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## Habitual abortion

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H A B I T U A L   A B O R T I O N

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## HABITUAL ABORTION

In this review, habitual abortion will be discussed under the headings of: definition, possible etiology, diagnosis, psychotherapy and present trends of hormone therapy. The conclusion of this paper will consist of a critical evaluation of this interesting problem.

### Definition

The precise definition of abortion is the termination of an intra-uterine pregnancy before the fetus has reached viability.<sup>1</sup> In our state of Nebraska the law describes an abortion as the termination of pregnancy before 20 weeks of gestation.<sup>2</sup> The majority of authorities include in the definition the fact that the fetus must weigh less than 400 grams and is less than 25 centimeters in length. It has been estimated the average probability that a pregnancy will end in spontaneous abortion ranges from 6% to 20%.<sup>3</sup> According to present day records, abortion accounts for about 400,000 fetal deaths yearly in the United States,<sup>4</sup> however, an abortion rate doesn't lend itself to precise summation and doesn't include criminal abortions which are probably as frequent or even more frequent than spontaneous abortion. This paper is concerned only with the habitual aborter and she is defined as any woman who has had at least three consecutive spontaneous abortions.<sup>5</sup>

### Etiology

The causes of abortion that have been described in the literature are numerous. Among them are dietary and vitamin deficiencies, uterine anomalies, malposition of the uterus, premature separation of the placenta, placenta previa, histamine deficiency, hemorrhagic diatheses, pathologic ova, incompetence of the internal cervical os, lowered metabolism, psychosomatic abnormalities and various abnormalities in the metabolism of estrogen, progesterone and chorionic gonadotrophin.

In an attempt to throw light on the still largely unknown causation of spontaneous abortion, Moya, et al in England<sup>6</sup> decided that every patient who was pregnant and had a history of being a habitual aborter and every pregnant patient who was threatening to abort would be subjected to the following procedures. They were admitted to the hospital for three days where a complete history and physical including past history was done, psychiatric and psychological testing, biochemical and hormonal tests run and all abortuses were examined by a pathologist. In the field of stress and exercising; using intercourse, car driving, exertion and emotional stress as possible precipitating factors, they could find no significant increase in factor or factors in the control group.

They next went to the diet problem and, although it was difficult

to get effective investigation results because of variability in actual food values, they were unable to find any evidence that diet had played a real part in causing any of the study cases to abort. The next step was to examine these women for possible uterine defects and noted that there were twice as many retroverted uteri among those who aborted. Vitamin C deficiency had about the same incidence in those women who aborted and those whose pregnancy went to term following threatened abortion. The author concluded that if Vitamin C was beneficial, it must be either because its effect is psychological or because the type of patient who tends to abort requires a higher blood level of this vitamin than the woman who does not. There was no evidence of a Vitamin E deficiency in those patients who only threatened to abort. The authors attempted to study possible thyroid deficiency by estimating serum cholesterol and in this group no evidence was found that thyroid deficiency was a causative factor in threatened abortion. The author admits that the serum cholesterol determination is quite crude and by using a more sensitive test it may be possible to correlate mild states of hypothyroidism with some abortions. The author found that when all hormone levels were normal 68% of the patients went to term; when hormones were low, only 29% went to term; when there was normal estrogen, and progesterone with low chorionic gonadotrophin

63% of the patients went to term; when there was low estrogen and progesterone with normal chorionic gonadotrophin 45% of the patients went to term. In general, then, it can be stated that if all hormone levels are normal the prognosis was more favorable than when all hormone levels are low. The authors next subjected this study group to psychiatric and psychological testing and they were able to divide all cases of threatened abortion into three main groups. Group one was called the Inadequate Reserve Group and it included women who were immature to most life situations and whose thinking centered mainly around their own needs. Group two was called the Inadequate Frustrated Group and included those women who tended to be obsessive and compulsive with fear of failure. The last group was a mixture of the two previous groups. The author then combined psychiatric and hormonal study of those who threatened to abort, but didn't. He was able to show that emotional stress appeared to cause a lowering in the hormonal blood levels and when psychiatric aid was given the hormonal blood levels returned to normal. Authors examined all placentas and fetuses of this group whenever possible. They could find no high percentage of fetal abnormalities and on microscopic examination although there were certain microscopic changes of a degenerative nature in the chorionic villi in the majority of women who aborted, they were not able to find



definite causative factors for these degenerative changes. Authors concluded that although this study was interesting and produced many interesting results, they still have no evidence to support any particular theory for the causation of abortion.

One can see by the past discussion that the etiology of abortion is very obscure and neither time nor space would allow the discussing of each. Therefore, I will only discuss the hormonal and psychic factors in abortion.

The conception and the maintenance of pregnancy depend upon the fertilization of a healthy ovum by a healthy sperm, the presence of a proper tubal and uterine environment and the existence of a suitable biochemical environment. If any of these factors is disturbed, spontaneous abortion or premature labor may result.

Following normal conception and implantation, almost immediately there appears in the maternal blood stream a hormone called chorionic gonadotrophin which is produced by the cytotrophoblast. The main function of this hormone is to maintain the corpus luteum until the placenta is capable of taking over the production of progesterone.<sup>7</sup> Usually the normal placenta will take over complete progesterone secretion at about day ninety. Deficiencies in this hormone are the result of cytotrophoblastic abnormalities which can be the result of poor ovum to start with or to abnormalities of the endometrium arising from inadequate hormone stimulation both before and after implantation.<sup>8</sup>

Progesterone is produced in small quantities by the mature follicle and after its rupture, the corpus luteum produces larger amounts of progesterone. Progesterone helps prepare the estrogen-primed endometrium for implantation and to maintain the decidue in a healthy state. This hormone also keeps the uterine muscle in a quiescent state sufficient enough to assume retention of the pregnancy and an adequate blood supply to insure normal gestation.<sup>9</sup> After normal fertilization and implantation the level of progesterone is maintained by the corpus luteum. It is felt that the placenta apparently begins progesterone production within a few hours after implantation and occasionally the placenta may be capable of supporting pregnancy as early as day twenty; in other cases it may not be able to support pregnancy until as late as day 140.<sup>7</sup>

No satisfactory method exists, as yet, for direct measurement of progesterone production. However, various chemical methods have been developed for assaying its major metabolite, the pregnanediol complex, in urine. When fertilization occurs and normal pregnancy follows, the excretion of pregnanediol is maintained during the postovulative period and the ensuing amenorrhea of gestation. During the first trimester, the excretion level is rather constant. Between the twelfth and fourteenth week of gestation the pregnanediol output begins to rise and reaches a maximum two to three weeks before parturition. The excretion level then falls rapidly and pregnanediol cannot be found in the urine two to four days after delivery.<sup>10</sup>

PREGNANEDIOL EXCRETION IN NORMAL PREGNANCY



D - Delivery

\* - Pregnanediol Excretion, mg. per 24 hours

It has been shown that pregnanediol excretion accounts for an average of 20% of the total progesterone. It is possible therefore, to make a rough estimate of the actual production of progesterone during pregnancy. Such estimates can only be rough approximations, however, since pregnanediol excretion represents a different fraction of total progesterone production in different individuals (varying from 7%-30%). Within these limits, it appears that progesterone production immediately after ovulation averages 10-25 mgm /24 hours. From day 20-80 about 25-50 mgm /24 hours. Between day 80-120 about 75 mgm /24 hours. Day 120-140 averages 100 mgm /24 hours. In the last trimester of pregnancy the production is in the order of 300-350 mgm, but range maybe from 130-2000 or more milligrams. Individual low levels of pregnanediol excretion have little significance, but persistently low levels that fall to and remain below normal indicate that abortion will ensue. On the other hand a normal pregnanediol level doesn't rule out the possibility of abortion from other causes.<sup>7</sup>

Since it is possible to establish the trend of pregnanediol excretion in a few days by testing urine specimens daily, it is felt that this information could be used to predict the fate of a pregnancy. One must remember that the non-endocrine factors may be the etiological factors in abortions and the pregnanediol tests will be useless in these cases. It has been shown that when pregnanediol determinations are begun early in pregnancy, a drop was observed in some cases before the onset of

symptoms. Thus, in cases of spontaneous threatened abortion and habitual abortion, serial pregnanediol estimations may be employed as an aid in evaluating the status of progesterone elaboration and as a guide in the prognosis of the fate of this pregnancy. In both conditions pregnanediol excretion studies may serve as a guide for the institution of progesterone therapy.<sup>11</sup>

RELATION OF PREGNANEDIOL EXCRETION TO CLINICAL COURSE OF THREATENED ABORTION<sup>12</sup>

Pregnanediol Excretion	No. of Cases	Clinical Results	
		Abortion	Retention
Normal	191	21% (40)	79% (151)
Decreased	144	97% (140)	3% (4)
Total	335	54% (180)	46% (155)

Estrógen is a hormone secreted by the theca cells of the maturing follicle and the corpus luteum. During early pregnancy the corpus luteum is the principal source of estrogen. However, it is also produced by the trophoblast and, as with progesterone, the placenta assumes the role of elaborating estrogen at about day ninety. The primary functions of estrogen is in preparing the endometrium for response to progesterone prior to the implantation. During pregnancy it is probably an essential factor in the maintenance of the decidua in a healthy state. It is also

thought that estrogen helps increase uterine vascularity and to produce uterine growth so as to accommodate the growing embryo.<sup>9</sup>

Estrogen production can also be followed by assay of its metabolites in urine. Estrogen production in early pregnancy is in the order of 0.1 /24 hours by day 100 and by day 120 to 2 mgm /24 hours. At day 140 it has reached 4 mgm /24 hours and from then the rise is very rapid until it reaches at term the average of 5 mgm per day. The estrogen metabolite measured in the urine accounts for about 10% of the actual estrogen production, therefore, the estrogen level varies from about 1 mgm shortly after fertilization to a level at term of approximately 120-4,000 mgm per day. The exact significance of either excessive or low estrogen in pregnancy is not clearly understood. Probably it is a balance between estrogen and progesterone which is essential, but at the present time no exact ratio can be demonstrated. Furthermore, low estrogen production in pregnancy is extremely rare.<sup>8</sup>

#### Diagnosis

Before discussing any form of treatment, I would like to present a few of the diagnostic signs and symptoms a woman will usually present when threatening to abort. Vaginal bleeding prior to the third trimester of pregnancy is an indication that abortion is threatening.<sup>13</sup> In the first 20 weeks of pregnancy any vaginal staining with or without colicky or cramping lower abdominal pain, may indicate threatened abortion.

Since only about 20% of those women manifesting vaginal bleeding at the above stage of pregnancy will carry their pregnancy to term, these symptoms should be regarded as an emergency.<sup>8</sup>

There is some question as to the exact source of this bleeding when seen in the first trimester. There are some who claim the bleeding is the result of decidual necrosis which is secondary to deficient production of progesterone by the corpus luteum.<sup>14</sup> Others believe separation of the placenta is a source of bleeding. Probably both of these factors are responsible because retroplacental bleeding in the decidua basalis would predispose to various degrees of placental separation.<sup>13</sup>

Almost as important as the fact the patient is bleeding is the character of the bleeding. Vaginal bleeding initially is bright red, subsequently becoming dark brown, is more often associated with eventual survival of the fetus. Dark brown discharge which later becomes bright red has a poor prognosis. In general, profuse and prolonged bleeding episodes is associated with the eventual loss of the pregnancy.<sup>3</sup> This fact is further substantiated in the following table.

RELATIONSHIP OF TIME OF ONSET OF INITIAL VAGINAL BLEEDING AND OUTCOME OF PREGNANCY

	Bleeding only at or near time of first missed flow-205 cases (22.9%)		Bleeding continued from first missed flow or developing later 689 cases (77.1%)	
Term or Premature Labor	195	95%	496	72%
Abortion, All Cases	10	5%	193	28%
Blighted Ova	4	40%	163	84%

Pain is usually preceded by bleeding in the first trimester abortion, while the reverse is true in the second trimester abortions. The character of the pain is also important not only in aiding to substantiate the diagnosis, but as an indication of the extent of the abortive process. Menstrual-like cramps in absence of bleeding may represent only exaggerated uterine irritability and may not necessarily portend abortion. Regular labor pains usually of severe intensity, accompanied by varying degree of vaginal bleeding, signifies that the uterus is endeavoring to expel the pregnancy and that the abortive process is quite far advanced.

One of the most important diagnostic procedures in a patient who is threatening to abort is a complete pelvic examination. Not infrequently you will find fetal tissue in the vaginal vault or being expelled from the cervical os. In other cases you may find the cervix extremely soft and partially dilated. Also, if the diagnosis is in question this gives you a good opportunity to estimate the size of the uterus and then



on subsequent examination you can see if the uterus is increasing in size. Failure of progressive uterine enlargement is a good indication that a fetal death has occurred and eventual expulsion of the products of conception will supervene.

The use of laboratory procedures is often of aid in making the diagnosis of threatened abortion. A positive pregnancy test means only that the chorionic tissue is still viable, the fetus may have already succumbed. A negative test is more significant in that it is a definite aid in selecting a more vigorous mode of therapy if bleeding persists.<sup>13</sup> Another fairly new laboratory test for pregnancy is the urinary pregnanediol level in the urine. Results to date indicate that pregnanediol determinations during amenorrhea are as accurate as the rabbit test in the diagnosis of pregnancy.<sup>15</sup>

Within the last decade much work has been done in trying to develop tests which would tell us which pregnancy is likely to or going to abort before actual signs and symptoms of abortion arise. The pregnanediol urine tests have been very helpful as a diagnostic aid, but unfortunately the laboratories in too many areas are unable to get reliable results because of poor technique and equipment or lack of skilled technicians.

It has been noted that many abnormalities of early pregnancy could be predicted by noting certain changes in the vaginal cytology. These changes are an increase in the acidophilic, mature estrogenic, or superficial type cells and a decrease in the basophilic, premenstrual or

intermediate type cells usually seen in preponderance in early pregnancy.<sup>17</sup> Today we have what is known as the Fern test. In this test the operator takes a smear from the cervical mucosa and then dries it in the air and looks for arborization on the slide under the microscope. Some feel the fern pattern is due to sodium chloride and a mucin-like substance,<sup>18</sup> others feel the arborization is due to a protein or carbohydrate solution that contains electrolyte.<sup>19</sup> The estrogen is believed to be responsible for the arborization through its control of NaCl metabolism. A fern pattern is no longer present when the progesterone reaches a high level on about the 22 day of the normal cycle.

The cytology of pregnancy is due to estrogen plus progesterone and it is generally accepted that a preponderance of superficial cells in a smear means a deficiency of progesterone in relation to estrogen. When the progesterone deficiency or the changes due to it are reversible, a significant increase in fetal salvage should be noted if these women are treated with progesterone. To test this hypothesis the author obtained vaginal smears from 583 women during the first four months of pregnancy. Women with more than 30% mature cells were given either oral progesterone 25 mgms, or identical oral placebos. Data confirmed that the abortion rate in those with abnormal smears was double that of the normal group (7.2% versus 3.5%). Progesterone in the dosage and form used was not significantly effective in increasing fetal sal-

vage in the group with progesterone deficient smears (6.5% versus 7.2% abortion). The author suggests using Pundel and VanMeensel method for separating those with abnormal smears into those with living trophoblasts capable of responding to therapy, and those with a degenerated trophoblast incapable of responding. This above separation is done by giving stilbestrol to all those having abnormal smears and he found that those who are apt to recover will show a reversion of the smear to normal where in those not apt to recover will show increase in cell maturity.<sup>18</sup>

Another test for diagnosing impending abortion is a qualitative evaluation of the exfoliated vaginal epithelial cells as interpreted in Papanicolaou smear. A trend toward increased eosinophilia of the exfoliated cells suggests an insecure pregnancy. It must be remembered that this is a highly specialized interpretation, only a qualitative estimation and subject to many inaccuracies of qualitative tests.<sup>20</sup>

There are numerous reports in the literature on the use of the "fern test" for determining what patients are likely to abort and the effects of therapy. In this one series the author took 299 unselected, consecutive private patients in the first and second trimester of pregnancy and did routine smear and staining of the cervical mucus. Of these, 48% were classified as being negative and of this group two aborted in the first trimester without assignable cause; this is a 1.4% loss. Fifty-two per cent were classified as being positive and

these were divided into groups according to therapy administered.

- Group I - Likely to abort because of poor obstetric history.  
Rx- Progesterone from the first visit on.
- Group II - Those who threatened to abort some time after the first visit.  
Rx- Progesterone from the time abortion first threatened.
- Group III - Those who would have been classified with Group I or II, but who either refused progesterone therapy or discontinued it against advice.
- Group IV - Those receiving no progesterone therapy.

The results in this series are as follows:

- Group I - Every possible case salvaged
- Group II - 81.8% salvage
- Group III - 14 abortions out of 15 patients
- Group IV - No abortions. This is expected because any patient threatening to abort was immediately transferred to either group II or group III according to therapy given.

This series indicates that cervical mucus smears in pregnancy are a good means of identifying women likely to abort and shows evidence that progesterone therapy is beneficial where there is actual evidence of a deficiency.<sup>21</sup>

#### Historical

Virtually all of the recent literature on pregnancy salvage in patients with a history of repeated abortion has been written against the background of a mathematical formulation devised by Malpas in 1938 and subsequently modified by Eastman in 1946. These papers have carried the weight of authority and have had incalculable influence, both as a

basis for professional counsel to patients and for the evaluation of methods of therapy.

In Malpa's origin work he determined that in any population the total number of instances of sequential abortion and stillbirth is made up of two groups of patients. First those whose pregnancies end in successive abortion because of chance succession of random and casual factors. In the second group are those who have repeated abortion due to a recurrent factor. In the population from which his material was drawn for this paper, the per cent of pregnancies ending in abortion was 18%. The total number of pregnant women in whom such recurrent factors occur is about 1%, as compared to about 17% of pregnant women who abort from random and accidental causes. From a statistical standpoint, the presence of a recurrent factor was inferred with reasonable certainty after the occurrence of three successive abortions. He then concluded that even after a woman has had three successive abortions the chance of her continuing to term in the fourth pregnancy are 27%, whether anything is done for her or not. Even if the recurrent causes of abortion could be removed, the treated patient would still be subject to the various casual factors which produce abortion in about 17% of all pregnancies and the best results that could be obtained from any specific therapy are about 83%.<sup>22</sup>

Malpas assigned values of 17 and 1 to x and y respectively. He figured if x represents the proportion of pregnancies that abort from non-recurrent causes in a given population and y represents the proportion that abort from recurrent causes, then the frequency of all spontaneous abortions is  $x - y$ . If they abort the first pregnancy they have an abortion expectancy of  $\frac{x+y}{x+y}$  in their next pregnancy. After two consecutive abortions, the chance of aborting in the third pregnancy is  $\frac{x+y}{x+y}$ . If after (n) consecutive spontaneous abortions the abortion expectancy is  $\frac{x^{n+1} + y}{x^n + y}$ .<sup>23</sup>

This arbitrary classification of causes into recurrent and non-recurrent groups seems quite unjustified. It would appear reasonable to suppose that for abortion, as for the common malformations, many changes in the hereditary-environment complex can cause the condition, and that each of these has a chance of recurrence somewhere between 0 and 100%, with only a few at either extreme. No such possibility is considered in Malpas' or Eastman's method.<sup>24</sup> Malpas also assumed that the frequency of spontaneous abortion was about 18% while the actual proportion of all pregnancies which terminate in spontaneous abortion lies between 7 - 11%. To get the value for y, Malpas took a group of 6,000 pregnancies and in this group were 84 women who had had three or more consecutive abortions or stillbirths. From this he concluded that

the proportion of women who had had three or more abortions was under 1% and thus assigned this value to  $y$ . He made no attempt to separate abortion and stillbirth, had no certainty that the abortions were spontaneous and no segregation of the primary from the secondary habitual aborter. To show the relationship between parity and abortion, Malpas compared his figures with those of Whitehouse. Again this was in error because the latter's figures were obtained from 3,000 gynecological patients and he also made no specific separation of his patients with history of abortion.<sup>23</sup>

A more recent study as to the prognosis of having a term pregnancy in a patient labeled as an habitual aborter was done by Eastman. To the factors  $x$  and  $y$ , Eastman assigned the values 9.6% and .4% respectively. Eastman's approach gives a woman with three consecutive abortions only a 16% chance of a viable infant, as compared with a 27% chance according to Malpas. Eastman used Malpas' formula and states that the risk that a woman will abort increases to 13% after one previous abortion, to 37% after two abortions, and to 84% after three abortions.<sup>25</sup> Again there is some question as to the reliability of Eastman's figures. The value of .4% for  $y$  was credited to Bishop who found that among 2687 patients there were 100 initial abortions—his definition of habitual abortion was "abortions for which no recognized organic cause such as syphilis or chronic nephritis can be found, occurring before the

28th week of pregnancy on more than one occasion." This definition of habitual abortion differs radically from that in common use, which requires a minimum of three consecutive abortions.<sup>22</sup>

The tendency for abortion to occur more often in certain women than in others indicates that at least some of the causes of abortion are recurrent, but leaves open the question of whether absolutely recurrent causes exist. It is not even clear whether women labelled as habitual aborters by the fact that they have had several successive abortions do represent a biologically distinct group that are constitutionally incapable of maintaining pregnancies. In a population where any pregnancy has roughly a 15% chance of aborting, then even if there are no recurrent causes, the chance of a woman aborting three times is roughly 15% or .3%, which is not very different from the estimates of the proportion of habitual abortions.<sup>3</sup>

In an attempt to obtain empirical data on the chance of a successful pregnancy following a sequence of three or more spontaneous abortions, Speert took a total of 17,490 obstetrical patients and subjected them to the following criteria. Every effort was made to eliminate cases in which there was a question as to sponticity, he also eliminated gynecologic patients and those applying for care after the onset of symptoms of abortion. Out of this total group of obstetrical patients, 121 cases met these criteria:



OUTCOME OF PREGNANCY IN RELATION TO NUMBER OF PREVIOUS CONSECUTIVE ABORTIONS

Previous AB	Patients	AB	Premature	Current Preg. Term	% Viable
3	66	7	7	52	89%
4	33	10	8	15	70%
<u>5 or more</u>	<u>22</u>	<u>6</u>	<u>3</u>	<u>13</u>	<u>73%</u>
Total	121	23	18	80	81%

The abortion sequence began with the first pregnancy in 62.8% of the patients and was preceded by a viable pregnancy in 37.2% of all cases. The overall proportion of the primary habitual aborters where pregnancies attained viability was 74%, in contrast to 93% for the group of secondary habitual aborters. This among women with the same number of abortions, a better prognosis is suggested for the patient who has once carried a pregnancy to viability than for the one who has aborted all previous pregnancies.

OUTCOME OF PREGNANCY IN RELATION TO NUMBER OF PREVIOUS PRIMARY CONSECUTIVE ABORTIONS

Previous AB	Patients	AB	Premature	Current Preg. Term	% Viable
3	37	7	3	27	81%
4	24	8	7	9	67%
<u>5 or more</u>	<u>15</u>	<u>5</u>	<u>2</u>	<u>8</u>	<u>67%</u>
	76	20	12	44	74%

OUTCOME OF PREGNANCY IN RELATION TO NUMBER OF PREVIOUS SECONDARY CONSECUTIVE ABORTIONS

Previous AB	Patients	AB	Premature	Current Preg. Term	% Viable
3	29	0	4	25	100%
4	9	2	1	6	78%
<u>5 or more</u>	<u>7</u>	<u>1</u>	<u>1</u>	<u>5</u>	<u>86%</u>
	45	3	6	36	93%

In each group the outcome was better for patients who had had only three previous abortions than those who had aborted more than three times, whereas no apparent difference existed between patients who had had four previous abortions and those who had aborted more than four times.

From this above series and from many similar studies in the literature the prognosis of having a viable pregnancy in a habitual aborter is much better than that proposed by Malpas and later by Eastman. There is considerable amount of confusion in the literature as to the prognosis and accepted therapy for habitual abortions. Much of this confusion is attributed to lack of standard diagnostic criteria of threatened abortion, heterogenous grouping of patients, inadequate numbers of patients, improper use of controls, inconstant dosage of therapeutic agents and combination of various regimes of management. Unfortunately this has resulted among many obstreticians a philosophy of nihilism concerning the specific benefits of therapy once a patient threatens to abort. This is detrimental to the profession as well as to the patient and subjects her to psychologic trauma which might otherwise be avoided, moreover, several recent studies emphasize the fact that the outlook may not be as dismal as one would believe.<sup>26</sup>

#### Management

In discussing therapy of habitual abortion we will mention only the hormonal benefits and not dwell on anatomical abnormalities. The

changing concepts of hormonal therapy through out the last half century are very fascinating. In 1900, an extract of the breast tissue was used, 1910 desicated ovarian tissue, 1920 aqueous corpus luteum, 1925 desicated corpus luteum, 1930 vitamin E, 1940 progesterone, 1945 estrogen and then estrogen and progesterone and in 1954 a combination of estrogen, progesterone and chorionic gonadatrophin.<sup>27</sup>

It is apparent that there is considerable diversity of opinion, not to say confusion, as to the nature and proper treatment of threatened and recurrent abortion. As stated previously, one important factor in this confusion is the obvious heterogeneity of these classifications and this difficulty is compounded by the reluctance of many clinicians to include proper controls in their studies. Another factor until recently was our inability to provide adequate mean to study the complex endocrine equilibrium which is involved in the process of gestation. Another factor that must be remembered before coming to any conclusion about any specific therapy; any treatment applied to a group of patients who will abort less than one-third of the time even if left alone, will look promising unless a simultaneous control group is available for comparison.<sup>5</sup>

We have already discussed the function of chorionic gonadrotrophin, progesterone and estrogen in normal pregnancy. Another hormone which is often used in treating habitual aborters is thyroid. The exact role of

this hormone in conception and in the maintenance of pregnancy cannot be stated in any exact terms. However, it has been established that thyroid hormone is essential to the development of normal germ cells as well as to the maintenance of a growing embryo. A survey of the literature would suggest that with one exception some have found each of the above hormones useful and others have found each one useless. The sole exception is thyroid hormone given when function tests indicate a deficiency: virtually everyone agrees that this form of hormone therapy is useful.<sup>7</sup>

When the thyroid function studies, anatomical abnormalities, blood incompatibilities and genetic factors can be ruled out one should strongly consider a hormone deficiency of some sort or, less likely, an emotional problem. I would now like to discuss several present day concepts of endocrine prophylaxis in habitual abortion.

In a series of 81 habitual aborters Stilbestrol was started early, before the period of pregnancy at which the patients last previous abortion had occurred. The dosage began with 2.5 mgm daily when started at 5 weeks, 5 mgm daily at 7 weeks, 10 mgm daily when started at 9 weeks and on up so that at the 25th week of gestation the patient would be taking 25 mgm daily. The dosage was then increased 5 mgm each week until 4 weeks before term when therapy was discontinued. The fetal salvage looks very impressive when compared with that expected in spontaneous cure. However, recent reports suggest that treatment of any sort, because

of its psychologic influence, raises the fetal salvage in these patients to figures that are very much higher than the spontaneous cure rate. The author of this series thought that Stilbesterol was capable of stimulating more normal secretion and metabolism of progesterone. Also, Stilbesterol will not maintain a defective trophoblast which is one of the advantages that it has over adequate therapy with progesterone.<sup>28</sup> In another series cytologic examinations of vaginal smears of habitual aborters was done and some showed the predominantly estrogen smear. This latter group was then treated with Stilbesterol and after treatment it was noted that those whose smear converted to show evidence of progesterone stimulation, went on to carry their pregnancies.

In an attempt to evaluate the benefits of Stilbestoral during pregnancy the authors gave Diethylstilbesterol in graduated amounts to 840 patients according to the schedule the Smiths used and compared their results with that of an identical placebo tablet given to 806 patients. They found that Stilbesterol didn't reduce the incidence of abortion, prematurity or postmaturity.<sup>29</sup> Also, another group found that the abortion rate was not significantly lower after Stilbestrol therapy than the rate in patients receiving no hormones at all.<sup>19</sup> At present there appear to be no statistical evidence for the value of Stilbestrol therapy.<sup>5</sup>

In threatened abortion, the prognostic significance of a low pregnanediol excretion is grave.<sup>12</sup> There is definite evidence, as well as

some inconclusive reports, of benefit from progesterone therapy particularly in cases where the patients' pregnanediol excretion is low.

Progesterone therapy has been highly successful in the hands of some while for others it has been useless. It is felt that if you can do pregnanediol excretion tests readily and correlate your deficiency with the amount of progesterone you give the results will be good. In the past, administration of progesterone has been on an empirical basis and certainly in amounts that are insufficient to raise blood levels to a normal value. With the advent of the orally effective progestational compounds, Norethynodrel and Norethindrone (Enovid and Norlutin), the clinician had available progestins that are capable of producing a profound progestational effect.

Proof of the actual benefit of progestational compounds when you cannot demonstrate a low pregnanediol excretion or when this test is not available, is lacking. Still progesterone has received a great deal of credit in saving pregnancies. A controlled study by Swyer and Daly treating identical groups with and without progesterone gave no significant improvement in fetal salvage with the use of the steroid. The first group of 60 patients was treated with progesterone in pellet form. Forty-eight living babies were produced, a success rate of 80%. Forty living babies resulted in the second group of 53 patients who received no treatment for a success rate of 75%. There is no statistical significance in this study.<sup>30</sup>

In an attempt to evaluate Stilbestrol therapy the author compared his results with those of Smith.<sup>28</sup> He found that many of his own patients had received this hormone in previous unsuccessful pregnancy and that his patients who received no treatment had better fetal salvage than those receiving Stilbesterol. The author could also find no rationale for using this hormone in early pregnancy when the endometrium is in an advanced secretory phase. He also found that nausea and vomiting are produced or increased by using Stilbestrol and this prevents normal nutritional intake.<sup>30</sup>

In a series of 121 patients Speert not only tried to get empirical data on the chances of successful pregnancy following a sequence of three or more spontaneous abortions, but also subjected 34 of this group to hormone therapy. Twenty-nine of this group were primary habitual aborters and were treated with hormones as follows: 19 received Stilbesterol, 5 received thyroid, 3 received Stilbestrol and progesterone, 2 received Stilbesterol and thyroid. He subjected the other five patients, secondary habitual aborters to the following hormone treatment: 4 received Stilbesterol and one received thyroid. Of the 24 patients treated with hormones there were 22 viable births and 12 abortions, or 65% salvage rate. Of the 87 patients who received no hormone therapy, 87% carried to viability. The author made no distinct as to what hormone produced the best results. However, while the figures are not significant, they

show that the good results achieved by the patients in this study cannot be described to hormonal therapy.<sup>23</sup>

There are several undesirable manifestations that may result from utilization of progesterone in the treatment of threatened abortion. Frequently the embryo has already expired at the time the patient is first seen. The administration of steroids may prolong the process and missed abortion is then encountered. There are also reports that genital anomalies will appear in female infants if the mother has been treated with progesterone during pregnancy. The anomalies consisted of an enlarged phallus, with or without varying degrees of fusion of the labioscrotal folds; no internal derangement of the internal genitalia was found.<sup>32</sup> It is postulated that partial masculinization of the female infants occurs only in those mothers receiving progestins in which there may be an abnormality of either the metabolism of the progestins or their transmission across the placenta.<sup>13</sup>

In another patient series, the endocrine therapy consisted of oral administration of conjugated estrogen, anhydrohydrox progesterone or orally absorbed progesterone or both, and the intramuscular administration of chorionic gonadotrophin. In each case, there was no clinical evidence of threatened abortion. This treatment is thought not to be indicated unless the very earliest stages of pregnancy are clinically normal. Conventional measures were not neglected, diets were evaluated vitamins and iron preparations prescribed, coitus was interdicted, and



adequate rest advised. No patient required sedation because of uterine contractions. All the patients were healthy white women with essentially negative, family, medical and surgical histories. Menstrual function was normal except where noted. There was no clinical or laboratory evidence of systemic or pelvic disease. The basal metabolic rate was on the plus side of zero except where noted and this was corrected by giving thyroid.

Because of the strict criteria used in this study only six patients comprised this report. These six patients had a total of 25 pregnancies prior to the present treatment. These 25 pregnancies had ended with 22 abortions and three live births. In six subsequent pregnancies, with treatment, six normal children were born. In four patients serial endocrine assays were done and some abnormality was noted in each patient. These abnormalities ranged from low pregnanediol levels to fluctuations in the excretion of estrogen and chorionic gonadotrophin; these abnormalities occurred at the time at which the patient had aborted in previous pregnancies.

Normally we expect that the corpus luteum will produce sufficient estrogen and progesterone to effect a healthy endometrial bed and that the early trophoblast will produce enough chorionic gonadotrophin to maintain the corpus luteum until such time as the chorio-placental system produces these endocrine substances in amounts sufficient to maintain pregnancy. An unusual phenomenon is the rapid increase and fall in the

excretion of chorionic gonadotrophin in the second and third months of gestation. It is strange that so many spontaneous abortions occur at the approximate time of this marked fluctuation in excretion of chorionic gonadotrophin. These fluctuations are also seen in the estrogen and progesterone levels. Because of this knowledge some had theorized that this fluctuation could initiate the process of abortion in a uterus which does not adapt itself to sudden changes in endocrine environment.

The author of this patient series believes endocrine treatment of repeated abortion is rational in theory for certain reasons. This therapy may be substitutive in nature. Supplying some of the factors necessary for normal environment and growth of the conceptus during time intervals in which there is malfunction of the corpus luteum and of the trophoblasts. He believes that these exogenous endocrine substances may prevent the initiation of the abortive process in uteri which do not tolerate marked fluctuations in endocrine environment.<sup>33</sup>

In the discussion following this interesting series it was noted that satisfactory results were present in 78-83% and it has been shown by Speert that 81% of his habitual aborters were carried to term without benefit of endocrine therapy. It was pointed out that in a series at another hospital when progesterone, whether supplemented with chorionic gonadotrophin was given to over 400 patients the incidence of salvage in threatened abortion was raised from 45% to 80%<sup>26</sup> in an

advanced secretory phase. He also found that nausea and vomiting are produced or increased by using Stilbesterol and this prevents normal nutritional intake.<sup>30</sup>

Our knowledge of the metabolism of the various hormones is quite incomplete and speculative. Those who criticize the endocrine treatment of habitual abortion on the basis that it is a hit-or-miss treatment probably have some justification. On the other hand, in these patients it is not possible to determine in time whether or not an endocrine deficiency or imbalance is present or will develop. One proceeds with the treatment in hope that the difficulty of the patient under consideration is due to a hormone deficiency or imbalance and that it can be corrected by the use of endocrine preparations. It must be understood that one cannot determine such deficiency states in time because if one waits until clinical evidence of threatened abortion appear or abnormal assay results are obtained, then one has waited at least in some cases, until the optimal time for treatment has passed. Furthermore, much has been written to the effect that many abortions are due to defective ova and it has been indicated that these are not amenable to therapy. It may well be, however, that many of these ova are defective at the time of their recovery, but that they would not be so had their early endocrine environment been normal.

As our understanding of endocrine metabolism during pregnancy is increased, more specific diagnostic procedures and therapeutic agents will become available which will eventually lift the shroud of uncertainty and pessimism that now envelops our conception of the etiology and treatment of abortion. For the present, an intelligent evaluation of the presenting symptoms and physical findings of the bleeding patient, coupled with a clear understanding of the various modes of therapy and their application, will yield gratifying results in handling threatened and recurrent abortion.

#### Psychotherapy

Before making any conclusion as to the proper treatment, if any, in habitual abortion, I would like to present several reports in which the patients received psychological support and no endocrine therapy.

Weil and Stewart felt that the majority of their patients who are habitual aborters seem to be of an immature, dependent type, either receiving inadequate support from their husbands and social group, or unable to utilize the available support even though they need it. They were able to show a correlation between a patient's emotions and her hormone levels.<sup>34,6</sup>

The second report is that of 32 patients who had had three or more previous abortions. These patients were subjected to a number of diagnostic procedures, including measurements of basal metabolic rate, glucose

tolerance, and urinary pregnanediol excretion. They were advised to take extra rest at the time their menses would have been due but received no other specific treatment that could have had any conceivable relation to the outcome of pregnancy. Without the benefit of any hormonal therapy, 29 patients, or 91%, reached the 28th week of pregnancy and 26 of the babies, or 81%, were carried to term and were viable. The author in this study laid great emphasis on the high degree of confidence that his patients had in his investigation and to this psychological support given unwittingly, he attributed a large measure of the success achieved.<sup>35</sup>

In recent years various functional pathways from the cerebral cortex through the higher autonomic centers and pituitary-adrenal axis have been described by way of which psychogenic sterility and abortion may occur. The work of Alvarez and Caldeyro-Barcia clearly demonstrated, by means of electromanometric recordings from balloons buried in the myometrium of a large series of pregnant women, that intense uterine contractions can occur in response to certain types of experimentally induced emotionally painful situations. Similarly, uterine irritability and ischemia in the face of emotional stress have been described. Also many obstetricians and psychiatrists have noticed a seeming relationship between emotional factors and habitual abortion.

In 145 patients who were found to be free of gynecologically discernible abortigenic conditions a special psychosomatic method of

therapy was offered. Of this group, 57 have delivered viable infants and 13 have miscarried, 21 were still in various stages of pregnancy, 6 dropped out before treatment was given and 48 are still in the pre-conceptional phase of therapy. The author considered only the patients in the study who, by virtue of delivery or abortion, responded successfully or unsuccessfully to psychotherapy. This group, among whom were 19 secondary aborters and 51 primary aborters, had, prior to treatment, a total of 290 pregnancies, 265 of which ended in miscarriages and 25 of which ended in viable births. Expressed comparatively, 91% of all pregnancies before treatment ended in abortion; with treatment, 19 per cent ended in abortion.<sup>36</sup>

#### Critical Review

One can readily see by the various reports presented in this paper that the ideal therapy for habitual abortion is much in question. Of more than speculative interest in this regard are the almost cyclic clinical trends which occur with the introduction and enthusiastic advocacy of new "therapies" for habitual abortion. Usually, and to some extent, in proportion to the professional stature and persuasiveness of the advocate, each new and therapeutically dramatic regimen is eagerly seized upon by corroborating fellow enthusiasts. In time, with more extensive and less suggestible usage, disenchantment usually sets in and in the process, the drug loses its efficacy.

This trend adds substance to Trudeau's nineteenth century admonition to young physicians: "Make haste to use the new drugs while they are still effective."

In this paper some of the present concepts of therapy in habitual abortion have been presented. One can readily see that there is no so called "cut and dried" therapeutic approach to handling this problem. All gynecologically discernible abortigenic conditions and all genetic aspects of abortion were omitted from this paper because of the vastness of the problem. I have tried to present not only the various modes of therapy, but also the advantages and disadvantages in each instance. The author hopes that from this paper he can better understand what is expected of the attending physician when presented with a habitual abortion problem.

Ideally, the treatment of the habitual aborter should commence in the preconceptional period. In actuality, treatment of the patient who periodically aborts becomes a comprehensive study to determine if possible, the underlying factors that are responsible for the recurrent pregnancy losses. These patients should first be given temperature charts so the actual time of ovulation can be determined and then, 24 hours after a normal menstrual period begins, perform a endometrial biopsy to see if the endometrium shows any evidence of progesterone

deficiency. Also, at the same time you can get routine blood work, thyroid function studies and correct any deficiencies that may be present. Special attention should be paid to the patients general health and diet. Next a thorough evaluation of the genital tract for any anatomic derangement should be made; a complete pelvic examination coupled with a hysterosalpingography will usually demonstrate any gynecologic problem which may be abortigenic. During the course of this preconceptional work-up, which may take several weeks, try to survey the patients' emotional makeup. If any obvious emotional difficulties are present, psychiatric consultation should be requested. Even in the absence of overt emotional difficulties, these patients should receive an abundance of reassurance and encouragement from their physician.

When the above things have been accomplished and the patient becomes ready for possible pregnancy the question arises as to whether this patient should be put on any hormones as a prophylactic measure. As one can see by reading the literature this problem is very debatable. Numerous reports indicate that those patients who received no endocrine therapy had as good or better fetal salvage than those treated with the various hormones.

I am of the opinion that if all the patients endocrine studies were within normal limits I would not start this patient on any drug therapy. During the early pregnancy frequent prenatal examinations, allowing adequate time for discussion of the patients problems and explanation



of her symptoms, will be of inestimable value in promoting a sense of security and relief of tension. I also feel that along with the psychotherapy you may also give the patient a placebo to further help to reassure her and help her believe she is actually receiving some visible therapy. Besides the routine prenatal tests, obtain frequent cervical mucus smears and look for any evidence of fern formation which may indicate a progesterone deficiency. If at all possible also run several pregnanediol excretion tests during the first trimester. If a definite progesterone deficiency can be established start the patient on a progestational agent, however, it must be explained to the family that there is always the possibility of having masculinization of the female infant if these drugs are used.

I have attempted to present some of the current concepts of therapy in habitual abortion so far as endocrine disorders are concerned. This author feels that in the last decade terrific advances have been made in endocrinology and that possibly in the near future we may have not only better diagnostic aids but also better therapeutic agents for use in certain habitual aborters. Until then these patients should have any endocrine deficiencies corrected if possible and they also should receive special attention from the attending physician as to possible emotional problems. It is my feeling the whole picture of habitual abortion is brighter than that previously painted by Malpas and Eastman.

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