12-17-2021

# Breakthroughs in hormonal male contraception

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**Breakthroughs in Hormonal Male Contraception**

## Abstract

**Objective:** Assess the efficacy of a nestorone plus testosterone gel at suppressing progestin levels and spermatogenesis.

**Design:** Systematic literature review.

**Methods:** Searches were done in PubMed and Dartmouth library using the terms nestorone, randomized control trial, human, and male. Limits used while searching included published in the last 10 years, randomized control trials, and English.

**Results:** Using the search criteria, the following three studies were found that met the inclusion/exclusion criteria of this study: Ilani et al, Zitzmann et al, and Anawalt et al. All three studies were found on PubMed and reference the Ilani et al study.

**Conclusion:** Nestorone plus testosterone gel is effective at suppressing progestin levels in the short-term and spermatogenesis over the course of several weeks. This drug has an efficacy similar to female oral contraceptives and a better efficacy than any existing non-invasive male contraceptive. The effective dose, level of compliance, and long-term side effects require further study.

## Introduction

Since 1960, the burden of using a reliable hormone-based contraceptive has been on the female partner in a heterosexual relationship. While condoms have been around since the 17th century, there has never been a reliable and reversible male pharmacological or hormonal contraceptive. Even so, the failure rate with modern condoms is still 13%, making their effectiveness much less than female hormonal contraceptives.[1] While vasectomies have a near 100% success rate and are somewhat reversible[2], only 2.4% of men worldwide choose this option.[3] The negative stigma and various misconceptions about vasectomies have contributed to their lack of popularity.

Nestorone (segesterone acetate) is a transdermal synthetic progestin gel which has been studied as a possible method of contraception since 1995.[4] In 2018, the FDA approved its contraceptive use as a vaginal ring when combined with ethinyl estradiol, under the trade name Annovera.[5] Currently, Nestorone has only been tested in stage II clinical trials as a male contraceptive, but there are still ongoing clinical trials that are evaluating its efficacy.

From what is known about Nestorone and its possible efficacy as a male contraceptive, it has little to no androgenic, estrogenic, or glucocorticoid activity.[6] Nestorone is thought to

inhibit gonadotropins by a mechanism other than acting on androgen receptors, directly inhibiting testosterone production.[7] To decrease the possible negative androgen effects that Nestorone may have, it has always been co-administered with transdermal testosterone.[8] An oral formulation of Nestorone was tested during its early development, but due to its poor GI absorption, decreased oral half-life, and lack of availability of an oral testosterone, transdermal administration has been accepted as the preferred route of administration.[7]

In analyzing the development of a hormonal male contraceptive, the main factors to look at are efficacy, ease of use, long-term compliance, and the minimization of adverse effects. This study analyzes three double-blinded randomized controlled trials which all used a combination Nestorone and testosterone transdermal gel to provide adequate gonadotropin suppression and prevention of pregnancy.

## Methods

An initial search of PubMed and Dartmouth library was performed in September 2020 using the terms nestorone, randomized controlled trial, human, and male. Limits included "published in the last 10 years, randomized controlled trials, English." This yielded 6 articles. Three articles were chosen based on their similar research methods and purposes. A search of the Cochrane Library and JMU Database failed to identify additional studies.

## Results

**Study #1**

*A New Combination of Testosterone and Nestorone Transdermal Gels for Male Hormonal Contraception*. *Ilani et al.*[7]

**Objective**: To compare and determine the effectiveness of a testosterone-based gel and a combination testosterone plus nestorone gel with regards to suppressing spermatogenesis.

| **Table 1. Patient Inclusion Criteria** |
|---|
| Male sex |
| Between 18 and 50 years old |
| No chronic illness |
| Normal physical exam, blood chemistries, and no evidence of a urinary tract infection |
| Two consecutive sperm concentrations of at least 15 million/ml |

**Study Design**

This was a randomized, double-blind, clinical trial consisting of 99 males, conducted at two different academic medical centers. Table 1 outlines the inclusion criteria.

Initially, 210 men were screened for the study, eventually leading to 99 participants. Reasons that screened individuals were not included in the study include: withdrawal of consent, low sperm count, substance abuse, abnormal chemistries, high BMI, high blood pressure, abnormal history and physical exam, and being lost to follow-up. The 99 study participants were randomized into three different groups and applied the trial drug daily for a period of 24 weeks. Group one self-administered a combination of 10 mg testosterone plus placebo gel. Group two self-administered a combination of 10 mg testosterone plus 8 mg nestorone gel. Group three self-administered a combination of 10 mg testosterone plus 12 mg nestorone gel. After the treatment period, the subjects were followed for a minimum of 12 weeks or until two consecutive semen samples had a sperm concentration of at least 15 million/ml. This concentration of sperm was observed in a previous study to serve at the baseline level for normal minimum sperm concentration.

Throughout the study, participants were required to use a secondary form of contraception, if engaging in sexual activities with their partner. Participants had serum concentrations of testosterone, free testosterone, nestorone, LH, FSH, Hgb, and semen concentrations obtained at regular intervals throughout the trial. In addition, other baseline labs included complete blood count, complete metabolic panel, lipid panel, and prostate specific antigen.

The goal of the study was to demonstrate the suppression of spermatogenesis to a level of no more than 1 million/ml by 20 weeks of daily use. The suppression of sperm concentration to less than this amount is considered by the study to be the cutoff for contraceptive efficacy and is comparable in efficacy to female oral contraceptive medications.

All semen analyses were performed by trained technologists using the standard techniques outlined in the World Health Organization *Laboratory Manual for the Examination of Human Sperm*.

**Study Results**

Of the 99 initial participants, 62 completed the study until at least week 20, with a near equal distribution of participants in each of the three study groups. Six additional participants who continued the trial through week 20 were later excluded due to nonadherence to the medication regimen. Data analysis was performed on the remaining 56 participants, per protocol.

There was a significantly higher percentage of participants who had a sperm concentration of 1 million/ml or less with the groups that used nestorone gel. Group one, who used testosterone plus placebo gel, only had 23% of participants achieve a sperm concentration of less than 1 million/ml, whereas groups two (testosterone plus nestorone 8mg) and three (testosterone plus nestorone 12mg) saw a suppression of 89% and 88%, respectively.

Serums testosterone and free testosterone levels saw no significant change throughout the trial in any group, but serum LH and FSH were significantly more suppressed in the groups receiving nestorone gel compared with the testosterone plus placebo group.

Participants in all groups had no significant changes in sexual desire, sexual activity, sexual enjoyment, satisfaction with erections, and fullness of erections when compared to baseline.

There were no serious adverse events leading to participants discontinuing the trial. Most participants that failed to complete the trail stated their reason as inconvenience of study visits or failure to come for follow-up visits. The most frequent side effects were acne (21%) and insomnia (6%) with no difference between treatment groups.

**Study Critique**

The lack of a pharmacologic "gold standard" for male contraception makes analysis of any male contraceptive trial difficult. The study's already small sample size (n=99) was further decreased to 56 participants after many failed to complete the trial period or completed the study but ended up being noncompliant with the medication. The study was successfully able to identify at least one participant that lied about their compliance, decreasing the likelihood of erroneous data. Though this discontinuation rate seems high, it is much less than the discontinuation rate of female contraceptive trials, which ranges from 32-49%. Furthermore, the study does suffer from only having healthy participants so extrapolation to a larger population is difficult.

Having multiple study locations and a standard for the analysis of sperm both likely helped to decrease any bias and increase the uniformity of the data. By choosing to have the study performed at academic hospitals, there was likely a diverse patient pool to choose participants from.

One downside to a nestorone gel contraceptive is that complete suppression of spermatogenesis has not been achievable to date.

**Study #2**

*Impact of Various Progestins With or Without Transdermal Testosterone on Gonadotropin Levels for Non-invasive Hormonal Male Contraception: A Randomized Clinical Trial. Zitzmann et al.*[9]

**Objective**

To evaluate and compare the effect of different oral or transdermal progestins on the suppression of both follicle stimulating hormone (FSH) and luteinizing hormone (LH) in healthy men.

| **Table 2. Patient Inclusion Criteria** |
| --- |
| Male sex |
| Between 18 and 50 years old |
| Normal mental and physical health |
| BMI between 18 and 33 $kg/m^2$ |

| Normal FSH, LH, Testosterone, and Sperm counts according to WHO Guideline |
|---|

**Study Design**

Fifty-six healthy Caucasian males that responded to a press advertisement were selected to participate in a randomized control trial. Table 2 outlines the inclusion criteria for this study. Each participant was placed into one of eight different treatment groups. This study used the following four progestins; cyproterone acetate (CPA), nestorone (NES), norethisterone acetate (NETA), and levonorgestrel (LNG). Each progestin was then further split into two different groups with differing dose amounts. Each treatment group underwent two phases. The first phase (two weeks) consisted of only the respective progestins being administered. The second phase (four weeks), 50 mg/day of transdermal testosterone gel was administered in combination with each respective progestin. The purpose of adding transdermal testosterone was to evaluate if testosterone could be added to provide normal androgenic function in men, while maintaining suppression of gonadotropin. After the four weeks of phase two, all participants completed a wash out period for three weeks. The study design is outlined in Table 3.

Each participant was instructed to take their respective progestin and record it in a drug diary, as well as keeping all drug containers. CPA, NETA, and LNG were all administered orally. The participants in the NES study groups all received 1 g of gel per day, containing either 2 mg of NES or 3 mg of NES, depending on their respective study group. Transdermal testosterone was administered through a 5g gel containing 50 mg of testosterone, that subjects applied each morning. This level of testosterone has been proven to provide serum testosterone concentrations within the normal level for one day.

Serum concentrations of FSH, LH and testosterone were all measured at weeks 0, 2,3,4,5,6,7,8, and 9. Target FSH and LH concentrations were both 0.5 IU/mL, a level that is consistent with spermatogenesis suppression. Additional safety parameters, resting blood pressure and heart rate, hematocrit, prostate specific antigen (PSA), insulin sensitivity, high-resolution C-reactive protein (hsCRP), and a lipid panel, were all collected at week 0,2,6, and after the three week washout period. All venous blood samples were collected after overnight fasting between 0800 and 1200 hours. While semen analysis was not the main purpose of this study, spermatozoa concentrations were measured at week 0, 6, and at the end of the washout period. Semen analysis was conducted in accordance with WHO standards.

| **Table 3. Study Design** | | | | |
|---|---|---|---|---|
| Group | Progestin | Dose | Route | *n* |
| 1 | Cyproterone Acetate | 10 mg/day | Oral | 7 |
| 2 | Cyproterone Acetate | 20 mg/day | Oral | 7 |
| 3 | Nestorone | 2 mg/day | Transdermal | 7 |
| 4 | Nestorone | 3 mg/day | Transdermal | 7 |
| 5 | Norethisterone Acetate | 5 mg/day | Oral | 7 |
| 6 | Norethisterone Acetate | 10 mg/day | Oral | 7 |
| 7 | Levonorgestrel | 120 µg/day | Oral | 7 |
| 8 | Levonorgestrel | 240 µg/day | Oral | 7 |

**Study Results**

Protocol compliance was measured by reviewing participants' drug dairies and counting empty study drug containers. Compliance was estimated to be over 95%. After the first phase (week 2), CPA was the only progestin that suppressed FSH and LH below 0.5 IU/mL. However, at the end of phase two (week 6) all trial groups, with the exception of NES 2 mg, suppressed FSH and LH below 0.5 IU/mL. Regarding the safety parameters measures, testosterone, hemoglobin, hematocrit, and insulin sensitivity all decreased markedly during the first phase. However, during the second phase and the addition of testosterone, all of these safety parameters increased to normal levels. The remaining safety parameters did not change throughout the study. There were no serious adverse events reported. The most common adverse events were 3 participants experiencing night sweats and 2 participants experiencing libido. Three participants dropped out of the study, however none were because of adverse events.

**Study Critique**

Strengths of this study include using a randomized control trial, using multiple doses of the same drug to determine appropriate dosages, having a period with progestins only to see the effects on no testosterone, and having no serious adverse events.

The biggest shortcoming of this study was the relatively small sample size of fifty-six, and the short six week time frame of the study. A further study, with a larger sample size and a longer study period, would be needed to fully understand the benefits and side effects of these

drugs. Larger sample sizes would also help to negate any interindividual transdermal absorption of NES or testosterone.

While this study was a randomized control trial, it was not blind. While the participants who knew what drug they were receiving most likely did not affect their FSH and LH concentrations, having a blind trial would help minimize any potential confounding variables. This study also did not use sperm concentrations as a marker for effective contraception. They used FSH and LH levels that have a correlation to sperm concentrations, however, FSH and LH levels are a surrogate outcome.

Lastly, the drugs used in this study were all provided by Bayer-Schering Pharma. While many companies make these different progestins, having the drugs provided by a pharmaceutical company raises the concern for a possible conflict of interest.

**Study #3**

*Combined nestorone-testosterone gel suppresses serum gonadotropins to concentrations associated with effective hormonal contraception in men*. *Anawalt et al.*[10]

Objective: Compare and determine the effectiveness of a testosterone-based gel and a combination testosterone plus nestorone gel with regards to suppressing serum LH and FSH concentrations.

**Study Design**

This was a randomized, double-blind, clinical trial consisting of 44 males, conducted at two different research institutions in Los Angeles, CA and Seattle, WA. Table 4 outlines the inclusion criteria.

| **Table 4. Patient Inclusion Criteria** |
|---|
| Male sex |
| Between 18 and 50 years old |
| No chronic illness |
| Normal physical exam, blood chemistries, and no evidence of a urinary tract infection |
| No use of anabolic steroids within 3 months |
| No moderate/severe depression (determined using the PHQ-9) |
| Sperm concentration of at least 15 million/ml |

Initially, 88 men were screened for the study, eventually leading to 44 participants. The 44 study participants were randomized into two different groups and applied the trial drug daily for a period of 28 days. Group one self-administered a 62.7 mg testosterone gel. Group two self-administered a combination of 62.5 mg testosterone plus 8.3 mg nestorone gel (NES+T).

After the treatment period, the subjects were followed for an additional 28 days which was considered a “washout period”. This occurred when serum testosterone, gonadotropin concentrations, complete blood count, complete metabolic panel results, and semen concentration returned to baseline or were within the normal ranges. The medication was provided in prefilled syringes and applied daily to the shoulders. Participants returned to the research center on a predetermined schedule seven times during the trial period.

Throughout the study, participants were asked to have any female sexual partner use a secondary form of contraception, if engaging in sexual activity. Participants had serum concentrations of testosterone, free testosterone, nestorone, LH, FSH, Hgb, and semen concentrations obtained at regular intervals throughout the trial. In addition, other baseline labs included complete blood count, complete metabolic panel, and prostate specific antigen.

The goal of the study was to demonstrate the suppression of LH and FSH to a level of no more than 1.0 IU/L by 28 days of daily use. The suppression of LH and FSH to this level is associated with the suppression of sperm concentrations to less than 1 million/ml, the level at which a medication can be declared an effective form of contraception.[10]

All hormone measurements and analyses were performed by trained technologists using previously validated and reported assays. Study analysis was performed per protocol.

**Study Results**

Of the 44 men who started the study, 4 participants withdrew early from the study. Two participants reported scheduling conflicts, one withdrew due to possible side effects, and one withdrew for personal reasons. Three men in the NES+T group were not included in the analysis because of lack of meeting inclusion criteria, leaving 37 men available for analysis. Participants in the NES+T study group report reported 89% everyday compliance.

Serum FSH and LH concentration in the NES+T group were significantly suppressed by day 7 and remained there throughout the entirety of the treatment period. By the fourth week, 84% of the NES+T group had FSH and LH concentrations below 1.0 IU/L, while only 16.7% of the testosterone only group had FSH and LH concentrations below 1.0 IU/L. By day 31, 3 days after stopping treatment, serum gonadotropins were not significantly suppressed. By day 56, 28 days after stopping treatment, serum gonadotropins were at baseline concentrations.

Nestorone serum concentration continued to rise throughout the treatment timeframe for the NES+T study group. After the 28-day treatment time frame, nestorone remained measurable for 72 hours and by day 56 was completely unmeasurable.

Sperm concentrations were measured at baseline and then on day 28 of treatment. The sperm concentration of the testosterone only group remained largely unchanged by day 28 with a level of 85 +/- 72 million/mL. The NES+T group’s sperm concentration decreased from 69 million/mL to 40+/- 43 million/mL. This is much lower concentration than the testosterone group but is still not at the <1 million/mL that is associated with effective contraception.

There were no serious adverse events leading to participants dropping out of the study. One participant in the testosterone only group reported decreased libido that could possibly be a result of the study. One participant in the NES+T group reported a sunburn over the site of gel application, and another reported a rash over the site of gel application, both which could possibly be related to the study. There was no change in any of the safety parameters being

measured. None of the participants reported any changes in psychosexual changes 1 weeks after treatment was stopped.

**Study Critique**

The study's already small sample size (n=44) was further decreased to 37 participants after many failed to complete the trial period or did but ended up being noncompliant with the medication. This study is very similar to the first study, where the study does suffer from only having healthy participants, so extrapolation to a larger population is difficult.

Strengths of this study include using a randomized control trial and having no serious adverse events.

One limitation of this study is that all doses of the trial medications were measured and placed into pre-filled syringes by pharmacists. It is unlikely that a consumer would be as precise with their dosages unless the administration method can be refined. Also, the length of the study was too short to measure the effectiveness at inhibiting spermatogenesis.

The efficacy of a gel as the route of administration must also be questioned. The trial did not take into account the effectiveness of the drug if it was washed or rubbed off after a certain period of time.

**Discussion**

**Table 5. Study Comparison**

| | **Ilani et al** | **Zitzmann et al** | **Anawalt et al** |
|---|---|---|---|
| **Participants, N** | 99 | 56 | 44 |
| **Population** | Healthy males age 18-50 | Healthy males age 18-50 | Healthy males age 18-50 |
| **Study Length** | 24 weeks | 6 weeks | 4 weeks |
| **Primary Interest** | Compare effectiveness of testosterone vs testosterone + NES in suppressing spermatogenesis | Compare effectiveness of 4 types of progestins in suppressing spermatogenesis | Compare the effectiveness of testosterone vs testosterone + NES in suppressing spermatogenesis |
| **Measurement of Efficacy** | Sperm count < 1 million/ mL | Serum FSH and LH concentration < 0.5 IU/mL | Serum FSH and LH concentration < 1 IU/L |

Pharmacologic contraception is still something that does not exist for the male population. Men have to either rely on barriers, spermicide, other nonpharmacologic methods of birth control or solely trust female contraception. These three novel trials were the first three

trials that showed efficacy in either the suppression of spermatogenesis or the decrease in levels of FSH and LH.

Due to the inability of testosterone to be absorbed enterally, these trials focused on the use of transdermal application. This both allowed for an increase in ease of application and the achievement of a steady state level of distribution once the medication was absorbed into the skin, all while remaining a non-invasive treatment.

An overview of the three studies is provided (Table 5). Due to its longer trial period, the Ilani et al study was the only one that focused on the suppression of spermatogenesis as a measurement of effectiveness. The other two trials, Zitzmann et al and Anawalt et al, used serum FSH and LH concentrations as a surrogate outcome for spermatogenesis.

While both Ilani et al and Anawalt et al compared the effectiveness of using NES+T versus only using testosterone for suppressing spermatogenesis, Zitzmann et al compared the effectiveness of 4 novel progestins, with and without testosterone, at suppressing spermatogenesis. For the purpose of this study, only the effectiveness of the nestorone group was discussed.

None of the trials reported any serious adverse events, but two common complaints observed were skin irritation, to include acne and sunburn, and a mild decrease in libido.

All three studies demonstrated the effectiveness of using NES gel at suppressing spermatogenesis. Ilani et al demonstrated that using either 8 mg of NES+Tgel or 12 mg of NES+T gel produced a sperm count < 1 million/mL for 89% and 88% of their respective study participants. Similarly, Anawalt et al found that using 8.3 mg NES +T gel suppressed serum FSH and LH to a concentration <1 IU/L in 84% of their study participants. Both Ilani et al and Anawalt et al used a control group that tested the effectiveness of testosterone only at suppressing spermatogenesis. Ilani et al demonstrated that only 23% of the participants administering testosterone only reached a sperm count of <1 million/mL and Anawalt et al demonstrated that only 16.7% of participants reached a FSH and LH concentration <1 IU/L. In comparison, Zitzmann et al tested the effectiveness of using 2 mg of NES and 3 mg NES, and found that on average all of the participants of the NES 3 mg group achieved a serum FSH and LH concentration <0.5 IU/mL, while on average none of the NES 2 mg group did. It is interesting to note that Zitzmann et al and Anawalt et al used different cutoff values for serum FSH and LH concentrations that correlate with adequate spermatogenesis. Both studies cite different sources for how they determine their respective cutoff values, but the cutoff value that Zitzmann et al used is 500 times higher than the cutoff value that Anawalt et al used.

Similar to female contraceptive trials, non-adherence remains an issue that plagues the effectiveness of medications. Each of the studies reported a compliance between 88 and 95%. This lack of complete compliance can result in a lower spermatogenesis rate, decreased suppression of progestins, and result in sperm rebound between periods of suppression. This failure to comply with a treatment regimen also translates to current accepted standards of contraception. Even though oral contraceptives have proven their high level of efficacy over the years, their levels of discontinuation over six months are 31% and 69%, respectively.[7]

**Conclusion**

Nestorone plus testosterone as a transdermal gel has shown promise in both spermatogenesis suppression and the decrease of progestins to levels reflective of a future decrease in spermatogenesis. All three trials used varying dosages of NES+T in an attempt to find the optimal dosage. The Ilani et al and the Anawalt et al trial both included a dosage of 8 mg NES which seems to be at or near the optimal dosage of NES. Further trials should be done to see if a dosage between 8 mg NES and 3 mg NES, the dosage used in the Zitzmann et al trial, would be the optimal dose. The lower dose of NES used in the Zitzmann et al trial was associated with less side effects but noted an ineffective level of progestin suppression.

Compliance with this medication remains one of the major issues with a male contraceptive. By combining the nestorone and testosterone gels into single use packets, application of the medication is simplified, potentially helping with compliance, acceptability, and overall effectiveness in the suppression of progestins and spermatogenesis. Patients must be educated on the transdermal application of this gel, as studies have shown that washing the application site will significantly affect the level of absorption if within a few hours of placement.[9]

The majority of men in these studies were satisfied with the NES+T gel as a method of contraception, and around 50% said they would use this as a primary method of contraception, if available. These studies support the development of NES+T as a suitable male contraceptive but require a longer trial period to further demonstrate the suppression of spermatogenesis.

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