

A Lower Dosage Levonorgestrel and Testosterone Combination Effectively Suppresses Spermatogenesis and Circulating Gonadotropin Levels with Fewer Metabolic Effects Than Higher Dosage Combinations

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ABSTRACT: Studies using exogenous high-dosage testosterone (T) or a combination regimen of physiologic T plus high-dosage levonorgestrel (LNG) administration in normal men have shown that oligozoospermia (<3 million/mL) or azoospermia can be achieved in the majority of the men. However, these hormonal regimens have been associated with significant weight gain and suppression of serum high-density lipoprotein (HDL) cholesterol levels. We hypothesized that a combination of physiologic exogenous testosterone and lower dosage LNG would result in uniform severe oligozoospermia or azoospermia in normal men but would cause fewer adverse metabolic side effects. We conducted a randomized, placebo-controlled, single-blind trial comparing 6 months of T enanthate (100 mg IM, weekly) plus LNG, 125 µg by mouth, daily (LNG 125; $n = 18$) or LNG, 250 µg by mouth, daily (LNG 250; $n = 18$) and compared these regimens with our previous study of the same dosage of T enanthate combined with placebo LNG (LNG 0; $n = 18$) or with 500 mg of LNG (LNG = 500; $n = 18$). All three combination regimens of T enanthate and LNG suppressed spermatogenesis more rapidly and resulted in significantly more uniform severe oligozoospermia (<1 million/mL) than the T-alone regimen. Severe oligozoospermia was achieved in 89% of the LNG 125, 89% of the LNG 250, and 78% of the LNG 500 groups, respectively, versus 56% of the men in LNG 0 ($P < 0.05$ for the combination groups vs. LNG 0), but there

were no significant differences between the combination regimens ($P = NS$). All four groups gained significant weight compared with their baselines, although the gain tended to be greater as the dosage of LNG increased (2.0 ± 0.9 , 2.9 ± 1.1 , 3.6 ± 1.0 , and 5.4 ± 1.0 kg gained, compared with baseline in the LNG 0, 125, 250, and 500 groups respectively; $P < 0.05$ compared with baseline). Serum levels of HDL cholesterol decreased in all of the groups, but the effect was larger as the dosage of LNG increased ($4 \pm 4\%$ vs. $13 \pm 4\%$, $20 \pm 3\%$, and $22 \pm 4\%$ decrease in HDL levels from baseline in the LNG 0, LNG 125, LNG 250, and LNG 500 groups respectively; $P = 0.06$ for LNG 125 compared with LNG 0, and $P < 0.05$ for LNG 250 and LNG 500 compared with LNG 0). We conclude that 1) the combination of physiologic exogenous T enanthate and LNG suppresses spermatogenesis more effectively than T enanthate alone and that 2) the combination regimen of T enanthate plus lower dosage LNG suppresses sperm production comparably to T enanthate plus higher dosage LNG, while causing less weight gain and HDL cholesterol suppression. A combination regimen of physiologic testosterone plus a low dosage of levonorgestrel offers great promise as a safe and effective male contraceptive regimen.

Key words: Male contraception, spermatogenesis, testosterone, levonorgestrel, gonadotropins.

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The administration of supraphysiologic dosages (200 mg weekly) of testosterone (T) can markedly suppress circulating gonadotropins and induce oligozoospermia (<3 million spermatozoa/mL), severe oligozoospermia (<1 million spermatozoa/mL), or azoospermia (Paulsen et al, 1982; World Health Organization Task Force, 1990; Cummings and Bremner, 1994; World Health Organization Task Force, 1996). In normal men, the suppression of sperm counts by exogenous high-dosage T to below 3 million spermatozoa/

mL has been shown to provide effective contraception, and suppression to below 1 million spermatozoa/mL is even more effective (World Health Organization Task Force, 1996). However, supraphysiologic T does not uniformly suppress spermatogenesis and is associated with significant weight gain and suppression of high-density lipoprotein cholesterol (HDL) levels (Cummings and Bremner, 1994; Merigiola et al, 1995).

Because exogenous progestins are known to suppress circulating gonadotropins and might synergistically suppress spermatogenesis when combined with exogenous T, various combination regimens of T plus a progestin such as levonorgestrel (LNG) and cyproterone acetate have been studied as potential male hormonal contraceptives (Cummings and Bremner, 1994). We previously demonstrated that the combination of a more physiologic dosage

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of exogenous T (100 mg, IM, weekly) and LNG (500 µg by mouth, daily) suppressed circulating gonadotropins and spermatogenesis more effectively and rapidly than the same dosage of T alone (Bebb et al, 1992). Although 94% of the normal men became oligoazoospermic to less than 3 million sperm/mL on the combination of T plus high-dosage LNG, compared with only 61% of the men on T alone, the men receiving combination therapy gained significantly more weight, and their HDL levels decreased more than those of the men who received T alone.

In the present study, we tested the hypothesis that reduction of the LNG dosage used in combination with T would uniformly induce severe oligoazoospermia or azoospermia in normal men. We further hypothesized that this treatment would result in fewer metabolic adverse effects than did T plus high-dosage LNG.

Methods

Subjects

Normal men, ages 20–46 years, were recruited by advertisement on bulletin boards, in newspapers, and on the radio. Inclusion criteria were a normal medical history and physical examination; the absence of current use of prescription medications; normal basal serum T, FSH, and LH levels; three successive normal seminal fluid analyses (sperm count greater than 20 million/ml and motility and oval forms greater than 50% after 48 hours of ejaculatory abstinence) on specimens collected at 2-week intervals; and normal values on routine hematology, blood chemistry, urinalysis, and fasting lipid profiles. Exclusion criteria included any history of significant acute or chronic medical illness, alcohol abuse, anabolic steroid use, or reproductive dysfunction.

After screening 104 men, 24 were excluded from entering the treatment phase of the study. Of these, eight were excluded for personal reasons, seven for low baseline sperm counts, four for hyperlipidemia, one for persistently abnormal liver function tests, one for persistent hematuria and hypertension, one for a history of significant psychiatric illness, and two for moving from the greater Seattle area before completing the control period.

Experimental Design

After meeting the screening criteria, subjects were entered into a 3-month control period during which monthly baseline serum hormone levels and biweekly seminal fluid analyses were performed while no hormones were administered. At the end of the control period, each subject was randomized in a single-blind, balanced design to one of two groups: 6 months each of T enanthate, 100 mg IM weekly, plus either LNG, 125 µg by mouth, daily (LNG 125) or LNG, 250 µg by mouth, daily (LNG 250). We compared them with our previously reported study of normal men who were randomized in an identical protocol to receive T enanthate, 100 mg IM weekly, plus either placebo LNG by mouth daily (LNG 0) or LNG, 500 µg by mouth, daily (LNG 500) (Bebb et al, 1992). No subject was enrolled in more than one of the four groups.

Following the treatment period, all subjects entered a recovery period that extended until two consecutive sperm concentrations were within the individual's control range. The study was approved by the University of Washington Human Subjects Review Committee and the Veterans Affairs Puget Sound Health Care System Research and Development Committee.

Measurements

Monthly interviews and physical examinations were performed by physicians throughout the study. Seminal fluid analysis was performed every 2 weeks on samples obtained by masturbation after 48 hours of abstinence. Monthly blood samples were obtained for measurement of serum T, FSH, and LH levels. During treatment, blood samples were drawn immediately prior to administration of T. Monthly nadir and peak serum LNG levels were measured prior to and 1 hour after LNG ingestion. Monthly urinalysis and measurement of blood counts and serum electrolytes, creatinine and hepatic function tests were performed. A lipid panel (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides levels) was performed on serum obtained following a 12-hour fast. This lipid panel was done once during the control period, once after the third and sixth months of the treatment period, and once during the recovery period. In the LNG 125 and LNG 250 groups, the lipid panels also included a determination of apolipoprotein A-I (apoA-I) levels.

Hormone and Lipid Assays—Serum testosterone levels were measured by radioimmunoassay with reagents from the World Health Organization (WHO)-matched reagent program by methods previously described (Matsumoto et al, 1983). The assay sensitivity was 0.017 nmol/L; the intra-assay and interassay variabilities were 5.1% and 9.8%, respectively. Serum FSH and LH levels were measured in the Delfia immunofluorometric assay (Wallac Oy, Turku, Finland). The sensitivities of the Delfia assays were <0.016 IU/L and <0.018 IU/L for FSH and LH, respectively. Intra-assay coefficients of variation were 2.3% for FSH and 2.8% for LH. Interassay coefficients of variation were 4.0% for FSH and 5.0% for LH. LNG levels were assayed by radioimmunoassay at the California Regional Primate Center (courtesy of Dr. Lisa Laughlin, University of California, Davis) (Ahsan et al, 1988). All samples from each individual were measured in the same hormone assays in order to avoid interassay variability. As an additional safeguard against assay variability, representative samples from individuals in each of the four groups were also measured in the same hormone assays. Hormone sensitivities were determined by the first point discernible from zero on standard curves.

Lipid analyses were performed on freshly prepared (unfrozen) plasma samples that were processed by centrifuge within hours of collection. Total plasma cholesterol and triglycerides were measured enzymatically at the Northwest Lipid Research Clinic (Seattle, Washington) on the Abbott Spectrum multichromatic instrument (Abbott Laboratories, North Chicago, Illinois), cholesterol was measured by a Trinder-type method, and triglycerides were measured by an ultraviolet light method (Warnick et al, 1982). HDL cholesterol was separated from plasma by precipitation with dextran sulfate-magnesium (Warnick, 1986). LDL

Table 1. Baseline clinical and biochemical parameters (mean \pm SEM)

Parameter	LNG 0	LNG 125	LNG 250	LNG 500
Age (years)	30 \pm 1.6	30.4 \pm 1.7	30.1 \pm 1.9	28.6 \pm 1.6
Weight (kg)	86.9 \pm 2.63	82.4 \pm 4.55	78.8 \pm 3.85	81 \pm 2.73
Testosterone (nmol/L)	26.3 \pm 1.7**	15.7 \pm 1.52	15.9 \pm 1	23.8 \pm 1.7**
Luteinizing hormone (IU/L)	4.1 \pm 0.42*	2.7 \pm 0.27	2.76 \pm 0.28	3.26 \pm 0.32
Follicle-stimulating hormone (IU/L)	3.32 \pm 0.44	2.5 \pm 0.27	3.15 \pm 0.4	2.7 \pm 0.3
Total cholesterol (mg/dl)	164 \pm 7.5	169 \pm 9.03	176 \pm 8.33	177 \pm 6.3
High-density lipoprotein (mg/dl)	49.1 \pm 2.8	48.4 \pm 3.5	46.8 \pm 3.1	50.6 \pm 2.9
ApoA1 (mg/dl)	NA	136 \pm 6.74	134 \pm 9.05	NA
Low-density lipoprotein (mg/dl)	101 \pm 6.3	104 \pm 8	108 \pm 6.8	112 \pm 7.6
Triglycerides (mg/dl)	68.5 \pm 12.1	84.4 \pm 11	105 \pm 10.5	73.2 \pm 6.9
Hematocrit (%)	45.7 \pm 0.65	43.8 \pm 0.54	44.6 \pm 0.59	46.2 \pm 0.84
Creatinine (mg/dl)	1.08 \pm 0.04	0.99 \pm 0.04	1.06 \pm 0.04	1.08 \pm 0.03
Serum glutamic-oxaloacetic transaminase (U/L)	25.2 \pm 2.5	27.2 \pm 1.38	28.8 \pm 1.8	23.9 \pm 2.5
Serum glutamic-pyruvic transaminase (U/L)	28.8 \pm 5.3	24.5 \pm 2.2	24.4 \pm 3.5	27.9 \pm 4.7
Serum γ -glutamyltransferase (U/L)	28.5 \pm 10.3	23 \pm 2.3	21.4 \pm 2.44	19.3 \pm 2.8
Alkaline phosphatase (U/L)	NA	71.2 \pm 3.53	69.9 \pm 3.69	NA

LNG indicates levonorgestrel; NA, not available.

* $P < 0.05$ compared to all other groups.

** $P < 0.05$ compared to LNG 125 and LNG 250.

was calculated indirectly by the Friedewald equation (Warnick, 1986).

Sperm Counts—Azoospermia was defined as two or more consecutive sperm counts of zero, and severe oligoazoospermia was defined as two or more consecutive counts below one million spermatozoa/mL, whereas oligoazoospermia was defined as two or more consecutive counts below three million spermatozoa/mL. Sperm count recovery was defined as the first of three normal sperm counts (>20 million/mL) with at least one value equal to the subject's mean baseline count. Sperm counts were determined by Coulter counter (Coulter Electronics, Inc., Hialeah, Florida), and concentrations below 15 million/mL were confirmed by direct determination using a hemocytometer (Gordon et al, 1965; Bremner et al, 1981). Sperm motility assessment was performed according to the WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction (WHO, 1992).

Statistical Analysis—The groups were compared by ANOVA with a Duncan's post hoc test. Because there were baseline differences in the T and LH levels between the four groups, the hormone data were also analyzed by analysis of covariance (ANCOVA), but the results yielded by the ANCOVA did not differ from those by the ANOVA. The analyses for oligoazoospermia, severe oligoazoospermia, and azoospermia were performed by a Kaplan-Meier curve with a log rank analysis and chi square analysis.

Results

Baseline Characteristics

The four groups were similar in all of their baseline characteristics, except for significant differences in T and LH levels (Table 1). The baseline T levels were significantly

higher in the LNG 0 and 500 groups, compared with the LNG 125 and 250 groups ($P < 0.05$), but they were not significantly different between the LNG 0 and 500 groups nor between the LNG 125 and LNG 250 groups ($P = NS$). The baseline LH levels were significantly higher in the LNG 0 groups than in the other three groups ($P < 0.05$).

69 of the 72 subjects completed the full 6 months of treatment. One subject in the LNG 0 and two subjects in the LNG 250 group dropped out of the study prior to completion. The LNG 0 subject, who stopped for personal reasons, had become severely oligoazoospermic after 5 months. One of the LNG 250 subjects dropped out of the study after 4 months of treatment because of depression, and the other LNG 250 subject stopped after 4 months of treatment because of weight gain and acne. Both of the LNG 250 subjects had become azoospermic. All three subjects were included in the analysis of response to treatment.

Response to Treatment

Sperm Counts—The four groups were analyzed according to whether they achieved oligoazoospermia (<3 million sperm/cc) or severe oligoazoospermia (<1 million sperm/cc) or azoospermia. All three of the groups receiving a combination treatment of LNG and T achieved oligoazoospermia, severe oligoazoospermia, and azoospermia significantly more uniformly and rapidly than did those on the T-alone regimen (Table 2, Figures 1 and 2). For all three measures of spermatogenic suppression—oligoazoospermia, severe oligoazoospermia, and azoospermia—identically significant differences were seen com-

Table 2. Effectiveness of suppressing sperm counts to levels associated with effective male contraception†

Sperm count	Percentage (n)			
	LNG 0	LNG 125	LNG 250	LNG 500
Oligozoospermia (<3 million sperm/ml)	61 (11)*	94 (17)	89 (16)	94 (17)
Severe oligozoospermia (<1 million sperm/ml)	56 (10)*	89 (16)	89 (16)	78 (14)
Azoospermia	33 (6)*	61 (11)	78 (14)	67 (12)

LNG indicates levonorgestrel.

† The sample size was 18 for all groups studied.

* $P < 0.05$ compared to all other groups.

pared with the T-alone regimen by 10 weeks (results for severe oligozoospermia are shown in Fig. 1). However, there were no significant differences between the three groups receiving combination T plus LNG therapy in percentage nor rapidity of oligozoospermia, severe oligozoospermia, or azoospermia achieved during the treatment period ($P = NS$). Sperm counts returned to baseline levels in the recovery period.

Hormones—There were no differences in testosterone levels during the treatment period in the four groups (26.4 ± 1.8 , 21.7 ± 2.1 , 17.7 ± 1 , 21.1 ± 1.7 nmol/L in the LNG 0, LNG 125, LNG 250, and LNG 500 groups respectively; $P = NS$). All four groups had significant suppression of FSH and LH levels during the treatment period compared with baseline ($P < 0.05$), but both FSH and LH levels were significantly more suppressed during treatment in all three groups of men receiving T plus LNG compared with the T-alone group ($P < 0.05$; Figure 3). Serum levels of T, FSH, and LH all recovered to baseline levels during the recovery period ($P = NS$ compared with baseline for all four groups).

Nadir and peak LNG levels during the treatment period increased as the LNG dose increased between the four

groups (Figure 4). Nadir levels were measured from sera drawn just prior to LNG administration, and peak levels were defined as the level of LNG 1 hour after administration of LNG.

Lipids—Total cholesterol levels did not change significantly during treatment in the four groups (percent change from baseline: (+) 4.7 ± 3.5 , (-) 6.0 ± 3.3 , (-) 2.0 ± 3.2 , and (-) $6.7 \pm 2.2\%$ in the LNG 0, LNG 125, LNG 250, and LNG 500 groups, respectively; $P = NS$ from baseline and between groups). LDL cholesterol and triglyceride levels did not change significantly from baseline in any of the four groups ($P = NS$). HDL cholesterol levels decreased in all four groups studied, but the decrease in HDL was greater as the dosage LNG increased (% change from baseline: (-) 3.7 ± 4.0 , (-) 13.4 ± 3.7 , (-) 20.2 ± 2.7 , (-) $21.7 \pm 3.6\%$; $P = 0.06$ for LNG 125, and $P < 0.05$ for LNG 250 and 500 compared with LNG 0; Figure 5). The apoA-I levels decreased in both the LNG 125 and LNG 250 groups, but apoA-I decreased significantly more in the LNG 250 group (percent decrease from baseline was as follows: 10.4 ± 3.4 vs. 18.6 ± 1.5 ; $P < 0.05$ between groups). All lipoprotein profiles returned to baseline during the recovery period in all four

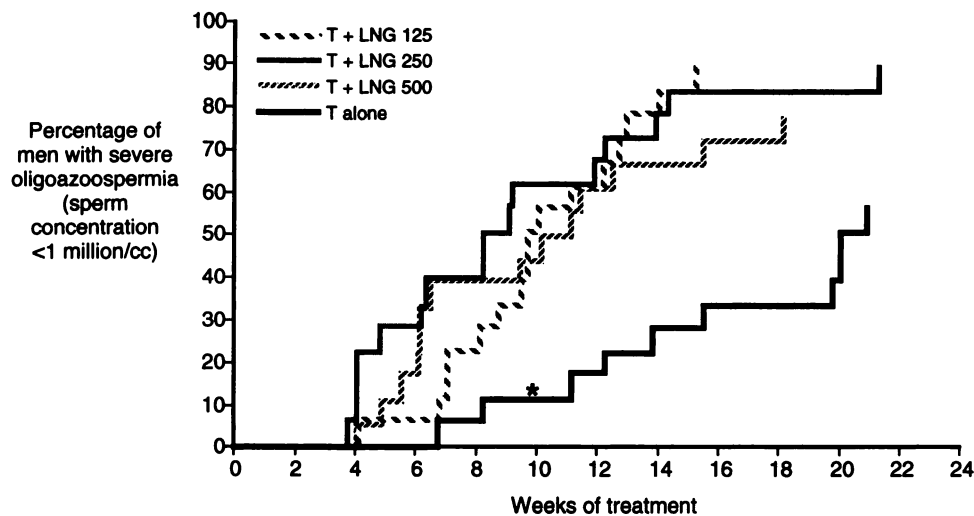


FIG. 1. Rapidity and uniformity of suppression to severe oligozoospermia (<1 million spermatazoa/mL) in normal men administered 6 months of T alone (100 mg/weekly), compared with three groups treated with T (100 mg/weekly) plus varying dosages of LNG. The combination of T plus low- or high-dosage LNG induced severe oligozoospermia more rapidly and uniformly than T alone. $P < 0.05$ compared with all other groups by week 10.

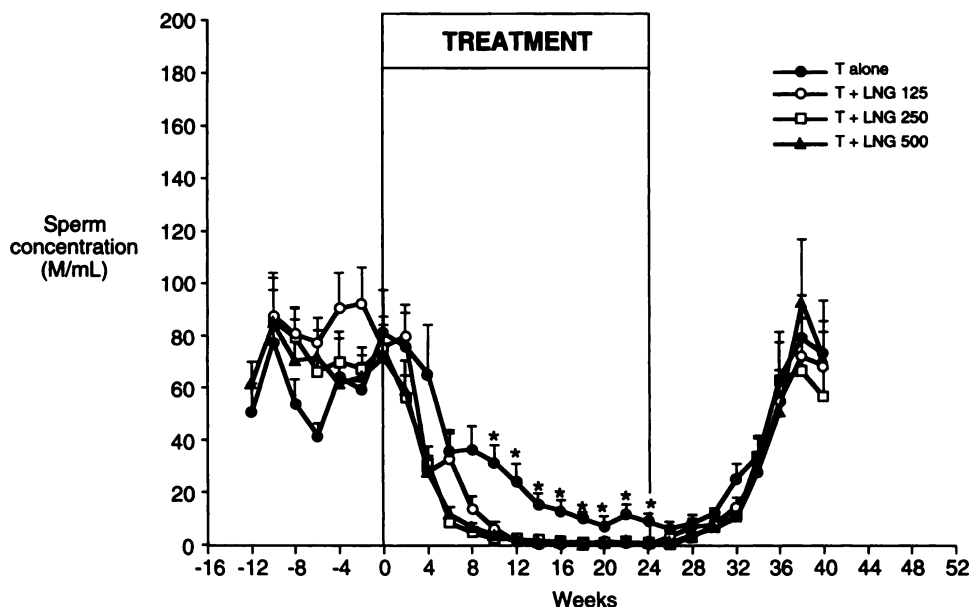


FIG. 2. Rapidity of suppression of sperm concentration in normal men administered 6 months of T alone (100 mg/weekly), compared with three groups treated with T plus varying dosages of LNG. The combination of T plus low- or high-dosage LNG suppressed sperm concentrations rapidly and significantly more than T alone. $P < 0.05$ compared with all other groups by week 10

groups ($P = \text{NS}$ compared with baseline for all lipid parameters in the four groups).

Hematologic Profiles, Blood Chemistries, and Urinalyses—Hematologic profiles, blood chemistries including bilirubin, liver transaminases, and alkaline phosphatase remained normal and without significant change from baseline during the treatment and recovery periods. No subject developed changes in urinalysis, including pyuria nor hematuria, during the study.

Weight Gain, Gynecomastia, and Acne—All four groups gained weight during treatment, but the LNG 0 and 125 groups gained the least (weight change compared with baseline; $P = \text{NS}$; Figure 5). Body weight decreased

to baseline during the recovery period. Six (33%) of the LNG 0, 14 (78%) of the LNG 125, 8 (44%) of the LNG 250, and 12 (66%) of the LNG 500 groups developed intermittent mild acne or a slight worsening of their baseline acne during the treatment period. One man in each of the LNG 0 and 125 groups had his baseline mild acne worsen enough to warrant treatment with oral doxycycline, and two other subjects who were both in the LNG 125 group developed transient, mildly tender, gynecomastia. Acne and gynecomastia were self-limited and resolved to baseline during the recovery period.

Discussion

In this study of the effects of exogenous T and lower dosage LNG, we determined that reducing the dosage of LNG from 500 μg daily to 125 or 250 μg daily still resulted in uniformly effective suppression of circulating gonadotropins and sperm concentrations. The percentage of men who achieved oligozoospermia (<3 million/cc), severe oligozoospermia (<1 million/cc) or azoospermia in the two combination regimens using exogenous testosterone (100 mg, IM, weekly) and the lower dosages of LNG was similar to the percentage achieved in our previously reported study of physiologic T and high-dosage LNG (Bebb et al, 1992). Furthermore, while the T plus lower dosage LNG combinations were as effective in suppressing circulating gonadotropins and spermatogenesis, they caused fewer androgenic side effects, such as weight

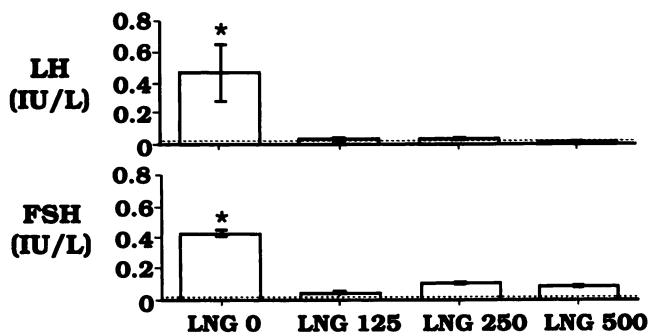


FIG. 3. Suppression of circulating gonadotropin levels (mean \pm SEM) in normal men administered 6 months of T alone (100 mg/weekly) compared with three groups treated with T (100 mg/weekly) plus varying dosages of LNG (month 5 or 6 of treatment). The combination of T plus low- or high-dosage LNG suppressed circulating gonadotropin levels significantly more than T alone. Values are mean \pm SEM ($n = 18$ for all groups). Dashed line signifies lower limit of assay detectability. * $P < 0.05$ compared with all other groups

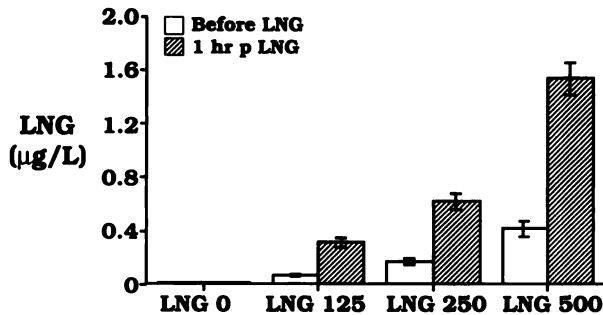


FIG. 4. LNG levels (mean \pm SEM) before and 1 hour after LNG administration in normal men administered 6 months of T alone (100 mg/weekly) compared with three groups treated with T (100 mg/weekly) plus varying dosages of LNG (month 5 or 6 of treatment). LNG levels increased proportionately to the dosage of LNG administered. Values are mean \pm SEM ($n = 18$ for all groups).

gain and HDL suppression, than the T plus higher dosage LNG regimen.

All three regimens of T plus LNG were much more effective than physiologic or supraphysiologic T administration alone in rapidly suppressing spermatogenesis to levels associated with effective contraception. In the WHO efficacy trial of the contraceptive effectiveness of high-dosage testosterone (200 mg/wk) in normal men, the pregnancy rates per 100 person-years were 0%, 2%, and 4% in the men whose sperm counts suppressed to azoospermia, ≤ 1 million/mL, ≤ 3 million/mL, respectively, and these failure rates were very comparable to rates of reversible female methods such as injectable and oral hormonal contraceptives (0.3 and 3 per 100 person-years) and the most common reversible male method, the condom, (12 per 100 person years), and these findings suggest that the combinations of T plus LNG used in our study would provide very effective reversible contraception in normal men (World Health Organization Task Force, 1996).

Some baseline differences existed between the groups of men, but these baseline differences do not appear to alter the conclusion that T plus low-dosage LNG is as effective as T plus high-dosage LNG and is more effective than T alone in suppression of gonadotropins and spermatogenesis. Although the T-alone treatment group had a higher mean baseline LH level and the T plus low-dosage LNG treatment groups had lower baseline T levels than the groups randomized to treatments of T alone or to T plus high-dosage LNG, Sertoli cell function and spermatogenesis as reflected by baseline FSH levels, and sperm counts were similar in all four groups. Furthermore, statistical analysis by ANCOVA that adjusted for baseline differences still yielded similar results.

Side effects of these hormonal contraceptive regimens were primarily androgenic effects. The T alone and T plus low-dosage LNG groups had less significant metabolic side effects during treatment than did the T plus high-

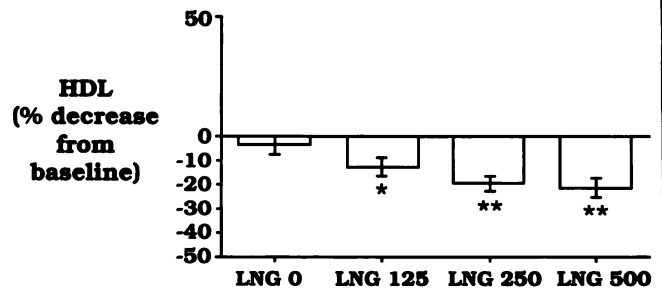


FIG. 5. Suppression of HDL levels (percentage change from baseline) in normal men administered 6 months of T alone (100 mg/weekly) compared with three groups treated with T (100 mg/weekly) plus varying dosages of LNG (month 5 or 6 of treatment). HDL levels decreased more in the groups receiving T plus LNG than in the T-alone group, but the decrease was greatest in the groups receiving the highest dosages of LNG. Values are mean \pm SEM ($n = 18$ for all groups). * $P = 0.06$ compared with LNG 0. ** $P < 0.05$ compared with LNG 0.

dosage LNG treatment group. All four hormone regimens suppressed HDL cholesterol levels without significantly changing low-density lipoprotein nor triglyceride levels, but the HDL cholesterol suppression was greatest in the T plus high-dosage LNG group. Suppression of circulating HDL cholesterol is undesirable because epidemiologic studies suggest that high HDL cholesterol levels are associated with a favorable cardiovascular risk profile, whereas low HDL cholesterol levels are associated with increased risk of coronary artery disease (NIH Consensus Development Panel, 1993). It appears likely that the suppression of HDL cholesterol from these hormone regimens is related to the total androgenic effect of T and LNG. A small study using a combination of the same dosage of T as our study and cyproterone acetate, an antiandrogenic progestin, did not cause HDL suppression in normal men (Merrigiola et al, 1996). Therefore, reduction of the testosterone or LNG dosages used in a combination contraceptive regimen might result in less androgenic suppression of HDL.

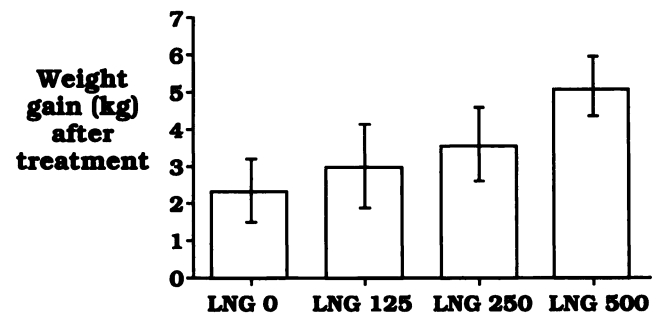


FIG. 6. Weight gain (change in kilograms from baseline) in normal men administered 6 months of T alone (100 mg/weekly) compared with three groups treated with T (100 mg/weekly) plus varying dosages of LNG (month 5 or 6 of treatment). Weight gain was greater in the groups receiving T plus LNG than in the T-alone group, but the weight gain was largest in the groups receiving the highest dosages of LNG. Values are mean \pm SEM ($n = 18$ for all groups).

Weight gain occurred during treatment in all four groups studied, but there was less weight gain in the T alone and T plus low-dosage LNG groups than the T plus high-dosage LNG group. Thus, it is likely that weight gain is also proportional to the increased androgenic effect from the higher dosages of LNG. Although weight gain is generally undesirable in normal healthy adults, it is possible that the weight gain was associated with a relatively greater increase in lean mass than fat mass, for androgens are known to increase lean mass. Exogenous high-dosage T administration in normal men and androgen replacement therapy in hypogonadal men have been shown to increase muscle strength and fat-free mass (Bhasin et al, 1996; Katznelson et al, 1996; Sih et al, 1997).

All four regimens were generally well tolerated as few other clinically significant side effects occurred, and only two subjects, both in the LNG 250 group, failed to complete the study because of symptoms potentially attributable to the hormone administration. One became depressed, and the other stopped because of weight gain (13 lb) and worsening of baseline acne. Complete blood chemistries, blood counts, and urinalyses remained normal and showed no significant changes during treatment in all four groups. Although many of the men developed mild acne or slight worsening of baseline acne during the treatment period, the acne was generally self-limited, and only two subjects required medical therapy for acne. Two subjects in the LNG 125 group developed gynecomastia. During the recovery period, acne, weight, sperm counts, and hormone levels returned to normal.

Nadir and peak LNG levels increased in a dose-dependent fashion during the treatment period. Mean and peak LNG levels measured in the T plus low-dosage and high-dosage LNG groups were comparable to levels achieved with LNG implants (Norplant) used for contraception in women (Fotherby, 1995). Therefore, it is possible that a long-acting form of LNG, such as LNG butanoate, could be co-administered parenterally with a long-acting testosterone ester, such as testosterone buciclate, in an effective male contraceptive regimen (Behre et al, 1995).

Physiologic exogenous testosterone and LNG act synergistically to suppress circulating gonadotropin levels and spermatogenesis. The combination induces a much more rapid and more uniform severe oligozoospermia than exogenous testosterone alone. The combination of T plus a low-dosage LNG resulted in a similarly effective suppression of spermatogenesis as T plus high-dosage LNG but with less significant androgenic metabolic side effects such as HDL suppression and weight gain. A combination hormone contraceptive regimen of T plus LNG, which synergistically suppressed spermatogenesis but with little weight gain or HDL suppression, might be achieved by reducing the total androgenic effect. Such a

regimen, which could include a lower dosage of T or LNG than we used, might be an effective, safe, and reversible male contraceptive.

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