Clinical trial with levo-norgestrel and testosterone oenanthate for male fertility control

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Abstract. Two groups of six men took levo-norgestrel (250 or 500 µg daily) by mouth and testosterone oenanthate (200 mg monthly, intramuscularly) for six months. A three months placebo period preceded the medication which was followed by a recovery phase of 6–10 months. Two volunteers withdrew due to side effects. The five men taking the low doses of levo-norgestrel (250 µg) exhibited a reduction in sperm count, but not azoospermia. The high dose of levo-norgestrel (500 µg) was more effective, sperm count was reduced to < 6 × 10⁶/ml in 3 of 5 volunteers and to < 17 × 10⁶/ml in the remainder. s-Testosterone, LH and FSH were decreased by the treatment. The men had no toxicological side effects or changes in libido and potency. During the recovery period sperm counts, sperm morphology, s-testosterone, LH and FSH returned to normal levels.

High doses of gestagens when given alone depress spermatogenesis (Heller et al. 1959) but at the same time loss of potency and libido occurred. The depression in sperm count is presumably due to inhibition of gonadotrophin release from the pituitary gland. The concomitant suppression of testicular androgen production is an undesirable side effect which may result in the sexual dysfunction observed. This unwanted effect on libido can be counteracted by simultaneous administration of androgen (Frick 1973), which may add to the suppression of LH and FSH release from the pituitary gland.

The object of this study was to evaluate the effect of an oral gestagen (levo-norgestrel), in the low doses comparable to those used in the female contraceptive pills, and combined with monthly injections of testosterone oenanthate.

Materials and Methods

Unpaid volunteers aged 25 to 45 years of proven fertility (1 or more children) were interviewed by a physician and by a psychiatrist (a WHO multicenter trial). A prior history of liver or other permanent diseases and a sperm count which was systematically less than 20 × 10⁶/ml during the placebo period and an unfavorable psychiatric report excluded a volunteer from the trial. The men were assigned to the treatment groups randomly in such a way that the two groups became of equal size. The trial lasted from 15 to 22 months. Only 2 men withdrew.

In group 1 placebo was administered daily to six men for 3 months, followed by levo-norgestrel (250 µg orally in one daily dose) plus testosterone oenanthate (200 mg...
Fig. 1.

s-Testosterone, s-LH, s-FSH, sperm count and percentage abnormal spermatozoa in volunteers No. 17, 20, 27, 33, and 42, before, during and after treatment with 250 µg levo-norgestrel daily and 200 mg testosterone enanthate monthly.
im in a monthly dose) for 6 months. One man withdrew after 2 months of drug treatment due to increasing acne on his back, a complaint also made during the placebo period. The men who completed the study were no 17, 20, 27, 33 and 42. The treatment period was followed by a recovery phase of 6 to 10 months.

In group 2 placebo was given daily to a further six men for 3 months followed by levo-norgestrel (500 µg orally in one daily dose) plus testosterone enanthate (200 mg im in a monthly dose) for 6 months. This was followed by a recovery phase of 6 to 10 months. One man was withdrawn after 3 months of steroid treatment, after psychiatric evaluation, due to a depressive mood change. This volunteer recovered within a month. Volunteers no 36, 38, 39, 40 and 43 completed the trial.

Seminal fluid samples were obtained approximately 2 weeks intervals by masturbation and analyzed for volume, sperm count, morphology and motility (Hammen 1946). Blood samples were drawn for s-LH, s-FSH and s-testosterone analyses at 2 weeks intervals between 8 a.m. and 6 p.m. and at the same time of the day for each volunteer. Hormone analyses were performed by radio-immunoassays (Hunter & Bennie 1979; Corker et al. 1978). During the trial the s-testosterone analysis was changed from one laboratory to another and this change was evaluated (see Appendix). Blood and liver function tests included determination of circulating haemoglobin, red cell and white cell counts, bilirubin, alkaline phosphatase, alanine-aminotransferase, cholesterol, triglycerides, creatinine and urea which were performed fortnightly. The values from placebo, treatment and recovery phases were compared in each individual with Student's t-test for pair differences. Every month the men underwent a physical examination which included blood pressure, body weight, testicular volume and an examination of the prostate. The volunteers were advised to use contraceptives. Changes in libido and potency was assessed by the same physician on the basis of responses to standard questions. Sperm count, percentage abnormal spermatozoa and hormone analyses were statistically evaluated as described in the Appendix.

Results

Ten of the twelve volunteers recruited for this study successfully completed all three phases. Sperm counts during the first 75 days of the treatment and recovery phase were excluded from the statistical analyses (see Appendix) since this is the duration of human spermatogenesis. A wide variation in sperm count was observed during the placebo period both within and between individuals (Figs. 1 and 2). Only one of five men (no 27) in group 1 (250 µg levo-norgestrel) became severely oligospermic (<2 x 10^6/ml) after 3 months of drug exposure and throughout the remaining three months of the treatment period; three men (no 17, 20 and 33) had sperm counts < 5 x 10^6/ml. The remaining volunteer (no 42) had a decrease of 57% to a mean level of 108 x 10^6/ml (Fig. 1). Thus one of the volunteers receiving 250 µg levo-norgestrel daily and 200 mg testosterone enanthate monthly became azoospermic.

In contrast, three of five men (i.e. no 36, 38 and 43) in group 2, 500 µg levo-norgestrel became severely oligospermic (<6 x 10^6/ml) during treatment (Fig. 2). Two men (no 39 and 40) had counts < 17 x 10^6/ml (Fig. 2). The severe oligospermia was observed in samples 1½ to 3½ months after beginning treatment. Azoospermia was seen in two men (no 36 and 38), but not continuously.

In the recovery phase a tendency for increase as well as decreases in sperm counts were observed (see Appendix). Placebo sperm counts were obtained in 7 of 10 volunteers (group 1 + 2). In two (no 42 and 39) of them the sperm count in the recovery phase remained below the placebo levels (Figs. 1 and 2) but in the normal published range; in one man (no 17) the counts in the recovery phase were not evaluated owing to the small number of observations.

The percentage of abnormal spermatozoa decreased slightly during the recovery phase in the 7 of 10 volunteers compared to the placebo period. During treatment the percentage of abnormal spermatozoa could not be consistently determined owing to the low sperm counts. The seminal fluid volume was unchanged.

Sperm motility decreased during the treatment period in only one (no 33) of five men in group 1, and in all five men in group 2. The motility returned to the level of placebo observations in the recovery phase.

s-Testosterone decreased significantly in all subjects during treatment (P < 0.02). No consistent difference was observed between the s-testosterone in samples drawn 2 weeks after injection of testosterone enanthate and in samples drawn 4 weeks after injection. s-Testosterone returned to normal levels after withdrawal of the 500 µg dose, but after the 250 µg dose the s-testosterone was significantly lower in the recovery phase when compared to the placebo period.

s-FSH and s-LH decreased significantly during treatment (s-FSH, group 1: P < 0.03; Group 2:
Fig. 2.

s-Testosterone, s-LH, s-FSH, sperm count and percentage abnormal spermatozoa in volunteers No. 36, 38, 39, 40, and 43, before, during and after treatment with 500 µg levo-norgestrel daily and 200 mg testosterone enanthate monthly.
P < 0.004 and s-LH, group 1: P < 0.02; group 2: P < 0.0005, except no 39 where P = 0.01). s-LH returned to placebo values in the recovery phase, while s-FSH increased in 6 subjects and decreased in 3 (see Appendix). In one subject (no 42) not enough observations of LH and FSH were made in the recovery phase to permit statistical analysis.

No serious side effects were observed. Serum bilirubin, alkaline phosphatase, alanine-amino-transferase, triglycerides, cholesterol, blood pressure were all unchanged in the three periods. No gynecomastia was observed. Body weights were unchanged in group 1, but in group 2 the body weights of 4 of 5 men increased between 2 and 7 kg during treatment. The body weights were still increasing in the recovery phase.

The volume of all the volunteers’ testes was slightly decreased (about 2 ml) during treatment and returned back to the size of placebo volume during the trial. Few complaints of changes in libido or potency were made during the placebo period and the treatment period.

Discussion

This is the first report of the inhibition of spermatogenesis in man by levo-norgestrel. Five of these men who took the 250 μg oral dose of levo-norgestrel every day exhibited a significant reduction in sperm counts and of the five men who took the higher dose of 500 μg daily three had severe oligospermia to azoospermia; the remaining two also had reduced sperm counts.

A previous report on the oral effect of levo-norgestrel in men found no systematic change in sperm counts probably because the dose was only 100 μg daily (Fotherby et al. 1972). There are reports on the use of oral norethisterone, norethindrone and norgestriene in men where the doses used are high (7 to 25 fold) compared to that used in female oral contraceptives (Brenner et al. 1975; Johansson & Nygren 1973; Coutinho & Melo 1973). However, no changes in sperm count were reported. Ulstein et al. (1975) observed sperm counts < 5 × 10⁶/ml (7 volunteers) during treatment with oral danazol combined with testosterone oenanthate (200 mg monthly) but the dose of gestagen was a thousand fold higher (600 mg daily) than in this study.

Parenteral administration of gestagens combined with parenteral androgens caused oligospermia and azoospermia (Melo & Coutinho 1977; Alvarez-Sanchez et al. 1977; Frick et al. 1977; Brenner et al. 1975). Testosterone oenanthate alone in weekly doses of 250 mg suppressed sperm counts below 3 × 10⁶/ml (Mauss et al. 1975). Steinberger et al. (1978) observed sperm counts at essentially azoospermic levels with testosterone oenanthate 200 mg injected every 10 to 12 days, but not every 3 weeks.

In our study a similar increase in body weight was observed (group 2) as in other studies (Melo & Coutinho 1977; Alvarez-Sanchez et al. 1977) but no serious side effects were observed. Only small changes in sperm count, percentage abnormal spermatozoa, s-FSH and s-testosterone were observed when the recovery phase values were compared with those of the placebo period. Such differences may be due to seasonal changes of unknown etiology.

In conclusion, the doses of levo-norgestrel and testosterone oenanthate used in our study for six months depressed sperm count in men. The doses at which this hormone combination cause clinical sterility remains to be determined.

Appendix

The measurements of the following parameters were analysed statistically: Sperm count, percentage of abnormal spermatozoa, s-testosterone, s-LH, and s-FSH. For each of these parameters, and for every volunteer, the values in each of the three phases (placebo, treatment, and recovery) the measurements were considered as being random samples from the same normally distributed population. Due to the length of spermatogenesis, the values of sperm counts and of the percentage of abnormal spermatozoa obtained during the first 75 days of the treatment and the recovery phases were not used in the analysis.

As a consequence of the model used, the measurements were averaged over time in each of the three phases for each person and for each parameter under study.

Tests of equality of the placebo and the recovery levels were performed by the Student's t-test, supplemented with the Welch (1937) modification, in the cases of variance-inhomogeneities. In order to detect tendencies which are common to the popu-
lation of volunteers, the fractions of the tests are depicted in one diagram, Fig. 3. (The fraction, f, of a test is the value of the test's distribution function taken at the observed point. The P-value is found as twice the smallest of the values f, and 1-f for a two-sided test). The interpretation of these diagrams is as follows: If no general tendencies are present, the points should vary randomly between 0 and 1. If the points huddle together in the ends of the interval, there is an indication of a general tendency of increase or decrease which may well be insignificant at the individual volunteers.

Tests of equality of the no treatment and the treatment levels of s-testosterone, s-LH, and s-FSH were again performed by the Welch test.

The values of s-testosterone were obtained from two different laboratories. Except for a few measurements, the values in a specific phase all stem from the same laboratory, and thus differences between the placebo and the recovery phases are due to either treatment effects or to the change of laboratory. Information from the laboratories seem to indicate that the two laboratories measure with different standard deviations but with the same mean. In the present material, the standard deviation is significant in the recovery phase as compared to the placebo phase, but it has not been possible to see whether this increase is due to the treatment or to the change of laboratory.

Acknowledgments

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**Fig. 3.** Fractions of the tests for equality of the placebo and the recovery levels of sperm count, percentage abnormal spermatozoa, s-testosterone, s-LH, and s-FSH.

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Fractions for tests of sperm count

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Fractions for tests of S-Testosterone

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Fractions for tests of S-FSH

* Values from volunteers in group 1
+ Values from volunteers in group 2

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References


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