

## Suppression of Spermatogenesis With Desogestrel and Testosterone Pellets is Not Enhanced by Addition of Finasteride

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**ABSTRACT:** Conversion of testosterone to dihydrotestosterone (DHT) by the action of 5 $\alpha$ -reductase can amplify androgen action. This may be of particular importance in the presence of low testosterone concentrations and may contribute to maintenance of spermatogenesis in a proportion of men receiving male contraceptive regimens. We therefore investigated whether the addition of finasteride, a 5 $\alpha$ -reductase inhibitor, to a prototype male hormonal contraceptive regimen consisting of desogestrel (150  $\mu$ g orally daily) and repeated administration of testosterone pellets (2  $\times$  200 mg per 12 weeks) would enhance suppression of spermatogenesis. Sixteen normal men were randomized to receive either the standard androgen/progestogen treatment alone (control group) or with finasteride (5 mg orally daily—FIN group) for 24 weeks. Both groups showed profound suppression of spermatogenesis with azoospermia being obtained in 6 of 8 subjects in the control group and in 5 of 7 in the FIN group. There were no significant differences between the groups

with respect to sperm concentrations. Significant suppression of luteinizing hormone and follicle-stimulating hormone was achieved within 2 weeks of treatment in both groups, while testosterone concentrations were maintained in the normal physiological range. DHT concentrations fell in both groups but were significantly lower in the FIN group. Gonadotropin and testosterone concentrations were similar for both regimens throughout the study. This study demonstrates the potential for long-term suppression of spermatogenesis using a combination of an oral progestogen with repeated administration of a depot preparation of testosterone. However, these data do not support the involvement of 5 $\alpha$ -reductase in maintaining residual spermatogenesis during gonadotropin suppression for hormonal male contraception.

Key words: Male contraception, 5 $\alpha$ -reductase, dihydrotestosterone.

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Suppression of gonadotropin secretion results in a reduction in spermatogenesis, which forms the basis of the hormonal approach to male contraception. However, in the great majority of regimens investigated, suppression of spermatogenesis is not complete, with a variable proportion of men (typically 30%–50%) maintaining a low rate of spermatogenesis. This level of spermatogenesis, though drastically reduced, is sufficient to result in significant risk of pregnancy (World Health Organization [WHO], 1990, 1996). For a regimen to have adequate contraceptive efficacy, it is likely that universal azoospermia is required but this has only been achieved in studies that included very small numbers of men (Merigiola et al, 1996; Wu et al, 1999).

The basis for this heterogeneity in response is unclear. Testosterone is the major intratesticular androgen and is

required for normal spermatogenesis. It can be converted to the more potent androgen, dihydrotestosterone (DHT) by the enzyme, 5 $\alpha$ -reductase, and differences in 5 $\alpha$ -reductase activity have been suggested to underlie differences in suppression of spermatogenesis during testosterone administration to men (Anderson et al, 1996). Inhibition of 5 $\alpha$ -reductase has been demonstrated to partially prevent the restoration of spermatogenesis by testosterone in a rat model, an effect that was apparent only at lower doses of testosterone (O'Donnell et al, 1996, 1999). This finding is consistent with the hypothesis that under conditions of reduced intratesticular testosterone concentrations, such as those that occur during administration of exogenous testosterone, 5 $\alpha$ -reductase may act as an amplifier of the effect of testosterone within the testis, thus providing direct trophic support to particular stages of spermatogenesis. The concurrent administration of an inhibitor of 5 $\alpha$ -reductase may therefore prevent amplification of the action of testosterone, resulting in a greater inhibition of spermatogenesis manifesting as an increased prevalence of azoospermia.

The objective of this study was to test this hypothesis directly. Combined administration of a progestogen with

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Table 1. Pretreatment values of subjects in the control and the finasteride (FIN) groups

Pretreatment Value	Control Group (n = 8)*	FIN Group (n = 7)*
Age, y	32 ± 1	30 ± 2
BMI, kg/m <sup>2</sup> †	23.3 ± 0.8	24.2 ± 1.3
Sperm concentration, ×10 <sup>6</sup> /mL	84 ± 19	60 ± 14
LH, IU/L	4.2 ± 0.6	2.9 ± 0.8
FSH, IU/L	6.0 ± 1.3	4.7 ± 1.3
Testosterone, nmol/L	26.5 ± 2.4	24.2 ± 1.6
DHT, nmol/L	1.60 ± 0.12	1.49 ± 0.10

\* Mean ± SEM.

† BMI indicates body mass index; LH, luteinizing hormone; FSH, follicle-stimulating hormone; and DHT, dihydrotestosterone.

testosterone results in increased suppression spermatogenesis while avoiding supraphysiological testosterone concentrations and is currently the most promising approach to hormonal male contraception (Meriggiola and Bremner, 1997). We have therefore investigated the effect of coadministration of the 5 $\alpha$ -reductase inhibitor, finasteride, on the degree of spermatogenic suppression achieved during administration of a prototype contraceptive regimen of testosterone with the progestogen, desogestrel, the primary objective being to achieve azoospermia in all men.

## Methods

### Subjects

Sixteen caucasian men aged 21 to 39 years (mean 31 years) were recruited from the local population. None had significant medical history or abnormality on examination and screening hematological and biochemical measures were within the normal range. Subjects submitted pretreatment semen samples on 2 occasions at least 2 weeks apart, which were assessed using WHO methodology (WHO, 1992). All men had sperm concentrations greater than 20 × 10<sup>6</sup>/mL (Table 1).

### Study Design and Medication

The study was a prospective randomized trial investigating the addition of finasteride to an androgen/progestin regimen. Subjects were randomized into 2 treatment groups. Both groups took 150  $\mu$ g of desogestrel (NV Organon, Oss, The Netherlands) by mouth daily for 24 weeks. In addition, on the first day of desogestrel treatment and 12 weeks later, 400-mg testosterone pellets (2 × 200 mg, NV Organon) were inserted subcutaneously under local anaesthetic into the anterior abdominal wall. One group (control) received the desogestrel and testosterone alone; the second group (FIN) also took 5 mg of oral finasteride (Proscar, Merck Sharp & Dohme Ltd, Hoddesdon, Herts, United Kingdom) daily for 24 weeks. All men gave informed written consent and this study received ethical approval from the Lothian Reproductive Medicine Ethical Review Committee. This study was carried out according to International Congress on Harmonization Good Clinical Practice guidelines.

Subjects were reviewed and examined 2 weeks after commencing medication and at 4-week intervals during the treatment phase and during the recovery phase of 16 weeks after finishing desogestrel. At each visit subjects were examined and adverse events or other health problems were recorded, semen samples were collected, and venipuncture was performed. Compliance was assessed by pill returns and direct questioning of subjects. Subjects were required to continue their current method of contraception throughout the study.

### Assays

Semen samples were submitted after 3–7 days of abstinence. Each semen sample was assessed for sperm concentration using WHO methodology (WHO, 1992). Oligospermic samples were examined so as to give a lower limit of quantification of concentration of 0.025 × 10<sup>6</sup>/mL. Azoospermia was confirmed by examination of the pellet following centrifugation of the ejaculate.

Blood samples were obtained between 0700 and 1200 hours at every visit. Samples were separated by centrifugation and serum was stored at –20°C until assay. Testosterone was measured by radioimmunoassay (RIA) as previously described (Corker and Davidson, 1978). Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by time-resolved immunofluorometric assay (DELFLIA, Wallac, Turku, Finland). Assay sensitivities were 0.15 IU/L and 0.125 IU/L, respectively. DHT was measured by RIA (DHT extraction RIA, Intertech, Bertrange, Luxembourg). Samples from individual subjects were measured in the same assay to reduce variability. Etonogestrel, the active metabolite of desogestrel, was measured by in-house RIA by Organon NV.

Blood was analyzed every 12 weeks for general hematological and biochemical values by routine autoanalyzer. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation with dextran sulphate-magnesium, and total cholesterol and triglycerides were measured enzymatically (Wood et al, 1987). Low-density lipoprotein cholesterol (LDL-C) was calculated indirectly (Friedewald et al, 1972).

### Behavioral Assessment

Sexual interest and activity were investigated pretreatment and at 12-week intervals during treatment and recovery. A structured interview was used to quantify sexual activity over the preceding 2 weeks and Frenken Sexual Experience Scales (SES) 2 and 3 were used to provide measures of psychosexual arousability and sexual motivation (Anderson et al, 1992; Martin et al, 2000). Subject's partners also returned a simple questionnaire at the same time points to record any perceived changes in subject's mood, sexual interest, and sexual activity (Martin et al, 2000).

### Power Calculation and Data Analysis

Testosterone alone can achieve azoospermia in approximately 70% of caucasian men. Assuming that this is achieved in the control group, to be 80% sure of detecting a 20% difference (90% azoospermia in the FIN group), 60 men per arm would be required. However, complete or near azoospermia is required for adequate contraceptive efficacy. The primary objective of this study was therefore to assess whether this was achieved in all men in either or both groups.

Results are presented as means  $\pm$  SEM. Hormonal data were log-transformed to correct nonequality of variance before analysis of variance (ANOVA) for repeated measures, and sperm concentrations were cube root-transformed prior to ANOVA. Paired *t*-tests were used to investigate at what time points a significant treatment effect was seen for each group. Analysis of covariance was used to test for an effect of finasteride after adjusting for baseline values. Categorical data were analyzed by Fisher's exact test.

## Results

Pretreatment sperm and hormonal concentrations are presented in Table 1. There were no significant differences between the 2 groups. One subject in the FIN group withdrew at 12 weeks of treatment for personal reasons. Testosterone pellets were extruded from 1 man in the FIN group after 20 weeks. He therefore stopped desogestrel and finasteride at that point and started the recovery phase. There were no significant adverse events experienced by any subject. Minor adverse events included increased appetite or weight (3), altered moods (3), and decreased libido (3). Compliance with oral medication was very high, as determined by pill returns and direct questioning of the subjects at each visit. Only 2.5% of pills dispensed were returned without having been taken. Subjects in the control group reported missing a median of 0.5 doses (range 0–3) out of a total of 168 doses during the 24-week treatment period. In the FIN group a median of 3.5 doses of both desogestrel and finasteride were reported missed per man (range 0–13). Etonogestrel concentrations determined at 20 weeks of treatment were  $628 \pm 128$  pg/mL in the control group and  $744 \pm 120$  pg/mL in the FIN group (not significant [ns]).

Sperm concentrations for the 2 treatment groups throughout the study are shown in Figure 1. Both groups showed a rapid and profound suppression of spermatogenesis ( $P < .001$ ). This was evident at 4 weeks of treatment in both control ( $P = .04$ ) and FIN ( $P < .001$ ) groups. There were no significant differences between the 2 groups at any time point. Overall, 11 out of 15 subjects (73%) became azoospermic within the 24 weeks of treatment, at the earliest by 8 weeks of treatment and the latest at 20 weeks. Azoospermia was achieved in 6 of 8 men (75%) in the control group and in 5 of 7 men (71%) in the FIN group. There were no significant differences between the 2 groups in the proportion of men becoming azoospermic or the duration of treatment required to achieve azoospermia. The 2 men in the control group with residual spermatogenesis had nadir concentrations of less than  $1 \times 10^6$ /mL ( $0.05$  and  $0.175 \times 10^6$ /mL). In the FIN group, 1 subject had a nadir sperm concentration of  $0.425 \times 10^6$ /mL and 1 subject maintained a concentration con-

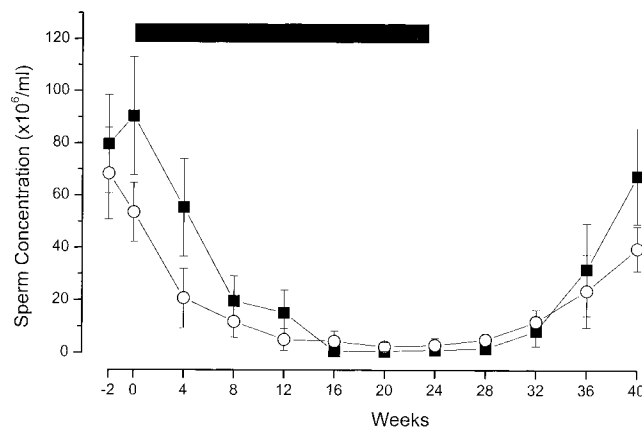


Figure 1. Sperm concentrations at pretreatment baseline (–2 to 0 weeks), during drug administration (weeks 0–24, indicated by bar), and following withdrawal of desogestrel  $\pm$  finasteride treatment. Control group, filled squares ( $n = 8$ ); finasteride group, open circles ( $n = 7$ ). Mean  $\pm$  SEM.

sistently above  $10 \times 10^6$ /mL. Serum etonogestrel concentration in this individual was 454 pg/mL at 20 weeks of treatment, which was within the range of other subjects, and only 3 drug doses were reported missed during the study. This individual was also noteworthy in that while LH concentration was suppressed to a similar degree in other subjects (to undetectable concentrations on 2 occasions), FSH suppression was much more variable, mean overall concentration during treatment being 4.6 IU/L compared with 0.9 IU/L in the other subjects in the FIN group. Serum DHT also fell to a similar degree to other subjects in the group. It cannot therefore be assumed that the basis for the lack of suppression of spermatogenesis in this individual was noncompliance.

Gonadotropin concentrations during the study are shown in Figure 2. All subjects showed significant suppression of both FSH (control,  $P = .003$ ; FIN,  $P < .001$ ) and LH (control,  $P = .016$ ; FIN,  $P = .011$ ) by 2 weeks of treatment. Concentrations of both gonadotropins remained suppressed throughout the treatment period and recovered to pretreatment levels within 4 weeks of stopping treatment. LH became undetectable in 6 of 8 men in the control group and in 6 of 7 in the FIN group during treatment. There were no significant differences between the 2 groups in either LH or FSH concentrations at any time point. Minor rises in FSH concentrations were observed in both treatment groups at 12 and 24 weeks of treatment, but these were not statistically significant.

Testosterone concentrations through the study are shown in Figure 3. Both groups showed a small but statistically significant decline in testosterone levels at 2 weeks of treatment (control,  $P = .007$ ; FIN,  $P = .023$ ), but mean testosterone levels were maintained in the normal physiological range throughout the study. At 16 weeks of treatment there was a transient increase in serum

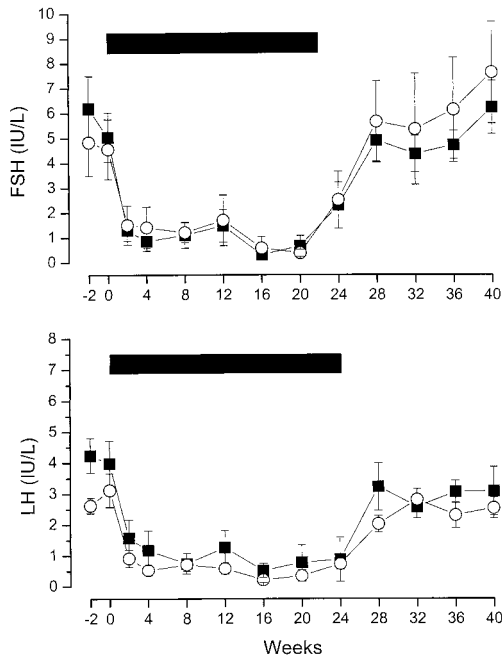


Figure 2. Gonadotropin concentrations at pretreatment baseline (–2 to 0 weeks), during drug administration (weeks 0–24, indicated by bar), and following withdrawal of desogestrel ± finasteride treatment. Control group, filled squares (n = 8); finasteride group, open circles (n = 7). Mean ± SEM.

testosterone concentrations following repeated insertion of testosterone pellets at 12 weeks. There were no significant differences in testosterone concentrations between the 2 treatment groups at any time point of the study.

Dihydrotestosterone concentrations pretreatment were similar in both groups. Both groups show a significant suppression of DHT from pretreatment concentrations at 4 weeks and for the remainder of the treatment period (control and FIN,  $P < .001$ ; Figure 4). During treatment at each time point, the DHT concentrations were significantly lower in the FIN group when compared with the control group ( $P = .01$  at 4 weeks,  $P = .001$  at 12 weeks,  $P = .024$  at 24 weeks). The DHT/testosterone ratio also fell in the FIN group, from  $0.063 \pm 0.008$  to  $0.026 \pm 0.005$  at 12 weeks ( $P < .02$ ) but was unchanged in the control group ( $0.065 \pm 0.008$  to  $0.052 \pm 0.004$ , ns). Similar results were obtained at 24 weeks of treatment. The 4 men who did not achieve azoospermia had DHT concentrations within the range of other subjects both pretreatment and during treatment.

Hematological and biochemical parameters were monitored throughout the study and no significantly abnormal results were noted. Both hemoglobin concentrations and hematocrit showed a small decline during treatment. The fall in hematocrit reached statistical significance when data were analyzed as 1 group, but not when treatment groups were analyzed separately (Table 2). There was no

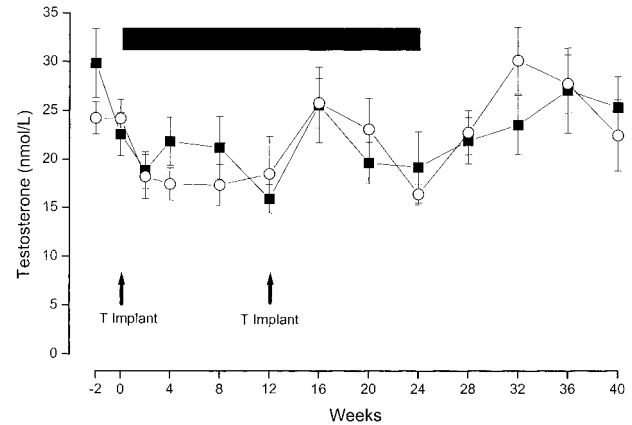


Figure 3. Testosterone concentrations at pretreatment baseline (–2 to 0 weeks), during drug administration (weeks 0–24, indicated by bar), and following withdrawal of desogestrel ± finasteride treatment. Testosterone pellets were inserted at weeks 0 and 12 as indicated by arrows. Control group, filled squares (n = 8); finasteride group, open circles (n = 7). Mean ± SEM.

change in total cholesterol, LDL-C, HDL-C, or triglycerides in either group during treatment and blood pressure was also unchanged throughout the study period (Table 2). Behavioral assessment data are shown in Table 3. There were no significant changes in either of the 2 psychometric tests used or the frequency of sexual activity. Questionnaires were returned by 7 and 6 partners in the control and FIN groups, respectively. Increased interest in sex was reported by 5 partners in the control group and by 2 in the FIN group. No partner reported a decline in interest in sex. The majority of partners reported no change in mood states with the exception being a tendency toward reporting increases in irritability, which was reported by 7 partners (5 and 2 partners in the control and FIN groups, respectively).

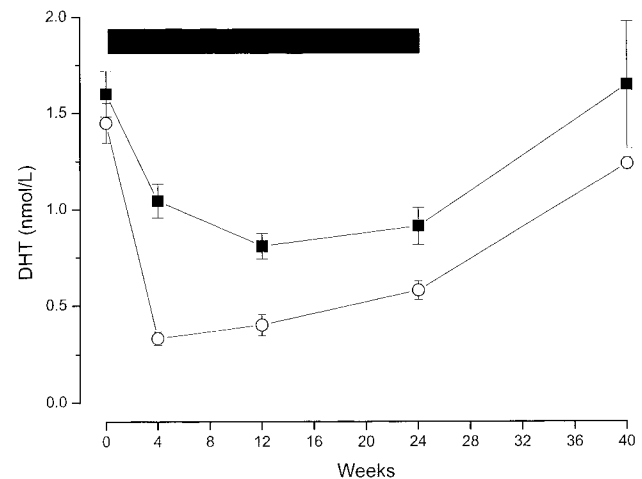


Figure 4. DHT concentrations at pretreatment baseline (0 weeks), during drug administration (weeks 0–24, indicated by bar), and following withdrawal of desogestrel ± finasteride treatment. Control group, filled squares (n = 8); finasteride group, open circles (n = 7). Mean ± SEM.

Table 2. Clinical and laboratory parameters of subjects in the control and finasteride groups before treatment, at 12 and 24 weeks of treatment, and at 16 weeks recovery\*

		0 wk	12 wk	24 wk	Recovery
Hemoglobin, g/L	Control	161 ± 4	153 ± 3	155 ± 3	157 ± 3
	FIN	154 ± 4	150 ± 3	150 ± 4	156 ± 3
Hematocrit	Control	0.46 ± 0.01	0.44 ± 0.01	0.44 ± 0.01	0.45 ± 0.01
	FIN	0.44 ± 0.01	0.43 ± 0.01	0.43 ± 0.01	0.44 ± 0.01
HDL cholesterol, mmol/L†	Control	1.38 ± 0.09	1.20 ± 0.09	1.13 ± 0.10	1.29 ± 0.09
	FIN	1.35 ± 0.19	1.27 ± 0.20	1.26 ± 0.20	1.26 ± 0.24
Total cholesterol, mmol/L	Control	5.12 ± 0.36	4.91 ± 0.29	4.85 ± 0.22	5.84 ± 0.30
	FIN	4.85 ± 0.23	4.54 ± 0.31	4.45 ± 0.33	4.44 ± 0.52
Diastolic BP, mm Hg	Control	71 ± 1	75 ± 3	73 ± 2	73 ± 2
	FIN	71 ± 4	73 ± 3	76 ± 2	78 ± 2
Systolic BP, mm Hg	Control	118 ± 4	123 ± 3	124 ± 4	121 ± 4
	FIN	117 ± 4	120 ± 4	133 ± 2	128 ± 2

\* Values are mean ± SEM. Control group, n = 8; finasteride group (FIN), n = 7.

† HDL indicates high-density lipoprotein; BP, blood pressure.

## Discussion

The combination of oral desogestrel with repeated administration of testosterone pellets resulted in profound suppression of spermatogenesis, with 11 of 15 subjects (73%) achieving azoospermia. A further 3 men had nadir sperm concentrations of less than  $0.5 \times 10^6/\text{mL}$ . The degree of suppression of spermatogenesis therefore compares very favorably with many other androgen-only or androgen/progestogen regimens previously investigated (Merigiola and Bremner, 1997; Nieschlag and Behre, 1998) and is the first demonstration of sustained suppression of spermatogenesis with repeated administration of a depot preparation of testosterone. This allowed maintenance of serum testosterone concentrations within the physiological range and contrasts with the unfavorable pharmacokinetics of injectable testosterone esters currently available (Behre and Nieschlag, 1998). Serum testosterone concentrations showed minor fluctuations over time with trough levels before and a transient rise after

the second insertion of testosterone pellets. FSH concentrations showed slight but not statistically significant rises at 12 and 24 weeks of treatment, coinciding with the nadir of testosterone concentrations. Such fluctuations were not seen for LH, which is consistent with a relatively greater effect of desogestrel on LH than FSH secretion (Wu et al, 1999). This regimen was not associated with significant changes in hemoglobin, hematocrit, or plasma lipoproteins, which is similar to results we previously obtained with a similar regimen used for a short time span (Martin et al, 2000), but different from the significant fall in lipoproteins, particularly HDL-C, reported using desogestrel alone or with testosterone enanthate (Wu et al, 1999). We have previously reported a minor fall in sex hormone binding globulin (SHBG) during oral desogestrel/testosterone pellet administration (Martin et al, 2000), which would be expected to reduce changes in free testosterone when total testosterone concentrations are slightly reduced. While the fall in HDL-C found here, particularly in the control group, did not reach statistical

Table 3. Behavioral assessment of subjects in the control and finasteride (FIN) groups before treatment, at 12 and 24 weeks of treatment, and at 16 weeks recovery\*

	0 wk	12 wk	24 wk	Recovery	
SES-2†	Control	-0.91 ± 0.11	-1.02 ± 0.17	-0.80 ± 0.06	-0.73 ± 0.16
	FIN	-0.99 ± 0.16	-0.73 ± 0.14	-1.05 ± 0.18	-1.12 ± 0.19
SES-3	Control	-0.08 ± 0.15	-0.28 ± 0.09	-0.33 ± 0.12	-0.07 ± 0.08
	FIN	-0.44 ± 0.09	-0.39 ± 0.23	-0.51 ± 0.05	-0.67 ± 0.10
Sexual activity	Control	6.0 ± 1.1	6.0 ± 0.8	5.7 ± 0.6	4.7 ± 1.4
	FIN	8.3 ± 1.6	8.0 ± 2.0	10.2 ± 1.0	9.2 ± 1.5

\* Sexual activity is the sum of number of times subjects reported sexual intercourse or masturbation within the preceding 2 weeks. Mean ± SEM. Control group, n = 8; FIN group, n = 7.

† SES indicates sexual experience scale.

significance, we have more recently found a significant fall of approximately 15% in a larger group of men (Anderson et al, 2000).

The enzyme, 5 $\alpha$ -reductase, converts testosterone to DHT, which interacts with the same androgen receptor as testosterone, but with greater affinity (Grino et al, 1990). 5 $\alpha$ -Reductase therefore effectively acts as an amplifier of androgen action. It is possible that this may contribute to the maintenance of spermatogenesis under certain conditions by amplification of androgen responses in the presence of low intratesticular testosterone concentrations. The ability of rat testicular tissue to convert testosterone to DHT in vitro has long been recognized (Nayfeh et al, 1966; Rivarola and Podestá, 1972) and is differentially distributed with greater activity in the seminiferous tubules than in the interstitium (Rivarola and Podestá, 1972). 5 $\alpha$ -Reductase activity has also been demonstrated in the human testis (Payne et al, 1973; Rivarola et al, 1973) and there appeared to be an increase in activity at the expected time of puberty (Rivarola et al, 1975) although data are very limited. The presence of messenger RNA (mRNA) for both isoenzymes of 5 $\alpha$ -reductase has been demonstrated in the male reproductive tract (Thigpen et al, 1993; Viger and Robaire, 1995). While mRNA and enzyme activity levels were very low in human testis, the presence of enzyme activity at pH 5.0 but not pH 7.0 is consistent with the presence of the type 2 enzyme (Thigpen et al, 1993). Conversely, the type 1 isoenzyme is present in the rat testis (Viger and Robaire, 1995). There may therefore be significant species difference in the testicular expression of 5 $\alpha$ -reductase isoenzymes. DHT can quantitatively support spermatogenesis at lower doses than are required with testosterone (Ahmad et al, 1973; Chen et al, 1994). Recently the role of 5 $\alpha$ -reductase in supporting spermatogenesis in the rat under conditions of reduced testosterone concentration has been clearly demonstrated using the inhibitor, L685-273 (O'Donnell et al, 1996, 1999). Inhibition of 5 $\alpha$ -reductase resulted in an increase in the dose of testosterone required to support spermatogenesis and reduced the progression of round spermatids through mid-spermiogenesis and the number of elongate spermatids produced.

Finasteride is a 4-azasteroid derivative that potently inhibits 5 $\alpha$ -reductase (Gormley et al, 1990). The dose given in the present study is sufficient to maximally reduce intraprostatic DHT concentrations (Geller 1990; McConnell et al, 1992) although intraprostatic testosterone concentrations were increased. A marked fall in serum DHT concentrations was demonstrated in the present study.

Previous studies using desogestrel with either testosterone pellets (Martin et al, 2000) or weekly testosterone enanthate injections (Wu et al, 1999) showed that a dose of 150  $\mu$ g is submaximal for full suppression of spermatogenesis. This dose was therefore chosen in the pre-

sent study to allow any additional effect of finasteride to be detected. While profound suppression of spermatogenesis was achieved, the lack of universal azoospermia demonstrates that this design aim was achieved. Administration of finasteride did not result in any increase in the degree of spermatogenic suppression achieved; in fact, the only individual in whom spermatogenesis was not profoundly suppressed was in that treatment group. While larger studies are required to detect significant differences in the proportion of men achieving azoospermia, crucially and pragmatically, azoospermia was not achieved in all subjects in the FIN group. Firstly, finasteride shows some selectivity for the type 2 5 $\alpha$ -reductase isoform (Andersson et al, 1991); thus, if the predominant isoform in the human testis is the type 1 isoform, it is possible that this underlies the lack of effect observed here. However, L685-273, the 5 $\alpha$ -reductase inhibitor that is effective in rodent testis (O'Donnell et al, 1999) also shows selectivity for the type 2 isoform. A second possible reason for the lack of effect of finasteride is that intratesticular testosterone concentrations were insufficiently suppressed, as the effect of higher doses of testosterone on spermatogenesis was unaffected by inhibition of 5 $\alpha$ -reductase (O'Donnell et al, 1999). Although LH was suppressed to undetectable concentrations in the majority of men in both groups using an assay of high sensitivity, it is possible that there remained sufficient intratesticular steroidogenesis to maintain testosterone concentrations sufficient to prevent an effect of finasteride. Third, it is possible that an increase in intratesticular testosterone secondary to finasteride, as found in the prostate, may have overridden any inhibitory effect of that drug. However, the clear demonstration of effect of L685-273, which might be expected to have similar effects on intratesticular testosterone concentrations, indicates that this is not a likely explanation.

Testosterone is an essential component of a hormonal male contraceptive regimen to maintain extragonadal androgen functions, but it is possible that inadequate depletion of intratesticular testosterone may provide some direct support to spermatogenesis. Administration of testosterone esters with short duration of action, such as testosterone enanthate, results in supraphysiological concentrations of testosterone, which are amplified by a reduction in SHBG concentrations. This may result in peak bioactive testosterone concentrations of up to 10-fold higher than normal (Anderson and Wu, 1996) and it is possible that these high concentrations may have a direct effect on spermatogenesis. It is clearly established that testosterone alone (ie, without FSH) can support spermatogenesis in the rat (Ahmad et al, 1973) and it is likely that this applies in humans (Matsumoto et al, 1984). The recent demonstration of apparently increased prevalence of azoospermia with a combination of desogestrel with 50 mg of testosterone enanthate per week compared with

100 mg per week provides indirect support for this (Wu et al, 1999). The increased prevalence of azoospermia in studies investigating the combination of the antiandrogen/progestogen cyproterone acetate with testosterone may also reflect antagonism of the action of testosterone within the testis (Meriggiola et al, 1996).

The testosterone pellets used in the present study have been shown to exhibit near zero order release (Handelsman et al, 1990; Jockenhövel et al, 1996) and throughout the present study testosterone concentrations were consistently maintained within the normal range. It is therefore possible that the basis for the maintenance of spermatogenesis in some men on the present regimen is different from that with other regimens based on short-acting testosterone esters and that 5 $\alpha$ -reductase is not involved. The androgen-dependence of 5 $\alpha$ -reductase activity (Andersson et al, 1989; George et al, 1991) may also underlie the involvement of 5 $\alpha$ -reductase in a testosterone-based contraceptive regimen, and not be pertinent to a progestogen-based regimen. A further possibility is that desogestrel may have some direct effect within the testis, as is suggested for other progestogens (Fotherby et al, 1972; Worgul et al, 1979; Cooke et al, 1991) including the possibility of a direct inhibitory effect on 5 $\alpha$ -reductase (Mauvais-Jarvis et al, 1974). It is not known whether desogestrel might have an inhibitory effect on 5 $\alpha$ -reductase, but a direct effect on steroidogenesis has been suggested (Kuhl et al, 1995). Thus the advantageous effects of the progestogen component of the present regimen may therefore have prevented demonstration of the involvement of 5 $\alpha$ -reductase.

Use of finasteride for treatment of benign prostatic hypertrophy is associated with an increased prevalence of reduced libido and impotence in older men (Gormley et al, 1992). In a placebo-controlled study of finasteride administration to normal young men, no consistent effect on sleep-related penile erection was found (Cunningham and Hirshkowitz, 1995). In the present study, none of the subjects or their partners reported any consistent effects on sexual interest, activity, or mood.

In conclusion, the combination of desogestrel with testosterone pellets resulted in profound suppression of spermatogenesis, but azoospermia was not achieved in all subjects. Administration of the 5 $\alpha$ -reductase inhibitor, finasteride, did not affect the degree of suppression of spermatogenesis. While these data support the development of desogestrel/testosterone combinations for male contraception, they do not provide support for the involvement of 5 $\alpha$ -reductase in the maintenance of spermatogenesis in men remaining oligozoospermic on such regimens.

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