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Use of progestational agents as a test for pregnancy

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THE USE OF PROGESTATIONAL AGENTS AS A TEST FOR PREGNANCY

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INTRODUCTION

As normal physiology becomes better understood and defined, simple diagnostic aids are as a result available. The normal physiology of menstruation has been explained only within the last twenty years. Based on this knowledge, there is a very simple non-specific test for pregnancy, that of induction of withdrawal bleeding by administration of progesterone to the estrogen-primed uterus.

THE HORMONAL BASIS OF MENSTRUATION

The normal menstrual cycle is under the control and influence of four hormones: follicle stimulating hormone (FSH) and luteotropic hormone (LH) from the anterior pituitary; and estrogen and progesterone from the ovaries.

FSH causes development of the ovarian follicles. FSH blood levels reach their peak during the first four to five days of the average twenty-eight day cycle, or during the time of the actual menstrual flow. The resultant development of the follicle produces estrogen, which gradually rises to a peak at day fourteen of the cycle. The estrogen produced is responsible for the development of the presecretory endometrium in preparation for possible implantation following ovulation, which occurs with the rupture of the follicle. The estrogen level drops slightly at this time, then rises again (possibly the result of progesterone acting on the follicle) to reach a peak at day eighteen to nineteen.

LH is at a high level at day fourteen and is responsible for development of the corpus luteum. The latter produces progesterone, which acts to maintain and further develop the endomentrium in its

secretory stage. The blood level of progesterone is at its peak at the same time the estrogen peak is reached. From this point, both estrogen and progesterone levels simultaneously decline to their minimal day one values, when menses begin. (See Figure 1, Appendix).

Administration of estrogen and/or progesterone to animals and humans (1,4) has demonstrated the following facts:

a) The removal of the ovaries causes bleeding.

b) Estrogen prevents the bleeding in (a), but following cessation of estrogen administration, there is bleeding.

c) If progesterone is given at the time estrogen is discontinued in (b), the bleeding is prevented; but the withdrawal of progesterone is followed by bleeding.

d) Progesterone withdrawal bleeding occurs even when estrogen has been given concomitantly with it, and even if the estrogen level is increased fourfold at the time of the progesterone withdrawal.

e) The average time of withdrawal bleeding for progesterone is 2.9 (range 2-4) days, while

for estrogen withdrawal, the average is 9.2 (range 5-16) days.

These facts constitute proof that withdrawal of progesterone is the basic cause for normal menstrual bleeding.

If implantation and pregnancy occur, progesterone from the corpus luteum increases steadily in the first trimester; and the placenta secretes increasing amounts in the second and third trimesters (10).

MECHANISM OF THE TEST

The preceding facts form the basis for testing for pregnancy. If there is amenorrhea of early pregnancy in a woman with previously normal menses, progesterone is present from endogenous production, and withdrawal of a relatively small exogenous source is of no consequence, and does not cause bleeding.

In the patient with the same background, i.e. previously normal menstrual history, but whose amenorrhea is the result of lack of progesterone, as in an anovulatory cycle, menstruation will follow the administration of 50 mg. of intramuscular progesterone for two days, in four days (12).

This test approaches 100% accuracy, when menses are not over several weeks overdue, and previous

menses were fairly regular; when menses are over three months overdue, the number of non-pregnant who do not bleed is increased (15).

ADVANTAGES OF THE TEST

The main advantage of the test is its accuracy at a very early state of pregnancy. Conventional biologic tests (frog, rabbit, rat) are based on the fact that chorionic gonadotropins are secreted by the cytotrophoblast of the chorion. The peak for these gonadotropins is reached at fifty to sixty days of gestation (10). These tests are not significantly sensitive to detect a gestation of less than one month's duration (from time of implantation).

There is also the psychological benefit of the occurance of a normal menstrual period in the non-pregnant woman, as further reassurance that she is not pregnant.

LIMITATIONS

The use of progesterone is limited by the absence of oral response, the short duration of activity, and the limited solubility of the product in suspension (3,6). However this factor is of greater importance with regard to prolonged therapy as in the inhibition of ovulation in contraceptive management,

and the past popular use for attempting to maintain pregnancy in threatened abortion.

NEW PROGESTATIONAL AGENTS (PROGESTINS)

Recently there has been a lot of work done with analogs of progesterone, and synthetic androgens which show progestational activity. It has been demonstrated that the higher homologs of 19-nor-testosterone show this increased progestational activity (3). Furthermore, these 19-nor-steroids are active orally, and with a daily dose show progestational effects on human endomentrium; and, this can be inhibited, if given prior to ovulation (pituitary inhibition resulting in inhibition of ovulation). Withdrawal bleeding follows discontinuation of the agent at one to four days (1% give no withdrawal bleeding, but when therapy is given before the tenth day of the amenorrheic phase, bleeding usually follows) (14).

Progestational agents available today include ethisterone, norethindrone or norethisterone, norethynodrel, and 17-alpha-hydroxyprogesterone acetate. All of these have oral progestational activity ranging from five to twenty-five times that of progesterone (3,12). The pituitary and ovaries have shown no

changes, and no fuctional impairment, with normal cycling or subsequent pregnancies following cyclic therapy or continuous administration for many months (12).

SIDE EFFECTS

The most serious complication reported to date from the use of progestins is the possible direct androgenic action on the female fetus (8). This virilism may be due to abnormal degradation or abnormal placental transmission, and is not mediated through the adrenals (10). Reviews of cases of female infant virilism related to maternal progestin administration have suggested that there are three factors: time in pregnancy; dosage; and duration of administration (7). It is possible to achieve increased phallic size with androgens at any stage of gestation, but the most critical and sensitive period is at six to twenty weeks, which is the time of labioscrotal fusion. Mild cases of virilism have been related to administration of twenty to forty milligrams of progestin per day (10). However, all of these reported cases have been related to prolonged therapy in connection with attempted maintenance of pregnancy in threatened abortion.

There have been a number of other side effects reported with the oral progestins, with the most prominent being related to gastrointestinal symptoms. The majority of these have been nausea and vomiting, less often bloating, weight gain, and jaundice associated with elevated bromsulphalein retention, the latter being peculiar to the alkyl derivatives (3). The nausea and vomiting are often alleviated by taking the medication at mealtime or with milk, particularly at bedtime, or with an antiemetic drug. Occasionally, the drug will have to be discontinued, because of persistant nausea and vomiting (12).

Infrequently, some women have complained of exacerbations of the usual menstrual molimina, with depression, irritability, and nervousness. There has also been swelling and tenderness of the breasts, which was not sufficiently annoying to discontinue the drug, and all of which regressed when the drug was finally discontinued (5,12).

Other very rarely reported complaints were vertigo, dyspnea, and increased libido (3,5,12).

Most of the side effects were reported subjectively and following cessation of administration of the progestin by several months (5). The overall

incidence was close to the placebo range, and in some contraceptive studies, may not have even differed from the placebo control patients (3).

REPORTED TEST SERIES

The Minnesota Series (15): This included three groups:

1) Three daily intramuscular doses of 2.5 mg. estradiol benzoate with 12.5 mg. progesterone. Withdrawal bleeding in the non-pregnant occurred usually four to five days after the last injection (range 2-15).
2) 100 mg. progesterone intramuscularly -- one dose only, with menses at five to six days (range 2-14).
3) 50 mg. anhydrohydroxyprogesterone with 0.02 mg. ethinyl estradiol orally with menses at two to four days (range 2-14).

In all three groups, none of the patients who subsequently were proven prgnant had any bleeding. Occasionally in the non-pregnant, bleeding was scanty or slightly prolonged. None of the female infants born had any signs of pseudohermaphroditism.

The Australian Series (13): This consisted of a group of patients with five to eight weeks amenorrhea who were given Orasecron (ethisterone 10 mg. with ethinyl

estradiol 0.05 mg.), five tablets every four hours for two days. The results were:

Total not bleeding.....36

Positive toad test, pregnant.....27

Negative toad test, pregnant..... 5

Orasecron test fallacious, not pregnant..... 4

Total bleeding.....21

Menses were at 2 to 7 days, and the toad tests were all negative.

Total spotting..... 5

Positive toad test and pregnant..... 3

Negative toad test, not pregnant..... 2

The Omaha Series (in cooperation with L. S. McGoogan, M.D., and the Squibb Institute for Medical Research): This consisted of 19 patients given ethinyl nortestosterone acetate, 2.5 mg. with ethinyl estradiol 0.05 mg. (Squibb's preparation Es402a-A), two tablets daily for three days. Based on the time of the last menstral period, time of gestation was from 5-20 weeks with 10 the average. This is approximately 6 weeks "overdue".

Total not pregnant.....10

Normal bleeding..... 7

The average time to onset of menses was

2.9 days. Frog tests were done on only two of these patients and both were negative.

Irregular bleeding..... 1

A D&C was done, and the microscopic showed irregular shedding without decidual reaction.

No bleeding..... 1

This patient never did have any bleeding, and there was no subsequent development of pregnancy. Two frog tests were done, and both were negative.

Unable to complete test..... 1

There was no subsequent development of pregnancy.

Total pregnant..... 9

No bleeding..... 9

All of these patients had subsequent development of pregnancy. Frog tests were done on two of them and both were positive.

Side effects: There were no reported side effects to the medication, except in one case, which was the one who was unable to complete the test. The

regimen was terminated after three tablets due to nausea, palpitations, and vertigo.

SUMMARY

Progesterone withdrawal is the basic mechanism in the causation of menstruation. There is a cyclic variation in the progesterone level in the normal cycle. When pregnancy intervenes the level is elevated. Exogenous administration of a substance with progestational activity, to women with previously regular cycles and with amenorrhea of short duration, and its subsequent withdrawal, constitutes a simple physiologic test for pregnancy. It approaches 100% accuracy, particularly during the time interval when biologic tests based on elevation of chorionic gonadotropin titers are insufficiently sensitive to be accurate.

There are a number of new agents available with oral progestational activity, with greatly increased potency over the parenteral route. Androgenic effects in the form of female infant virilization have been reported, but have been due to the prolonged use of high doses. Gastrointestinal symptoms have been the most troublesome of the side effects, but have not been difficult to overcome with careful administration in relation to food intake or antiemetic drugs.

The Omaha test series reported here supports

the high level of accuracy previously reported for this type of test in two other series.

CONCLUSIONS

There are several currently available oral progestational agents which are capable of being used for withdrawal bleeding as a test of pregnancy. Accuracy of this type of test approaches 100%. It is useful at the time when biologic tests are inaccurate. Side effects are minimal. Effects on the fetus for the dosage used in this test are of no consequence.

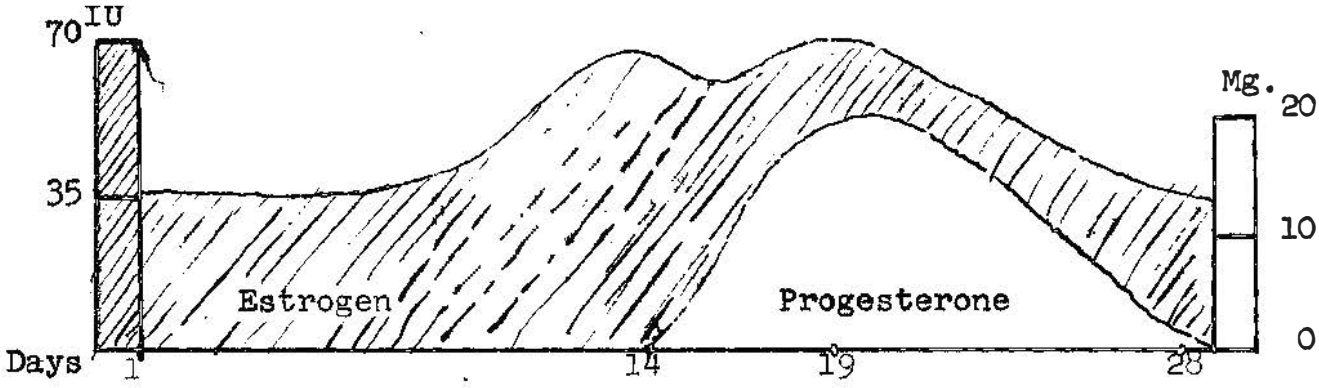

Figure I: THE RELATIONSHIP OF ESTROGEN AND PROGESTERONE IN MENSTRUATION

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