PROGESTERONE IMPLANTATION IN HABITUAL ABORTION

BY

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The woman who suffers a series of spontaneous abortions has attracted clinical as well as theoretical interest for many years. The most striking feature of reports in the recent literature (Bacharach, 1940; Smith, 1948; Bevis, 1951; Bishop and Richards, 1952) is the uniformity of the results claimed for various methods of treatment; as these nearly all indicate a success rate of the order of 80%, it is perhaps surprising that any problem should still be thought to exist. Few clinicians, however, would regard the matter as settled, and the search for the best form of treatment continues. It seems that, in spite of eagerness to publish series of cases treated in various ways, there has been great reluctance to compare the results of treatment with what really happens in the absence of specific therapy, as opposed to what, on theoretical grounds, has been expected to happen, based, for example, on the calculations by Malpas (1938) and Eastman (1947). Since it is unlikely that all the forms of treatment, which according to their respective authors prove so successful, can be influencing the exciting causes of repeated abortion, real doubt arises whether these series of treated cases may not in fact be comparable with the populations described by Malpas and by Eastman—that, in fact, the prognosis for the untreated patient may be much better than has generally been supposed. An alternative explanation could be that psychic factors are of paramount importance and that all the treatments are effective simply by giving the needed psychological boost.

The key role of progesterone in the maintenance of pregnancy has long been appreciated both experimentally and clinically. The fact that the site of its production changes from the corpus luteum to the placenta at about the twelfth to sixteenth week of gestation has suggested that at this critical time, at which so many spontaneous abortions seem to occur, the smooth take-over may not be accomplished, leading to a temporary or permanent fall in progesterone production, which might be responsible for the abortions. There is also the possibility that, in the habitual aborter, production of progesterone may be inadequate at all times. For both these theoretical reasons, the administration of progesterone has been advocated, both in the treatment of threatened abortion and in the prophylaxis of habitual abortion. Since the intramuscular injection of progesterone is certain to lead to considerable fluctuations of the progesterone level within the body, such treatment, it would seem, might do more harm than good. The slow absorption of the steroid from fused pellets implanted beneath the deep fascia suggests that this mode of administration might well be more appropriate. Good results from this treatment have, in fact, been claimed (Bishop, Richards, and Doll, 1950; Bishop and Richards, 1952).

We have been interested in this problem for some years and have been implanting progesterone in the same way as Bishop and Richards since 1947, but, because we have remained unconvinced that the successes claimed in the past for any form of treatment have been justified, we have not hesitated to treat approximately alternate cases, leaving the remainder without specific therapy but receiving the usual antenatal care. (The control patients attending St. Helier Hospital were given inert oral tablets.) We thus have a series of untreated control habitual aborters, the outcome of whose pregnancies can be compared with that of the patients who were implanted.

We have also made use of this clinical material in the attempt, by studying pregnanediol excretion, to obtain evidence for or against the theories of progesterone deficiency outlined above.

Material and Methods

The patients in this series have attended University College Hospital or St. Helier Hospital. They have all had two or more consecutive spontaneous abortions before the twentieth week, and none has been included in whom complicating factors (such as positive Wassermann reaction, extensive cervical tear, uterine malformation, associated medical disease, etc.) of obvious potential significance had been found. Preliminary investigation had been extensive in some patients (such as those complaining of infertility and seen in the first place in the fertility clinic) or absent in the case of those referred from the antenatal clinic. The assignment to the control or the treated group was on the basis of alternate cases at St. Helier Hospital and at random at University College Hospital. Implantation, by the technique described by Bishop, Richards, and Doll (1950), of six 25-mg. pellets of progesterone within the gluteal muscles about 5 cm. below the iliac crest, was carried out as soon as the pregnancy was diagnosed, and, in any case, not later than the tenth week of gestation or the time of the earliest previous abortion.

The outcome of pregnancy is now known in 113 patients, of whom 53 were controls and 60 had received progesterone implants. The distribution of previous abortions and the numbers of primary and secondary cases (the latter having had full-term pregnancies before the abortion sequence) are shown in Table I.

TABLE I.—*Distribution of Previous Abortions and Division into Primary and Secondary Cases in the Patients Included in the Series*

	No. of Previous Consecutive Abortions				Primary	Secondary	Total
	2	3	4	More than 4			
Controls	33	15	3	2	42	11	53
Received progesterone implants	33	16	7	4	45	15	60
Total	66	31	10	6	87	26	113

Pregnanediol estimation was performed on first morning urine specimens by the method of Sommerville, Marrian, and Kellar (1948), or, prior to the publication of that method, by a modification of the Guterman procedure (Swyer, 1949a, 1949b). The drawbacks of first morning specimens, as compared with 24-hour collections, are fully appreciated, but the likelihood of obtaining repeated 24-hour collections from out-patients is, of course, small. In this series a total of 355 determinations of pregnanediol excretion were made, 203 being on specimens from the control patients or the treated patients before implantation, and 152 on specimens from patients after implantation. One or more assays were made on specimens from 43 treated and 43 control patients; in each group, 18 patients provided

five or more consecutive specimens on which assays were made. In addition, 47 patients taken at random from the antenatal clinic were asked to provide a first morning specimen, on which pregnanediol assay was performed.

The Outcome of Pregnancy

Of the 60 patients who received progesterone implants, 48 were delivered of live babies, 11 aborted before the twentieth week, and one, who had previously had four pregnancies, none of which went beyond the twentieth week, delivered at 27 weeks a live baby which survived only five hours. In terms of living children, therefore, there was a successful outcome in 80% of cases. There were three caesarean sections for obstetric indications and one breech delivery. One patient delivered at 36 weeks a premature baby which survived.

Of the 53 patients who received no specific therapy, 40 were delivered of live babies and 13 aborted. A successful outcome was thus obtained in 75% of cases. There were two caesarean sections and two twin pregnancies, all of which were successful. One patient delivered at 34 weeks a premature baby which survived.

For the entire series (Table II) the success rate was 77.9%, and it is clear that the difference in the outcome for treated and untreated patients is not statistically significant

TABLE II.—Outcome of Pregnancy in 113 Patients with Two or More Consecutive Previous Abortions

	Aborted	Live Birth	Total	% Success
Controls ..	13	40	53	75.5
Received progesterone implants	12	48	60	80.
Combined ..	25	88	113	77.9

($\chi^2=0.124$, $P>0.7$), since a far greater difference could easily occur merely on a chance basis.

It will doubtless be objected that patients with a history of only two previous consecutive abortions are not necessarily "habitual aborters" and that therefore our series might contain a considerable number of patients whose previous abortions were due to the operation of non-recurrent chance factors. For these, progesterone implantation would not be expected to affect the outcome of subsequent pregnancies, so that a difference between control and treated groups would not be anticipated. The likelihood of such a "dilution" is, in fact, shown by the comparatively small number of women who do have more than two consecutive abortions, there being only 47 cases with three or more abortions in our series, which is drawn from more than 12,000 pregnant women. The distribution of these patients (Table I) is 20 controls and 27 implanted cases; the outcome of their pregnancies is given in Table III, from which

TABLE III.—Outcome of Pregnancy in 47 Patients with Three or More Consecutive Abortions

	Aborted	Live Birth	Total	% Success
Controls ..	9	11	20	55.0
Received progesterone implants	7	20	27	74.
Combined ..	16	31	47	66.

it will be seen that in the treated group the success rate was 74%, while in the control group it was 55%, the combined success rate being 66%. The difference between control and treated groups is not statistically significant ($\chi^2=1.107$, $P>0.2$), the likelihood of such a difference occurring on a chance basis being greater than 1 in 5. However, reference to Table I shows that the record of the previous abortions of the patients in the treated group is, in fact, worse than that of the control patients (11 with four or more abortions in the former, as against only 5 with four or more abortions in the latter); although this

difference is a random sampling effect, it does seem possible that, had the control group had an equally bad past obstetric history, the difference in outcome of pregnancy for the two groups might have been greater. All we can say, therefore, is that our limited data do not give clear evidence of a beneficial effect from progesterone implantation, and that the outcome of pregnancy in the untreated patients was far better than would have been expected on the basis of the calculations of Malpas and of Eastman.

Pregnanediol Excretion

In order to see whether different patterns of pregnanediol excretion are found in habitual aborters with and without progesterone implants, and in unselected antenatal

FIG. 1.—Scatter diagram of pregnanediol excretion in untreated habitual aborters.

FIG. 2.—Scatter diagram of pregnanediol excretion in habitual aborters treated with progesterone implants.

patients, the assay values have been plotted in relation to the period of gestation to which they refer (Figs. 1 and 2). It is at once evident that wide scatter is seen in the first two groups and that no distinct differences are apparent.

Further analysis of the data was made by studying the regression of pregnanediol excretion on period of gestation for the three groups by standard statistical methods. Because relatively few assays were performed during the later stages of pregnancy, and because the variance seemed to increase during these stages, it was decided that it would be

safer to exclude all values obtained after the twenty-fifth week. Calculations were therefore based on 198 values in the control habitual aborter group, 141 values in the treated habitual aborter group, and 44 values in the unselected antenatal group. In the first place, it was found that in each group the slope was significant and that there was no significant departure from linearity (Table IV). It therefore became permissible to compare the three linear regressions (shown in Fig. 3). The analysis of variance for differences between the individual slopes and positions of the regression lines is given in Table V. It shows that there is no significance in the differences between the slopes (it will be recalled that to determine the unselected antenatal group regression line only roughly one-third the number of assays were used as were available for the other two lines, which

TABLE IV.—Analysis of Variance for Slope and Departure from Linearity

Group	Sources of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F.
Control habitual aborters	Linear regression	813.39	1	813.39	7.57†
	Departure from linearity	2,539.85	19	133.68	1.24
	Residual	19,010.1	177	107.402	—
	Total	22,363.34	197	—	—
Treated habitual aborters	Linear regression	574.40	1	574.40	7.11†
	Departure from linearity	1,740.51	18	96.70	1.20
	Residual	9,769.93	121	80.743	—
	Total	12,084.84	140	—	—
Unselected antenatal patients	Linear regression	412.83	1	412.83	6.09*
	Departure from linearity	1,058.44	13	81.42	1.20
	Residual	1,965.43	29	67.773	—
	Total	3,436.7	43	—	—

* Significant ($P < 0.05$). † Highly significant ($P < 0.01$).

FIG. 3.—The regression of pregnanediol output on duration of pregnancy for treated and untreated habitual aborters and for unselected antenatal patients.

TABLE V.—Analysis of Variance for Difference Between Slopes and Position of Regression Lines

Sources of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F.
Overall slope	1,455.47	1	1,455.47	15.47†
Difference between individual slopes	116.66	2	58.33	0.62
Difference between average slope and slope of group means	261.37	1	261.37	2.78
About regression of group means	399.94	1	399.94	4.25*
About individual lines	5,338.79	50	106.776	1.136
Residual	30,745.46	327	94.023	—

* Significant ($P < 0.05$). † Highly significant ($P < 0.01$).

are obviously indistinguishable). There is, however, a significant variation about the regression of the group means—that is, the relative positions of the lines. This indicates that the regression line for the unselected antenatal group is, if anything, placed at a lower level than that of the other two.

The data, therefore, do not provide evidence for a diminished output of pregnanediol in the habitual aborters, as compared with unselected antenatal patients, or for an increase in pregnanediol excretion in those habitual aborters who were given progesterone implants.

Trends in Pregnanediol Excretion

In 18 control and 18 treated habitual aborters five or more consecutive pregnanediol assays had been performed. In studying these, it seemed that for each group three main

FIG. 4.—Serial pregnanediol estimations in untreated habitual aborters.

FIG. 5.—Serial pregnanediol estimations in habitual aborters treated with progesterone implants.

patterns of excretion could be postulated, though, as will be seen in Figs. 4 and 5 which attempt to display the data, this conclusion might appear to be rather far-fetched. It seemed, however, that one group of patients produced a pattern of excretion which began at low levels and rose more or less steadily; a second group had an irregularly fluctuating pattern, with no marked tendency to climb during the first 25 weeks or so; while in a third the general tendency was to show relatively high levels in the early

stages of pregnancy, but to fall later on. This last is the pattern referred to earlier as a theoretical possibility in habitual abortion; it occurred in seven out of the 18 controls and in six out of the similar number of implanted habitual aborters studied, and perhaps, therefore, strengthens the theoretical argument. It is doubtful, however, whether progesterone implantation has had the desired effect of eliminating the occurrence of the postulated fall in pregnanediol excretion. Perhaps the dose administered was grossly inadequate. If a fall in progesterone production, after an initial adequacy, is in fact an important cause of habitual abortion, it is not surprising that no overall deficiency of pregnanediol excretion in the habitual aborter group is apparent.

Further information on the causal connexion between failing progesterone production, as reflected by diminishing pregnanediol excretion, and abortion can be obtained by examining the pregnanediol assay values in those patients in the series who aborted. There were 15 patients who aborted and on whom pregnanediol excretion studies had been made; six of these were controls and nine had had implants. Of the controls, four showed low pregnanediol excretion, but in the other two adequate values were obtained, an output of 22 mg. being recorded on the day one of them aborted. Of the treated patients, only one showed an indubitably low value, the excretion being probably or certainly adequate in the remainder—for example, values of 12, 14, 15 mg. on the actual day of abortion. These data therefore suggest that a high proportion of the abortions in this series have occurred in spite of apparently adequate progesterone metabolism. On the other hand, one of the implanted patients, whose pregnanediol excretion fell and who threatened to abort, was given progesterone by intramuscular injection; the threat passed off, the pregnanediol excretion rose (Fig. 5), and eventually the pregnancy terminated successfully. Clearly, then, progesterone deficiency could be responsible for some of the tragedies.

Discussion

In their first series Bishop, Richards, and Doll reported on 45 cases of habitual abortion treated by progesterone implantation, the success rate being 86% for those patients who had had two previous abortions, 89% for those with three, and 75% for those with four or more. They compared these results with the calculations of Eastman on the expected outcome of pregnancy after repeated abortions, and concluded that, provided the true incidence of recurring abortions is not much less than 0.1%, their treatment had been of real value. In their second series Bishop and Richards added a further 40 cases, and for the combined group of 85 patients the success rates were 85%, 76%, and 67% for patients with histories of two, three, and four or more previous abortions respectively. Their conclusions remained unaltered, though they acknowledged the report by Bevis (1951) on 32 patients with three or more successive abortions, who had 81% of live births without any specific therapy but who had been subjected to extensive investigation.

The question naturally arose whether the similarity of the results was not, in fact, due to the psychotherapeutic effects, both of extensive investigation and of progesterone implantation. They wrote: "There is, of course, an obvious way of settling the question whether a progesterone implant is endocrinologically or merely psychologically therapeutic—namely, to treat alternate cases with implants of progesterone and an inert compound such as cholesterol." The present report, though not fulfilling these criteria, in that our control patients received no specific therapy, would seem to provide no strong support for the endocrine therapeutic efficacy of progesterone implants. However, the data from our control patients raises some doubt about the validity of the Eastman calculations.

A number of objections can be raised, both against these calculations and against the principle of comparing the

results of treatment of a condition in one population with the outcome of that condition (whether untreated, treated in the same way, or treated in a different way) in another population and at another time. Since most of the latter are fairly obvious, we may confine our attention to the former. Eastman's calculations make the assumption that 10% of all pregnancies terminate in spontaneous abortion and that a recurrent factor causes 0.4% to abort repeatedly. Both these assumptions are dubious, the true incidence of spontaneous abortion being unknown but very likely higher than 10%, while the 0.4% is simply the incidence Bishop (1937) had found for women with two or more recurrent spontaneous abortions before the fifth month in a series of 2,687 cases at Guy's Hospital. In that same series the incidence of three or more spontaneous abortions was 0.1%—but this was constituted by no more than three cases. Another fallacy in the argument is the concept of a "recurrent" factor. While it is true that such a factor may exist in every pregnancy in some woman (such, for example, as a gross uterine malformation), it is equally true that factors may recur in some of a series of pregnancies but become non-operative later. The effect of maternal syphilis is an obvious instance, while it is also well known that the changes undergone by the uterus during each pregnancy make it better adapted to accommodate a subsequent one. The frequent occurrence of abortion—premature stillbirth—livebirth sequences bears testimony to the waning influence of "recurrent" factors, at least in some patients.

Eastman's calculations lead to the prediction that the spontaneous cure rate would be 86.8% after one abortion, 63.1% after two abortions, and 16.4% after three. If his calculations are extended one stage further the predicted spontaneous cure rate after four abortions would be 2%—a figure with which few obstetricians of experience would agree.

Malpas's figures, based on similar calculations, were comparable—78% after one, 62% after two, 27% after three, and 6% after four abortions. The results we obtained in the control group—75% for 53 patients with two or more previous consecutive abortions, and 55% for 20 patients with three or more abortions—are clearly quite different from the predicted figures, and suggest either that the population we were sampling was not comparable with those which provided the basis for the Malpas and Eastman calculations or that those calculations were themselves fallacious. We incline towards the latter possibility.

Our data on pregnanediol excretion, though far from conclusive, give but little rational support for the use of progesterone implantation in the way we have employed it (which was the same as that used by Bishop and Richards). It is, of course, well known that pregnanediol is not the only metabolite of progesterone, and it is generally conceded that pregnanediol excretion may not reflect at all accurately the actual levels of progesterone turnover. Nevertheless, some difference would certainly have been expected between its excretion in habitual aborters and in "normal" patients, as well as between that of the controls and the implanted patients, if habitual aborters were deficient in progesterone and implantation corrected that deficiency. Moreover, though our data do provide some evidence for the occurrence of a temporary fall in progesterone production in some cases, implantation did not appear to lessen the incidence of such a fall. Finally, several of the abortions in our series occurred while pregnanediol excretion was apparently adequate, thus suggesting other causal factors.

The full discussion of these other factors is outside the scope of this paper, though mention should at least be made of germ-plasm defects, which, as Streeter (1931) has stressed, may be a more important cause of abortions than abnormal uterine environment, the factor favoured by Mall and Meyer (1921). Strong evidence in support of this theory comes from the studies of Hertig and Rock (1949), who recovered a series of 28 early human ova, 12 of which were abnormal in spite of perfectly normal endometria, and who

concluded, "... the evidence, such as it is, indicates that the defective fertilized ovum is due to intrinsic germ-plasm quality rather than to its environment, and is the main factor in the production of spontaneous abortion." If this view be correct, a therapeutically nihilistic attitude towards spontaneous abortion, be it isolated or repeated, seems inevitable until such time as we can exert a more direct influence on the germ-plasm itself.

We must, however, mention the report by Jones and Delfs (1951), who studied extensively the endocrine patterns in women with histories of abortions, and who based therapy (with thyroid, progesterone, and vitamin E) on the finding of deficiencies of these factors. There were 74 pregnancies in their series in women who had had three or more consecutive abortions; 41 gave indications of hormone deficiency and were treated appropriately, 35 going to term (85% success); 23, also apparently deficient, were left untreated, and only five went to term (22% success); while 10 patients who presented no evidence of hormone deficiency were given no treatment and had five term pregnancies (50%). It is difficult to reconcile these figures with our own, but it may be pointed out that the considerably greater success rate in the treated deficient cases, as compared with the untreated non-deficient cases, seems to argue strongly in favour of a psychological effect of the treatment, in addition to, if not in place of, its endocrinological effect.

Summary

The outcome of pregnancy in a series of 113 women who, prior to the pregnancy in question, had had two or more consecutive spontaneous abortions before the twentieth week has been studied. The 53 control patients, who received no specific therapy, produced 39 live babies (75% success); 60 patients received implants of six 25-mg. pellets of progesterone and gave birth to 48 live babies (80%). This difference is not significant. In the control group 20 patients had had three or more consecutive abortions and produced 11 live babies (55%); in the implanted group 27 patients had had three or more previous abortions and produced 20 live babies (74%). Again the difference is not significant. The success rate for the control group is far higher than currently accepted estimates would have had one expect, and the calculations on which these estimates have been based are criticized.

Studies of pregnanediol excretion on these patients provide no support for the view that progesterone deficiency is an important cause of repeated abortion, and failed to show any influence from the implanted progesterone. They gave some evidence for the development of a temporary fall in progesterone production in some cases, but none for the reduction of the incidence of such a development in the implanted patients. Many of the abortions seemed to occur in spite of adequate pregnanediol excretion.

If, as seems likely, germ-plasm defects account for more abortions than do abnormalities of uterine environment, a pessimistic view of any therapeutic attempts appears justifiable. On the other hand, the prognosis for the untreated patient who has suffered a series of abortions in former pregnancies may be much better than has hitherto been supposed.

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PAIN IN THE TRUNK

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Symptoms referable to the moving parts of the body are often encountered in both physical and psychological medicine, and considerable difficulties are apt to attend differential diagnosis. On the one hand, pain, though of organic provenance, may continue unaltered for long periods without giving rise to much in the way of physical signs. This is a particularly common feature of symptoms occurring in the trunk, and it is a well-known fact that backache, for example, may continue without appreciable alteration for years. On the other hand, pain of equal persistence setting up no objective signs to explain its source characterizes a number of psychogenic disorders. Moreover, nothing prevents a psychiatrically ill patient from developing a disorder of the moving parts irrespective of the mental state. Problems then arise that can be solved only by close collaboration between the two disciplines concerned.

It is our common experience that patients with purely psychiatric disorders have often received some years' physiotherapy before the true nature of their symptoms has been realized. Again, we find that, in a patient with obvious neurosis, symptoms of organic origin are often mistakenly dismissed as part of the psychiatric syndrome. Once detected, organic disorders can frequently be successfully treated in their own right, irrespective of concurrent psychiatric disability.

We have found that the greatest difficulties arise when the complaint is of pain in the trunk. Some cases are first seen in the psychological medicine, others in the physical medicine, department.

While we concern ourselves here with symptoms and signs affecting the back, exactly similar considerations apply to the other moving parts of the body. Our purpose in dealing with a restricted field is to draw attention to the fact that much so-called neurotic backache has an organic component. A relatively simple physical examination on the one hand and the consideration of various psychiatric criteria on the other make it fairly easy to decide how much weight to give to each factor.