Journal of Andrology, Vol. 25, No. 5, September/October 2004

Male Hormonal Contraception: Suppression of Spermatogenesis by Injectable Testosterone Undecanoate Alone or With Levonorgestrel Implants in Chinese Men

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ABSTRACT: Monthly injections of testosterone undecanoate (TU) act as a male contraceptive by reversibly suppressing spermatogenesis to azoospermia or severe oligoazoospermia in 95% of Chinese men. In 5% of Chinese men, however, monthly TU administered alone fails to suppress spermatogenesis into contraceptive ranges, or sperm ''rebound,'' leading to occurrences of pregnancy during treatment. Since combinations of progestins and androgens are associated with greater degrees of sperm suppression in white men, we hypothesized that the combination of TU and the progestin levonorgestrel (LNG) would result in improved spermatogenic suppression in Chinese men. Sixty-two healthy Chinese men were randomly assigned to one of the following 3 regimens: group I (n = 21) received 4 LNG rods (75 mg each), which were followed 4 weeks later by 500 mg of TU by intramuscular (IM) injection every 8 weeks for 24 weeks; group II (n = 20) received 4 LNG implants, which were followed 4 weeks later by 1000 mg of TU by IM injection every 8 weeks for 24 weeks; and group III (n = 21) received TU 1000 mg by IM injection every 8 weeks for 24 weeks. Sperm counts, serum testosterone (T), luteinizing hormone, follicle-stimulating hormone, and LNG were measured every 2 weeks before, during, and after treatment. During treatment, group II demonstrated a trend toward a greater attainment of azoospermia than groups I and III (90% vs 62% [group I] vs 67% [group III]; $P = .09$). Attainments of either azoospermia or oligozoospermia (sperm density, $<3 \times 10^6$/mL) were 95%, 100%, and 86% for groups I, II, and III, respectively ($P > .05$ for comparisons between groups). Spermatogenesis in all subjects returned to the normal range after the implants were removed. No serious adverse events and no significant changes in serum chemistry occurred during the study. These results demonstrate that the combination of IM injections of high-dose TU every 2 months and LNG implants is associated with marked suppression of spermatogenesis in Chinese men. The combination of high-dose TU every 2 months and LNG implants is a promising candidate for future large-scale efficacy studies of hormonal male contraception in Chinese men.

Key words: Androgens, contraceptive, progestins, family planning.
J Androl 2004;25:720–727

Efforts to develop a safe, reversible hormonal contraceptive for men have used the administration of exogenous testosterone (T) to inhibit the secretion of pituitary gonadotropins and thereby suppress spermatogenesis (Anawalt and Amory, 2001; Anderson and Baird, 2002). Previous multicenter efficacy studies of weekly intramuscular (IM) T enanthate have demonstrated that T-induced azoospermia is an effective contraceptive; however, some men on T-alone regimens do not suppress spermatogenesis to levels low enough to make pregnancy unlikely (World Health Organization, 1990, 1996). In these trials, Asian men demonstrated higher attainments of azoospermia than their non-Asian counterparts. This led to the hypothesis that T-alone regimens might prove effective for hormonal contraception in Chinese men, and previous small studies of Chinese men have reported high degrees of azoospermia with T-alone regimens (Zhang et al, 1999). However, recently, a large, contraceptive efficacy trial enrolling more than 300 men conducted in China using the long-acting androgen T undecanoate (TU) alone showed that some men did not have sperm count suppression to azoospermia or severe oligozoospermia (Gu et al, 2003). Some men who had initially suppressed to azoospermia exhibited ''sperm rebound,'' and for one of these men and his partner, a pregnancy occurred. In populations of white men, the addition of progestins to T-based contraceptive regimens improves rates of azoospermia compared with T-alone regimens (Bebb et al, 1996; Handelsman et al, 1996; Meriggiola et al, 1996, 1998; Anawalt et al, 1999, 2000; Kamischke et al, 2000, 2001; Kinninburgh et al, 2001; Gonzalo et al, 2002), but this approach has not been tested extensively in Chinese men. Since sperm counts in Chinese men appear to be more easily suppressed by hormonal regimens, we hypothesized that a combination of TU with an implant con-

Supported in part by a grant from the CICCR Program of the Contraceptive Research and Development (CONRAD) Program, Eastern Virginia Medical School, USA, Subproject (CIG-99-37).

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Received for publication December 20, 2003; accepted for publication March 15, 2004.

taining the progestin levonorgestrel (LNG) would enhance sperm suppression in Chinese men and result in a contraceptive regimen suitable for large-scale testing and use.

This study had 2 goals: first, we sought to determine whether delaying the administration of the androgen after exposure to the progestin implant would significantly improve suppression of spermatogenesis, and second, we sought to determine if additive suppression of spermatogenesis mediated by the progestin implant could be maintained with a lower androgen dose. Therefore, we conducted a prospective 3-arm trial of injections of TU alone and with the progestin LNG administered by means of an implant shown previously to suppress sperm counts in normal men (Gao et al, 1999; He et al, 2001) to determine the safety, reversibility, and spermatogenic suppression of this combination in normal Chinese men.

Materials and Methods

Subjects

Sixty-two healthy Chinese men, aged 22–35 years, were enrolled in this study. Inclusion criteria were as follows: a normal medical history and physical examination; normal serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and T; sperm counts of greater than 20 million per milliliter with normal values for motility and morphology on semen analyses; and normal values on routine hematology, blood chemistry, and fasting lipid profile. Individuals having a history of chronic medical illness, taking chronic medications or anabolic steroids, or experiencing current or prior drug or alcohol abuse were excluded from the study. The Ethical Review Committee of the Shanghai Institute of Planned Parenthood Research approved the study, and all subjects gave written informed prior to participation.

TU and LNG Implants

The LNG implants each contained 75 mg of LNG (Shanghai Da Hua Pharmaceutical Co, Shanghai, China) and are designed to release between 50 and 100 μg of LNG daily. The injectable TU was suspended in tea-seed oil at a concentration of 125 mg/mL (Xian Ju Pharmaceutical Co, Zhe Jiang, China). The same batch of TU was used throughout the study.

Study Design

This was a randomized, 3-arm open-label trial consisting of a 4-week control period, a 28-week (groups I and II) or 24-week (group III) treatment period, and a 12- to 16-week recovery period. At the beginning of the treatment period (week 0), 4 LNG rods were implanted under the skin of each subject (in groups I and II). Four weeks after insertion, subjects began receiving TU at a dose of 500 mg (group I) or 1000 mg (group II) by IM injection every 8 weeks for 24 weeks. The 4-week delay prior to the addition of the T was added to the protocol to see if a period of exposure only to a progestin would reduce the time required to achieve azoospermia. At the end of week 28, the LNG implants were removed. Subjects in group III received 1000 mg of TU by IM injection beginning at week 0 and every 8 weeks thereafter for 24 weeks. All injections were given by the study nurse in either a single injection of 4 mL (500-mg group) or two 4-mL injections (1000-mg groups) in the gluteus muscles; no subject missed an injection. After the completion of the treatment period, the subjects were followed until serum T, FSH, and LH had recovered to pretreatment levels and until sperm counts were greater than 20 million per milliliter on 2 consecutive occasions.

Throughout the study, subjects were asked to provide semen samples every 2 weeks by masturbation after 2–7 days of sexual abstinence and to undergo a monthly physical examination. Blood samples for analysis of serum levels of T, LH, and FSH were drawn every 2 weeks throughout the study immediately prior to the injection of TU. Serum LNG levels were measured every 2 weeks in groups I and II during the study period. Blood counts, blood chemistries, and a fasting lipid panel were measured at the beginning of the study, every 8 weeks during treatment period, and at the end of the recovery period. All serum samples were centrifuged and stored at −70°C until analysis. Subjects were questioned monthly by one of the investigators about their general well-being, and any changes were noted in the study chart. Libido and sexual function were assessed by a simple questionnaire used previously by our group (Gao et al, 1999).

Since limited data were available on the use of TU at 8-week intervals, it was estimated that the rate of azoospermia in the TU-alone group would be 60% and that the rate of azoospermia in the combination groups would be 90%. Therefore, a sample size of 20 per group was calculated to have a 70% power to find a 30% difference in the proportion of subjects achieving azoospermia between these groups at a α value (1-sided) of .05.

Measurements

Semen analyses were performed according to World Health Organization (1992) guidelines. Suppression to azoospermia was defined as the absence of sperm from the seminal fluid, even after centrifugation, in 2 or more consecutive specimens. Sperm rebound was defined as a recurrence of sperm in the ejaculate after the subject had achieved azoospermia. Severe oligozoospermia was defined as 2 or more counts of between 0 and 3 million sperm per milliliter. Plasma FSH, LH, and T levels were measured by immunoenzymetric assay (Serozyme, Rome, Italy). The lower limit of quantification (LLQ) of FSH was 0.3 IU/L; intra- and interassay coefficients of variation were 4.6% and 13.8%, respectively. The LLQ of LH was 0.35 IU/L; intra- and interassay coefficients of variation were 5.0% and 14.5%, respectively. The LLQ of T was 0.4 nmol/L; intra- and interassay coefficients of variation were 6.3% and 14.0%, respectively. LNG levels were measured by radioimmunoassay (Immunometrics, London, United Kingdom); the intra-assay and interassay coefficients of variation were 6.9% and 15.4%, respectively.

Statistics

Data are presented as the mean ± standard error of the mean. Baseline values were computed as the mean of the 2 visits prior

Table 1. *Baseline characteristics of study subjects, who were randomly assigned to group I (4 LNG implants plus 500 mg of TU every 8 weeks); group II (4 LNG implants plus 1000 mg of TU every 8 weeks); or group III (1000 mg of TU every 8 weeks)**

Characteristic	Group I (n = 21)	Group II (n = 20)	Group III (n = 21)	*P*
Age (y)	32 ± 0.7	32 ± 0.8	32 ± 0.7	.85
Weight (kg)	65 ± 2.5	62 ± 2.4	62 ± 2.6	.43
BMI (kg/m^2)	23 ± 0.6	23 ± 0.6	22 ± 0.8	.46
Testis volume (cm^3)	21 ± 0.7	22 ± 0.7	22 ± 0.7	.40
Sperm concentration (10^6/mL)	85 ± 5.0	84 ± 7.1	68 ± 8.0	.56
Ejaculaste volume (mL)	2.3 ± 0.3	2.6 ± 0.4	2.5 ± 0.3	.80

* LNG indicates levonorgestrel; TU, testosterone undecanoate; and BMI, body mass index.

to the treatment phase. Proportions of subjects attaining azoospermia or severe oligospermia were compared using the extended Fisher exact test. Variations in sperm counts and hormone levels within each treatment group across time and between treatment groups at a given time point were compared by analysis of variance for repeated measures, followed by a post hoc test (PC+ version 10.0, SPSS Inc, Chicago, Ill). For all analyses, $P = .05$ was considered significant.

Results

Subjects

The baseline characteristics of the study subjects are shown in Table 1. There were no significant baseline differences among the 3 groups in any parameter. During the study, no serious adverse side effects were reported, and only minor postinjection discomfort was reported, despite the large injection volume. There were no serious complications with the LNG implants, such as infection or extrusion. Several subjects had mild-to-moderate bruising at the implant site that lasted for up to 2 weeks. No significant changes in self-reported perceptions of mood or well-being were reported upon questioning by the clinicians involved in the study or revealed by the sexual function questionnaire, either during the 4-week period after LNG implantation or during TU treatment. In addition, no significant change in body weight was observed during the study. A small reduction in testicular volume was noted during treatment, but this reversed completely during recovery (data not shown). After enrollment, no subjects discontinued participation in the study, and all subjects were followed until study completion.

Sperm Concentrations

Sperm concentrations decreased significantly compared to baseline in all 3 groups from week 8 of treatment until 10 weeks into recovery. Suppression of sperm concentrations was significantly greater in group II at several time points during treatment compared with that in groups I and III (Figure 1).

Sperm rebound after the attainment of azoospermia was noted in 3 subjects in group II, 1 subject in group III, and no subjects in group I. In group II, 1 subject exhibited azoospermia by week 20 but had a sperm count of 3 mil-

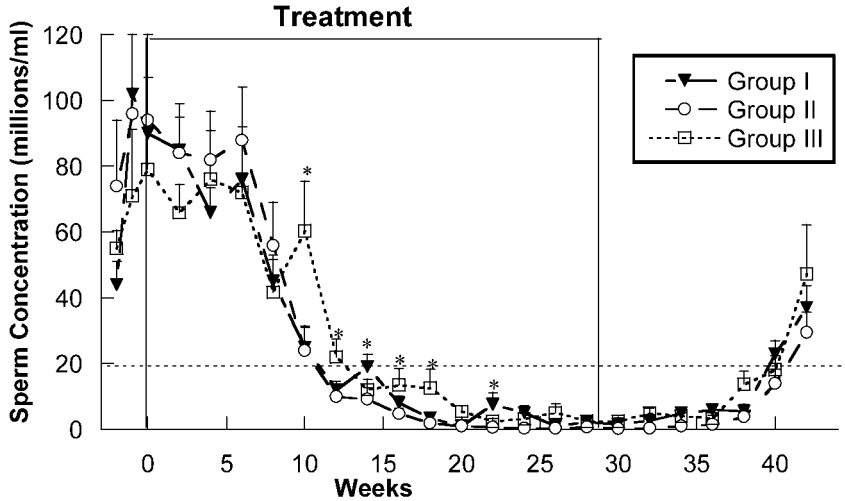

Figure 1. Mean sperm concentrations before, during, and after treatment (±SEM) in healthy men treated with levonorgestrel (LNG) implants plus 500 mg of testosterone undecanoate (TU) (group I), LNG implants plus 1000 mg of TU (group II), or 1000 mg of TU alone (group III). Vertical lines denote the treatment period for groups I and II; the treatment period for group III ends at 24 weeks. The dashed line denotes the lower limit of the normal range. * $P < .05$ compared with group II.

Table 2. *Rates of azoospermia and oligozoospermia and mean time to azoospermia during treatment in Chinese men who were randomly assigned to group I (4 LNG implants plus 500 mg of TU every 8 weeks); group II (4 LNG implants plus 1000 mg of TU every 8 weeks); or group III (1000 mg of TU every 8 weeks by study group); subjects (%)**

	Group I (n = 21)	Group II (n = 20)	Group III (n = 21)
Azoospermia	13 (62)	18 (90)	14 (67)
<1 million/mL	3 (14)	2 (10)	2 (10)
<3 million/mL	4 (19)	0	2 (10)
>3 million/mL	1 (5)	0	3 (14)
Mean time to azoospermia (wk)	17.8 ± 1.5	15.0 ± 1.2	17.7 ± 2.1

* LNG indicates levonorgestrel; TU, testosterone undecanoate.

lion/mL at week 28. A second subject was azoospermic by week 12 but had a sperm count of 0.2 million/mL at week 24; the third subject was azoospermic by week 14 but had a sperm count of 2 million/mL at week 24. In group III, 1 subject who was azoospermic at week 12 had a sperm count of 4 million/mL at week 16.

Attainment of Azoospermia and Oligozoospermia

During treatment, group II demonstrated a trend toward a greater attainment of azoospermia than groups I and III (90% vs 62% [group I] vs 67% [group III] $P = .09$) (Table 2). Rates of either azoospermia or severe oligozoospermia (sperm density, $<1 \times 10^6$/mL) were 76%, 100%, and 77% for groups I, II, and III, respectively ($P > .05$ for comparisons between groups), and rates of either azoospermia or oligozoospermia (sperm density, $<3 \times 10^6$/mL) were 95%, 100%, and 86% ($P > .05$) (Table 2). In group I, the earliest any subject reached azoospermia was 12 weeks into treatment; in group II, 1 man achieved azoospermia at week 8, and 4 men were azoospermic by week 12, while in group III, 1 subject reached azoospermia at week 4, but no other subject reached azoospermia until after week 10. The mean time to azoospermia in subjects was 18 ± 1.5, 15 ± 1.2, and 18 ± 2.1 weeks in groups I, II, and III, respectively ($P = .43$). Spermatogenesis in all subjects returned to the normal range (>20 million sperm per milliliter) after the implants were removed, and the injections ceased after a mean of 3–4 months in all groups.

Reproductive Hormones

The mean serum T was significantly elevated above baseline following all TU injections in the 2 groups receiving 1000 mg of TU (Figure 2). The mean treatment (weeks 16–24) serum T concentration increased in the groups receiving 1000 mg of TU but decreased in the group receiving 500 mg of TU (Figure 2) ($P < .001$ for group I vs groups II and III). The serum LH and FSH were significantly decreased compared to baseline throughout the treatment period, even during the initial period prior to TU treatment (ie, with LNG alone) in groups I and II. Compared with group II, the serum LH and FSH in

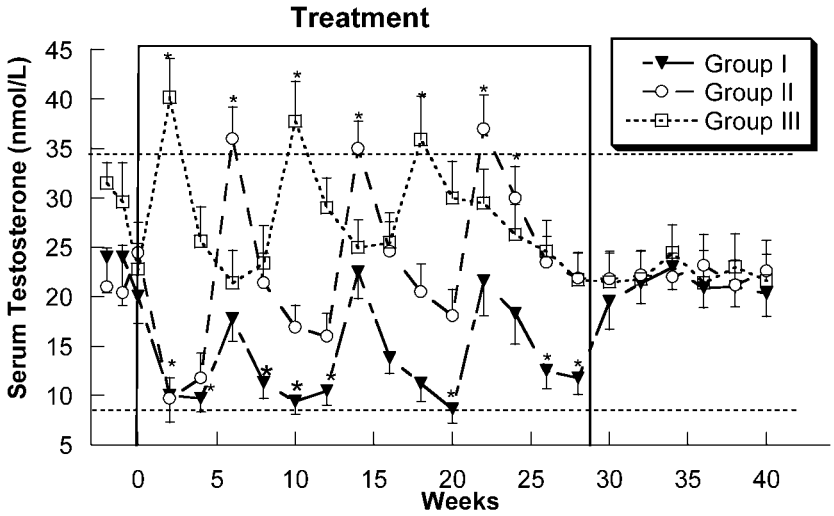

Figure 2. Mean serum testosterone (T) concentrations before, during, and after treatment (±SEM) in healthy men treated with levonorgestrel (LNG) implants plus 500 mg of testosterone undecanoate (TU) (group I), LNG implants plus 1000 mg of TU (group II), or 1000 mg of TU alone (group III). In groups I and II, TU was administered at weeks 4, 12, and 20, while in group III, TU was administered at weeks 0, 8, and 16. Vertical lines denote the treatment period for groups I and II; the treatment period for group III ends at 24 weeks. Dashed lines denote the normal range. * $P < .05$ compared with baseline.

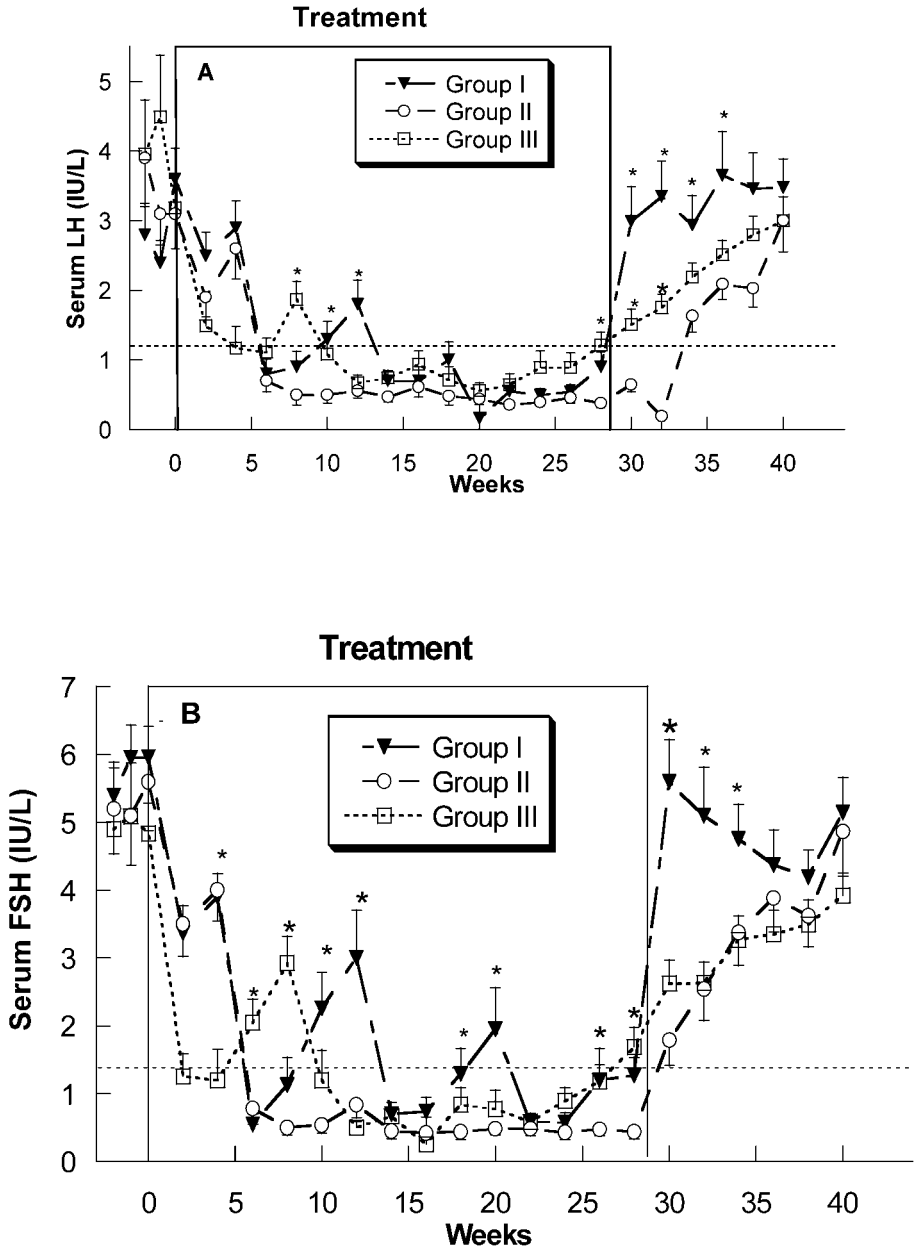

Figure 3. Mean serum luteinizing hormone (LH) **(A)** and follicle-stimulating hormone (FSH) **(B)** concentrations before, during, and after treatment (±SEM) in healthy men treated with levonorgestrel (LNG) implants plus 500 mg of testosterone undecanoate (TU) (group I), LNG implants plus 1000 mg of TU (group II), or 1000 mg of TU alone (group III). In groups I and II, TU was administered at weeks 4, 12, and 20, while in group III, TU was administered at weeks 0, 8, and 16. Vertical lines denote the treatment period for groups I and II; the treatment period for group III ends at 24 weeks. The dashed line denotes the lower limit of the normal range. * $P < .05$ compared with group II.

groups I and III were significantly elevated at several points during treatment (Figure 3A and B). The mean treatment (weeks 16–24) serum LH and FSH concentrations decreased by 67% and 79% (group I), 85% and 91% (group II), and 83% and 87% (group III) during treatment ($P < .05$ for group I vs groups II and III). Serum LNG levels were stably and significantly elevated, with a mean level of 0.48 ± 0.02 ng/mL in group II and 0.59 ± 0.05 ng/mL in group I ($P < .05$ for group I vs group II) throughout the 28-week treatment period in groups I and II (Figure 4).

Lipid and Blood Chemistry Effects

All groups demonstrated statistically significant reductions in total and high-density lipoprotein (HDL) cholesterol during treatment (Table 3). There were no significant changes in serum chemistries or hematocrit during the study (data not shown).

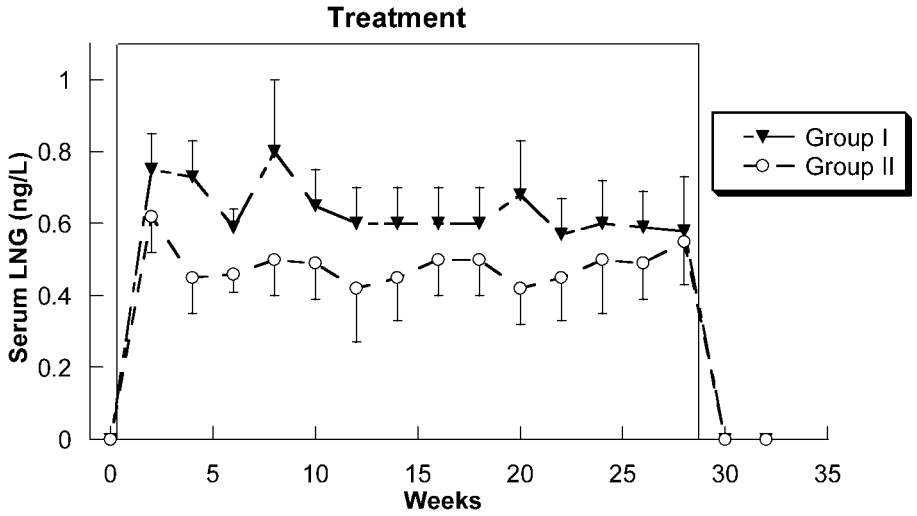

Figure 4. Mean serum levonorgestrel (LNG) concentrations before, during, and after treatment (±SEM) in healthy men treated with LNG implants plus 500 mg of testosterone undecanoate (TU) (group I) or LNG implants plus 1000 mg of TU (group II). Vertical lines denote the treatment period.

Discussion

This study demonstrates that the combination of LNG implants and IM injections of TU every 2 months results in the suppression of spermatogenesis to a degree that would allow its use as a male contraceptive in Chinese men. In our study, sperm suppression and attainment of azoospermia were determined by both the dose of TU and the coadministration of LNG. The combination of high-dose TU and LNG implants in group II resulted in the attainment of azoospermia in 90% of men, and all subjects in this group achieved suppression of spermatogenesis to either severe oligozoospermia or azoospermia. These results, and the fact that this combination of infrequent injections and an implant is likely to function well in ''real-world'' settings, make the combination of high-dose TU and LNG implants an attractive option for large-scale contraceptive efficacy testing in Chinese men.

That the attainment of azoospermia in group II was not significantly greater than that seen in groups I and III was likely due to inadequate power with this study design. Given the difficulty in demonstrating significant improvements in the percentage of men achieving azoospermia in contraceptive studies in which attainment of azoospermia

Table 3. *Lipid effects during treatment in Chinese men who were randomly assigned to group I (4 LNG implants plus 500 mg of TU every 8 weeks); group II (4 LNG implants plus 1000 mg of TU every 8 weeks); group III (1000 mg of TU every 8 weeks)†*

		Treatment Week				Recovery Week	
	Baseline	4	12‡	20‡	28‡	8	16
Total cholesterol (mg/dL)							
Group I	164 ± 8.4	160 ± 8.9	149 ± 9.0	143 ± 8.2*	150 ± 8.3	169 ± 6.6	168 ± 7.2
Group II	163 ± 9.0	13.8 ± 7.2*	139 ± 8.5*	138 ± 7.8*	142 ± 10.0*	169 ± 7.9	167 ± 7.0
Group III	165 ± 7.2	ND	161 ± 8.0	154 ± 7.1	159 ± 9.5	164 ± 9.0	171 ± 7.7
HDL cholesterol (mg/dL)							
Group I	52 ± 3.2	48 ± 2.9	42 ± 3.4*	36 ± 2.7*	36 ± 2.7*	50 ± 3.5	49 ± 3.9
Group II	48 ± 1.9	42 ± 1.8*	35 ± 2.1*	32 ± 2.2*	34 ± 2.0*	44 ± 2.5	47 ± 2.0
Group III	51 ± 2.6	ND	46 ± 2.9	40 ± 2.4*	42 ± 1.8*	43 ± 2.0*	47 ± 1.5
Triglycerides (mg/dL)							
Group I	164 ± 8.4	160 ± 8.9	150 ± 9.0	144 ± 8.2	150 ± 8.3	169 ± 6.6	168 ± 7.3
Group II	163 ± 9.0	138 ± 7.2	138 ± 8.5	138 ± 7.7	142 ± 10.0	169 ± 7.9	167 ± 7.0
Group III	165 ± 7.2	ND	161 ± 8.0	154 ± 7.1	159 ± 9.5	163 ± 9.0	171 ± 7.7

† LNG indicates levonorgestrel; TU, testosterone undecanoate; ND, not done; and HDL, high-density lipoprotein.
‡ Weeks 8, 16, and 24 for group III.
* $P < .05$ compared to baseline.

exceeds 60%–70%, future contraceptive studies will require larger sample sizes to be adequately powered to detect significant differences between regimens.

Sperm suppression, particularly in groups I and III of this study, was inferior to that reported previously in Chinese men receiving TU alone at 4-week intervals (Gu et al, 2003). This is likely due to inadequate androgen levels during the later 4 weeks of the 8-week TU injection interval used in this study. Analysis of the changes in serum gonadotropins over time shows that, particularly in the case of serum FSH in the group receiving the lower dose of TU, FSH rose to be within the normal range prior to the next TU injection. This finding demonstrates the primary importance of the androgen in spermatogenic suppression by androgen/progestin male hormonal contraceptive combinations. In our subjects receiving 1000 mg of TU alone every 8 weeks (group III), the attainment of azoospermia was lower than has been reported in Chinese men receiving 500–1000 mg of TU every 4–6 weeks (Zhang et al, 1999; Gu et al, 2003). This difference is likely also due to the elevations in FSH seen in this group at the end of the 8-week injection interval (Narula et al, 2002).

Since less frequent injections of T are viewed more favorably by prospective male contraceptive users (Martin et al, 2000), the combination of a progestin such as LNG with T will likely be necessary if T injections are to be given at intervals longer than 4–6 weeks, even in Asian men. It is notable that the average LNG levels in group II were lower than those in group I, despite the use of identical implants in both of these groups. This is likely due to greater suppression of sex hormone binding globulin (SHBG) mediated by the higher dose of T in this group. Such a decrease in SHBG has been shown to increase ''free'' LNG, which is metabolized more quickly, resulting in lower circulating levels of total hormone (Alvarez et al, 1998). This also likely decreased the serum T levels in group II and compared to group III.

During treatment, 3 subjects administered the high-dose TU and LNG (group II) experienced ''sperm rebound'' after achieving azoospermia. This observation is consistent with prior experiences in trials of hormonal contraceptives in Chinese men, especially in subjects receiving injections at longer intervals (Gu et al, 2003). In none of these individuals did the sperm counts during ''rebound'' exceed 3 million sperm per milliliter. This suggests that once azoospermia is obtained on this regimen, sperm count elevations to the degree at which the risk of fertility is high are uncommon.

The efficacy of spermatogenic suppression in group II was superior to that induced by combinations of T enanthate and oral LNG in non-Asian men (Bebb et al, 1996; Anawalt et al, 1999; Kamischke et al, 2001) but was similar to those seen with T enanthate and LNG administered by implant (Gonzalo et al, 2002). In general, it remains a mystery why Asian men exhibit greater degrees of spermatogenic suppression on hormonal contraceptive regimens. It has been suggested that Asian men have a smaller spermatogenic reserve than white men, despite comparable semen parameters at baseline (Johnson et al, 1998). Differences between ethnic groups in feedback sensitivity at the pituitary are present only at T doses lower than those used in contraceptive studies (Wang et al, 1998). Genetically, Asian men have a larger number of CAG repeats in their androgen receptors (Edwards et al, 1992), which may confer greater response to T-based contraceptive regimens (von Eckardstein et al, 2002). Other investigators, however, have not found CAG repeat length to predict the difference between individuals who suppress to azoospermia on hormonal contraceptive regimens and those who do not (Yu and Handelsman, 2001).

On average, individuals in group II achieved azoospermia by 15 weeks, 3 weeks sooner than individuals in either group I or III. This time course of azoospermia is somewhat slower than that seen in other androgen/progestin contraceptive trials (Bebb et al, 1996; Handelsman et al, 1996; Meriggiola et al, 1996, 1998; Anawalt et al, 1999, 2000; Kamischke et al, 2000, 2001; Kinninburgh et al, 2001; Gonzalo et al, 2002) and is likely due to the 4-week delay in administering TU after the insertion of the LNG implants. It is probable that more rapid attainment of azoospermia could be achieved by administering the TU and LNG simultaneously, and this will be done in future trials of this combination.

There were no serious adverse side effects in this study; however, a significant 20%–30% reduction in serum HDL cholesterol was seen in the 2 groups in which men were receiving both TU and LNG. The long-term consequences of this are unknown but might lead to an increased risk of atherosclerosis over time (Liu et al, 2003; Wu and von Eckardstein, 2003).

In conclusion, we have demonstrated that the combination of high-dose IM TU every 2 months and LNG implants leads to a marked spermatogenic suppression in Chinese men. This combination was well tolerated and associated with no serious adverse side effects. Given its high degree of efficacy, minimal side effects, and potential ''real-world'' utility among men, the combination of TU every 2 months and LNG implants is a promising candidate for a large-scale efficacy trial in Chinese men.

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