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Use of stilbestrol in the treatment of abortion

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THE USE OF STILBESTROL IN THE TREATMENT OF ABORTION

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INTRODUCTION

Abortions have been a problem for obstetrical and gynecological men for many years. There has been great disagreement in the past of what the definition of abortion consisted. Several different definitions have been given but to me the best definition was given by Greenhill in his text.[1] He states, "We apply the word abortion to all interruptions of pregnancy before the child is viable." Anything past this time is spoken of as a premature delivery, premature labor or "miscarriage."

Several different types of abortions are described. These are:

1. Habitual abortion meaning that at least three successive pregnancies have been interrupted.

2. Threatened abortion is indicated by a bloody discharge from the uterus accompanied sometimes by pain in the back and the pelvis.

3. Inevitable abortion is similar to threatened abortion but more intense in symptoms.

4. Incomplete abortion indicates that the process of labor has started but the uterus is incompletely emptied.

5. Complete abortion indicates that the products of conception have been completely emptied from the uterus.

6. Missed abortion is like incomplete abortion but indicates that the whole product of conception is in the uterus and that the fetus is dead.

7. Theraputic abortion is described as being induced due to the patients physical or mental condition for theraputic reasons of these conditions.

This paper will be concerned for the most part with threatened and habitual abortion and the response of these to treatment with stilbestrol. The incidence, etiology and pathogenesis will be discussed first. This will be followed by the theories of which stilbestrol reacts in the body and the suggestive treatment with results of many observers will be presented with tables from their articles. This being followed by the summary.

INCIDENCE

There are certain stages that an abortion must go through during its progress. These are threatened, inevitable, incomplete and complete. The threatened abortion is indicated, as mentioned before, by uterine bleeding and cramps. It is impossible to say whether a threatened abortion is salvageable or not when it is first seen. Therefore all abortions should be considered salvageable until proven otherwise. It is true that some threatened abortions would not go on through the progressive stages to complete abortions whether treated or untreated. Therefore the percentage of cures are those that would go on the complete abortion. The percentage is not determinable so the definite number of cures cannot be stated.

In general 25% of pregnancies and in abortion of induced, therapuetic or spontaneous,[3] of which 8% are said to be spontaneous. Other authors maintain different percentages ranging from 6% to 13%. Hertig[2] states that spontaneous abortion occured in 10.6% of 1150 cases over

a period of six years of private practice in Boston.

It is difficult to evaluate the figures of threatened abortion. It seems that different authors have different ideas of what threatened abortions consist. Some say the symptoms are uterine cramps with bleeding, others say there need not be any cramps and others say cramps without bleeding indicates threatened abortion. The incidence ranges from .94% reported by Javert and Stander[4] in New York to 4% reported by Rutherford[5] from the Boston Lying-In Hospital. However, most spontaneous abortions are preceded by threatened abortion and it seems to me that threatened abortion should be of a much greater incidence than spontaneous. However, observations and follow up cases do not indicate as such. It would seem plausible that spontaneous abortions, as reported above, plus threatened abortions, as reported above, would give a more accurate estimate as to the incidence of threatened abortion.

Habitual abortions are about .4% of all pregnancies. Approximately 4.1% of all the spontaneous abortions are accounted for by habitual abortions.

ETIOLOGY

There is no definite statement that can be made for the underlying cause for abortion. There is logical reasoning to think that the endometrium would show a thrombosis of the decidual sinusoids with resultant necrosis and hemorrhages into the decidua. This is based on the ob-

servation made by Hertig at the Boston Lying-In Hospital and the Hospital for Women. He states that the cause for the condition at the placental site of a normal pregnancy is the encroachment of the placenta on the endometrial site, and states that it is evident in this manner why all spontaneous abortions do not present an abnormal ova. Some of the other causes for abortion may be present also. These are:

1. Ovular:
   (a) Immaturity of the ova.
2. Maternal:
   (a) Low implantation in the uterus.
   (b) Endometrium not at the stage for which implantation is necessary.
   (c) Inflammatory disease.
   (d) Uterine abnormalities.
   (e) Blood dyscrasia.
   (f) Low hormonal levels.
   (g) Diabetes.
3. Paternal:
   (a) Immature sperm.
4. Fetal:
   (a) Interference with umbilical cord.
   (b) Hydraminous.
   (c) Non viable fetus.

HISTORY OF EARLY STUDIES

Diethylstilbestrol is a synethetic estrogen that acts like the natural occurring estrogens of the body. It was founded in 1938 by Dodds and coworkers[6]. It was demonstrated by him to be much more effective than the natural occurring estrogen of the human body and in ovariectomized rats showed a definite increase in the

size of the uterus[7].

The following year The Council of Pharmacology and Chemistry authorized certain investigators[8] the publication of experimental evidence they had prepared on humans. Forty-two women with menopausal syndromes were the subjects of study. Studies were directed to vaginal epithelium made several times a week. At this early date it gave wide promise for human therapy because it could be taken orally and was easily absorbable. It presented a great deal of estrogenic activity evidenced by: 1. follicular and estrous type of vaginal smears. 2. Vaginal cornification and withdrawal of bleeding. 3. Endometrial hyperplasia. 4. Proliferation of mammary tissue. 5. Inhibition of lactation. Toxic effects at this early date were noted by two investigators. In treating forty-six cases one group[9] found three to have nausea and vomiting. Another group[10] exhibited only one with toxic symptoms in fifty-one.

Pencharz[11] demonstrated that diethylstilbestrol was a very potent estrogenic substance by the use of hypophysectomized rats. Table I will demonstrate the findings of this investigator. Simpson[12] varified these studies.

Diethylstilbestrol was first used for threatened and habitual abortion in 1942[13]. At this time experimental studies showed that twenty-five milligrams given in anterior wall of the cervix and five milligrams taken

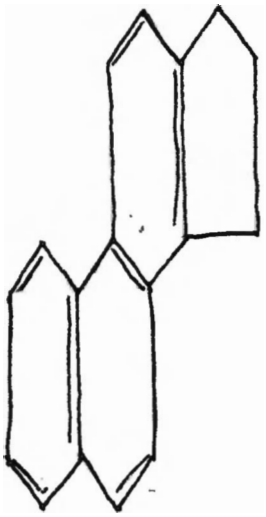
orally every fifteen minutes until the pains stopped preserved some of the threatened abortions. The use of the drug has progressed rapidly to the present day. There are many indications for the substance which will be mentioned later.

CHEMISTRY

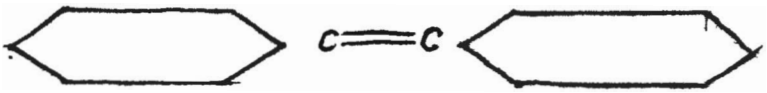
Diethystilbestrol although having action that duplicates or simulates estrogens is not the latter in chemical structure. The estrogens possess the cyclopentenophenanthrene nucleus while the synthetic compound is made up of a diphenylethylene nucleus. (Figure I) Dodds[6], experimenting with the 4, 4' dihydroxystilbene structure found that the alkyl group C_2H_5 substituted for R_1 and R_2 (Figure II) made the most potent compound.

PHARMACOLOGICAL ACTION AND TOXICOLOGY (after Davison[13], Goodman and Gillman)[14]

Synthetic estrogens are capable of producing all the physiological effects of the natural estrogens. They cause marked proliferation of the vaginal mucosa, change the external genitalia from senile appearance to the appearance of childbearing years. They change the pH of the vagina from about 6.5 to 4.0. Smaller doses of the substance will cause endometrial proliferation while larger doses produce hyperplasia of the endometrium. Uterine bleeding may be caused by the prolonged use of the drug but most often the bleeding comes with withdrawal of the substance. Lactation is suppressed by the synthetic estrogen just as it is by the natural occurring estrogens.

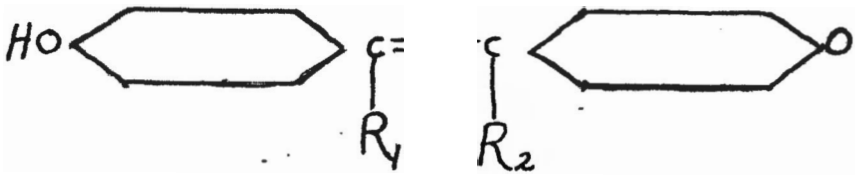


Cyclopentenophenanthrene Nucleus



Phenylethylene Nucleus

Figure I



4,4' Dihydroxystilbene

Figure II

Figures I, II after Goodman & Gilman

Overdosage of diethylstilbestrol will produce toxic symptoms that may be associated with overactivity of estrogenic compounds. The symptoms most often exhibited are nausea and vomiting. Bleeding, painful breasts and vaginal irritation may be present from continous therapy. Blood studies and liver function tests performed at the time of administration of the drug have revealed no evidence of toxicity. Long administration of the drug fails to produce any toxic evidence in the blood or urine. In cases that are seen at autopsy, the liver, kidneys and adrenals show no changes that may be attributed to diethylstilbestrol.

INDICATION FOR STILBESTROL

1. Menopausal syndrome 2. Supression lactation 3. Senile vaginitis 4. Gonorrheal vaginitis 5. Threatened abortion 6. Habitual abortion 7. Pre-eclampsia 8. Eclampsia 9. Carcinoma of the prostate 10. Kraurosis vulva 11. Pruritis vulvae

BASIS OF DIETHYLSTILBESTROL IN ABORTION

In the last century much emphasis has been placed on the importance of endocrine factors as the cause of abortion. The emphasis particularly relating to the placenta and corpus luteum.[16] There are a number of reports from several different laboratories that abortions are sometimes preceded by a decrease in pregnandiol levels that are suggestive of premature failure of

the corpus luteum or a decrease or inadequate function of the placenta.[17-20] However, the same investigators report that some normal pregnancies have low pregnandiol titers while others with high titers threaten to abort.

There is a high incidence of low pregnandiol titers accompanied by low blood and urine estrogens.[16] With the corpus luteum manufacturing these substances it is understandable that both could be low in corpus luteum deficiency. Hamblen[19] thinks that there is a synergistic action between both estrogen and progesterone.

Smith and Smith have done a great deal of study on the hormonal effect of pregnancy. They observed in 1936[21] that an increase in estrogen excretion was followed by a decrease in chorionic gonadotropin. In 1938[22] they administered estrogen to pregnant women and after withdrawal of the estrogen found that there was a decrease in chorionic gonadotropin. Studies of both pregnant and non-pregnant women had indicated to these investigators that a rise in estrogen always preceded any increased secretion of progesterone. This observation led them to believe that there is some relationship of the estrogen to the corpus luteum in non-pregnant women and to the utilization of chorionic gonadotropin in pregnancy for the production ofprogesterone.

Progesterone depressing the rate of estrogen

oxidation and inhibiting the pituitary property of estrogen was demonstrated by Smith in 1944.[23] Therefore in any attempt to enhance progesterone secretion by estrogen therapy the latter must be given in doses larger than could be metabolized by the body. Replacement therapy of estrogen and progesterone over a prolonged period of time as indicated in pregnancy is impossible.[24] For this reason a more practical and physiological approach would be some method of stimulating the placental steroid hormone secretion. The administration of chorionic gonadotropin is contraindicated because with the increased estrogen level the chorionic gonadotropin is increased in the circulation and there is inadequate utilization for the production of placental steroid.

Smith in her studies of estrogen metabolism of women produced a clearer understanding of the physiological process involved for the production of estrogen and progesterone. These are:

1. That progesterone facilitates the metabolic conversion of estrogens and depresses their rate of inactivation.

2. That the estrogen inactivation products plays an important part in the stimulation of steroid secretions.

3. The production of progesterone during the luteal phase of menustrual cycle and the thirty-eighth week of pregnancy is sufficient enough to reduce estrogen inactivation to such an extent to remove the stimulus for sex steroid secretions.

It was found that diethylstilbestrol was not suppressed in its pituitary effect by progesterone. With this proven it is logical to think that the pituitary gland could produce chorionic gonadotropin to stimulate the production of progesterone.

It can be assumed by the above that there is a definite cooperation between estrogen, chorionic gonadotropin and progesterone. Chorionic gonadotropin is needed for production of estrogen and progesterone was shown by Smith[25] and that progesterone will depress the inactivation of estrogen. It is stated also by the above investigator that stilbestrol is not given to replace the estrogen but is given to stimulate the secretion of estrogen and progesterone.

Karnaky[7] postulated that diethylstilbestrol worked in one of four ways or in a combination of two or more of the following:

1. Keeping or raising the estrogenic level above the normal estrogenic level.
2. Keeping the sodium, calcium, potassium, magnesium and phosphorus ions from being concentrated at level which produce uterine contractions.
3. Keeping estrogenic-ionic ratio from being optimum for labor.
4. Stilbestrol may stimulate the corpus luteum to produce more progesterone.

Karnaky thinks that it is possible stilbestrol causes an increase in the utilization of chorionic gonadotropin and suggests that there is an active utilization

of chorionic gonadotropin by the placenta to produce estrogen and progesterone. An abnormal metabolism of estrogen and progesterone may be the result of a deficiency thus resulting in inadequate utilization, more rapid destruction and less complete conversion so that a normal hormonal balance may be kept to preserve pregnancy. The synthetic estrogen may cause an opposite effect on the above situation and thus working by some mechanism to inhibit abortion or miscarriage.

Stilbestrol may replace the natural occurring estrogen and by doing so may stimulate the placenta directly to cause an increase in the production of estrogen and progesterone. The synthetic compound may cause the placenta to utilize chorionic gonadotropin giving an increase in both estrogen and progesterone.[26] This last statement is in agreement with the observation made by Smith as stated before.

It has been found that from eight to twenty-four days before the onset of labor the estrogens gain a maximum level in the body. (Figure III) Between this peak level and the time of onset of labor a progressive change in the steroid level of the body is characterized by progesterone and estrogen withdrawal. There is a gradual decrease in the conversion of the substance and some increase in the rate of destruction. If false labor begins the estrogen and progesterone decreases thus getting

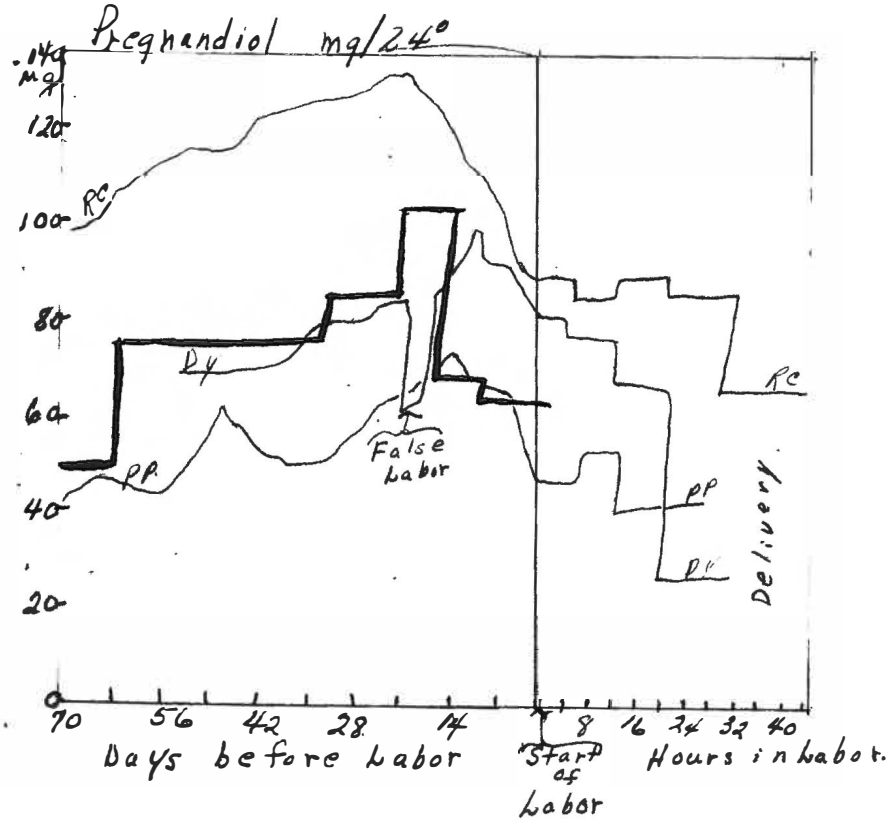


FIGURE III

Urinary pregnandiol during the last ten weeks of normal pregnancy and during labor. Heavy black line = composite curve based on 63 specimens from fourteen individuals followed to term. Letters indicate patients.*

* After Smith

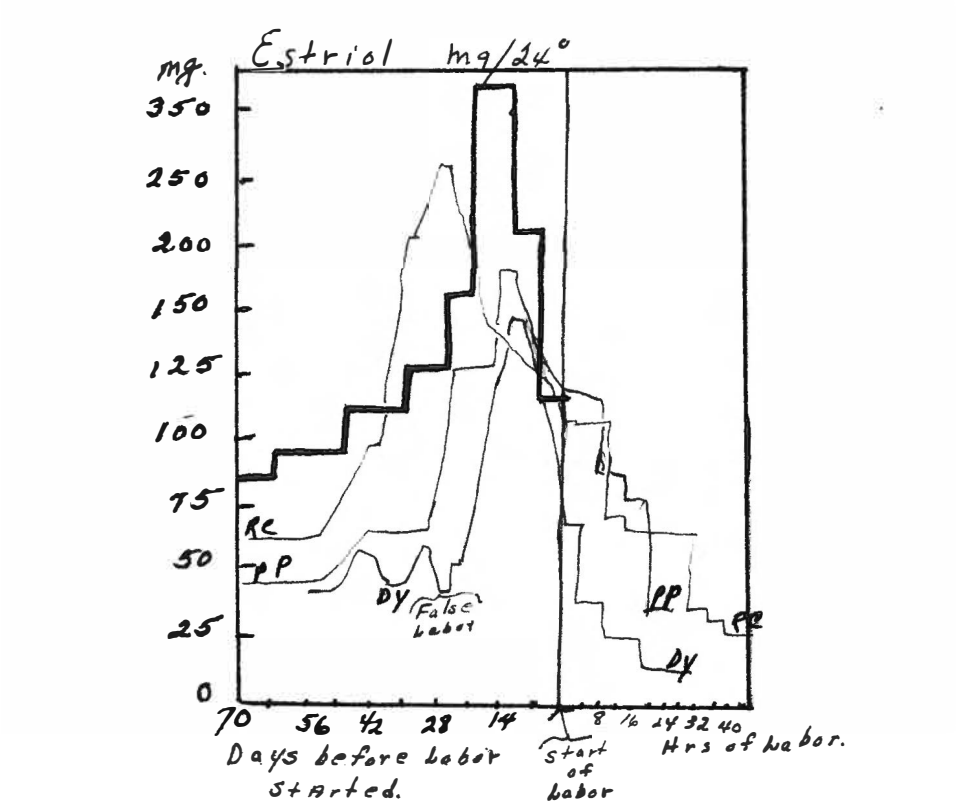


FIGURE IV

Urinary estriol during the last 10 weeks of normal pregnancy and during labor. Heavy black line — composite curve based on 66 specimens from 15 individuals followed to term. Letters indicate patients. *

* After Smith

an increased sensitivity of the uterus. When the membranes rupture there is definite evidence of decreased estrogen and progesterone.[23]

Estriol is the end product of the conversion of estradiol to estriol and the irreversible estrone estriol conversion is facilitated by the presence of progestin. The level of urinary estriol, therefore, when considered with the urinary estrogens provide an index of progestin secretion and utilization. In both figures III and IV the pregnandiol and estriol excretion run parallel during the last ten weeks of pregnancy.

TREATMENT

Diethylstilbestrol has proven to be of great value in the prevention and care of threatened abortion and habitual abortion. Whether or not it is of value in cases that are not of hormonal etiology is not known. It seems illogical to me that abortion with an etiology such as fibromata, immature sperm, cancer of the uterus, etcetera, can be saved by the administration of stilbestrol. On the other hand if diseases such as diabetes, pituitary disease, ovarian disease and other glandular diseases are present it seems logical that there is an upset in metabolism of the body. In this situation diethylstilbestrol may be of some benefit. If the condition is of inadequate female hormonal harmony, the synthetic estrogen is indicated definitely.

Karanky[7] in early trials of stilbestrol indicated that stilbestrol given in adequate dosage could prevent threatened abortion, premature labor and habitual abortion. His treatment of these cases consisted of twenty-five milligrams of stilbestrol injected into the anterior wall of the cervix. This is followed by twenty-five milligrams administered orally every fifteen minutes as long as there are any pains. After the cesation of pain, ten milligrams are taken every hour for six doses, followed by five milligrams every hour for six doses. After this therapy the patient is given ten milligrams every night until the eight month of pregnancy at which time it is stopped. The injection of the material into the anterior wall of the cervix is not necessary if the bleeding and cramps are not to severe. He feels that this is governed by each independent case.

It is thought by Karnaky that uterine bleeding and cramps may be stopped immediately by anterior cervical wall injection of twenty-five to two hundred milligrams of stilbestrol. The hard contracting uterus may be converted to a softened condition in thirty to sixty seconds and remain softened from six, eight, to twenty-four hours following the cervical injection.

The toxic effects are minimal in this study. No intrauterine deaths in twenty cases was reported after dosages of two thousand five hundred to six thousand milligrams of stilbestrol. Sixteen mothers have given

birth to sixteen normal babies and ten more cases were still under observation. Sterile women were given ten milligrams of stilbestrol every night until the seventh month. If there was any uterine bleeding or cramps they were treated as above.

Karnaky[22] a few years later made another study of the synthetic estrogen. He used all types of gynecological cases. He selected one hundred and thirty-six cases in which the dosages of the synthetic compound was increased from one to five milligrams by mouth every three to seven days until some were taking one hundred milligrams of stilbestrol a day. Routine urinalysis and blood counts were taken on these patients and no evidence of any pathology could be ascertained. There was no evidence of any other toxic effects of the patients. The patients in the above incidence also were treated with IM. injection once or twice a week with two hundred and fifty milligrams of the compound. One woman accidently killed while under treatment revealed no gross or microscopic pathology of any of the organs of the body.

Thirty-one normally pregnant women were treated with one hundred milligrams of diethylstilbestrol daily from the third month of pregnancy until term. All the babies were born normally and appeared normal with the exception of a darkened areola around the nipples, labia and linea alba similar in intensity to that of the mother, indicating that stilbestrol is shared by

the fetus. During the period of gestation ten of the cases were injected with a single five hundred milligram dose. All became nauseated and vomited. The author of the article states that it takes five hundred milligrams of the substance to cause nausea and vomiting in pregnant women while only seventy-five hundredths to five milligrams causes nausea and vomiting in non-pregnant women.

Rosenblum and Melinkoff[28] followed ninty-six cases of threatened abortion, premature labor and habitual abortions. The threatened abortion was diagnosed by uterine bleeding and uterine cramps. Habitual abortion was diagnosed by three previous cessations of pregnancy and threatened premature labor was determined by the development of pains hard enough to simulate real labor.

Threatened abortion was treated by bed rest and diethylstilbestrol, five to twenty-five milligrams for the first dose. This was followed by twenty-five milligrams every hour until symptoms had disappeared. Forty-eight hours after bleeding stopped the patient was allowed out of bed. After cessation of all symptoms five milligrams of stilbestrol was given three times a day until the thirty-sixth week of pregnancy. Later it was thought that the placenta was developed enough so that the drug could be discontinued at the end of the twentieth week.

Threatened premature labor was treated exactly as threatened abortion. Habitual abortion was treated differently. In these cases, the investigators began very early in pregnancy, five milligrams of stilbestrol three times a day. This dosage was increased five milligrams per day at weekly intervals until the thirty-fifth week of pregnancy at which time it was stopped.

These investigators report very favorable results. There were rare reports of nausea and vomiting, but no other ill effects were noted. Darkening of the areola, linea alba and congestion of the breasts were noted in both mother and baby. One baby was born with multiple deformities and survived only a few minutes. Two toxemias appeared. One appeared immediately after a normal delivery, the other at six and one-half months gestation. The latter was treated by elective caesarian section and a normal living child was delivered. The mother made an uneventful recovery. The other toxic patients condition improved immediately after the spontaneous delivery and her recovery was uneventful.

The final results of the ninty-six patients treated were:

1. Ninty-three resulted in normal spontaneous labor without complications.
2. Two toxemias with delivery of normal babies - one by section, the other spontaneous.
3. One baby delivered at seven months with multiple deformities and living only a few minutes.

Smith and Smith have made the most extensive and most reliable study on the problem of stilbestrol in the prevention of pregnancy accidents. They have contributions from 117 obstetricians throughout the United States. These men have followed the recommended treatment suggested by Smith, etal, and were willing to pool their results to make a good survey and study for the treatment of pregnancy accidents.

The dosage recommended for use was as follows:

1. Thirty milligrams per day starting the sixteenth week of gestation.
2. Dosage increased five milligrams per day at weekly intervals until the thirty-fifth week.
3. Stilbestrol therapy stopped at the end of thirty-fifth week.

This recommended dose was given to diabetic patients, patients with previous history of pre-eclampsia, toxemia and any other condition that might complicate the second trimester of pregnancy.

In case of earlier pregnancy accidents of the first trimester the dosage was as follows:

1. Five milligrams daily starting the second week after the last menstrual period.
2. Increase daily dosage five milligrams every other week until the sixteenth week.
3. Increase daily dosage five milligrams weekly thereafter until the thirty-fifth week.
4. At the end of the thirty-fifth week stop stilbestrol treatment.

Hertig and Livingstone[24] report that 40% of the threatened abortions would not abort if no treatment was given. He indicated the highest percentage of cures that were observed was 50%. In Smith's series the percentage of cures was increased to 72%. (Table I) This was probably due to the administration of stilbestrol.

Prophylatic stilbestrol was given to 272 patients based on past history. Of the cases, 215 gave a history of one or more abortions previously, forty-one had histories of sterility for two to ten years and sixteen patients had been treated surgically. 135 of these patients had previously aborted two or more times, 105 (83%) of the patients carried to the twenty-eight week and 78% had living and well babies. (Table II)

In the abortion sequence pointed out by Smith and Smith, Eastman calculated that after two previous abortions a woman has a 62% chance of carrying the next pregnancy. The spontaneous cure rate drops to 16.4% after the third abortion and after the fourth and fifth abortion it is 2% and.5% respectively. According to Smith and Smith's tabulated cases of 127 patients the role of stilbestrol in habitual abortion can not be disputed. (Table III)

TABLE I

Stilbestrol for abortion: Definitely for threatened abortion, (bleeding with or without cramps; weeks six to twenty-one).

Previous abortions	Number of cases	Carried to 28 weeks (%)	L and W babies
0	143	74	70
1	46	88	77
2	17	82	72
3 or more	13	83	82
Total	219	78	72

(Including nine cases of which six aborted because of low dosage; fifteen cases of overdosage of which four aborted.)

TABLE II

Stilbestrol for abortion prophylactically (on the back of past history.)

Indic. for therapy	Number of cases	Carried to 28 weeks (%)	L and W babies
Infertility (2-10 yrs.)	41	86	82
Surgical reasons	16	81	75
Prev. abort.			
1	80	87	83
2	65	82	77
3	41	87	80
4 or more	29	67	52
Total	272	83	78

(Includes nine cases on too low of dosage of which three aborted and thirteen cases on too high of dosage of which seven aborted.)

TABLE III

Stilbestrol for chronic abortions: Repeated consecutive abortions preceding therapy; No supplementary therapy.

Previous abortions	Number of cases	Carried to 28 wks.		L and W babies	
		Number	%	Number	%
2	67	56	84	54	81
3	38	33	87	33	87
4	17	11	65	10	59
5	5	2	40	1	20
Total	127	102	80	90	77

Tables I, II, III after Smith[25]

SUMMARY

The evidence that estrogen rise always precedes the increased secretion of progestrin is suggestive that there is a definite relationship between estrogen and the corpus luteum. There is also evidence of chorionic gonadotropin utilization for the production of progestion by its corresponding level to that of estrogen. Progesterone depresses the rate of estrogen oxidation and inhibits its pituitary property. If the progestin secretion is to be increased, estrogens must be given in larger doses than could be metabolized by the body.

The chemical structures of estrogen and stilbestrol, although being different, have similar effects on the body. Stilbestrol is not given to replace the estrogen but is given to cause stimulation for the production of estrogen and progesterone. This synthetic substance is not suppressed in its pituitary effect by progesterone. With this property the synthetic estrogen can stimulate the production of chorionic gonadotropin which is needed for the production of estrogen and progesterone.

Diethylstilbestrol may work in several different ways but it is the consensus of opinion of most investigators that the synthetic substance causes the placenta to utilize chorionic gonadotropin for production of estrogen and progesterone.

Several series of cases were reported in which stilbestrol was used for threatened and habitual abortion. The dosage varied in these series, but when adequate amounts were given the results were favorable. Different methods of stilbestrol administrations were also mentioned. If the abortion is caused by some factor other than endocrine, the administration of stilbestrol is not indicated.

The dosage of stilbestrol should be large enough to avert the symptoms of abortion but should not be at a level high enough to cause toxic symptoms.

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