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DOUBLE-BLIND STUDY OF EFFECT OF 17-HYDROXYPROGESTERONE CAPROATE ON ABORTION RATE

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After many years of use and a large number of publications there is still no good evidence to indicate that progestogens have a valid role in the treatment of patients with a history of abortion.

In many of the published series the amount of material administered has been inadequate in the light of current concepts of progesterone secretion in pregnancy (Zander, 1959) and inadequate control observations have invalidated much published data. To assess the salvage rate in treated pregnancies and then compare it with that found for previous untreated pregnancies in the same patients ignores the number of pregnancies that would have reached viability if no treatment had been given at all.

Malpas (1938) produced a theoretical estimate that any woman with a history of three consecutive abortions

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had a 73% chance of aborting in the next pregnancy. His prognosis provides the background to many claims that a satisfactory treatment exists for this group of women. This gloomy theoretical figure is not supported by the observed incidence of abortion in similar patients who have remained untreated. Warburton and Fraser (1959) found that the risk of abortion in patients with a history of two previous miscarriages was 23%, rising to 26% after three abortions. Specific treatment should be associated with an abortion rate lower than this. To assess the effect of a progestational agent it appears reasonable to administer this preparation only to those individuals showing evidence of a low or declining progesterone production.

The purpose of this paper is to present the results of a double-blind study of treatment with a progestogen in 50 patients selected for treatment on this basis. If progesterone treatment is of material assistance to these individuals then there should be a significant difference in the salvage rate from those receiving an adequate dose of the active preparation compared with those receiving a placebo.

Method and Materials

Preparation and Dosage

The progestogen used was 17-hydroxyprogesterone caproate. It was supplied by the manufacturers in a strength of 250 mg./ml. with 1 ml. of solution in each ampoule. The presentation of the active preparation and the placebo was identical with the exception of the letters A and B on the ampoules. The correct identity of these substances is not known to any person taking part in this study.

Although it has been shown that there is a close correlation between pregnanediol excretion and placental progesterone content throughout pregnancy (Shearman, 1959), it is accepted that urinary pregnanediol excretion is an inexact reflection of progesterone secretion. Recovery of pregnanediol after administration of progesterone varies, but is usually less than 20% (Loraine, 1958). Pregnanediol is not an excretory product of 17-hydroxyprogesterone caproate. Since constancy of dosage in different individuals is essential in such an investigation as this, we have assumed that an average of 10% of secreted progesterone can be recovered from the urine as pregnanediol. In a small series of spontaneous first-trimester abortions studied previously (Shearman, 1959) excretion of pregnanediol was found to be up to 5 mg./24 hours less than that found in normal patients. Therefore a dose scale was settled on as follows: up to 8th week, 250 mg./week; 8th to 11th week, 375 mg./week; 12th to 16th week, 500 mg./week; 17th to 20th week, 375 mg./week; 21st to 24th week, 250 mg./week. No treatment was given after the 24th week. The decision to withdraw steroids slowly after the 16th week rather than abruptly was arbitrary, based on the generalization that it would be less likely to cause disturbance of the pregnancy.

Selection of Patients

Patients presenting to the sterility clinic at the Royal Hospital for Women, Paddington, or the endocrine clinic at King George V Memorial Hospital, Camperdown, with a history of two or more consecutive abortions were initially selected for study. Since we wished to assess the effect of the progestogen in patients where the only observed abnormality was a low or falling pregnanediol excretion, further selection then took place. Four patients showing uterine reduplication on hysterography were excluded. In the remaining patients pregnanediol was assayed once weekly from as early in pregnancy as possible. The excretion of pregnanediol in normal patients has been previously studied (Shearman, 1959). Patients showing persistently normal levels were not treated and have therefore been excluded from this study. There have been no abortions in this group so far.

This final selection left a group of 50 patients who were treated on the following criteria: (1) if the 24-hour excretion of pregnanediol was less than that shown in Table I; or (2) if there was a fall in pregnanediol excretion of more than 2.5 mg./24 hours from one week to the next, provided this occurred before the twelfth week.

TABLE I

Week of pregnancy	7	8	9	10	11	12	13	14
Pregnanediol (mg./24 hours) ..	5	6	6·5	7	7·5	8	8·5	9

Method of Assay.—Pregnanediol was assayed by the method of Klopper, Michie, and Brown (1955). All assays were performed in duplicate on aliquots of 24-hour urine specimens.

Results

Of the 50 patients so far selected for treatment, 10 have aborted. Of these 50, 27 have received solution A and five have aborted; 23 have received solution B and five have aborted. These results are shown in Table II.

TABLE II.—*Results*

	No. of Patients Treated	No. of Abortions
Solution A ..	27	5 (18·5%)
„ B ..	23	5 (21·7%)
Total	50	10 (20%)

In order to determine that the cases were not unfairly distributed one way or the other, the average pregnanediol excretion has been determined in all treated patients proceeding to viability, and this is shown in Table III. There is no significant difference in the figures from week to week in either group. It will be seen that the mean excretion is essentially the same as that established in normal patients (Shearman, 1959).

TABLE III.—*Mean Pregnanediol Excretion in Treated Patients Reaching Viability. Excretion is Expressed as mg./24 Hours*

Week of Pregnancy:	7	8	9	10	11	12	13	14
Solution A ..	8·9	10·1	10·5	11·5	10·7	10·5	12·0	12·8
„ B ..	7·8	10·6	11·7	11·7	10·2	12·0	12 1	13·2

In all patients in whom pregnancy progressed to viability pregnanediol excretion returned to normal values after the institution of treatment. This was true irrespective of the solution used. Typical curves are shown in Fig. 1.

On the other hand, with one exception, in patients aborting pregnanediol remained at a low level until abortion occurred despite the administration of either preparation (Fig. 2). The exception was a patient who received solution A after a fall of 4 mg./24 hours in pregnanediol excretion between the sixth and seventh

week. Abortion occurred in the 14th week with a pregnanediol excretion of 17.4 mg./24 hours. The foetus had an exomphalos.

Unnecessary delay in starting treatment could perhaps be blamed for foetal loss in those patients in whom abortion occurred. The delay in treatment has been calculated from the interval between the date of collection of the urine specimen giving results that indicated the necessity for treatment and the first injection. This mean delay was 6.4 days in patients who aborted and 6.5 days in those who did not abort. The interval between the first injection and the subsequent abortion is also of importance in this context, as treatment starting only hours or a few days before abortion may not be regarded as an effective trial. Those patients receiving solution A who aborted had a mean interval of 18.8 days, while in those receiving solution B the interval was 25.2 days. These figures are not significantly different.

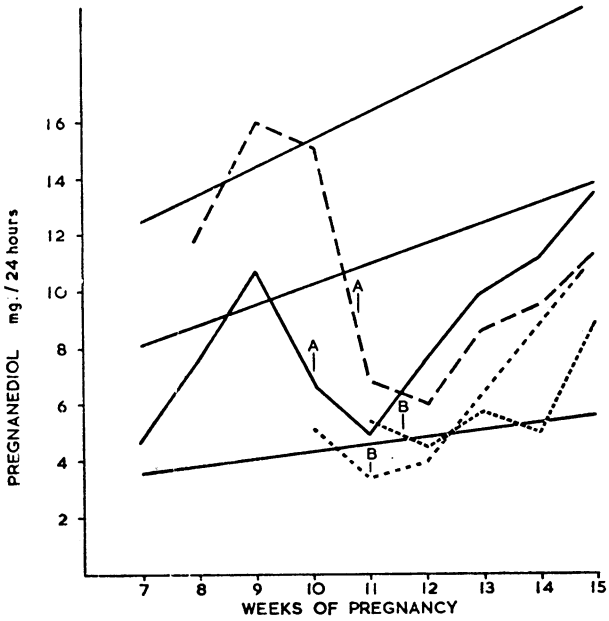

FIG. 1.—Pregnanediol excretion in four patients treated because of low or falling pregnanediol excretion in whom pregnancy progressed to viability. The letters A and B indicate the time of the first injection and the solution used. The pattern observed was similar irrespective of the solution used.

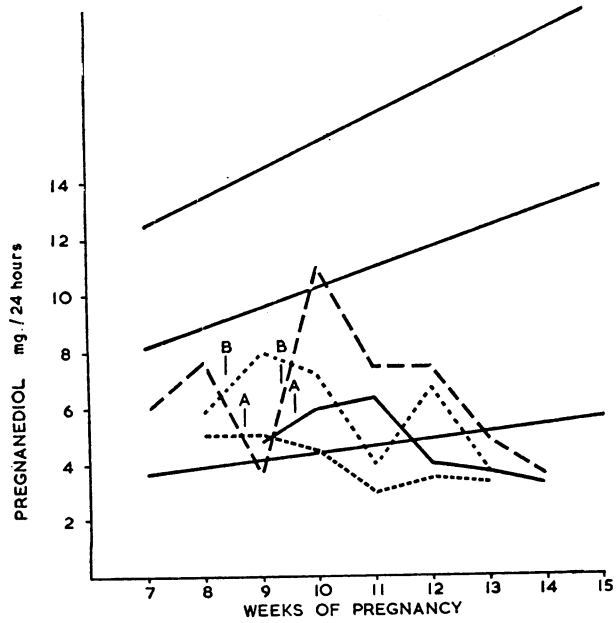

FIG. 2.—Pregnanediol excretion in four patients treated because of low or falling pregnanediol excretion who subsequently aborted. The letters A and B indicate the time of the first injection and the solution used. The pattern observed was similar irrespective of the solution used.

Type of Abortus

We felt that it was important to obtain a detailed description of the abortus wherever possible, and this has been done in 6 of the 10 patients. The essential findings were as follows.

Solution A.—(1) Intact amniotic sac and scanty chorionic tissue. No embryo was seen. ("Blighted ovum.") (2) The foetus and chorionic tissue appeared normal. (3) The only abnormality was an exomphalos. Sections of chorionic tissue appeared normal.

Solution B.—(1) Foetus and chorionic tissue appeared normal. (2) "Blighted ovum" with intact amniotic sac and scanty chorionic tissue. No embryo was seen. (3) "Blighted ovum" with intact amniotic sac and scanty chorionic tissue. No embryo was seen.

Therefore, of the six abortuses recovered, three were instances of blighted ova, one had an exomphalos, and two appeared to be normal.

Discussion

Malpas (1938) wrote, "The very best results that could be obtained from any specific therapy are about 83% (salvage rate)." It is an intriguing fact that almost all of the published methods claiming success in the management of recurrent abortion show a salvage rate in the vicinity of 80% (Javert, 1957), whether the methods used be as disparate as the administration of thyroid extract, oestrogens, progestogens before or after conception, chorionic gonadotrophin, psychotherapy, or the non-specific use of antisyphilitic preparations.

There is a good deal of evidence that many first-trimester abortions are preceded by a fall in pregnanediol excretion (Borth and de Watteville, 1952; Alder and Krieger, 1957; Shearman, 1959), so the use of a progestational agent appears at first sight to be rational. However, there is no valid evidence that would permit one to decide whether these patients abort because progesterone secretion declines or whether the factor responsible for the abortion also causes the fall in progesterone secretion.

Because of this lack of evidence and the expense of this type of treatment, we felt that a double-blind study of the effect of a progestogen was both justifiable and necessary. The identity of the preparations in this double-blind study is still not known to us, but our results so far indicate that progestational therapy administered to women with evidence of a low or falling pregnanediol excretion is not associated with a salvage rate materially different from that found in women receiving either a placebo or any other form of published treatment, or apparently no treatment at all.

If one accepts that a falling pregnanediol excretion reflects a qualitatively similar pattern in progesterone secretion the evidence would suggest that not all patients showing this fall will abort and that in those who do there is no causal connexion between inadequate progesterone secretion and ultimate abortion. Rather it would appear that *both* are the result of the basic

cause of spontaneous abortion, which still remains unknown.

Although only six of the abortuses have been recovered for detailed study, four of them were grossly abnormal. The abnormalities were distributed evenly between patients who received either solution A or solution B. It remains to be determined whether these abnormalities are environmentally or genetically determined.

It has taken over three years to collect the 50 cases published in this paper, and because of this relatively small number the investigation will continue to ensure that small, but perhaps ultimately significant, differences do not escape detection.

Summary

Fifty patients have been treated in a double-blind study of the effect of 17-hydroxyprogesterone caproate on abortion rate. Only patients showing a low or falling pregnanediol excretion were treated and included in this study. Of those receiving solution A, 18.5% aborted; of those receiving solution B, 21.7% aborted. The overall incidence of foetal wastage is 20%. Whichever of these solutions contains the progestogen these results do not so far support the claims that progestational therapy is of specific value in the prevention of abortion. This study is continuing.

Of six abortuses examined, four were grossly abnormal.

We are grateful to Dr. B. L. Reid for examining the aborted material and to Professor Bruce T. Mayes for his continued interest in this work. The technical skill of Mrs. Sheila Nisbet, Mr. Alan Clarke, and Miss Gwen Davidson is greatly appreciated. The preparations used in this study were made available by Dr. Jurgen Friebel, Schering AG, Berlin.

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METHYLDOPA IN THE TREATMENT OF HYPERTENSION

BY

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Hypertensive patients have been shown to be highly sensitive to the pressor effect of catecholamines (Goldenberg *et al.*, 1948), although evidence for increased production of these adrenergic amines is absent in most forms of hypertension (von Euler, 1956).

Irrespective of the exact role of catecholamines in hypertension, control of their endogenous production might provide a means of lowering blood-pressure. Methyldopa is a compound shown *in vitro* to be an effective inhibitor of the decarboxylation of dihydroxyphenylalanine, a precursor of catecholamines (Sourkes, 1954). This effect was subsequently confirmed pharmacologically (Reichel and Dengler, 1958). Inhibition of 5-hydroxytryptophan, tyrosine, and tryptophan decarboxylation was also demonstrated (Oates *et al.*, 1960). On administration of methyldopa to hypertensive patients it immediately proved to be an antihypertensive agent (Oates *et al.*, 1960). This warranted a more extensive study in order to assess its value either as a sole agent or in combination with other drugs in the treatment of hypertension. Possible toxic effects of the drug on the liver, kidneys, and blood picture, and certain aspects of the catecholamine metabolism during administration of methyldopa, have been studied.

Materials and Methods

Twenty-eight subjects with persistent hypertension were selected for this study, their ages ranging from 22 to 72 (average 46 years). Seventeen had essential hypertension, eight had malignant hypertension (with papillary oedema), two had hypertension with stenosis of a renal artery, and one had a phaeochromocytoma. All patients, except two with essential hypertension, had a urea clearance above 35%. Blood-pressure measurements were made by the arm-cuff-auscultatory technique. Methyldopa was administered as the L-isomer ("aldomet") supplied as capsules or film-coated tablets containing 250 mg. of the drug.† The toxicity of the drug was checked in each patient with serial analysis of the liver-function test and complete blood-cell counts. The urinary metanephrines were assayed in three cases by the method of Pisano (1960). The urinary excretion of catecholamines was determined in one patient by the method of De Schaepdrijver (1958). The protocols of individual studies are considered below in the appropriate sections.

Effect of Methyldopa on Blood-pressure

Acute Effect

Twenty-three hypertensive patients received the drug during their stay in hospital, their blood-pressure being taken three to five times daily in both the recumbent and the standing position. After two days in hospital a placebo capsule was given three times daily for two days to seven patients, after which they received methyldopa capsules on a similar schedule in daily doses ranging from 750 to 2,750 mg. for 2 to 10 days. When necessary the dose was increased every third day. Fourteen subjects were started immediately on methyl-

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