# CONTROL OF FERTILITY BY MONTHLY INJECTIONS OF A MIXTURE OF NORGESTREL AND A LONG-ACTING ESTROGEN

A Preliminary Report

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## ABSTRACT

Fifty women were treated over 550 menstrual cycles with a long-acting injectable mixture of 25 mg norgestrel and 5 mg estradiol hexa-hydro-benzoate administered monthly. The treatment proved to produce sterility in all patients when injections were given between 28 and 30 day intervals. Minor changes in menstrual pattern were reported but cyclic bleeding similar to menstruation was preserved in 75% of all the cycles.

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## INTRODUCTION

Several attempts have been made in the last decade to use long-acting progesterone derivatives as injectable contraceptives (1-8). Successful trials were carried out with hydroxyprogesterone caproate, dihydroxyprogesterone acetophenide, 6α-methyl-17α-hydroxyprogesterone acetate and more recently, norethisterone enanthate. These progestins have been used alone or in combination with a long-acting estrogen. Persistent and sometimes undesirable menstrual irregularities of varying degrees were observed in most patients who received high doses of these progestins. With low doses and using an estrogen-progestin combination, cyclic bleeding similar to menstruation could be preserved in the majority of cycles (9).

In the present study, the contraceptive effectiveness of a totally synthetic progestagen, norgestrel (DL-13β,ethyl-17α-ethynyl-17β hydroxygon-4-en-3-one), chemically related to the 19-nortestosterone derivatives, was evaluated. Norgestrel is not estrogenic in acute test and also is not converted to estrogen in vivo, as determined by chronic bio assay procedures. Available evidence suggests that the biological activity is found in the D-enantiomer. The L-enantiomer is inactive (10).

## MATERIALS AND METHODS

Case selection was limited to 50 healthy normal patients of proven fertility as indicated by at least one successful pregnancy. The patients were between 16 and 35 years of age with an average of 18 years. Pregnancies ranged from 1 to 13 with an average of 5. After complete pre-treatment physical examination with a special emphasis on breast and pelvis, each patient received on Day 5 of the menstrual cycle, an intramuscular injection of a mixture of 25 mg norgestrel in aqueous suspension and 5 mg estradiol hexabenzoate in peanut oil. Injections were given at subsequent intervals of 28 to 30 days, for a period ranging from 1 to 14 months, with an average of 11 injections for each patient. Vaginal cytology was performed on all patients at 6-month intervals. Endometrial biopsies were also performed on twenty patients.

## RESULTS

No pregnancy occurred during the treatment indicating that the injectable mixture was 100% effective as a contraceptive agent during the study period which lasted 550 cycles. Cycle length, duration and intensity of menstrual flow, before and during the treatment, are summarized in Figure 1.

The average cycle length prior to the first injection was 29 days with a range of 24 to 33 days. The average cycle length during treatment was 32 days with 75% of all the cycles between 24 and 33 days. The number of cycles in which patients bled from 2 to 5 days decreased from 88% before the injection to 65% during treatment. However, the 97% of all the cycles, the duration of flow was still

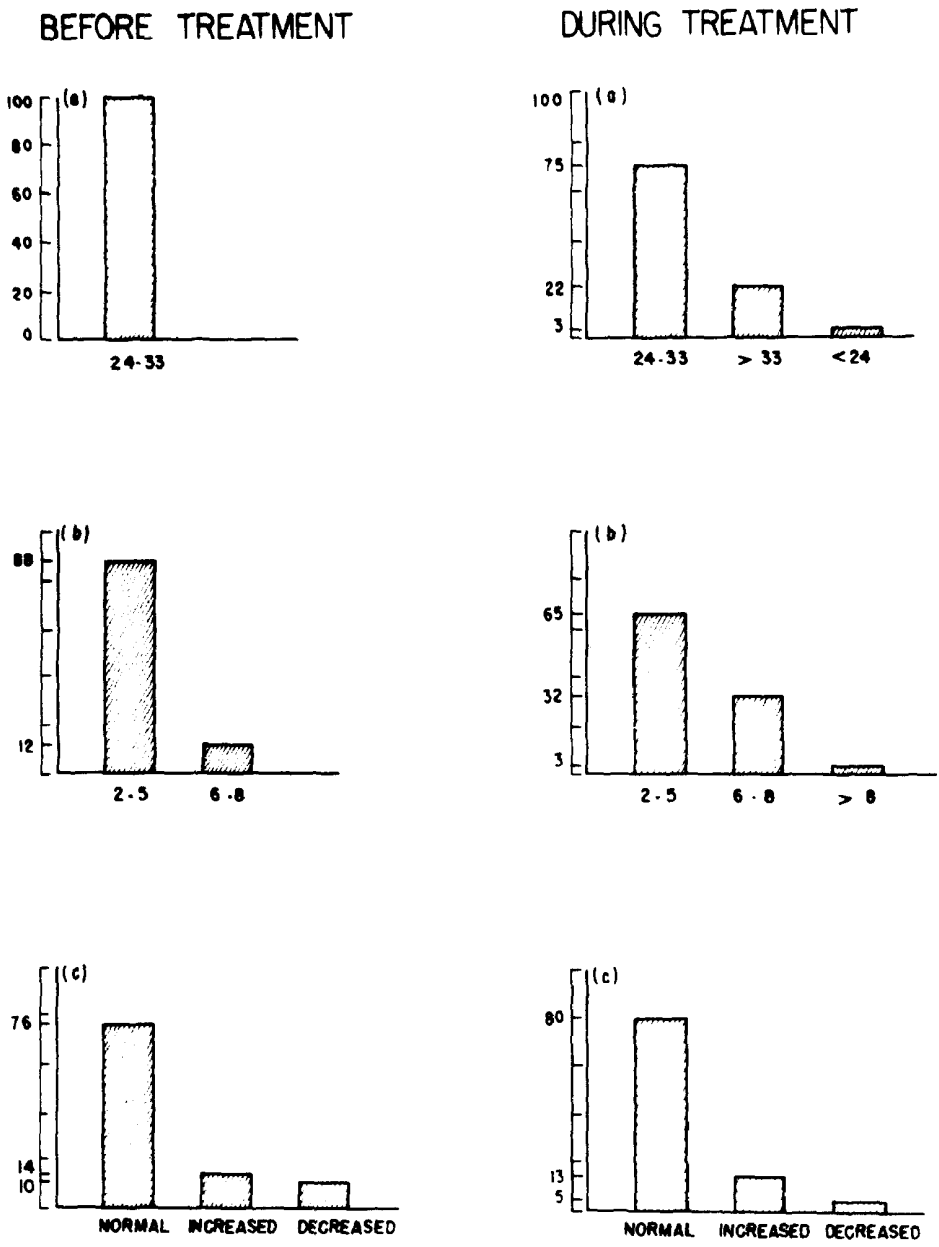


Figure 1: Comparison of (a) cycle length, (b) duration of menstrual flow, and (c) intensity of menstrual flow before and during treatment. The ordinate shows percentage of cycles.

from 2 to 8 days. The amount of flow was considered to be normal in 80% of all the treatment cycles, whereas before treatment, it was considered normal in only 76% of all cycles.

An increase in weight occurred in most patients during the treatment period. The weight change was greater than 4 kg for 60% of the patients. In 24% of the patients, the weight increase was less than 4 kg but greater than 2 kg. There was no appreciable weight change in only 16% of the patients. Spotting occurred in 9% of the cycles. Other complaints such as headache, dizziness, abdominal pain, etc., were reported in less than 5% of all the cycles.

## DISCUSSION

The present study shows that a mixture of estradiol hexabenzoate with the synthetic progestin, norgestrel, can be used effectively as an injectable contraceptive. The study also shows that the monthly administration of the contraceptive mixture allows cyclic bleeding similar to menstruation providing, therefore, a practical and simple method of cycle control. The amount of biologically active progestin used in association with the estrogen to provide one month of contraception is approximately 12.5 mg, in view of the fact that one-half of the total injection mixture is represented by inactive L-norgestrel. The present injectable mixture compares favourably to results previously reported with a monthly injectable estrogen-progestogen combination using a different progestin, medroxyprogesterone acetate (9).

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