Acceptability of an injectable male contraceptive regimen of norethisterone enanthate and testosterone undecanoate for men

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BACKGROUND: We assessed attitudes towards and acceptability of male hormonal contraception among volunteers participating in a clinical trial of a prototype regimen, consisting of progestin and testosterone injections. METHODS: After completing screening, eligible men were randomly assigned to the no-treatment group (n = 40) or to receive injections of norethisterone enanthate and testosterone undecanoate or placebo at different intervals (n = 50) according to a blocked randomization list. They underwent self-administered questionnaires. RESULTS: The average age of the participants was approximately 28 years; most were involved in a stable relationship and had no children. Ninety-two percentage of the respondents thought that men and women should share responsibility for contraception and 75% said they would try a hormonal contraceptive if available. At the end of the treatment phase, 66% of the participants said that they would use such a method, and most rated its acceptability very highly; none reported it to be unacceptable. The injections themselves were indicated as the biggest disadvantage. No significant changes in sexual function or mood states were detected among the men who underwent hormone injections. CONCLUSIONS: The contraceptive tested in this study was well accepted by the participants over the course of 1 year.

Key words: acceptability/male hormonal contraception/testosterone

Introduction

Despite some scepticism regarding the potential demand for new male methods of contraception (Potts, 1996), results of population-based studies of men’s fertility and contraceptive preferences indicate that, globally, a high percentage of men approve of family planning and use some form of contraception themselves (Posner and Mboj, 1989; Ezeh et al., 1996; Grady et al., 1996; Ringheim, 1996; Drennam, 1998).

The introduction of hormonal methods of male fertility regulation to the market seems to be imminent now (Anderson and Baird, 2002; Meriggiola et al., 2002; Wang and Swerdloff, 2002; Waites, 2003; Kamischke and Nieschlag, 2004).

Limited research has been done on the features that could influence men’s acceptance of hormonal contraceptive methods for their use (WHO, 1980; Hulton and Falkingham, 1996). Some of the most important attributes that would make such a method highly acceptable include high level and rapid onset of effectiveness, with the most acceptable methods being more effective than those presently available; convenience, not coitus-dependent, easy to use and does not interfere with a couple’s daily routine; reversibility; no or limited actual or perceived side effects; long-term safety; low cost and favourable physical properties, including odour and comfort. However, acceptability is dependent not only on factors related to the method but also on the user’s—or potential user’s—personal preferences, characteristics and situation. Characteristics of potential male contraceptive users were investigated in an early study, and users were described as being more pro-social and introspective, whereas non-users were seen as more assertive, conventional and self-seeking (Gough, 1979).

A few large-scale surveys performed in different countries have recently been published. The results of these studies show a high potential level of acceptability of hormonal methods of male fertility regulation (Glasier et al., 2000; Martin et al., 2000; Heinemann et al., 2005a).

Experience acquired during the development of female contraceptives has informed researchers of the importance of addressing users’ perspectives early in the male contraceptive
development process. It is critical, at the product development stage, to collect as much information as possible on the acceptability of this new form of contraception, on characteristics that would make it more attractive and on perceptions or misinformation that could alienate potential users. There has been little research on the acceptability of a potential hormonal contraceptive method for men; in particular, studies performed by sampling men participating in clinical trials of hormonal contraception are lacking. Participants in a clinical trial are uniquely positioned to offer their perspectives about the investigational method’s ability to meet their needs, the appropriate steps to improve its marketability and the factors motivating and constraining the successful introduction of a new contraceptive method. Therefore, in this study, we assessed the attitudes regarding hormonal contraception among male volunteers participating in a 1-year study of an injectable contraceptive regimen consisting of progesterin and testosterone preparations.

Materials and methods

Population, randomization and treatment

Of the 200 healthy Italian men interviewed at the study center of the University of Bologna, Bologna, Italy, between July 2000 and May 2002, 122 were screened for eligibility to participate in a clinical trial designed to test the efficacy of a prototype hormonal male contraceptive regimen in suppressing spermatogenesis. The study consisted of a baseline phase lasting at least 4 weeks, a treatment phase lasting 48 weeks and a recovery phase that lasted until each volunteer had at least two sperm counts within his own baseline range. The men were informed that the study consisted of a treatment group (TXT group) which would receive drug or placebo injections at different intervals and of a no-treatment group (N-TXT group) which would be asked only to complete a series of questionnaires at regular intervals. They were told that they would be randomized to one of the two groups without any possibility of choice. Ninety of the 122 screened men were determined to be eligible and were enrolled. Thirty-two of the screened men (26%) were considered not to be eligible for the study (N-ELIGIBLE group) for medical or personal reasons including the desire to use the experimental method as their only means of contraception (n = 5), a lack of commitment for the required length of time (n = 13), fear of injections (n = 7), fear of prostate ultrasound (n = 6) and failure to meet the study entry criterion for normal sperm count (n = 1).

The ninety enrolled men completed the baseline phase and were then randomized to either the N-TXT group (n = 40) or the TXT group (n = 50). Men in the TXT group received one of several regimens of norethisterone enanthate combined with testosterone undecanoate (TU), injected at 6-, 8- or 12-week intervals; therefore, the TXT group was made up of several subgroups. The assignment to a study group was performed according to a blocked randomization list created by a statistician (SAS for Windows NT, version 6.12; Statistical Analysis System, SAS Institute, Cary, NC, USA); the allocation of a randomization number to a subject was linked in a chronologically ascending manner to the sequence of arrival of the subjects to the study centre. Details of the protocol and results of the clinical trial have been reported elsewhere (Meriggiola et al., 2005).

The study was conducted in a single-blind fashion, and the participants were told to which treatment subgroup they were allocated only at the end of the study. The person who administered the questionnaires was trained by a psychosocial scientist and was blinded to the treatments. No blinding was possible between the N-TXT and the TXT groups.

All 90 men provided responses to weekly and monthly questionnaires on sexual function and mood; 84 men completed the entire study period. One aim of the study was to develop and validate instruments to monitor sexual function, behaviour and mood in large-scale clinical trials; results of these efforts will be reported elsewhere. At the end of the study, men in the TXT group were asked to further questions on the acceptability of the hormonal regimen. The study lasted an average of 72 weeks, including baseline, treatment and recovery phases. The follow up was completed at the end of June 2004. At the end of the study, all men were paid a small fee (1500€) as compensation for travel expenses to and from the study centre.

Main outcome measures

Main outcomes of the acceptability component of the study were attitudes towards contraception, motivation to participate in the clinical trial, reactions to the various treatment regimens, overall assessment of the method and reports of physical status, mood, sexual function and behaviour. Secondary outcomes were background characteristics of participants, contraceptive history and reports of partners’ reactions.

Study instruments

At baseline, all screened volunteers were asked to complete a Background questionnaire (BAK). On the first visit, enrolled study participants were asked to complete a Baseline Mood and Behaviour questionnaire (BMB) before receiving their first hormone injections. During the treatment period of the study, on each visit to the clinic (i.e. at 6-, 8- or 12-week intervals), all study participants completed a Treatment Mood and Behaviour questionnaire (TMB). On each visit, study participants also completed a Profile of Mood State questionnaire (POMS) (Lorr and McNair, 1980). At a follow-up clinic visit 12 weeks after the final hormone injection (TXT group) or 64 weeks after initiation of the study (N-TXT group), study participants completed a Recovery Mood and Behaviour questionnaire (RMB) which included the same questions as those in the TMB regarding changes in mood, sexual function and behaviour.

On the final visit to the clinic (on average, 72 weeks after the initiation of the study), all participants of the TXT group who completed the treatment (n = 44) filled in the Final Treatment questionnaire (FTA). For the purposes of this instrument, the investigator cited the time needed to achieve sperm suppression (<1 × 10⁹/ml) or the recovery of the sperm count as based on the results of their previous study of a similar combination of hormones (12 or 18 weeks respectively) (Meriggiola et al., 2003b).

The questionnaires (BMB, TMB, RMB and FTA) were developed specifically for this study and included a selection of questions taken from other questionnaires designed for different purposes (Reynolds et al., 1988; O’Leary et al., 1995; Corty et al., 1996; Feiger et al., 1996; Clayton et al., 1997; Derogatis, 1997; Rosen, 1998). The questionnaires were self-administered. The first step in the research was the translation of all questionnaires to be appropriate for Italian-speaking people. The translation consisted of the following steps, which comply with international recommendations (Brislin, 1970; Anonymous, 1997; Herdman et al., 1998):

- Forward translation: two translators translated all questionnaires independently. The two versions of the translation were compared, differences were discussed and a final translation was agreed upon by consensus.
- Backward translation: a new bilingual translator then translated this agreed-upon version of the Italian translation back into English. The translators discussed and resolved all discrepancies between the original English forms and the English back-translation.
- Pre-test: before administering these questionnaires to study subjects, they were tested in a group of 15 male volunteers. These men...
read the questionnaires, gave their opinion about understandability and made suggestions for any final changes. At the end of this stage, the questionnaires were considered ready to be used in the present study.

Details on the content of the questionnaires, time and modality of administration are reported in Table I.

Statistics
This study was designed to complement a pilot clinical study that had already been approved and the sample size fixed (n = 50) (Meriggiola et al., 2005). Most of the data that we report are descriptive. Comparison analyses were performed on the acceptability results obtained at the beginning and at the end of the treatment phase (Figure 3). For the predetermined subjects’ number of this study, an effect size of 25% and a P < 0.05, the power is >0.8. All questionnaires were completed. Continuous data were reported as mean ± SD. Categorical data were reported as frequency and percentage and analysed by means of the Pearson’s chi-square test evaluated by the Monte Carlo method for small samples and by means of the paired McNemar test. Statistical evaluations were performed by the SPSS/PC+ package (version 8.0; SPSS Inc., Chicago, IL, USA) (Snedecor and Cochran, 1989; Norusis, 1998) on a personal computer. A two-tailed P < 0.05 was considered statistically significant. Because there were only a few differences in attitudes and acceptability among TXT, N-TXT and N-ELIGIBLE groups, background data are shown combined for the three groups. Where present, significant differences are described in the text.

Results

Demographic characteristics of study population
All 122 screened men agreed to provide baseline information by responding to the BAK. The demographic characteristics of these volunteers (TXT, N-TXT and N-ELIGIBLE groups) are reported in Table II. Ninety volunteers met the eligibility criteria and chose to enrol in the study. No significant differences in age range, marital status or educational level were found among these groups or among the various treatment subgroups which, when combined, made up the TXT group. Most of the participants were in a stable relationship (married or regular partner), with no children. Educational level did not vary among groups, whereas a higher number of study participants in the N-TXT group considered themselves religious compared with the TXT group and to the volunteers who were not eligible to participate in the study (Table II). The proportion of men who reported practising religion was similar in the different groups: 29, 26 and 32% in the TXT, N-TXT and N-ELIGIBLE groups, respectively. In the background questions, subjects describing themselves as non-religious (n = 34) were younger (25.8 ± 4.48 versus 28.2 ± 5.60 years; P = 0.026) and more likely to be single (13/24 versus 16/66 in the religious group; P = 0.03). No differences in any responses to any items in the treatment phase questionnaires were noted when comparing religious (n = 66) and non-religious (n = 24) study participants.

We also compared fathers’ and childless men’s responses to the questionnaires. Fathers were older (37.7 ± 4.6 versus 26.4 ± 4.4 years; P = 0.0005) and more likely to have a partner (100%...
in the father group versus 65% in the group of men with no children \( P = 0.009 \). No other differences between these two populations of study participants were described in our analyses.

**Attitudes towards contraception**

At baseline, there were no significant differences in reported contraceptive use among the three groups (N-TXT, TXT and N-ELIGIBLE groups). The most widely used contraceptive in this population was the condom, followed by withdrawal and oral contraceptives. But 62% of the respondents (75/122) indicated that condoms are an unsatisfactory contraceptive option for men. On the contrary, the female pill was considered the best available method by 57% of the respondents (70/122). Table III presents data on current and ever use of various contraceptive methods among the TXT and N-TXT groups.

Overall, 92% of the participants (112/122) agreed that men and women should share responsibilities for contraception, even though only 38% (46/122) of the men overall would assume full responsibility for contraception (Figure 1). Seventy-five percentage of the volunteers (92/122) indicated that they would try a new male contraceptive if available, and 74% (90/122) thought that the female partner would welcome the use of such a method (Figure 2).

Questions on the acceptability of this specific hormonal contraceptive regimen were asked at the beginning and at the end of the treatment phase only to the 50 participants in the TXT group. Forty-four of these participants completed the treatment phase. Of the six participants (14%) who dropped out in the treatment phase, two subjects dropped out at the very beginning of this phase, because they did not like injections and thus did not even respond to the first acceptability question. Another subject complained of loss of libido, and the other three subjects dropped out for reasons unrelated to the study protocol. Therefore, at least three men (6%) among the 48 who responded to the question at the beginning of the treatment phase judged the regimen not acceptable enough to complete the study. At the beginning of the study, 36 of 48 (75%) of the men in the TXT group indicated that they would use such an injectable hormonal method for contraception if it were commercially available (Figure 3), whereas at the end of the treatment phase, 31 of 47 men (66%) expressed a willingness to use it \( (P \neq NS \) beginning versus end of the study). Among the six participants who responded that they would not use such a method, the injection frequency was given as the major obstacle to use. Among the 44 participants who completed the 1-year exposure to the method, rating of this method was very high. None of the participants judged it to be unacceptable (Figure 4). The 44 men who completed the study were questioned about their perceptions of the potential advantages and disadvantages of the method. The injections, regardless of the frequency, were considered to be the biggest disadvantage, as stated by 32% of the study participants (14/44), followed by the absence of protection from sexually transmitted infections, as stated by 25% (11/44) of the men (Figure 5).

Thirty percent of the study participants (13/44) agreed that the biggest advantage of the method was that it offered an alternative to condoms; 27% (12/44) described the most significant advantage as being male control over contraception (Figure 5).

![Figure 1](https://academic.oup.com/humrep/article-abstract/21/8/2033/2938610)

![Figure 2](https://academic.oup.com/humrep/article-abstract/21/8/2033/2938610)

| Table III. Current and ever contraceptive use among the men enrolled in the study |
|-------------------|------------------|--------------------------|------------------|------------------|
| Method           | TXT Ever method (%) | TXT Current method (%) | N-TXT Ever method (%) | N-TXT Current method (%) |
| Condom           | 94 (%)             | 29 (%)                  | 100 (%)            | 26 (%)            |
| Withdrawal       | 66 (%)             | 7 (%)                   | 73 (%)             | 5 (%)             |
| Vasectomy        | – (%)              | – (%)                   | – (%)              | – (%)             |
| Rhythm           | 12 (%)             | 3 (%)                   | 11 (%)             | – (%)             |
| Spermicide       | 3 (%)              | – (%)                   | – (%)              | – (%)             |
| Oral pill        | 76 (%)             | 58 (%)                  | 59 (%)             | 68 (%)            |
| Female barrier   | 3 (%)              | 3 (%)                   | – (%)              | – (%)             |
| IUD (hormonal)   | – (%)              | – (%)                   | – (%)              | – (%)             |
| IUD              | – (%)              | – (%)                   | – (%)              | – (%)             |
| Injectable       | – (%)              | – (%)                   | – (%)              | – (%)             |
| None             | – (%)              | 7 (%)                   | – (%)              | 25 (%)            |

IUD, Intrauterine device.

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**Figure 1.** Responses (%) given by the study volunteers (all groups combined) to the following statements. Left panel: men and women should share the responsibility for contraception equally. Right panel: I would like to relieve my partner of the responsibility for contraception.
A 12-week delay to achieve contraceptive effectiveness was judged unacceptable by 39% (17/44) of the participants; however, 64% (28/44) of the participants felt that an 18-week delay for return to fertility after discontinuation of the method would be acceptable. The acceptability of specific injection intervals appeared to be related to the length of the interval between injections, with 75% (33/44), 84% (37/44) and 84% (37/44) of men finding 8-, 10- and 12-week injection intervals to be acceptable, respectively. However, these differences were not significant. Sixty-two percentage of the study participants (31/50) reported that they would pay between 10 and 20 euros monthly for such a male contraceptive; 32% (16/50) said that they would pay 10 euros (the current price of the female contraceptive pill in Italy). Only 6% (3/50) of the participants were willing to pay a maximum of less than 10 euros; none of the respondents would pay more than 20 euros per month.

**Sexual function and mood**

Questions were asked to all enrolled participants in both the groups (n = 90) regarding sexual function and mood, as described in the Methods section and Table I. No significant changes in any measured parameters of sexual function and mood were recorded in any group at any time throughout the study periods. Sex drive, appetite, insomnia, sweating, snoring, lethargy, relaxation, tension, energy, irritability, anger, frequency of intercourse, masturbation, sexual desires, sexual fantasies, arousal and spontaneous erections were all unchanged throughout the study.
Discussion
In this study, we assessed attitudes towards and acceptability of an experimental hormonal contraceptive regimen among men who volunteered to take part in a year-long clinical trial. Ninety men were randomly assigned to receive an androgen–progestin regimen \((n = 50)\) or no treatment \((n = 40)\) for 48 weeks. All the men were asked to answer questions about their attitudes towards male contraception, and those who were randomized to receive the hormones were questioned on various aspects of acceptability of this prototype hormonal contraceptive regimen.

Ninety-five percent of the men agreed that men and women should share the responsibility of contraceptive use. Despite the widespread use of condoms among the study population, most of the men indicated that they were using them, because no other choice was available for male use, and 79% of them said that they would try a new male contraceptive if it were available. The satisfaction with this hormonal contraceptive regimen was very high among the men who tested it for 1 year, and 61% of them rated it excellent or good (Figure 4). Sixty-six percent of these men expressed their willingness to use it if it were commercially available (Figure 3). Most of the men reported that an alternative to condoms and the control over contraception were the major advantages offered by this contraceptive regimen. Major drawbacks of this method were the injections and the lack of protection from sexually transmitted infections.

Hormones suppress fertility in men by depriving the testes of the stimulatory effects of gonadotrophins and of intratesticular testosterone and thereby inhibiting sperm production (Meriggiola and Brenner, 1997). Achieving this goal has represented a major challenge for researchers over the last decades, and only recently have hormone regimens that can reliably suppress sperm production to a level compatible with acceptable contraceptive protection been developed (Meriggiola et al., 2003a). Because of the lack of such products, studies investigating the attitudes of men towards hormonal contraception are scarce (Ringheim, 1995; Martin et al., 2000). The few published studies reported high acceptability of potential or hypothetical hormonal contraceptive methods, with a few differences attributed to the various cultural backgrounds of the populations studied (Martin et al., 2000; Heinemann et al., 2005a,b). The liberal attitude towards hormonal contraception in this study is not surprising, because these men volunteered to participate in a study on hormonal male contraception. However, the high acceptability level of this contraceptive at the end of the study period is of particular interest, because these study participants had already tested it for 1 year. This form of contraception is often indicated for 1 year, and 61% of them rated the method either excellent or good, and another 23% felt that it was acceptable (Figure 4).

The injections themselves were judged as the major disadvantage by 32% of the men, regardless of their frequency. It has been suggested that men find formulations with which they are familiar as commonly used female contraceptives to be more acceptable than those that are relatively or totally unknown (Martin et al., 2000). According to the United Nations report on world contraceptive use, the use of injectable female contraceptives in Italy is negligible (United Nations Department of Economic and Social Affairs Population Division, 2004). It is therefore possible to speculate that the Italian men enrolled in this trial were less familiar with injectable contraceptives and were, therefore, more apprehensive about the method. These results suggest the need to pursue research on non-injectable formulations suitable for men who want to take responsibility for contraception but who, for cultural or personal reasons, do not like injections. Among non-injectable regimens, oral and implantable formulations should be considered for testing in further studies. Results from preliminary studies on implantable regimens have indeed shown promise in terms of sperm suppression (Anderson et al., 2002). As with contraceptive methods for women, different routes of administration will be acceptable to different subsets of the population; no single method for men will meet all men’s needs.

As expected, the satisfaction with the frequency of injections tended to be related to the injection intervals, but no significant difference was found between the acceptability of an 8- and fathering children. This population of men may not be willing to give up control of fertility. Seventy-nine percent of the study population indicated that they would use this contraceptive method if it were available, and 74% thought that their partner would like it. These results indicate a high degree of acceptance for this new form of male contraception.

Most acceptability studies conducted to date have surveyed men about potential characteristics of a hypothetical hormonal contraceptive regimen (Hall, 1971; Balswick, 1972; Keith et al., 1975; Diller and Hembree, 1977; Gough, 1979; Martin et al., 2000; Heinemann et al., 2005a,b). In this study, we interviewed a population undergoing a clinical trial and therefore actually exposed to an experimental contraceptive regimen. It is recognized that clinical trial study participants can be atypical in that they are self-selected, receive compensation for their participation and are more attentively monitored than is the general population. Although a study population may not be representative of the overall community of men, it should be noted that clinical trials offer a unique opportunity to collect information regarding method preferences from study participants who are highly informed, experienced in using the method and who have been given time to think about it. Study participants are supposed to be less influenced by future promotional information that can aim at changing the method’s image (Keller, 1979). In this study, we questioned men who used the experimental hormonal regimen for 1 year. The high satisfaction with this method reported by the men both at the beginning and at the end of this trial might suggest a strong demand for and use of it, once it is on the market. Indeed, 61% of the participants rated the method either excellent or good, and another 23% felt that it was acceptable (Figure 4).

As expected, the satisfaction with the frequency of injections tended to be related to the injection intervals, but no significant difference was found between the acceptability of an 8- and 16-week interval. However, 50% of the men who took injections every 4 weeks rated it excellent or good, and another 23% felt that it was acceptable (Figure 4). The injection intervals themselves were judged as the major disadvantage by 32% of the men, regardless of their frequency. It has been suggested that men find formulations with which they are familiar as commonly used female contraceptives to be more acceptable than those that are relatively or totally unknown (Martin et al., 2000). According to the United Nations report on world contraceptive use, the use of injectable female contraceptives in Italy is negligible (United Nations Department of Economic and Social Affairs Population Division, 2004). It is therefore possible to speculate that the Italian men enrolled in this trial were less familiar with injectable contraceptives and were, therefore, more apprehensive about the method. These results suggest the need to pursue research on non-injectable formulations suitable for men who want to take responsibility for contraception but who, for cultural or personal reasons, do not like injections. Among non-injectable regimens, oral and implantable formulations should be considered for testing in further studies. Results from preliminary studies on implantable regimens have indeed shown promise in terms of sperm suppression (Anderson et al., 2002). As with contraceptive methods for women, different routes of administration will be acceptable to different subsets of the population; no single method for men will meet all men’s needs.

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12-week injection interval. The time required before the contraceptive regimen became effective (12 weeks) and, at discontinuation, the time needed for fertility to recover (18 weeks) were considered unacceptable by less than half of the participants. Among published studies, the hormonal formulations with the most rapid onset of effect take about 3 months to become effective, whereas most of the regimens seem to take even longer (Ly et al., 2005). Potential users may view this time as too long. Therefore, these results suggest that efforts should be put in to increase the speed of onset of spermatogenic suppression as well as of recovery.

A well-known and important factor that influences the satisfaction with a contraceptive is its interference with sexual functioning. There are numerous ways in which a hormonal contraceptive regimen may affect sexual function, one of which is the creation of a non-physiological hormonal milieu. With respect to male methods, there is a risk of producing testosterone levels that are either stimulatory or inhibitory to sexual function. This is one of the reasons why a basic goal of hormonal regulation of male fertility is the maintenance of testosterone concentrations within the normal range. The testosterone formulations used in early studies were not able to mimic physiological testosterone levels. In fact, most of them caused significant rises in circulating testosterone concentrations soon after injection and a decrease below the normal range just before the next injection, a so-called burst effect. Thus, perceived changes in some aspects of sexual function have been reported in previous contraceptive trials (Anderson et al., 1992; Bagatell et al., 1994; Sjoegren and Gottlieb, 2001). Other androgen formulations inducing more physiological circulating testosterone levels have been developed and include patches, gels and long-acting injectables such as testosterone decanoate or testosterone pellets (Brady et al., 2004, 2006; Hay et al., 2005). In this study, one of these formulations, the injectable TU, which produces and maintains testosterone levels within the normal range for up to 12 weeks in hypogonadal men, was used (Von Eckardstein and Nieschlag, 2002). With this TU formulation, serum testosterone levels varied between the higher and the lower end of the normal range over the course of 8- or 12-week intervals between injections. However, these fluctuations, which occur over a relatively long period of time (8 or 12 weeks), are probably not sharp or sudden enough to be noticed by the men. The study participants, in fact, did not report any changes in mood or sexual function over the course of the study. In conclusion, the results of our study show that the contraceptive regimen tested in this study was very well accepted by the study participants who tested it for 1 year. The complaints about injections by some of the men suggest the need to pursue research on alternative formulations that do not require injections, such as oral, longer-acting (depot or implants) regimens.

Acknowledgements

Financial support for this study was provided by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization (Project ID A05104) and by Schering A.G. (Berlin, Germany), by the Clinic of Obstetrics and Gynecology S. Orsola Hospital, University of Bologna and the University of Washington, Center for Research in Reproduction and Contraception.

We thank Dr. Kathryn M. Yount for her work prior to and in the early stages of the study.

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Submitted on January 11, 2006; resubmitted on February 27, 2006; accepted on March 6, 2006.