

Combined Administration of Levonorgestrel and Testosterone Induces More Rapid and Effective Suppression of Spermatogenesis Than Testosterone Alone: A Promising Male Contraceptive Approach*

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ABSTRACT

Studies using high dose testosterone (T) administration in normal men as a male contraceptive have resulted in azoospermia rates of only 50–70%. Previous studies of T and progestogen combinations have shown comparable rates of azoospermia, but have been uncontrolled or used T in doses less than that associated with maximal suppression of sperm production. We conducted a randomized, placebo-controlled, single blind trial comparing 6 months of T enanthate administration (100 mg, im, weekly) with the same dose of T enanthate in conjunction with the progestogen levonorgestrel (LNG; 500 µg, orally, daily) in 36 normal men, aged 20–42 yr (n = 18 in each group). The primary end points were induction of azoospermia or severe oligospermia (<3 million sperm/mL).

The combination of T plus LNG was much more effective in suppressing sperm production than T alone. Sixty-seven percent of the T plus LNG group (12 of 18) and 33% of the T alone group (6 of 18) achieved azoospermia by 6 months (P = 0.06). Severe oligospermia or

azoospermia developed in 94% of the T plus LNG (17 of 18) group compared to 61% of the T alone group (11 of 18; P < 0.05). T plus LNG also suppressed sperm production more rapidly than T alone. Time to azoospermia was 9.9 ± 1.0 vs. 15.3 ± 1.9 weeks in the T plus LNG and T alone groups, respectively (mean ± SEM; P < 0.05).

Serum high density lipoprotein cholesterol decreased 21.7 ± 3.6% in men given T plus LNG (P < 0.05), compared to only a 1.8 ± 3.8% decrease in men in the T alone group. Average weight gain was 5.3 ± 0.8 kg in the T plus LNG group and 2.3 ± 0.9 kg in the T alone group (P < 0.05). Acne and increase in hemoglobin were similar in the two groups.

We conclude that combination hormonal therapy with T plus a progestogen might offer a reversible male contraceptive approach with a more rapid onset of action and more reliable induction of both azoospermia and severe oligospermia than T alone. (*J Clin Endocrinol Metab* 81: 757–762, 1996)

HORMONAL contraceptive development for men has lagged far behind contraceptive developments for women. Since its invention by Gabriello Fallopio in 1564, the condom has remained the only effective reversible male contraceptive available (1). Increasing concerns regarding global overpopulation with resulting socioeconomic and environmental problems as well as surveys showing that the majority of men wish to participate in family planning and would use a safe, rapidly effective, reliable, and fully reversible male contraceptive have stimulated research in this area (2–4).

Human spermatogenesis is dependent upon the actions of both LH and FSH (5–7). Methods of hormonal contraception

for men have, therefore, centered on attempts to suppress gonadotropins. Hormonal regimens have included testosterone (T) alone and in combination with progestogens, antiandrogens, and GnRH agonists and antagonists (2, 8–10). Previous studies of T alone as a male contraceptive used high dosages, (e.g. 200 mg T enanthate/week, im), but resulted in azoospermia (zero sperm count) in only 50–70% of normal men (2, 8, 9). Although high dosages of T have been tolerated well, there has been concern regarding suppression of high density lipoprotein (HDL) cholesterol levels (11) and possible effects on the prostate gland (12).

T in combination with progestational agents produced rates of azoospermia comparable to those obtained with high dose T alone (9, 13, 14). However, previous studies using combinations of T with a progestogen have been nonrandomized, used historical controls, or used dose schedules of T insufficient to induce maximal suppression of sperm production (9, 13, 14).

In this present study, we tested the hypothesis that the combination of the progestogen levonorgestrel (LNG) plus T would suppress sperm production more effectively than T alone. The T dose in this study (100 mg T enanthate, im, weekly) has been demonstrated to suppress sperm production (15) without reducing HDL cholesterol levels (16). LNG

Received April 19, 1995. Revision received June 14, 1995. Rerevision received September 7, 1995. Accepted September 22, 1995.

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* This work was supported by CONRAD CSA-92-102, the Mellon Foundation, NIH Grants P50-HD-12629 and RR-37, and Veterans Affairs research funds.

† Supported by a fellowship grant from the British Columbia Health Research Foundation.

‡ Andrew W. Mellon Foundation Research Fellow.

was used as the progestogen because it is one of the most potent progestogens available to suppress gonadotropins, and extensive clinical experience exists in women using both oral and implantable (Norplant, Wyeth-Ayerst Laboratories, Philadelphia, PA) contraceptives (17, 18). In addition, LNG serum assays are available to monitor treatment (19). Finally, long acting preparations of androgens and progestogens that are either currently available or being developed would provide more practical contraception if the combination proved to be effective and safe (18, 20).

Subjects and Methods

Subjects

Normal men, aged 20–42 yr, were recruited by advertisement on bulletin boards, in newspapers, and on the radio. Inclusion criteria included a normal medical history and physical examination; the absence of current use of prescription medications; normal basal serum LH, FSH, and T levels; three successive normal seminal fluid analyses (sperm count >20 million/mL and motility and oval forms >50% after 48 h of abstinence) on specimens collected at 2-week intervals; and normal values on routine hematology, blood chemistry, urinalysis, and fasting lipid profile [total cholesterol (C), <6.22 mmol/L (240 mg/dL); HDL-C, >0.91 mmol/L (35 mg/dL); low density lipoprotein cholesterol (LDL-C), <4.14 mmol/L (160 mg/dL); triglycerides, <2.83 mmol/L (250 mg/dL)]. Exclusion criteria included any history of significant acute or chronic medical illness, alcohol abuse, anabolic steroid use, or reproductive dysfunction.

Of 48 men screened, 8 were excluded, and 2 dropped out for personal reasons before receiving any active drug. Of those excluded, 4 men had low baseline sperm counts, 3 had elevated baseline lipid levels, and 1 had a history of a major psychiatric illness. Of the remaining 38 subjects, 20 were randomized to the T plus LNG group and 18 to the T alone group. Two subjects in the T plus LNG group were removed from the study after 2 months of active treatment, 1 for protocol violations and the other due to nondrug-related angioedema (rechallenging the subject subsequently with LNG and T enanthate did not reproduce the angioedema).

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 given. At the end of the control period, each subject was randomized in a single blind, balanced design to receive either LNG (500 µg/day, orally) plus T enanthate (100 mg/week, im) or placebo orally daily plus T enanthate (100 mg/week, im). This active treatment phase lasted 6 months. All injections were given by the investigators or their assistants. Logbooks were kept to monitor injections and weekly pill counts. Subjects who missed more than one injection or more than three pills in any 1 month were counted as protocol violations and were then discontinued from the treatment phase and entered the recovery phase. After the 6-month treatment period, each subject entered a posttreatment recovery period until three sperm counts were within the individual's pretreatment range. The study was approved by the University of Washington human subjects review committee and the Veterans Affairs Medical Center research and development committee.

Monitoring

Monthly interviews and physical examinations were performed by physicians throughout the entire study. Seminal fluid analysis was performed every 2 weeks on samples obtained by masturbation after 48 h of abstinence. Monthly blood samples were obtained for measurement of serum LH, FSH, and T (during treatment, samples were drawn immediately before T treatment). Monthly peak and nadir serum LNG levels were obtained by measuring levels before and 1 h after a LNG (or placebo) dose. To monitor for any adverse effects or illness, monthly urinalysis, blood count, electrolytes, creatinine, and hepatic function were analyzed. A lipid panel (total C, HDL-C, LDL-C, and triglycerides)

was measured after a 12-h fast once in each of the three study periods for each subject.

Hormone and lipid assays

Serum LH and FSH levels were analyzed using the Delfia fluoroimmunoassay (Wallac Oy, Turku, Finland). The sensitivities of the Delfia assays were less than 0.019 IU/L and less than 0.016 IU/L for LH and FSH, respectively. Intraassay coefficients of variation were 4.5% for LH and 5.9% for FSH. Interassay coefficients of variation were 7.4% for LH and 9.3% for FSH. Serum T levels were measured by RIA using reagents from the WHO Matched Reagent Program by methods previously described (21). The assay sensitivity was 0.35 nmol/L; the inter- and intraassay variabilities were 8.1% and 4.1%, respectively. LNG levels were assayed by RIA at the California Regional Primate Center (Courtesy of Dr. Lisa Laughlin, University of California-Davis) (19). All samples from each individual were measured in the same assay to avoid interassay variability. Hormone assay sensitivities were determined by the first point discernible from zero on standard curves.

Lipid analyses were performed at the Northwest Lipid Research Clinic (Seattle, WA). HDL-C was separated from plasma by precipitation with dextran sulfate-magnesium, using the method of Warnick *et al.* (22). Total C and triglycerides in plasma were measured enzymatically (23) with an Abbott Spectrum multichromatic instrument (Abbott Laboratories, North Chicago, IL), C by a Trinder-type method and triglycerides by a UV method. LDL-C was calculated indirectly, using the formula LDL-C = total C - (HDL-C + triglycerides/2.2) (2) (24).

Sperm counts

Azoospermia was defined as two or more consecutive sperm counts of zero, and severe oligospermia as two or more counts between zero and 3 million spermatozoa/mL. Sperm count recovery was defined as the first of three normal sperm counts (>20 million) with at least one value equal to the subject's mean baseline count. Sperm counts were determined by Coulter counter (Coulter Electronics, Hialeah, FL), and concentrations below 15 million/mL were confirmed by direct determination using a hemocytometer (25, 26). Sperm motility assessment was performed according to the WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction (27).

Statistical analysis

The study was designed to detect a significant difference between the two groups if 60% of one group and 90% of the other became azoospermic or severely oligospermic. We expected approximately 60% of men in the T alone group to become azoospermic because in previous studies 50–70% of Caucasian men achieved azoospermia with T enanthate alone (8, 9). The number of men attaining azoospermia or severe oligospermia in each group was compared using Fisher's exact test. Analysis of sperm counts was performed by repeated measures ANOVA after log transformation to adjust for skewness in the distribution of data. Hormone and chemistry data were analyzed by repeated measures ANOVA followed by unpaired or paired *t* test as appropriate. Gonadotropin data were further analyzed by analysis of covariance (ANCOVA) to adjust for any baseline differences in LH and FSH. Statistical analysis was carried out on a Macintosh IIsi computer using Statview 4.02 (Abacus Concepts, Berkeley, CA).

Results

Baseline demographic, clinical, and biochemical characteristics of the 36 subjects at the time of randomization are shown in Table 1. There were no significant baseline differences between the 2 study groups with respect to age, weight, seminal fluid analysis, FSH, T, serum chemistry, or lipid analyses. Baseline serum LH was slightly, but significantly, higher in the T alone group than in the T plus LNG group (mean ± SEM, 4.08 ± 0.28 vs. 3.12 ± 0.24 IU/L; *P* < 0.05, by unpaired *t* test).

Thirty-four subjects completed the full 6 months of treat-

TABLE 1. Baseline demographic, clinical, and biochemical parameters

| Baseline parameters | T alone ^a | T plus LNG ^a |
|-----------------------------------|----------------------|--------------------------|
| No. of subjects | 18 | 18 |
| Age (yr) | 30.3 ± 1.6 | 28.6 ± 1.6 |
| Wt (kg) | 85.9 ± 2.4 | 79.7 ± 2.3 |
| Sperm conc. (M/mL) ^b | 61.0 ± 7.9 | 68.9 ± 7.1 |
| Sperm motility (%) | 63 ± 6 | 67 ± 7 |
| Ejaculate vol (mL) | 2.7 ± 0.2 | 3.6 ± 0.3 |
| LH (IU/L) | 4.08 ± 0.28 | 3.12 ± 0.24 ^c |
| FSH (IU/L) | 3.35 ± 0.43 | 2.65 ± 0.27 |
| Testosterone (nmol/L) | 25.6 ± 1.3 | 23.7 ± 1.6 |
| Total cholesterol (mmol/L) | 4.29 ± 0.21 | 4.59 ± 0.17 |
| LDL (mmol/L) | 2.66 ± 0.17 | 2.89 ± 0.20 |
| HDL (mmol/L) | 1.25 ± 0.08 | 1.31 ± 0.08 |
| Triglycerides (mmol/L) | 0.80 ± 0.14 | 0.83 ± 0.08 |
| Hemoglobin (g/L) | 153 ± 2 | 156 ± 2 |
| Aspartate aminotransferase (IU/L) | 25.4 ± 1.9 | 25.3 ± 2.4 |

^a Values are mean ± SEM.

^b Sperm concentration in millions per mL.

^c $P < 0.05$ between the T alone and T plus LNG groups.

ment. One subject in each group withdrew after 5 months of treatment, one for personal reasons and the other to travel. The subject in the T plus LNG group had attained azoospermia, and the subject in the T alone group was severely oligospermic at 5 months. Both of these subjects were included in the analysis.

Sperm counts

T plus LNG resulted in greater suppression of sperm counts than T alone (Fig. 1). At the end of the treatment period, 67% (12 of 18) of the men in T plus LNG group had achieved azoospermia compared to only 33% (6 of 18) of those in the T alone group ($P = 0.06$; Table 2). Severe oligospermia rates at 6 months were 94% (17 of 18) for the T plus LNG group and 61% (11 of 18) of the T alone group ($P < 0.05$; Table 2).

As shown in Fig. 1, in addition to reducing sperm counts in a greater percentage of men, T plus LNG also suppressed sperm counts more rapidly than T alone. Average time to azoospermia was 9.9 ± 1.0 weeks in the T plus LNG group compared to 15.3 ± 1.9 weeks in the T alone group (mean ± SEM; $P < 0.05$; Table 2). The average time to oligospermia was 8.9 ± 0.9 weeks in the T plus LNG group compared to 14.4 ± 1.9 weeks in the T alone group ($P < 0.01$; Table 2). The recovery of sperm counts was not significantly different between the two groups. Recovery occurred at 10.2 ± 0.9 weeks in the T alone group compared to 13.7 ± 1.1 weeks in the T plus LNG group.

Gonadotropins and T

Both LH and FSH in each group decreased significantly during the treatment period ($P < 0.0001$; Fig. 2). Both LH and FSH levels were significantly lower and more rapidly suppressed in the T plus LNG group than in the T alone group. During the 6 months of treatment, the mean LH level was 0.65 ± 0.18 IU/L in the T alone group compared to 0.05 ± 0.01 IU/L in the T plus LNG group ($P < 0.05$, by ANCOVA). FSH levels during this same period were 0.49 ± 0.14 IU/L in the T alone group compared to 0.12 ± 0.04 IU/L in the T plus LNG group ($P < 0.05$, by ANCOVA). Gonadotropin levels remained detectable in both groups at all times.

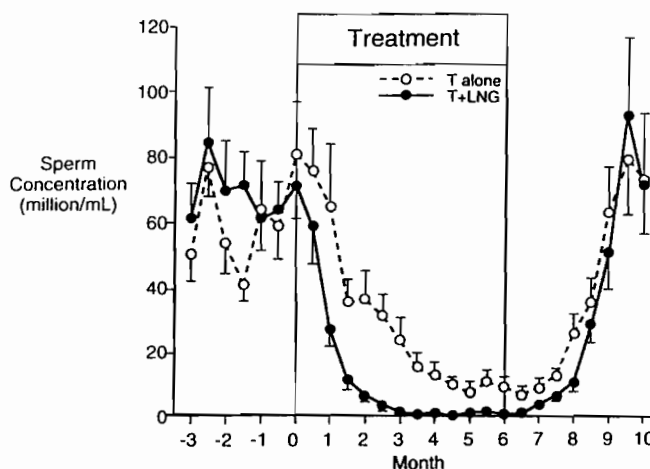


FIG. 1. Mean monthly sperm concentration (million per mL) during the control (−3 to 0 months), treatment (0–6 months), and recovery (6–10 months) periods in normal men treated with T alone (○) compared to those treated with T plus LNG (●). T plus LNG suppressed sperm concentrations more rapidly and effectively than T alone (see text). Values are the mean ± SEM (n = 18 for each group).

TABLE 2. Effectiveness (total numbers of subjects achieving either azoospermia or oligospermia at 6 months) and rapidity of onset of azoospermia and oligospermia

| | Azoospermia ^a | | Oligospermia ^b | |
|---------|--------------------------|------------------------|---------------------------|------------------------|
| | No. (%) ^c | Weeks ^d | No. (%) ^c | Weeks ^d |
| T alone | 6/18 (33) | 15.3 ± 1.9 | 11/18 (61) | 14.4 ± 1.9 |
| T + LNG | 12/18 (67) ^e | 9.9 ± 1.0 ^f | 17/18 (94) ^f | 8.9 ± 0.9 ^g |

The percentage is given in parentheses.

^a Azoospermia is defined by two or more consecutive sperm counts of zero.

^b Oligospermia is defined by two or more consecutive sperm counts less than 3 million per mL.

^c Number of men achieving azoospermia or oligospermia.

^d Number of weeks to the onset of azoospermia or oligospermia (mean ± SEM).

^e $P = 0.06$ compared to T alone.

^f $P < 0.05$ compared to T alone.

^g $P < 0.01$ compared to T alone.

The percent decrease from baseline gonadotropin levels to week 12 of treatment was significantly greater in the T plus LNG group. The mean percent decrease in LH was $88.4 \pm 3.5\%$ for the T alone group compared to $99.1 \pm 0.2\%$ for T plus LNG ($P < 0.01$). The mean percent decrease in FSH was $85.5 \pm 4.1\%$ for the T alone group compared to $96.6 \pm 1.2\%$ for the T plus LNG group ($P < 0.05$).

T levels did not change significantly during either treatment or recovery in the two groups. Values during the treatment period were 28.0 ± 1.4 and 22.0 ± 1.2 nmol/L (807 ± 40 and 634 ± 35 ng/dL; $P = \text{NS}$) for the T alone and T plus LNG groups, respectively.

LNG levels

Mean treatment LNG levels immediately before and 1 h after the daily dose were 0.41 ± 0.06 and 1.52 ± 0.11 µg/L, respectively, in the LNG plus TE group ($P < 0.0001$). Mean LNG levels were below the level of detection in all men receiving T alone.

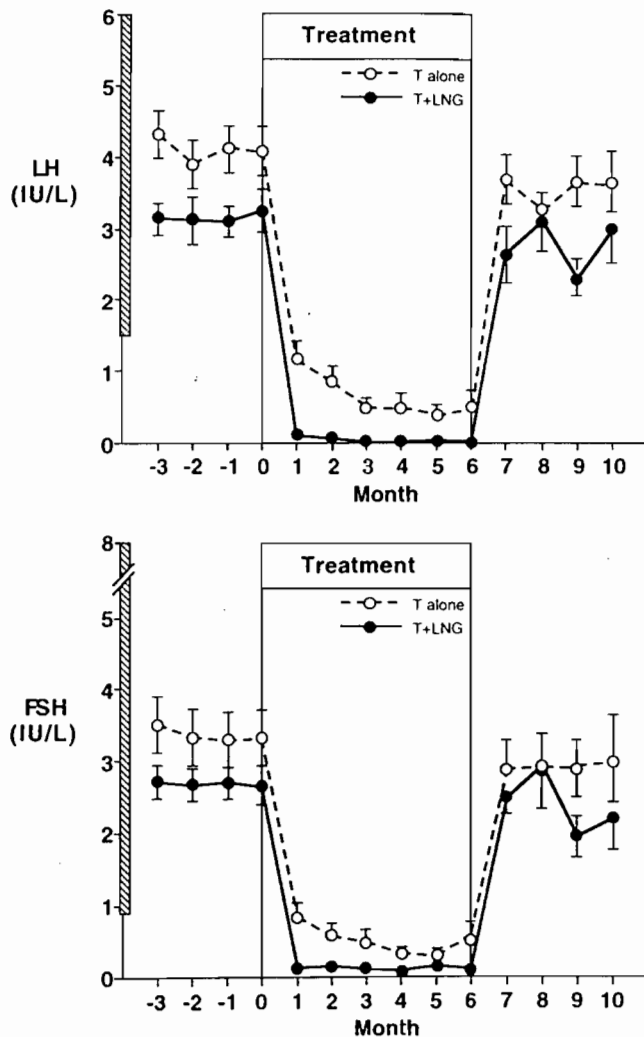


FIG. 2. Mean monthly serum LH (top) and FSH (bottom) levels during the control (–3 to 0 months), treatment (0–6 months), and recovery (6–10 months) periods in normal men treated with T alone (○) compared to those treated with T plus LNG (●). T plus LNG suppressed both LH and FSH more rapidly and effectively than T alone (see text). Values are mean \pm SEM ($n = 18$ for each group). Hatched bars on the ordinate axis represent the normal ranges for serum gonadotropins.

Blood chemistry and hematology

There were no significant differences in aspartate aminotransferase levels, serum hemoglobin, hematocrit, routine blood chemistry, or urinalysis between the two groups during any phase of the study. Serum hemoglobin increased during treatment in both the T alone group (158 ± 2 compared to 153 ± 2 g/L in the control period; $P < 0.05$) and the T plus LNG group (163 ± 2 compared to 156 ± 2 g/L during the control period; $P < 0.05$).

Lipid parameters

There were no significant changes in HDL, LDL, total C, or triglycerides in the group receiving T alone (Table 3). Triglycerides and LDL did not change significantly in the T plus LNG group. In contrast, HDL-C decreased from an

TABLE 3. Mean lipid values (millimoles per L; mean \pm SEM) in the T alone and T plus LNG groups during the three phases of study

| | Control | Treatment | Recovery |
|-------------------|-----------------|-----------------------|-----------------|
| T alone | | | |
| Total cholesterol | 4.29 ± 0.21 | 4.45 ± 0.19 | 4.72 ± 0.26 |
| HDL | 1.25 ± 0.08 | 1.24 ± 0.10 | 1.33 ± 0.11 |
| LDL | 2.66 ± 0.17 | 2.76 ± 0.18 | 2.89 ± 0.24 |
| Triglycerides | 0.80 ± 0.14 | 0.91 ± 0.10 | 1.01 ± 0.16 |
| T plus LNG | | | |
| Total cholesterol | 4.59 ± 0.17 | 4.29 ± 0.21^a | 4.53 ± 0.19 |
| HDL | 1.31 ± 0.08 | $1.01 \pm 0.05^{b,c}$ | 1.31 ± 0.06 |
| LDL | 2.89 ± 0.20 | 2.75 ± 0.26 | 2.70 ± 0.11 |
| Triglycerides | 0.83 ± 0.08 | 0.76 ± 0.10 | 0.96 ± 0.15 |

^a $P < 0.05$ compared to control.

^b $P < 0.001$ compared to control.

^c $P < 0.05$ compared to T alone group.

average of 1.31 ± 0.08 mmol/L (50.7 ± 2.9 mg/dL) to 1.01 ± 0.05 mmol/L (38.9 ± 2.0 mg/dL) in the T plus LNG group ($P < 0.001$). Total C also decreased significantly in the T plus LNG group from 4.59 ± 0.16 mmol/L (177.2 ± 6.3 mg/dL) to 4.29 ± 0.21 mmol/L (165.7 ± 8.0 mg/dL; $P < 0.05$).

Compliance and clinical findings

Compliance was excellent during the study, as evidenced by the fact that only one subject was dismissed for protocol violations. Significant increases in body weight occurred in both treatment groups. The T alone group gained an average of 2.3 ± 0.9 kg ($P < 0.05$) compared to an average weight gain of 5.3 ± 0.8 kg ($P < 0.001$) in the T plus LNG group. The difference in weight gain between the two groups was statistically significant ($P < 0.05$).

Blood pressure did not change significantly during any phase of the study in either the T alone or T plus LNG group. No consistent behavioral changes, gynecomastia, or libido or sexual dysfunction were reported in either group. Acne was noted in 10 of 18 subjects in the T alone group and in 15 of 18 subjects in the T plus LNG group ($P = \text{NS}$ between the two groups). Except for two men, all of the subjects with acne rated it as slight or mild. One subject in the T alone group who had a previous history of acne was given isotretinoin near the end of the treatment period, and one subject in the T plus LNG group received topical therapy.

Discussion

We found that the combination of T plus LNG was more effective than T alone in the suppression of sperm production in normal men. Men who received T plus LNG were more likely to become azoospermic or severely oligospermic, and the onset of spermatogenic suppression was approximately 5 weeks faster in these subjects. Completeness and speed of onset of spermatogenic suppression are key components of any potentially successful male contraceptive method. The present study shows that the combination of T plus LNG offers advantages over T alone in both of these areas. Complete recovery of sperm counts occurred in both study groups, and the rapidity of recovery was not significantly different. Therefore, the combination of an androgen and a progestogen offers a promising male hormonal contraceptive strategy.

We chose the end point of azoospermia because the contraceptive efficacy of T-induced azoospermia has previously been established (8). In a WHO-sponsored study, only one pregnancy occurred during 1486 months of use in men who attained azoospermia during high dose T treatment. Thus, the contraceptive efficacy of T-induced azoospermia (0.8 pregnancies/100 person yr) is comparable to or better than that of combination estrogen-progestogen oral contraceptives for women (3.0 pregnancies/100 person yr) and superior to the use of condoms (12.0 pregnancies/100 person yr) (8). However, only 65% of subjects in the WHO study became azoospermic. Presently, a large study is being conducted to investigate the contraceptive efficacy of lesser degrees of spermatogenic suppression (28). Preliminary results suggest that the development of a sperm concentration of less than 3 million/mL is sufficient to achieve contraceptive efficacy rates comparable to those obtained with the female oral contraceptive pill or the intrauterine device (28). Therefore, a combination hormonal regimen such as T plus LNG that produced either azoospermia or severe oligospermia in 94% of subjects could potentially be an effective contraceptive method.

Previous studies using T in combination with progestogens such as depo-medroxyprogesterone acetate have found rates of azoospermia and oligospermia comparable to those induced by high dose T administration alone (9). However, in these studies T has generally been given monthly using a number of doses less than that associated with maximal suppression of spermatogenesis, and comparison has been made to historical controls, unlike the present randomized controlled trial (13, 14, 29–32).

The mechanism of action of hormone-based contraceptive regimens is the suppression of gonadotropin release from the pituitary sufficient to impair sperm production (5). Studies in men have shown that progestogens can decrease serum gonadotropins (33), and when used in combination with T, an additive suppressive effect on both serum LH and FSH is observed (34). In the present study, T plus LNG suppressed gonadotropin levels more rapidly and effectively than T alone, similar to the reduction of sperm counts. Both LH and FSH levels during the treatment period were significantly lower in the T plus LNG group compared to those in the group given T alone. The physiological significance of the small differences in baseline LH levels is unclear, given that there were no differences in baseline sperm concentrations. Compared with men receiving T alone, T plus LNG resulted in a highly significantly greater percent reduction in both LH and FSH levels. Mechanistically, this greater relative reduction in both FSH and LH in the T plus LNG group could explain the higher rates of azoospermia and oligospermia observed in these subjects. It is reasonable to expect that a greater perturbation from normal homeostasis (*i.e.* relatively greater percent gonadotropin reduction) would result in greater suppressive effects on sperm production.

It is also possible that LNG could exert a direct testicular effect. Progestogens have some 5 α -reductase inhibitory activity and could, therefore, decrease testicular dihydrotestosterone levels (35). In previous trials using T as the sole contraceptive method, different dihydrotestosterone levels

have been postulated as a mechanism to explain why some subjects become azoospermic and others do not (36).

We found that both the T plus LNG and T alone regimens were well tolerated. Moderate weight gain occurred in both groups, with a greater weight gain in the T plus LNG group. Despite these clinically significant weight increases, no subject from either group expressed concern with the weight change, nor was weight gain a factor in compliance or dropouts. Hemoglobin levels increased significantly in both groups, consistent with the known effects of T on erythropoiesis, but there was no significant difference between the two study groups. The increase in acne was generally mild and not sufficient to result in termination from the study for any subject. The one subject given isotretinoin had a previous history of significant acne. There was no consistent change in libido or feeling of well-being in either group. Liver tests, chemistry panels, urinalysis, and blood pressure were unaffected.

Of the lipid parameters measured, only the decrease in HDL-C was significantly different in the two study groups. This association between lower HDL-C and high dose androgen alone or certain progestogen-androgen combination contraceptive regimens has been demonstrated previously (37). Although lower HDL levels have been associated with an increased risk for atherosclerotic heart disease (38–40), this does not necessarily imply that a T plus LNG hormonal regimen would increase the risk of vascular disease in recipients. The potential does, however, exist, and further studies are warranted using lower doses of LNG or newer progestogens, such as desogestrel (41), in combination with T to determine whether the effect on lipids could be minimized without loss of contraceptive efficacy.

In summary, we have shown that 6 months of treatment with T enanthate (100 mg/week, im) in conjunction with LNG (500 μ g/day) is a more effective and rapidly acting method than T alone for suppressing sperm production to azoospermia or severe oligospermia. Furthermore, with the exceptions of a lowering of HDL-C and an increase in weight, the combination of T and LNG was well tolerated. Progestogen-androgen combinations hold promise as an effective approach to achieve reversible contraception for men.

Acknowledgments

We are indebted to the following, without whose dedicated assistance the completion of this study would not have been possible: Ms. Elaine Rost for her assistance in organizing and coordinating this project and preparing the manuscript; Ms. Consuela Pete, Ms. Jennifer Bullock, Ms. Dorothy McGuinness, Ms. Elizabeth Van Gaver, and Mr. Arlen Sarkissian for their technical assistance; Ms. Liza Noonan for help with biostatistical analysis; Drs. Carrie Bagatell and David Gruenewald for their help in examining subjects; Dr. Lisa Laughlin and Dr. Richard Blye for the serum LNG level analysis; Wyeth-Ayerst for providing Levonorgestrel; and the nurses and staff of the University of Washington Clinical Research Center.

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