the post-partum period, previous emotional disturbance and previous contraceptive methods. An effort was made to evaluate current stresses. A Minnesota Multiphasic Personality Inventory (M.M.P.I.) was recorded in most instances. In order to obtain a broad spectrum of experience, we accepted referrals from our staff obstetricians, screened psychiatric patients who had used the drugs and interviewed mothers referred by local pediatricians. Many were referred because they did not like the drug effects, though some, referred as control patients, turned out to have noted changes too.

Fifty patients have been interviewed thus far, all but one were using the medication as oral contraceptives. Eleven were psychiatric inpatients at the time of interview. The drugs involved were Ovulen (ethyndiol acetate), Enovid (Enavid, norethynodrel with mestranol), Ortho Novum (norethindrone) and Norlutin. The patients ranged in age from 26 to 43, the latter being the only patient over 36. Most had one or more children, and most had used mechanical contraceptives without difficulty before they started the use of the hormones. Changes were noted from one week to six months after drug therapy started.

Adverse Reactions

Twenty-eight patients reported undesirable effects, including the previously cited psychotic reaction. Nineteen reported lability of mood, with depression and tearful spells, irritability, loss of interest in their environment and two reported suicidal ideation. One patient in this group (the only psychiatric patient hospitalized in connection with the use of these medicines) came in with a recurrence of depression following the institution of contraceptive therapy. Nine depressed patients had marked decrement in sexual interest, and one described her orgasm as less intense. Two others had a complete menopausal-like syndrome, with hot flushes, etc. In only two depressed patients was there an increase in sexual activity or drive, one to the point of nymphomania. This patient also showed a considerable peak in her mania scale on the M.M.P.I. when tested just after stopping the drug, with return to normal several months later. Two patients who became depressed were in psychoanalysis, and it was their therapists' opinion that the drug was responsible, since they could see no relationship to anything current in the analysis or the environment. One depressed patient reported vivid red green visual hallucinosis of geometric patterns, persisting with closing of the eyes. Severe migraine-like headaches followed the disappearance of hallucinosis, possibly related to arteriolar changes similar to those vascular changes seen in the endometria of patients suffering from headaches

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on oral contraceptive agents (4). Seven other patients presented a syndrome of lethargy, disinterest and marked decrease in sexual interest, one suffering a concomitant thrombophlebitis. One further patient reported nervousness and irritability with increased sexual drive while receiving cyclic therapy for persistent amenorrhea of endocrine origin. During an evaluation of Enovid (5 mg. daily) as a therapeutic agent for post-partum psychoneurotic depression, one patient showed elated mood and behaviour, with an elevation of the mania scale of the M.M.P.I. Substitution of placebo brought an end to the elated state without recurrence of depression, and the abnormal psychological test material returned to normal values at the same time.

At the time of interview, most of those who reported adverse effects had discontinued the drugs themselves or on the advice of their physician. Our only clue to the incidence of adverse reactions comes from six patients who because of emotional distress dropped out of a study of 150 patients evaluating Ovulen as contraceptive agent. Except for the hospitalized patient, the M.M.P.I. profiles on these patients were unremarkable.

Beneficial Effects

Eleven patients, six of whom were psychiatric patients, noted effects of a more acceptable kind. Seven described feelings of increased well-being and "vigour", and four of them also experienced amelioration of their usual premenstrual tension syndrome. The oldest patient, probably in early menopause, experienced lethargy, depressed feelings, irritability and decreased interest in sex when she stopped medication. Two of these seven women also experienced increases in sexual drive, and one noted improvement in orgasmic pleasure. Two of this group reported being generally less nervous, and one described herself as having gained 30 pounds with moon facies and hirsutism. One patient in this group also noted relief of her symptoms of rheumatoid arthritis, and stopped only because of persistent uncontrollable spotting.

Only two psychiatric patients noted undesirable effects, while six thought the medication had desirable effects. The non-psychiatric subjects felt they had not experienced similar depressed feeling states in the past.

Discussion

Concurrent stresses as such did not seem causal in these reactions; rather, the patient complained of increased susceptibility to the usual kind of stresses they encountered. As previously stated, our two analytic patients became depressed for no detectable reason other than the medication. There was a low incidence of previous post-partum reaction, confined to "third day blues". Moral conflict seemed negligible, since most had used mechanical contraceptives previously. Only the patient who reported nymphomania mentioned and evidenced guilt over increased sexual drive.

Several studies have demonstrated very low levels of endogenous hormone production while taking these drugs (5), which may account for the "pseudo-menopausal" syndrome seen in two patients. Both of these had hot flushes and tachycardia, associated with gross reduction in the frequency and amount of menstrual bleeding while on drug, with return to normal after stopping the drug. Several observations suggest the possibility that some patients convert these hormones to steroids with glucocorticoid activity. One was of our patient with reversible weight gain, moon facies, and hirsutism. Another patient experienced symptom relief similar to that reported by Gilbert *et al.* (6) in arthritic patients whose steroid dosage could be reduced while they were receiving oral contraceptives. A recent study of serum-lipids in patients receiving an oral contraceptive (Anovlar) demonstrated a significant rise, especially of low density lipoprotein. Low density lipoprotein reached levels "typical for post-menopausal women" (7).

Progesterone is known to exert a sedative effect in the C.N.S., as reflected in E.E.G. slowing in humans (8) and lessened sensitivity to induced convulsions in animals (9). The progestins have also been shown to alter arousal thresholds for stimuli in the hypothalamus of various animals (10). Many of our women

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described themselves as "different from before and not as responsive to the environment" as they had been. The increased narcissistic preoccupation these women describe is very reminiscent of the descriptions by Benedek of women in the progesterone phase of the menstrual cycle (11). These data also conform to the description of the anxiety and depressive symptoms seen in large numbers of pregnant women, which subside after parturition without notable after-effect.

Hampson's review (12) of data bearing on peak times of sexual desire indicates that these occur during the oestrogen phase of the cycle and immediately before the menses, when progesterone levels are falling. In a recent seminar, Dr. William Masters reported clinical data similar to ours, with loss of libido in patients receiving medication for more than 18 months. Another member of the same panel, Dr. John Eichenlaub, estimated that 20 per cent. of his patients showed much keener interest toward the end of the menstrual flow, with virtually complete disinterest later in the month. He reported that these same patients showed substantially impaired response during pregnancy (13). We have elicited similar reports of loss of sexual desire and orgasmic pleasure throughout pregnancy in a recent clinical psychiatric survey of post-partum obstetrical patients (14). This suggests that the complaints of diminished sexual desire reported by 16 of the 50 patients may be related to the progestins in the mixture.

Summary

Fifty women, including eleven psychiatric patients, were interviewed about their experience with oral contraceptive agents. Twenty-eight had adverse effects, eleven had beneficial effects and the others noted no change. Depressive feelings, accompanied by lethargy and decreased interest in sex were the most frequent complaint of the twenty-eight patients responding adversely. Visual hallucinosis followed by migraine headache was reported by one, while two of them reported symptoms suggesting a menopausal syndrome. Seven of the fifty women described increased wellbeing and vigour, and four reported decreased premenstrual emotional disturbance. Two patients described changes suggesting conversion of these hormones to others with glucocorticoid activity. Historical data regarding emotional disturbances at times of hormonal change (premenstrual and post-partum) were not predictive as to type of reaction, nor did M.M.P.I. data show deviation from normal at the time of testing except in the psychiatric patients.

Further replication of these data is needed, since adequate controls were not obtained. Further clinical observations may help to clarify the factors determining such responses.

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