

## CONTRACEPTION

### OVULATION INHIBITION FOLLOWING VAGINAL ADMINISTRATION OF PILLS CONTAINING NORETHINDRONE AND MESTRANOL

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#### ABSTRACT

Plasma levels of estradiol and progesterone were investigated in women using daily vaginal pills containing 1 mg norethindrone and 50 mcg mestranol. Of 13 treatment cycles in ten women using one vaginal pill daily, six were ovulatory and seven anovulatory. All 12 cycles in ten women using two vaginal pills daily were anovulatory.

#### INTRODUCTION

We have shown that inhibition of ovulation may be achieved by daily vaginal administration of contraceptive pills (1). The pills used in the first pilot trials contained dl-norgestrel 500 mcg and ethynyl-estradiol 50 mcg. In a comparative study between oral and vaginal administration of this combined pill, it was found that plasma levels of l-norgestrel rise at a slower pace and reach a lower peak value after vaginal placement than after oral administration of the same pill (2). Plasma levels of l-norgestrel obtained twelve hours after administration on days 1, 5, 10, 15 and 20 of a treatment cycle show that the levels are lower when the pill is administered by the vaginal route. Nonetheless ovulation was inhibited in women using the vaginal pill as consistently as in those taking the same pill by oral route.

Recently we have shown that vaginal placement may be used as a method of conception control, having a continuation rate which compares favorably with other methods of contraception. In a study conducted in our Family Planning Unit, 124 women used vaginal pills for periods ranging from 6 to 20 months. 1,438 woman-months of use were recorded with no pregnancies. Cycle control in vaginal pill users was as good as with oral administration and menstrual disturbances occurred rarely. Vaginal discharge did not appear to be a serious problem and other side effects usually associated with pill use, such as nausea and headache, were less frequent with vaginal pill than with the oral pill (3).

The success of the first clinical trial prompted us to try other compounds for possible use in vaginal pill which could have advantages such as lower price or greater local availability than the combination used in our first clinical trials. We report now on the effects on ovulation of the combination norethindrone-mestranol administered by vaginal route.

Submitted for publication February 7, 1984  
Accepted for publication March 12, 1984

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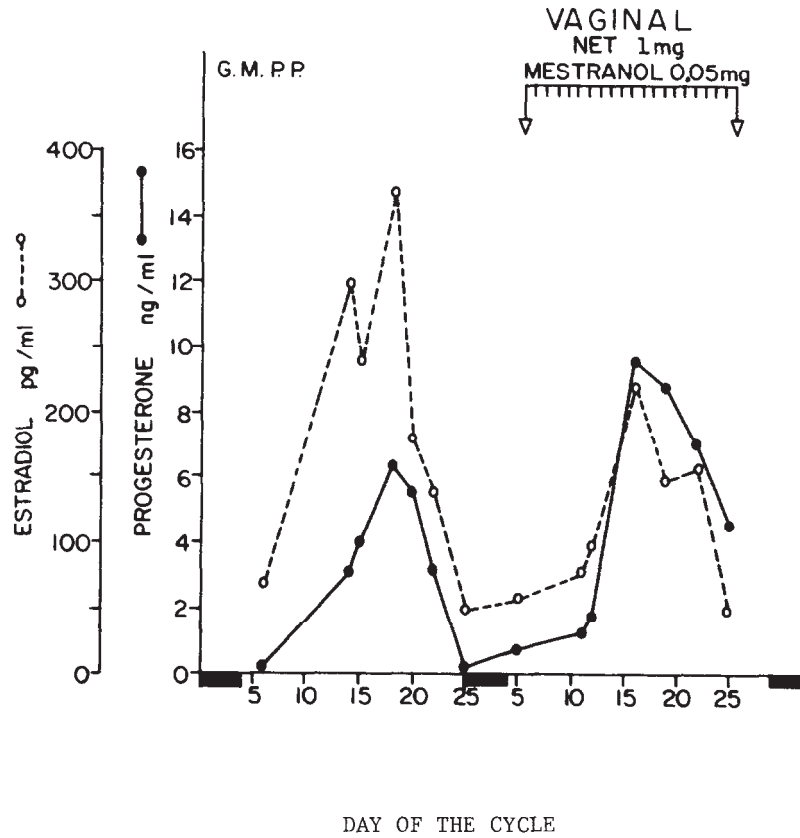


Fig.1. Estradiol and progesterone plasma levels in a control and treatment cycle. Treatment consisted of daily vaginal administration of one pill. Note rise in both estradiol and progesterone, typical of ovulation, in both cycles.

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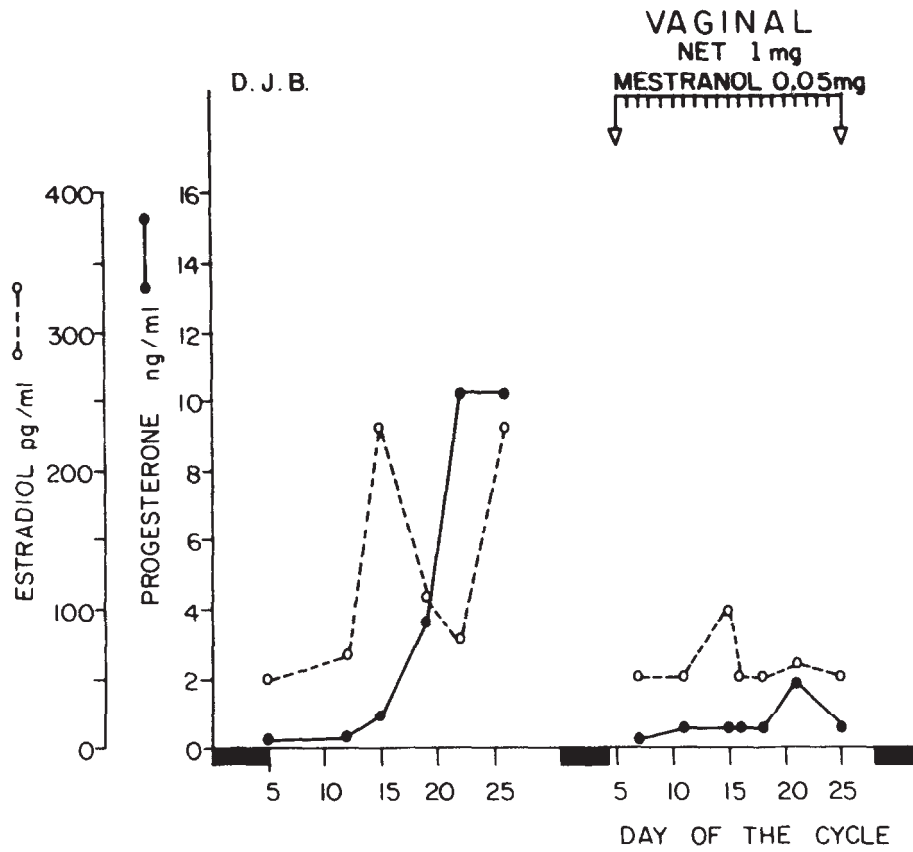


Fig.2. Estradiol and progesterone plasma levels in a control and in a treated cycle. Treatment consisted of daily vaginal administration of one pill. Note ovulation suppression in treatment cycle.

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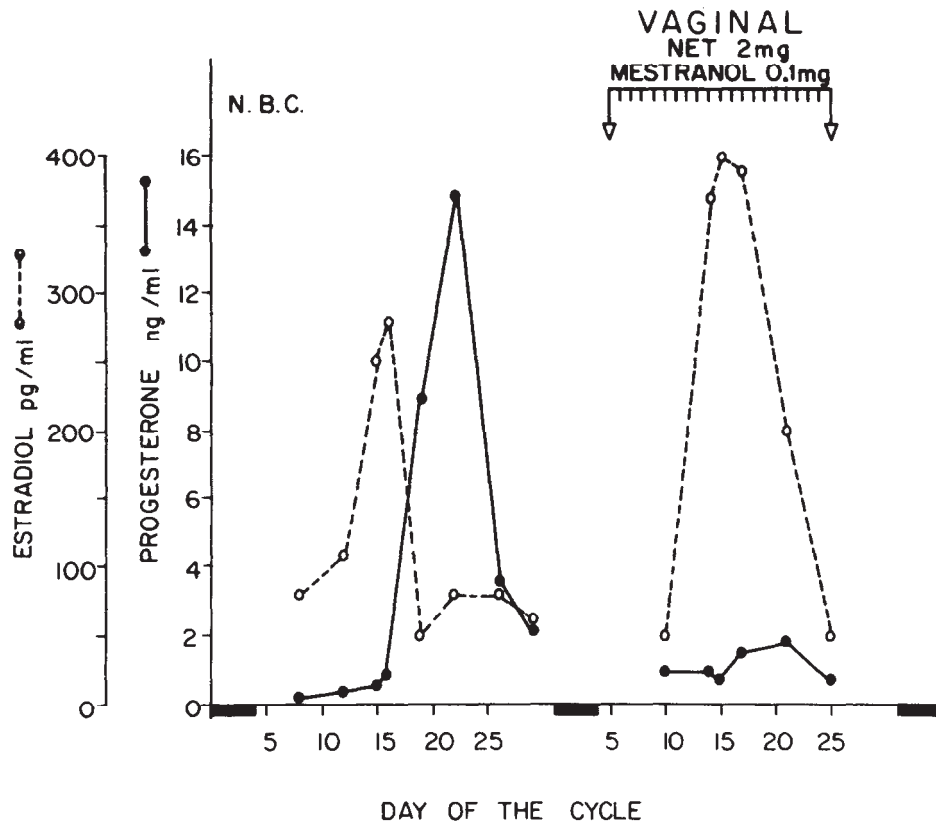


Fig.3. Estradiol and progesterone plasma levels in a control and in a treated cycle. Daily vaginal administration of two pills. Note suppression of progesterone rise and elevation of plasma estradiol in treatment cycle.

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### PATIENTS AND METHODS

Twenty healthy women 21-28 years of age volunteered for the study. All patients were using a copper T intrauterine contraceptive device for one year or longer. Blood samples were provided 2-3 times a week during a control pre-treatment cycle and during one or more treatment cycles. Plasma estradiol and progesterone were measured by radioimmunoassay (RTA) according to the method of Thorneycroft and Stone (4).

Each of two groups of 10 women was instructed to insert either one or two pills daily for 21 days in the vagina, always at the same time of the day. The pill used contained norethindrone 1 mg and mestranol 50 mcg.

### RESULTS

A total of 25 treatment cycles was available for analysis. Of the ten women inserting one pill daily, 13 treatment cycles were available. In six of these cycles, both progesterone and estradiol levels remained within the normal ovulatory pattern, indicating that ovulation occurred (Fig.1). In the remaining 7 cycles, no pre-ovulatory estrogen peak nor post-ovulatory progesterone rise occurred, indicating that no ovulation took place (Fig.2).

Of the ten women inserting two pills daily, 12 cycles were available for analysis. In all twelve cycles, no rise in progesterone levels occurred, indicating that ovulation was suppressed. In some cycles estradiol levels rose above 300 pg/ml but progesterone levels remained below 2ng/ml (Fig.3). Except for one patient who complained of vaginal irritation with pruritus, no side effects associated with vaginal pill insertion occurred.

### DISCUSSION

The pioneering studies of Mishell and collaborators with the contraceptive vaginal ring (CVR) have demonstrated vaginal absorption of several contraceptive steroids and have shown their efficacy in conception control (5,6). Vaginal rings were shown to be as effective as the oral contraceptive pill and continuation rates were comparable to those of low dose oral contraceptives. However, CVR had few but significant drawbacks. It could provoke erosion of the vaginal wall, interfere with coitus, and retain and release unpleasant odor. In order to overcome these disadvantages of the ring while preserving the advantages of the vaginal route of administration, we have proposed vaginal administration of a contraceptive pill as an alternative to CVRs.

In a previous study we have shown that a combination pill containing dl-norgestrel and ethynylestradiol could inhibit ovulation. The present study shows that another combined pill containing norethindrone and mestranol may be as effective as the norgestrel-ethynylestradiol combination. In order to obtain contraceptive efficacy, 2 mg of norethindrone and 100 mcg of mestranol have to be administered daily. The requirement for higher dose by the vaginal route as compared to the oral route stems from the fact that much lower blood levels of the steroids are obtained through vaginal absorption. This dose could be contained in a single tablet if the compounds tested in this study are to be used as a vaginal pill contraceptive.

#### Acknowledgement

This study was supported by the Rockefeller Foundation.

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