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Effects of ethinyl estradiol on semen quality and various hormonal parameters in a eugonadal male

Horst Lübbert, M.D.*
Inka Leo-Roßberg, M.D.
Jürgen Hammerstein, M.D.

Hospital for Women, Department of Gynaecological Endocrinology and Reproductive Medicine, Free University of Berlin, Berlin, Germany

Objective: To determine the influence of estrogens on male fertility.

Design: A 36-year-old eugonadal male was subjected to two different regimens of treatment with ethinyl estradiol (EE_2). Sperm quality, immunoreactive luteinizing hormone (LH) and follicle-stimulating Hormone (FSH), testosterone (T), estrone (E_1), estradiol (E_2), dehydroepiandrosterone sulfate (DHEAS), prolactin (PRL) and sex hormone-binding globulin were determined at intervals of 2 weeks for 315 days.

Setting: A gender dysphoria clinic.

Patient: A transsexual male nurse.

Main Outcome Measures: It was hypothesized (and confirmed) that by comparing the effects of increasing and constant dose of EE_2 on fertility parameters, differences in estrogen-sensitivity would show more clearly. Furthermore, this procedure served to find the minimal dose of EE_2 for complete testicular suppression.

Results: Low doses of EE_2 (20 μg/d) had no negative effect on sperm motility and density for a period of approximately 4 weeks, whereas high doses (60 μg/d) reduced motility already after a few days and led to a pronounced decrease in sperm density after 2 weeks. After discontinuation of therapy, motility normalized faster than sperm density. Under increasing doses of EE_2 there was a constant decrease of FSH that occurred several weeks earlier than that of LH. Under constant dose of EE_2 (60 μg/d) the decrease of LH was delayed (with respect to FSH) by only a few days. The decrease in T showed a stronger correlation with that of FSH than with that of LH. Volume and fructose content of the seminal fluid correlated with the decrease in T. Rebound effects were observed for FSH, LH, T, and fructose during the therapy-free interval. Ethinyl estradiol therapy had no influence on the serum concentrations of E_1, E_2, and PRL. Estrone was the dominant estrogen before and after therapy with EE_2. Adrenal gland activity was markedly suppressed by EE_2, as reflected by the decrease in DHEAS.

Conclusion: The suppressive effect of EE_2 on FSH and sperm motility was more pronounced and consistent than on LH and sperm density. The T decrease appears to be mainly caused by a direct effect of EE_2 on the testes. Fertil Steril 1992;58:603–8

Key Words: Male fertility, estrogens, sperm quality, gonadotropins, testosterone

The influence of estrogens on male fertility has not been fully clarified. In disorders involving hyperestrogenemia (e.g., estradiol [E_2]-producing adrenal gland tumors), suppressive effects on gonadotropins and sperm quality have been observed (1). On the other hand, gonadotropin release and sperm quality may be improved by administration of antiestrogens (2–4). However, serum E_2 and estrone (E_1) analysis in subfertile males is useful only in patients with markedly increased estrogen levels because physiological variations are frequently

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* Reprint requests: Horst Lübbert, M.D., Klinikum Steglitz der FU Berlin, Hindenburgdamm 30, D-1000 Berlin 45, Germany.

within the range of assay variations. Thus, it is difficult to assess the importance of serum estrogen values for male fertility. In the majority of publications (1–4), the effect of estrogens on luteinizing hormone (LH) and follicle-stimulating hormone (FSH), prolactin (PRL), free and total testosterone (T), E_1, E_2, and dehydroepiandrosterone sulfate (DHEAS) is described independently of sperm parameters or of one another. Furthermore, most of these studies were of short duration. Trends showing only after long-term administration were therefore not demonstrable. We describe the treatment of a eugonadal male transsexual with ethinyl estradiol (EE_2) over a period of almost 1 year. The serum parameters mentioned above and sperm parameters were determined simultaneously in 14-day intervals. This and the employment of two different types of therapy (staircase therapy versus constant-dose therapy) enabled us to detect differences in response that are otherwise not seen, e.g., the higher negative response of FSH than that of LH to estrogens.

MATERIALS AND METHODS

Treatment Plan

A 36-year-old eugonadal transsexual male was treated in three phases as follows (Fig. 1) [1] The first phase ranged from 1 to 140 days: Oral administration (in the evening) of increasing doses of EE_2. The daily dose was increased by 10 μg at intervals of 2 weeks up to a maximum dose of 80 μg/d (so-called staircase therapy). [2] The second phase was a therapy-free interval and lasted from days 141 to 240. [3] The third phase lasted from days 241 to 315. The patient received a constant dose of 60 μg EE_2/d.

It was hypothesized that by comparing the effects of increasing and constant doses of EE_2 on fertility parameters, differences in estrogen sensitivity would show more clearly. Furthermore, this procedure served to find the minimal dose of EE_2 for complete testicular suppression while maintaining or increasing personal well-being. During the above treatment, no other medication was given. The patient (a male nurse) had given his informed consent. No ethical objections were put up by the institutional reviewers. All parameters (spermiogram, hormones, and sex hormone-binding globulin [SHBG]) were determined at intervals of approximately 14 days.

Sperm Analysis

After 3 to 4 days of sexual abstinence, sperm was obtained by masturbation and analyzed according to the World Health Organization standards (5). Analysis was started 30 minutes after ejaculation and included spermatozoal density, total number of spermatozoa, qualitative and quantitative motility, morphology, percentage of nonvital sperms, ejaculate volume. Initial fructose in sperm plasma served as a marker of vesicular function and 4-hour fructose (fructolysis) as a parameter for sperm vitality and metabolic activity.

Serum Analysis

Plasma LH, FSH, and PRL concentrations were measured by delayed fluoroimmunoassay (Delfia) supplied by Pharmacia (Wallac, Turku, Finland). The intra-assay and interassay coefficient of variation (CV) was <7%.

The sensitivity was 0.05 mIU/ML for LH and FSH and 1.4 mIU for PRL. Testosterone, E_1, and E_2 were determined by radioimmunoassay (RIA) using specific antisera after extraction and separation of individual steroids on celite columns according to the method of Abraham et al. (6). The antiserum for T was bought from Abraham, the antiserum for E_1 from bioMerieux (Marcy-l'Etoile, France), and the antiserum for E_2 (Anti-17β-Estradiol-6-[CMO]) from Steranti (St. Albans, United Kingdom). The sensitivity was 2 to 6 pg/mL for E_1, 2 to 7 pg/mL for E_2, and 8 pg/mL for T. Dehydroepiandrosterone sulfate was measured without preliminary chromatography by use of a solid-phase RIA kit (Hermann Biermann GmbH, Bad Nauheim, Germany). The sensitivity for DHEAS was 0.021 μg/mL. Intra-assay and interassay CVs were <8% for all steroids. Serum analysis for SHBG was also performed with a Delfia kit supplied by Pharmacia. The intra-assay and interassay CV was <9%. The sensitivity was 0.8 nmol/L.

RESULTS

Effect of EE_2 on Sperm Quality

Staircase Therapy

Sperm density ($\times 10^6$/mL) and total sperm count ($\times 10^6$/ejaculate) remained unchanged with dosages of up to 50 μg EE_2/d (80th day of treatment). When the therapy was continued with a higher dosage, the sperm count dropped below 1,000/mL within the following 14 days.

No negative effect was observed on motility, percentage of vital sperm, or normal-shaped sperm with

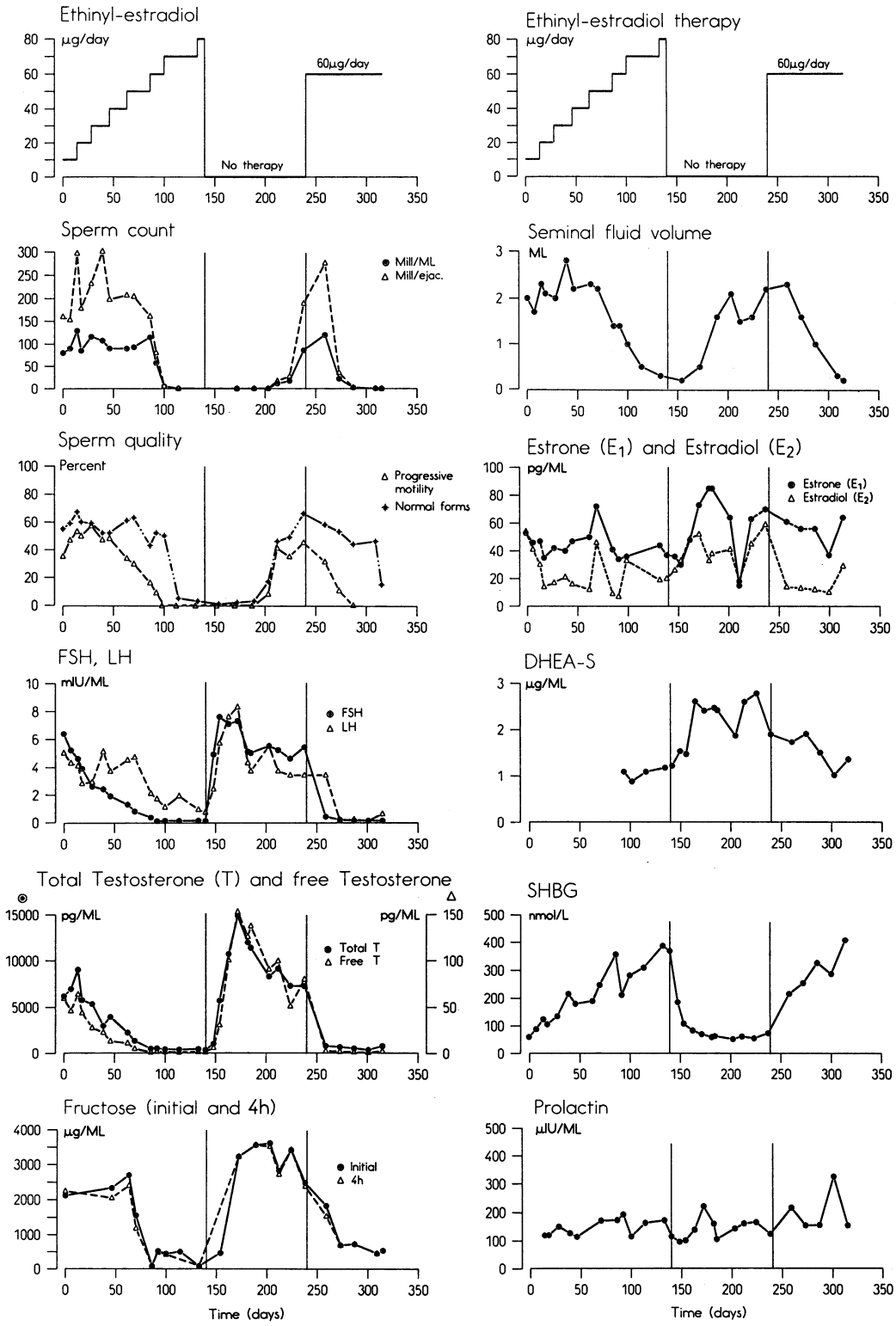

Figure 1 Treatment of a 36-year-old eugonadal male transsexual with EE_2. The study period was 315 days, divided into three phases. [1] The first phase ranged from 1 to 140 days: oral administration (in the evening) of increasing doses of EE_2. The daily dose was increased by 10 µg at intervals of 2 weeks up to a maximum dose of 80 µg/d (so-called staircase therapy). [2] The second phase was a therapy-free interval and lasted from days 141 to 240. [3] The third phase lasted from days 241 to 315. The patient received a constant dose of 60 µg EE_2/d. The effect of EE_2 on the following parameters was determined. [1] Sperm quality (sperm density, motility, morphology, ejaculate volume, and fructose content); [2] FSH, LH, T, E_1, E_2, DHEAS, and PRL; [3] SHBG.

dosages up to 20 μg EE_2/d (day 30). However, within the following 70 days (dose increase to 60 μg EE_2/d), these parameters went down to zero (day 100). With an FSH level of 1 mIU/mL and a T value of 1,500 pg/mL (day 70), progressive motility fell below the 30% mark. Up to that point, serum LH had not decreased and, at 5 mIU/mL, was within the normal range. The seminal plasma volume decreased rapidly from day 70 on and reached 0.3 mL with a dose of 80 μg EE_2/d (initial value approximately 2 mL).

Constant-Dose Therapy

At 60 μg EE_2/d, sperm density and sperm count decreased rapidly after day 20 of the therapy (compare staircase therapy). Sperm motility and all other qualitative parameters deteriorated immediately after the start of therapy. On day 50 (twice as early as under the staircase therapy) no motile sperms were detectable. Seminal plasma decreased rapidly from day 20.

Therapy-Free Interval (Recovery Phase)

Sperm motility and the other qualitative parameters returned to normal faster than the sperm count. Pretherapeutic normal values were obtained after 70 days (motility) and 100 days, respectively (sperm count). Compared with sperm density, motility, and other qualitative parameters, seminal plasma volume recovered fastest (60 days).

Effect of EE_2 on Serum Concentrations of FSH and LH

Staircase Therapy

Increasing doses of EE_2 led to a constant decrease of FSH down to values within the minimal detectable range (day 90), whereas LH remained almost unchanged up to a dose of 50 μg EE_2/day (day 70). A marked decline of LH was observed only after a further dose increase. Under 80 μg EE_2/d, the LH value went down <1 mIU/mL on day 140. At a dose of 20 μg EE_2/d, the FSH graph intersected the LH graph (25th day of therapy).

Constant-Dose Therapy

Constant-dose EE_2 (60 μg/d) administration also led to a much faster reaction of FSH than of LH: on day 20 (day 260 of our study), FSH was already markedly suppressed, whereas LH was still within the normal range. Maximal suppression of both gonadotropins was observed a few days later. During the therapy-free interval the rebound effect was almost identical for FSH and LH.

Effect of EE_2 on Serum Concentrations of Total and Free T

Staircase Therapy

Free and total T declined continuously. This decline was parallel to that of FSH but not to that of LH (dissociation of the decrease of LH and T).

Constant-Dose Therapy

At 60 μg EE_2/d, the dissociation of LH and T levels described above was observed also under this therapy: on day 20 (day 260 of the study), the LH value was still within the normal range, whereas maximal suppression of T (and FSH) was already accomplished. During the therapy-free interval a rebound effect was detectable.

Effect of EE_2 on Fructose Content of Seminal Plasma

Staircase Therapy

The fructose content of seminal fluid remained almost unchanged up to a dose of 50 μg EE_2/d (day 70). Subsequently, it decreased rapidly.

Constant-Dose Therapy

A rapid decrease of the fructose content was observed immediately after starting this therapy of 60 μg/d of EE_2. During the therapy-free interval a slight rebound effect was detectable.

Effect of EE_2 on Serum Concentrations E_2 and E_1

Serum E_2 and E_1 levels as well as their ratio of concentration remained largely unchanged during all study phases. Even in the complete absence of testicular T production (T < 500 pg/mL, gonadotropins < 1 mIU/mL), E_2 and E_1 remained within the normal range. Estrone continued to be the dominant estrogen.

Effect of EE_2 on Serum Concentrations of DHEAS, SHBG, and PRL

High dosages of EE_2 (60 μg/d) reduced the serum DHEAS concentration approximately by one half. The concentration of SHBG was markedly increased. This increase was almost linear in both types of therapy, although under constant dose it

was somewhat steeper. An eightfold increase of SHBG was achieved after 80 days when 60 μg EE_2/d was administered (315th day of the study). No significant change of the PRL level was demonstrable.

DISCUSSION

In a healthy, eugonadal male low estrogen doses (10 to 20 μg EE_2/d) did not have an acute negative effect (i.e., for approximately 4 weeks) on sperm count and motility. Higher doses of EE_2 and longer duration of therapy led to a clearly more sensitive reaction of sperm motility than of sperm count. This was observed in both types of EE_2 therapy (increasing versus constant dose) and also during the recovery period. One possible explanation is that there is a different effect of estrogens on the epididymis and testes. The close correlation between FSH, T, and motility indicates that motility is mainly dependent on FSH and T. This is substantiated by studies involving tamoxifen, clomiphene, and testolactone administration to subfertile males. Under these antiestrogens, the increase of FSH was usually more pronounced than that of LH (3, 4, 7–9), or at least comparable (2). In the majority of cases, administration of these antiestrogens also caused an increase of T (2, 3, 7–9).

Ethinyl estradiol had a markedly stronger suppressive effect on FSH than on LH. This observation is in agreement with that of other authors (10). The higher sensitivity of FSH was especially substantiated by staircase therapy. Other estrogens and antiestrogens also seem to act stronger on FSH than on LH (1, 11, 12). Gooren et al. (11) were able to demonstrate that (endogenous as well as exogenous) estrogens scarcely inhibit basal LH secretion and that certain antiestrogens (tamoxifen, clomiphene citrate [CC]) have a more pronounced stimulative effect on LH secretion in the luteinizing hormone-releasing hormone (LH-RH) test than on basal LH secretion. The opposite was observed regarding FSH: tamoxifen caused only a slight increase of FSH in the LH-RH test but had a stronger impact on basal FSH. In a patient with endogenous hyperestrogenism (tumor of the adrenal cortex), basal FSH secretion was more suppressed than LH (1). However, not all authors observed this increased sensitivity of FSH to estrogens (13, 14). This was probably because of the experimental design. Intravenous low-dose administration of native E_2 (48 and 90 μg/d, respectively) for 3 to 4 days either did not cause any suppression of immunoreactive and bioactive FSH (13) or had an identical effect on both types of gonadotropins (14). In our experiments, the differential effect of EE_2 on FSH and LH was only demonstrable in a limited range of dose and time. As shown by others (1, 11, 12), estrogens seem to suppress bioactive rather than immunoreactive LH. Tamoxifen seems to have the opposite effect: it leads to an increase especially of bioactive and to a lesser degree of immunoreactive LH (12). Therefore, the dissociation of the decrease of LH and T in our study may have two different causes. [1] The decline of T was mainly because of a decrease of bioactive LH that remained hidden because only the immunoreactive LH was determined. [2] Ethinyl estradiol suppresses T production mainly through a direct impact on Leydig's cells.

The second possibility appears more likely because LH values remained almost unchanged up to a dosage of 50 μg EE_2/d (day 70). If the first explanation was more apt, a continuous decrease of total LH would have been likely. The inhibition of steroidogenic enzymes by E_2 also indicates a direct impact of EE_2 on Leydig's cells (15, 16).

Serum concentrations of E_1 and E_2 in this normal eugonadal male were comparable with those of women just after menopause, also regarding the preponderance of estrone ($E_1 > E_2$). Our results in this respect are in good agreement with those of other authors (17, 18). Because high dosages of EE_2 lead to maximal suppression of Leydig's cells ($T < 500$ pg/mL = castration value) without causing E_1 or E_2 to decrease, it must be assumed that estrogens are largely produced by peripheral sources. This is already postulated in older publications (19). As in postmenopause, androstenedione is the main precursor of aromatization. The role of extraglandular aromatization in estrogen production in the male was elucidated by experiments with aromatase inhibitors. Testolactone causes a decline of total and/or free T and of E_2 (8, 9, 20). Tamoxifen and CC (E_2 receptor antagonists) lead to a rise of both steroids (E_2 and T) because of increased activity of Leydig's cells and increased peripheral aromatization of T to E_2 (2, 3, 7). Although adrenal steroid production was inhibited by EE_2 in our study (decline of DHEAS), this was without significance for peripheral estrogen levels.

As expected, SHBG levels increased with increasing EE_2 dosages and were inversely correlated with T concentrations. This parameter was used to control estrogen intake (compliance). With a constant dose of 60 μg EE_2/d, the latency period between EE_2 administration and maximal SHBG increase was at least 80 days (days 241 to 315 of our study). Because

the study was suspended on day 315, the maximum increase of SHBG could not be determined.

Prolactin levels were independent of the therapy in our study. There is controversy in the literature regarding the effect of estrogen receptor antagonists (e.g., tamoxifen) on serum PRL concentrations. Both increases (3) and decreases (7) are reported. Our results indicate that PRL (at least in the eugonadal male) is no estrogen-sensitive parameter.

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