0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(8):3640–3649

Suppression of Spermatogenesis by Etonogestrel Implants with Depot Testosterone: Potential for Long-Acting Male Contraception

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The coadministration of a progestogen with testosterone increases the degree of suppression of spermatogenesis and is one approach to the development of hormonal male contraception. Depot formulations may allow a reduction in dosage, minimizing adverse effects. We have investigated the effects of a sc implant containing the progestogen etonogestrel (Implanon) with depot testosterone on spermatogenesis in normal men. Twenty-eight men were randomized to receive either one or two etonogestrel implants, removed after 24 wk. All men additionally received 400 mg testosterone pellets on d 1 and at 12 wk. Four men withdrew during the study, three because of side effects. Testosterone concentrations remained within the physiological range during treatment, although they were overall slightly reduced, compared with pretreatment. Both groups showed marked suppression of spermatogenesis, nine men in each group achieving azoospermia (64% and 75% in the one- and two-implant groups, respectively). Sperm concentrations in 13/14 men in the two-implant group fell to 0.1 × 10^6/ml or less. Spermatogenic suppression was more variable in the one-implant group, with partial recovery in three men. Incomplete suppression of spermatogenesis in the one-implant group was associated with less complete suppression of gonadotropins. There were no significant changes in body weight, hemoglobin, hematocrit, or high-density lipoprotein cholesterol concentrations during treatment. These data demonstrate that etonogestrel implants with depot testosterone provide effective suppression of spermatogenesis with reduced metabolic effects and are, therefore, a promising approach to the development of long-acting yet reversible male contraception. (*J Clin Endocrinol Metab* 87: 3640–3649, 2002)

THE SUPPRESSION OF gonadotropin secretion in men results in depletion of intratesticular testosterone and spermatogenic arrest. Reliable suppression of spermatogenesis to near azoospermia is required for a viable hormonal method of male contraception and has been demonstrated to be achievable (1, 2). However, many steroidal regimens thus far investigated involve supraphysiological doses of testosterone, which result in side effects and unfavorable metabolic changes including a fall in high-density lipoprotein C (HDL-C) concentration (3–5). The combination of a progestogen with testosterone increases the degree of suppression of spermatogenesis, compared with testosterone alone, and allows a marked reduction in testosterone dosage (6–8). Several progestogens have been investigated in this context, including levonorgestrel, medroxyprogesterone acetate, cyproterone acetate, and norethisterone enanthate using both oral and injectable preparations (5–9). Administration of the oral gestagen desogestrel in combination with testosterone results in a high prevalence of azoospermia but still has impact on nonreproductive metabolism (10–12).

Long-acting hormonal preparations may have significant advantages in addition to convenience. In particular, lower total drug dosage may be required for equivalent biological effect, with, therefore, potentially fewer side effects and long-term risks. This dose-sparing effect has been demonstrated in a comparison of injectable *vs.* depot testosterone (13), in which a greater than 50% reduction in testosterone dose was achieved with the depot formulation while maintaining similar suppression of spermatogenesis. Compared with oral administration, implants will also reduce the exposure of the liver to high postabsorptive doses of drug, which may further reduce effects on lipoproteins and SHBG concentrations. Progestogen depot preparations with 6- to 12-wk injection intervals have been investigated (6), but there is limited evidence as to the efficacy of long-acting progestogen-containing implants (14). A subdermal implant containing etonogestrel, the active metabolite of the orally active desogestrel, has been developed and recently licensed for use as a female contraceptive (Implanon, N.V. Organon, Oss, The Netherlands), a single implant providing contraceptive protection for 3 yr (15). In combination with depot testosterone, these implants may, therefore, provide a contraceptive regimen for male contraception with a long administration interval and minimizing potentially adverse nonreproductive effects. Testosterone pellets have some disadvantages but provide the most stable testosterone concentrations among currently available preparations (16). We and others have previously demonstrated that repeated administration can successfully maintain testosterone concentrations in the physiological range for at least 1 yr in male contraceptive trials (12, 17, 18).

We here evaluated this combination in a phase II clinical trial. The primary objective of this study was to assess the use of etonogestrel implants in combination with testosterone pellets for suppression of gonadotropin secretion and sper-

Abbreviations: HDL-C, High-density lipoprotein C; LDL-C, low-density lipoprotein cholesterol; pro-αC, inhibin forms containing pro and αC.

matogenesis in normal men. The dose of testosterone was chosen to provide physiological replacement without by itself having a significant suppressive effect on spermatogenesis (19). Secondary objectives included pharmacokinetic and dose-finding information by comparison of one *vs.* two etonogestrel implants, assessment of duration of action over a 24-wk treatment period, and monitoring metabolic and behavioral effects.

Subjects and Methods

Subjects

Twenty-eight Caucasian men aged 21–39 yr (mean, 31 yr) were recruited from the local population. All men gave informed written consent, and this study received ethical approval from the Lothian Reproductive Medicine Ethical Review Committee. The study was performed to good clinical practice standards. 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 two occasions at least 2 wk apart, which were assessed using World Health Organization methods (20) in a laboratory that participates in the United Kingdom national external quality assessment scheme for semen analysis. Pretreatment sperm concentrations were greater than 20×10^6/ml in all men, and motility and morphology were within normal ranges for the local population.

Study design and medication

The study was a prospective, randomized trial investigating the use of etonogestrel implants with depot administration of testosterone in the form of sc pellets. Subjects were randomized into two treatment groups. Group I received a single etonogestrel implant; group II received two etonogestrel implants. Etonogestrel sc implants (Implanon, N.V. Organon) were 4 cm long, contained 68 mg etonogestrel, and were inserted under local anesthetic into the medial aspect of the nondominant upper arm. Additionally, on the day of etonogestrel implant insertion and 12 wk later, all subjects received 400 mg testosterone pellets (2×200 mg, N.V. Organon) inserted sc under local anesthetic into the anterior abdominal wall. After 24 wk of treatment, the etonogestrel implants were removed under local anesthetic. The testosterone pellets dissolve completely and do not require removal.

Subjects were reviewed 2 wk after commencing medication, and at 4-wk intervals during the 24-wk treatment phase and during the recovery phase of 16 wk after etonogestrel implant removal. At each visit subjects were examined and adverse events or other health problems recorded, semen samples produced, and venepuncture performed. Subjects were required to continue their current method of contraception throughout the study.

Assays

Semen samples were submitted after 3–7 d of abstinence. Each semen sample was assessed for sperm concentration using World Health Organization methodology (20). Oligozoospermic samples were examined to give a lower limit of quantification of concentration of 0.025×10^6/ml. Azoospermia was confirmed by careful examination of the pellet following centrifugation of the ejaculate.

Blood samples were obtained between 0700 and 1200 h at every visit. Samples were separated by centrifugation and serum stored at −20 C until assay. Testosterone was measured by RIA and LH and FSH by time-resolved immunofluorometric assay (DELFIA, Wallac, Inc., Turku, Finland), SHBG by immunoradiometric assay (DPC, Los Angeles, CA). Methodologies were as previously described (21, 22). Assay sensitivity was 0.15 IU/liter for LH and 0.125 IU/liter for FSH. Intraassay and interassay coefficients of variation were less than 5% and less than 9%, respectively, for testosterone, LH, and FSH. Inhibin B and inhibin forms containing pro and αC (pro-αC) immunoreactivity were measured in serum and seminal plasma as previously described (23–25). Assay sensitivities for inhibin B and pro-αC were 15 and 3 pg/ml, respectively, and coefficients of variation 15% (inhibin B) and 7.3% (pro-αC). 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 (N.V. Organon). Samples were analyzed for general hematological and biochemical values, including total cholesterol, HDL-C, and low-density lipoprotein cholesterol (LDL-C), and by routine autoanalyzer at 12-wk intervals.

Behavioral assessment

Sexual interest and activity were investigated before treatment, at 12 and 24 wk of treatment, and at the end of recovery. A structured interview was used to quantify sexual activity over the preceding 2 wk, and the Frenken Sexual Experience Scale 2 was used to provide a measure of psychosexual arousability (26, 27).

Data analysis

Results are presented as mean ± SEM. Serum hormonal data were log transformed to correct nonequality of variance before ANOVA for repeated measures, and sperm concentrations were cube root transformed before ANOVA. Paired *t* tests were used to investigate at what time points a significant treatment effect was seen for each group, *e.g.* to analyze fluctuations in gonadotropin concentration during treatment. Seminal plasma inhibin B was analyzed by nonparametric testing (Friedman test and Spearman correlation). Categorical data were analyzed by Fisher's exact test.

Results

Subjects, adverse events, and withdrawals

Pretreatment values for the subjects are shown in Table 1. There were no significant differences between groups in age; body mass index; sperm concentration; or LH, FSH, or testosterone concentrations.

There were no episodes of extrusion or other significant complications of the testosterone pellets during the study. All etonogestrel implant insertions were uncomplicated, and no subjects reported discomfort or any other implant-related complications during the course of the study. Implant removal was generally uncomplicated, although in one individual one of the two implants was found to be in two pieces at the time of removal. Removal of the second, shorter length of that implant was completed without difficulty under local anesthesia a few days later. The subject reported no trauma to the area. Examination of the implant by the manufacturer did not identify a specific reason that implant was in two pieces. None of the data from this individual was distinguishable from the rest of the group and are thus included in the analysis.

Four men withdrew before completing 24 wk of treatment. One man in group I withdrew at 12-wk treatment because of perceived reduction in ejaculate volume, which was not confirmed by semen analysis. Three men withdrew from group II: one at 12 wk because of mood changes, one at 12 wk

TABLE 1. Pretreatment values of subjects in the two treatment groups

Pretreatment value	Group I (n = 14)	Group II (n = 14)
Age (yr)	32 ± 1	30 ± 2
Body mass index (kg/m^2)	23.3 ± 0.8	24.2 ± 1.3
Sperm concentration ($\times 10^6$/ml)	68 ± 9	60 ± 9
LH (IU/liter)	5.0 ± 0.8	4.1 ± 0.3
FSH (IU/liter)	5.0 ± 0.6	4.4 ± 0.4
Testosterone (nmol/liter)	24.1 ± 0.9	24.1 ± 1.3

Groups I and II reflect administration of one or two etonogestrel implants, respectively. Data are mean ± SEM.

because of change in personal circumstances unrelated to the study, and one at 16 wk with increased fatigue. There was no change in weight (Table 2) or blood pressure during the study in either treatment group.

Testosteroneand etonogestrel concentrations

Serum testosterone concentrations remained within the physiological range throughout the treatment period in both groups (Fig. 1a) with minor fluctuations in keeping with the schedule of testosterone administration. There was an initial fall at the start of treatment to a nadir at 12 wk ($P < 0.001$ in both groups), the time of administration of the second dose of testosterone. Testosterone rose at 16 wk to concentrations not significantly different from pretreatment and then again showed a gradual decline until 24 wk, at which time the etonogestrel implants were removed. Testosterone concentrations during treatment were slightly lower in group II, compared with group I, but this difference did not reach statistical significance. Testosterone concentrations below the normal range (10 nmol/liter) were detected in three men in group I and six men in group II. These values were all at 12-wk of treatment, with none of the subjects having concentrations less than 10 nmol/liter at the second trough at wk 24. At wk 12 and 24, testosterone concentrations of individual subjects were an average of 69% and 71% of pretreatment concentrations in group I and 56% and 60% in group II. Mean 4-wk testosterone concentrations during testosterone/etonogestrel administration were 19.0 ± 0.6 nmol/liter in group I and 15.4 ± 0.5 nmol/liter in group II. During the recovery phase, testosterone concentrations rapidly returned to pretreatment concentrations. Calculated free testosterone concentrations (28) were significantly reduced in both treatment groups at both 12- and 24-wk treatment during testosterone/etonogestrel administration (both $P < 0.001$, Table 2) and returned to pretreatment concentrations during the recovery phase.

Etonogestrel concentrations were highest 2 wk after implant insertion, with concentrations that were similar in the two groups, 467 ± 194 pg/ml in group I and 528 ± 69 pg/ml in group II (Fig. 1b). Thereafter, however, there was a clear dose dependency, concentrations in group II being approximately 2-fold higher than in group I ($P < 0.001$) during the remainder of the treatment phase. Etonogestrel concentrations in both groups showed a gradual decline during the treatment phase, falling after 24 wk to 60% of the concentration at 4 wk in group I and to 56% in group II.

Sperm concentration

All men in both treatment groups showed a profound suppression of sperm concentration ($P < 0.001$, Fig. 2) during etonogestrel/testosterone administration. During the course of the treatment phase, nine men in each group became azoospermic. Taking into account those men who withdrew from the study without achieving azoospermia, this gives a prevalence of azoospermia of 64% in group I and 75% in group II. Although there was a trend toward more complete suppression of sperm concentrations in group II, this did not achieve statistical significance either overall or at any single time point. In group I, sperm concentrations in 10, 13, and 14 men (of 14) fell below the thresholds of 1, 3, and 5×10^6/ml. In group II, sperm concentration fell to 0.1×10^6/ml or less in 13 of 14 men. Only one man in the study, in group II, maintained a sperm concentration of more than 5×10^6/ml throughout the study. Sperm concentration in this individual reached a nadir of 7.8×10^6/ml at the end of the treatment phase (24 wk). This man weighed 68 kg, less than the mean for the whole group, and gonadotropin concentrations were suppressed to a similar degree to other men. Of the four individuals who withdrew from treatment during the course of the study, two became azoospermic (both at 12 wk, one from each dosage group), and in the other two men spermatozoa were detectable only in the ejaculate pellet after centrifugation in their final treatment sample, at 12 and 16 wk (both group II).

TABLE 2. Weight, SHBG, calculated free testosterone, and lipid concentrations and hematological parameters pretreatment, during treatment and after 16 wk recovery in men receiving testosterone pellets with either one or two etonogestrel implants

		Pretreatment	12 wk	24 wk	Recovery
Weight (kg)	Group I	84.7 ± 3.0	82.8 ± 2.8	83.1 ± 2.5	83.8 ± 3.1
	Group II	77.2 ± 2.9	78.5 ± 2.9	76.1 ± 2.7	77.2 ± 3.0
SHBG[a] (nmol/liter)	Group I	30.8 ± 2.7	26.5 ± 2.8	27.3 ± 2.7	32.7 ± 2.9
	Group II	31.4 ± 6.6	24.6 ± 2.8	28.3 ± 3.5	30.3 ± 3.9
Free testosterone (nmol/liter)[b]	Group I	0.58 ± 0.04	0.40 ± 0.03	0.41 ± 0.05	0.50 ± 0.10
	Group II	0.58 ± 0.04	0.30 ± 0.02	0.32 ± 0.03	0.56 ± 0.04
Cholesterol (mmol/liter)	Group I	4.8 ± 0.3	4.9 ± 0.2	4.5 ± 0.2	4.7 ± 0.3
	Group II	4.9 ± 0.2	4.8 ± 0.1	5.0 ± 0.2	5.3 ± 0.2
HDL-C (mmol/liter)	Group I	1.4 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.1
	Group II	1.20 ± 0.06	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
LDL-C[a] (mmol/liter)	Group I	2.7 ± 0.4	3.2 ± 0.3	2.8 ± 0.2	2.8 ± 0.3
	Group II	2.8 ± 0.2	3.1 ± 0.1	3.3 ± 0.2	3.5 ± 0.2
Hemoglobin (g/liter)	Group I	150 ± 2	147 ± 2	146 ± 3	145 ± 3
	Group II	151 ± 2	150 ± 2	148 ± 3	155 ± 2
Hematocrit	Group I	0.42 ± 0.01	0.42 ± 0.01	0.42 ± 0.01	0.43 ± 0.01
	Group II	0.43 ± 0.01	0.43 ± 0.01	0.42 ± 0.01	0.45 ± 0.01

Groups I and II reflect administration of one or two etonogestrel implants, respectively.

[a] SHBG concentrations were significantly lower at 12 and 24 wk treatment than pretreatment when both groups were analyzed together, but not separately. LDL-C concentrations showed a significant increase during treatment in both treatment groups.

[b] Free testosterone concentrations were significantly reduced in both treatment groups. There were no significant changes during treatment in any of the other parameters. Mean ± SEM, n = 14 per group.

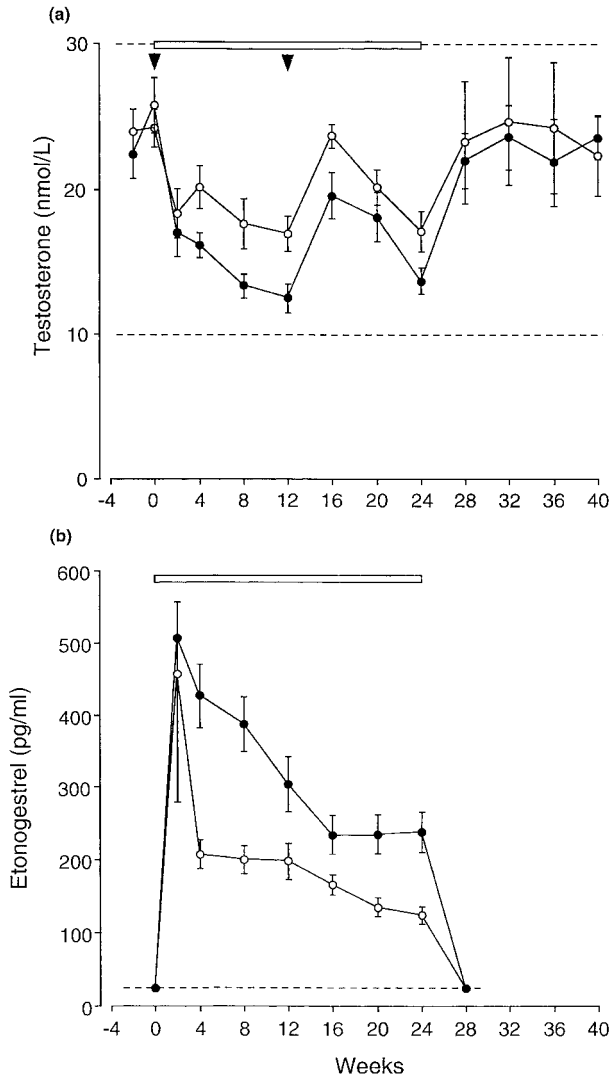

FIG. 1. Testosterone (a) and etonogestrel (b) concentrations during etonogestrel/testosterone treatment. The duration of etonogestrel treatment is indicated by the *bar*, and the *arrows* indicate the time points at which testosterone pellets (400 mg) were administered. ○, Group I; ●, group II. The *dotted lines* (a) indicate the normal range and limit of detection of the assay (b). Mean SEM, n = 14/group.

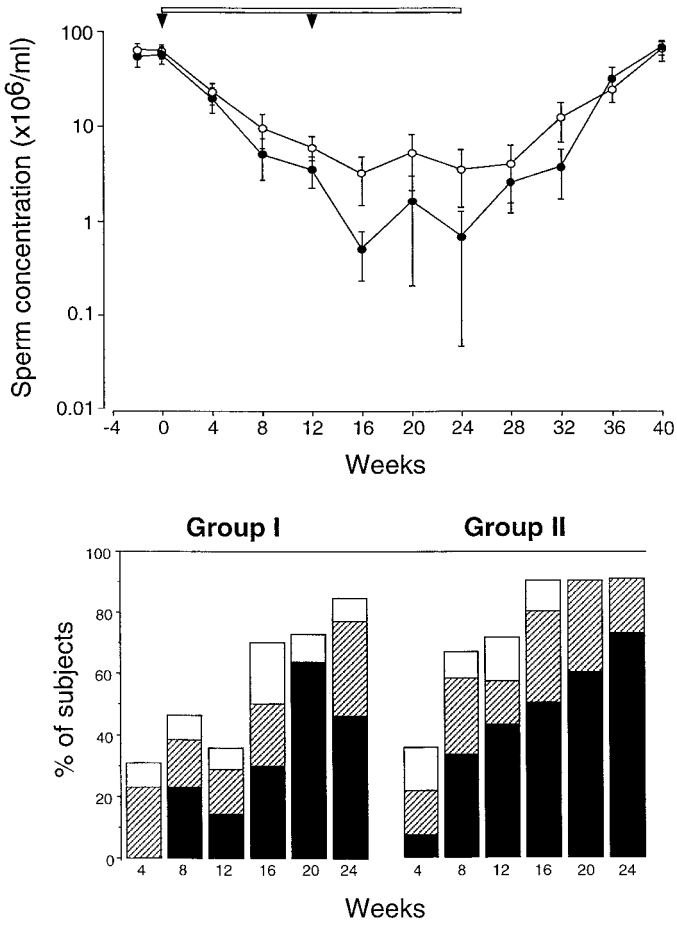

FIG. 2. Sperm concentrations (a) during etonogestrel/testosterone treatment. The duration of etonogestrel treatment is indicated by the *bar*, and the *arrows* indicate the time points at which testosterone pellets (400 mg) were administered. ○, Group I; ●, group II. Mean SEM, n = 14/group. Note *logarithmic scale* on ordinate. Percentages of men in each group (b) achieving azoospermia (■), sperm concentrations of 1×10^6/ml or less (▨) and 3×10^6/ml or less (□) at each time point during etonogestrel/testosterone treatment.

A clearer difference in the spermatogenic response to treatment was, however, seen in the pattern of suppression during the second half of the treatment phase, with more variable suppression in group I. Five men in that group showed partial recovery of spermatogenesis during continuing treatment, sperm concentration rising in three men from 2–4 $\times$ 10^6/ml at 16 wk to more than 20×10^6/ml at 24 wk and from azoospermia to the presence of low concentrations ($<1 \times 10^6$/ml) of spermatozoa in another two men. This pattern of suppression followed by evidence of partial recovery was not seen in any men in group II, all of whom were azoospermic or showed nadir sperm concentrations at 24 wk. Recovery in group I, however, was not always associated with incomplete suppression because two men who did not achieve azoospermia showed nadir sperm concentrations at 24 wk of treatment.

There was no clear relationship between maintenance of spermatogenesis during treatment and weight. Mean weight (range) of the seven men in group I who were azoospermic at the end of treatment was 81 kg (74–94 kg), whereas in the men who showed incomplete suppression it was 89 kg (77–109 kg). In group II, the three individuals who showed incomplete suppression of spermatogenesis weighed 84, 69, and 68 kg (overall group mean, 75 kg), with the individual weighing 68 kg maintaining the highest sperm concentration.

Other reproductive hormones

There was marked suppression in the concentrations of both LH and FSH during etonogestrel/testosterone administration ($P < 0.001$, Fig. 3). Overall, there was no significant difference in either LH or FSH concentrations between the two treatment groups, and there were no significant differences at any of the individual time points. There were fluctuations in both LH and FSH concentrations in both groups at 12 and 24 wk, reciprocal to changes in testosterone concentrations. Following readministration of testosterone at 12 wk, concentrations of both gonadotropins fell at 16 wk (LH:

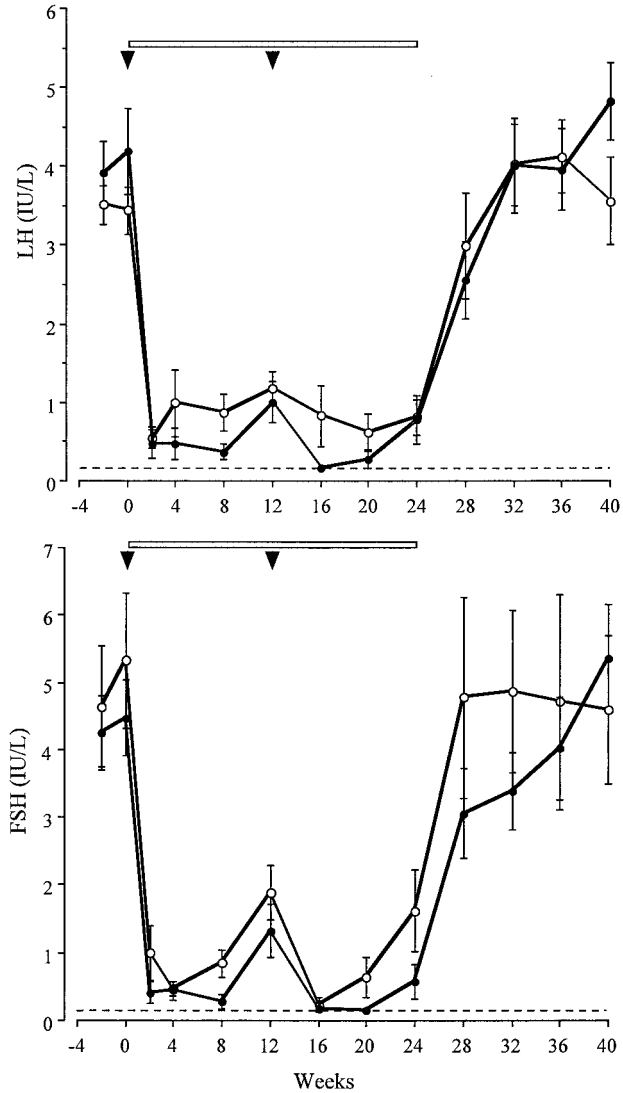

FIG. 3. Gonadotropin concentrations during etonogestrel/testosterone treatment. The duration of etonogestrel treatment is indicated by the *bar*, and the *arrows* indicate the time points at which testosterone pellets (400 mg) were administered. ○, Group I; ●, group II. The *dotted lines* indicate the limit of detection of the assays, and the *arrows* on the ordinate indicate the lower limit of the normal ranges. Mean SEM, n = 14/group.

$P = 0.02$ in both groups; FSH: $P = 0.001$ group I, $P = 0.005$ group II). A small rise in FSH concentrations at 24 wk was also observed in group I, but this did not reach statistical significance. Combining data from 12 and 24 wk, FSH was undetectable in 4% and 26% of samples in group I and II, respectively, and LH was undetectable in 21% and 48%. By comparison, at 8 and 16 wk, FSH was undetectable in 38% and 64% of samples in groups I and II, respectively, and LH was undetectable in 45% and 65% of samples. Concentrations of both hormones were not significantly different from pretreatment throughout the recovery phase.

Analysis of mean LH and FSH concentrations during treatment by degree of suppression of spermatogenesis in group I showed significant differences in LH ($P = 0.022$) but not FSH between those men who were azoospermic at the end of the study (n = 6; data not included from the subject who withdrew) and those in whom spermatogenesis was maintained or showed recovery during the treatment phase and were thus not azoospermic at the end of the treatment phase (n = 7, Fig. 4). Similar statistical analysis was not possible in group II because of the more consistent suppression of spermatogenesis. This method of analysis, however, did allow the demonstration that there were no differences in either mean treatment LH or FSH concentrations between group II and the azoospermic men in group I (Fig. 4), although both LH ($P = 0.01$) and FSH ($P = 0.003$) were significantly lower in group II than in the nonazoospermic men in group I. Mean treatment concentration of LH in the individual in group II who showed significant ongoing sperm concentrations was 0.81 IU/liter, and concentration of FSH was 0.49 IU/liter, compared with group means of 0.48 ± 0.10 and 0.49 ± 0.12 IU/liter, respectively. Similarly, less suppressed mean LH concentrations (1.47, 1.20, and 0.98 IU/liter) were also found in three other individuals in group II, all of whom showed relatively slow suppression of spermatogenesis with sperm concentrations of approximately 10×10^6/ml at 12 wk (group mean, 3.8×10^6/ml at that time point) but all of whom subsequently became azoospermic.

There were no significant differences in SHBG concentrations between the two groups. SHBG concentrations showed a small fall during testosterone/etonogestrel treatment (Table 2). This did not reach statistical significance when the two groups were analyzed separately but was significant at both 12 and 24 wk of treatment ($P = 0.013$) when the groups were analyzed together. SHBG concentrations showed a significant increase during the recovery phase to pretreatment concentrations (Table 2).

Inhibin B concentrations in peripheral blood showed no significant changes over the study period in either group (Fig. 5) or when analyzed as a single group. Pro-αC inhibin fell markedly during treatment with concentrations dropping to approximately half of pretreatment levels after 4 wk of treatment in both groups ($P = 0.004$, group I; $P < 0.001$, group II, with no significant differences between groups). Pro-αC remained suppressed for the duration of treatment, although there were changes during treatment in parallel to changes in gonadotropin secretion: Concentrations were at their nadir at 4 wk and rose significantly at 12 wk of treatment ($P = 0.001$, $P = 0.014$ in the groups I and II, respectively) with similar concentrations at 24 wk. Pro-αC concentrations rose following removal of etonogestrel implants and were similar to pretreatment at the end of the recovery period.

Seminal plasma inhibin B concentrations before treatment showed a marked variation among subjects, as previously described (25). There was a significant fall in seminal plasma inhibin B concentrations during treatment in group II ($P = 0.02$), which was seen at 4 wk of treatment (Fig. 5). This decline continued for the duration of treatment, by the end of which mean inhibin B had fallen from 2700 to 190 pg/ml and had become undetectable in 5 of 14 men. However, two of these five men did not achieve azoospermia, and the range of detectable concentrations in those men who did achieve azoospermia was 93–440 pg/ml. There was no overall significant change in seminal plasma inhibin B concentrations in group I, although inhibin B became undetectable in two

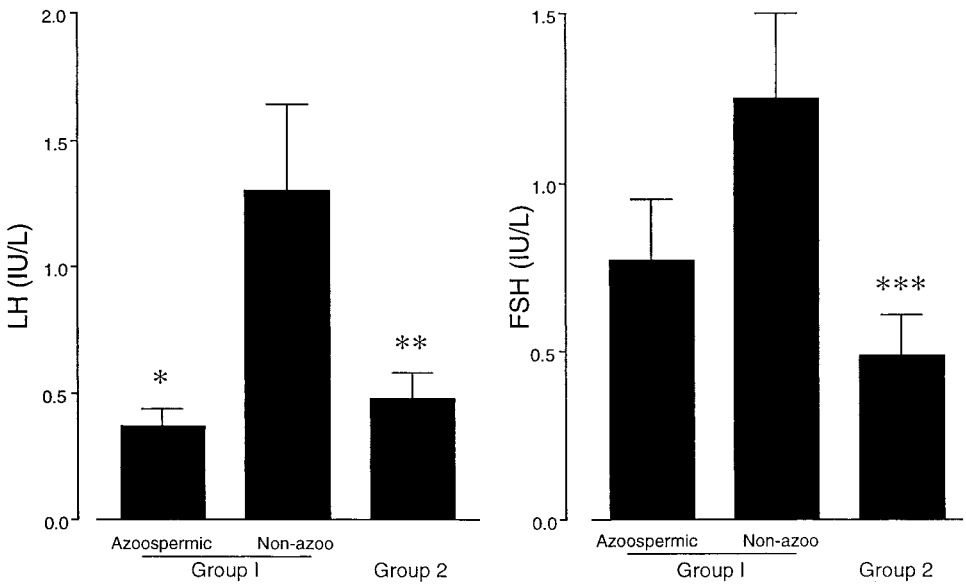

FIG. 4. Serum concentrations of LH and FSH during etonogestrel/testosterone treatment. Data are mean ± SEM of average hormone concentrations at all time points during treatment; subjects in group I were divided into those who were azoospermic at the end of the treatment period (n = 6) and those who were not (n = 7), *vs.* all subjects in group II (n = 14). *Asterisks* indicate significant differences, compared with the nonazoospermic, one-implant group. *, $P = 0.02$; **, $P = 0.01$; ***, $P = 0.003$.

men and fell to less than 50 pg/ml (approximately 5% of pretreatment) in another five men. There was a significant positive relationship between sperm concentration and seminal plasma inhibin B concentration at the end of treatment in group I ($P = 0.03$).

Lipids and hematology

HDL-C concentrations showed a small (<10%) fall over the course of treatment (Table 2), which was not statistically significant. Because there were no differences between the two groups, the data were also analyzed as a single group, again showing no significant change in HDL-C concentration. There were no significant changes in total cholesterol concentrations in either treatment group during treatment. LDL-C concentrations showed significant increases during treatment in both implant groups (group I, $P = 0.03$; group II, $P = 0.01$), which, however, were not reversed during the recovery phase (Table 2).

There was no significant change in hemoglobin concentration or hematocrit through the duration of the study in either treatment group (Table 2). There were no significant alterations or abnormalities in any of the clinical biochemical markers.

Behavioral assessments

Sexual activity was recorded as the sum of sexual intercourse and masturbation in the preceding 2 wk and showed no change during the course of the study in either group or when both groups were analyzed together (Table 3). Similarly, there was no change in the Frenken Sexual Experience Scale 2 score during the course of the study (Table 3).

Discussion

The combination of etonogestrel implants with testosterone pellets resulted in profound suppression of spermatogenesis, with sperm concentrations of less than 1×10^6/ml (in fact, $<0.1 \times 10^6$/ml) in 13 of 14 men (92%) in group II and 10 of 14 men (71%) in group I. This degree of efficacy is similar to that achieved with other combinations of testosterone with progestogen (5, 8–10) or GnRH antagonist (29, 30) but with reduced nonreproductive effects. There are no previous data on the effects on spermatogenesis of these or similar progestogen implants in Caucasian men. This degree of spermatogenic suppression was achieved with a daily steroid dose of approximately 100 μg etonogestrel (group II, two implants) and 4.8 mg testosterone. Comparison with studies of oral desogestrel (10, 11), which is converted into etonogestrel by nonlimiting first-pass hepatic metabolism (31), reveals the enhanced efficacy of implant preparations. Serum etonogestrel concentrations of approximately 1200 pg/ml were reported for 300 μg desogestrel and 500–800 pg/ml for 150 μg desogestrel (10, 11), compared with approximately 400 pg/ml at 8 wk in group II. Higher rates of etonogestrel release over the initial days after insertion may in fact be advantageous in augmenting suppression of gonadotropin secretion. The dose administered in the present study is, therefore, lower than in studies investigating the effects of oral desogestrel, yet the degree of spermatogenic suppression was similar, consistent with a dose-sparing effect of preparations with near zero-order release. This relatively low dose of etonogestrel and the avoidance of first-pass hepatic effects are also likely to have contributed to the lack of significant effect on HDL-C and SHBG concentrations because the decreases observed in combination studies are similar to those with oral desogestrel administered alone (10).

Dose sparing has also been demonstrated with testosterone pellets, compared with weekly injections of testosterone enanthate (13). All hormonal-based male contraceptive regimens require the administration of testosterone, both to contribute to gonadotropin suppression and prevent testosterone deficiency. The characteristics of the testosterone preparation are, therefore, central to the efficacy of the regimen. The optimum preparation of testosterone would provide constant and consistent physiological concentrations with an infrequent administration schedule. No such preparation is yet available. The dose of testosterone in the

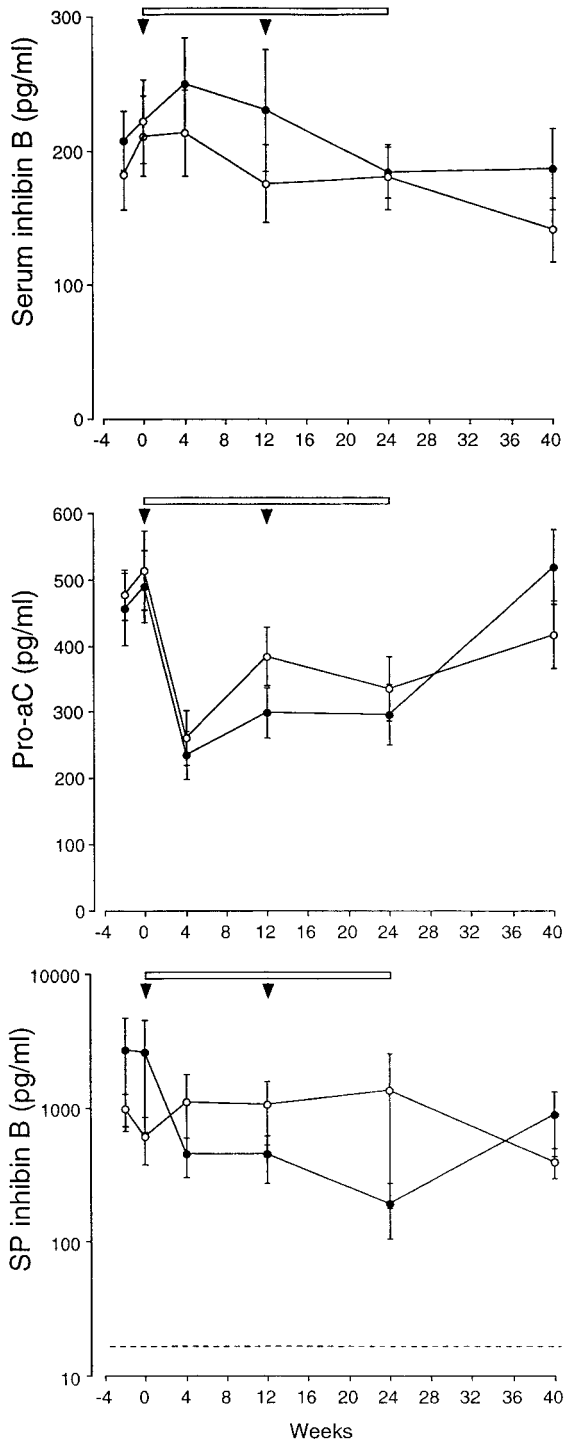

FIG. 5. Serum concentrations of inhibin B (a), pro-αC (b), and seminal plasma (SP) concentrations (c) of inhibin B during etonogestrel/testosterone treatment. The duration of etonogestrel treatment is indicated by the *bar*, and the *arrows* indicate the time points at which testosterone pellets (400 mg) were administered. ○, Group I; ●, group II. The *dotted line* indicates the limit of detection of the assay (c). Mean SEM, n = 14/group. Note the logarithmic ordinate (c).

present study resulted in a modest overall fall in serum testosterone concentrations, although pretreatment morning venesection is likely to overestimate average testosterone concentrations (32). Furthermore, the dose administered is similar to the mean daily production rate of 3.7 mg/d (33) and is, therefore, an appropriate near-physiological replacement dose. Although trough concentrations were 56–71% of pretreatment levels, the probably more meaningful average testosterone concentrations during treatment were 19 nmol/liter in group I and 15 nmol/liter in group II. None of the men in this study showed any signs of testosterone deficiency or excess; in particular, there was no evidence of subphysiological replacement despite the overall fall in serum testosterone concentrations. The long-term implications of such alterations in average serum concentrations (either positive or deleterious) are uncertain and will require investigation in appropriately designed studies of sufficient power and duration. The choice of appropriate replacement dose is complicated by 3-fold range of normality in serum testosterone concentrations, the relevance of which as an epidemiological risk factor is uncertain (34, 35). That the dose used here was at the threshold of effectiveness is illustrated by the fluctuations in gonadotropin concentrations during treatment, with significantly enhanced suppression evident following readministration of testosterone at 12 wk. The use of a relatively low dose of testosterone has the further advantage of not masking the effect of etonogestrel.

Many studies of prototype male contraceptive regimens have used testosterone enanthate, which requires weekly administration and has unsatisfactory pharmacokinetics (36). The resultant supraphysiological testosterone concentrations may act directly to maintain spermatogenesis in some men (22, 37). Recently longer-acting im preparations of testosterone undecanoate have been developed, with promising results (5, 38, 39). An alternative approach to the maintenance of physiological testosterone concentrations is by frequent administration, and daily transdermal administration has been demonstrated to provide this in hypogonadal men (40). Transdermal administration of testosterone, however, appears to result in markedly less suppression of spermatogenesis even when combined with an effective dose of progestogen (41, 42) despite the daily testosterone dose being the same as demonstrated to provide replacement in hypogonadal men. The absorption characteristics of the testosterone preparation and resulting variability in serum concentrations are thus crucial to the effectiveness of a given dose, confirming the advantages of a depot preparation. The main disadvantages of testosterone pellets are the need for a minor surgical procedure and occasional complications, particularly extrusion, which, however, did not occur in the present study involving 52 episodes of testosterone pellet insertion. Testosterone pellets, therefore, remain a valuable prototype allowing investigation of the effects of a preparation with close to zero order release characteristics, and the present data clearly demonstrate the effective contribution of repeated administration of this preparation for the suppression of spermatogenesis. Repeated administration of a higher dose of testosterone pellets (800–1200 mg per 3 months) given alone (17) resulted in a similar degree of spermatogenic suppression to that seen in the single etonogestrel implant group in the present study. A testosterone-only group was not included in the protocol because this dose of testosterone pellets has been previously demonstrated to have no signif-

TABLE 3. Sexual activity and Frenken Sexual Experience Scale 2 score (psychosexual arousability) during testosterone/etonogestrel implant administration

		Pretreatment	12 wk	24 wk	Recovery
Sexual activity	Group I	5.4 ± 1.3	6.0 ± 1.0	4.9 ± 0.6	5.1 ± 1.5
	Group II	7.6 ± 2.0	7.7 ± 1.7	6.8 ± 1.7	6.6 ± 1.3
SES 2	Group I	−1.07 ± 0.12	−1.08 ± 0.13	−1.23 ± 0.14	−1.16 ± 0.18
	Group II	−0.91 ± 0.11	−0.83 ± 0.10	−0.94 ± 0.12	−1.08 ± 0.14

Sexual activity is the sum of the number of acts of sexual intercourse and masturbation in the preceding 2 wk. Data are mean ± SEM, n = 14 per group.

icant suppressive effect on spermatogenesis when administered alone (19).

The validity of the present approach to avoid supraphysiological testosterone replacement is further supported by the absence of any change in weight, hemoglobin concentration, hematocrit, and HDL-C concentration. A variety of other progestogens have been investigated with testosterone as potential male contraceptive agents over the preceding decades and include oral levonorgestrel and cyproterone acetate (7, 8, 41, 43, 44), and injectable formulations of medroxyprogesterone acetate and norethisterone enanthate (5, 6, 45, 46). In general, these regimens have resulted in marked suppression of spermatogenesis but have frequently also resulted in potentially adverse metabolic effects, most commonly a decrease in HDL-C (3, 5, 8, 47). Increases in LDL-C as in the present study have been reported with other progestogen-T regimens (5, 41), and decreases have also been reported (10). Increases in hemoglobin concentration and hematocrit have also been frequently documented in these studies, probably reflecting the supraphysiological dose of testosterone administered. The exception to these changes is with administration of cyproterone acetate with testosterone, which resulted in a dose-dependent fall in hemoglobin and hematocrit, with no change in HDL-C concentrations (7). These hematopoietic effects may result from the antiandrogenic effect of cyproterone. Because the nonreproductive effects of both progestogens (4) and testosterone (48) in men are dose dependent, the advantages of minimizing steroid dosage by using progestogen implants in combination with physiological replacement using a depot formulation of testosterone are clear.

One previous study has reported the effects of implant formulations of progestogen with testosterone on spermatogenesis in Chinese men (14). In that study, two implants each containing 75 mg levonorgestrel were administered for 16 wk, with testosterone undecanoate 250 mg im every 4 wk introduced after 3 wk. Six men became azoospermic, but in four men sperm concentrations remained in the normal range. Although this was a relatively low dose of testosterone undecanoate, compared with other studies (5) and serum testosterone concentrations were not reported, the dose of testosterone is similar to that administered in the present study. The etonogestrel implants used here, therefore, appear to result in considerably greater suppression of spermatogenesis than the levonorgestrel implants currently available. Implants also have the advantage of rapid reversibility on removal, in contrast to injectable depot progestogens, *e.g.* medroxyprogesterone acetate, whose duration of action can be prolonged (49).

Although azoospermia was induced in the same number of men in each dosage group, there was evidence of lesser suppression of spermatogenesis in group I. In particular, there was evidence of partial recovery of spermatogenesis during the second half of the study in some men in that group, which was not seen in group II. These data, therefore, indicate that the decline in etonogestrel concentrations over the course of the treatment period fell below the threshold needed for ongoing suppression of gonadotrophins and spermatogenesis in some but not all men. A relationship between the degree of suppression of gonadotrophins and spermatogenesis was also shown both by treatment group and in individuals in group II who showed slower or less complete suppression of spermatogenesis. LH but not FSH concentrations were significantly more suppressed in men in group I who became azoospermic, compared with those who did not. The contribution of the administered dose of testosterone to gonadotropin suppression was clearly shown by the partial escape of gonadotropin at 12 wk of treatment when testosterone concentrations were at their nadir at the time of readministration. This is consistent with the incomplete degree of gonadotropin suppression achieved by desogestrel alone (10). It also appears that the present dose of two etonogestrel implants results in slower, less complete suppression than achievable with higher doses (300 μg) of oral desogestrel, which, in combination with the same testosterone regimen used here, resulted in complete suppression of spermatogenesis in all men studied in both Caucasian and Chinese populations (12). It is thus likely that further increasing the dose of etonogestrel might result in greater suppression than achieved with two implants as presently formulated. An increase in the dose of testosterone might also increase the degree of suppression and prevent the partial escape of gonadotropins observed at the nadir of testosterone concentrations.

Further evidence of a less complete effect of this dose of etonogestrel on spermatogenesis than achieved with oral desogestrel is indicated by the degree of suppression of seminal plasma concentrations of inhibin B. We have previously demonstrated that treatment with oral desogestrel (300 μg) in combination with a similar testosterone regimen to the present study resulted in seminal plasma inhibin B becoming undetectable in all men after 8 wk of treatment (27). The present data show that, although inhibin B concentrations in the ejaculate appear much more responsive to changes in the activity of the seminiferous epithelium than circulating concentrations, suppression to undetectable concentrations does not accurately reflect induction of azoospermia. Although group I did not show a significant fall in seminal inhibin B, there was a positive correlation between sperm and inhibin concentrations at the end of treatment. Further studies are

required to investigate the potential value of its measurement for comparison between treatment groups as an index of the degree of regression of the seminiferous epithelium and may shed light on the residual proliferation of germ cells and interaction with Sertoli cells under such circumstances. As previously noted, pro-αC closely reflects changes in gonadotropin concentrations (27, 50).

In conclusion, these results demonstrate that effective suppression of spermatogenesis can be achieved by implants of testosterone and etonogestrel, even when both are administered at relatively low doses, thus minimizing nonreproductive side effects. It is likely that the stability of circulating concentrations of both hormones is central to this enhanced efficacy. Implants of synthetic androgen, currently under investigation (51, 52), may be an appropriate substitute for the testosterone pellets used here and provide a way forward to the development of an effective, truly long-duration yet reversible male contraceptive.

Acknowledgments

We are grateful to N.V. Organon for the gift of testosterone and etonogestrel implants and the etonogestrel assays, Anne Mayo for assistance with the care of the subjects, and Neil Hollow for performing the immunoassays.

Received February 1, 2002. Accepted May 10, 2002.

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This work was supported by a Special Project Grant of the Medical Research Council and the Department for International Development to the Contraceptive Development Network (Grant G9523250).

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