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## Vitamin E in pregnancy

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VITAMIN E IN PREGNANCY

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## INTRODUCTION

In 1921, Evans and his colleagues, while working with rats on deficiency diets, discovered vitamin E. It was first called a substance X, later given the name vitamin E.

The most important role that this vitamin plays is found in pregnancy. In this paper the value of vitamin E in recurrent abortions, abruptio placenta and sterility will be discussed.

## VITAMIN E

In 1921 Evans and Bishop discovered Vitamin E, first termed a substance X which was present in natural foodstuff and necessary for reproduction. In working with rats on supposedly complete dietaries, they found, with both growth and external appearance normal, animals would exhibit normal oestrus cycle and would breed, ovulate and conceive, yet be unable to experience a normal gestation through the invariable occurrence of fetal death. They discovered that the addition of various natural foods would cure such in the following gestation. The requisite quantity was small and extracts of foods such as fresh leaves of lettuce, dry cereals, (e.g. whole wheat) wheat germ oil, were efficacious. Their work has been confirmed in many laboratories. (7)

Vitamin E is a light yellow oil which is clear, solidifying at about 0° C. (21) It is a fat soluble vitamin, being almost insoluble in water and remarkably stable to light, heat, air, and many other ordinary chemical reagents. It is stable to acid and alkali at normal temperature. The vitamin is rather unstable in the presence of certain fats and salts. Lard, at a level of two per cent of the ration, destroys or renders ineffective the

vitamin E in wheat germ oil, but not at a lower level. This may be explained by suggesting that in high fat diets the vitamin is taken up by the fat and excreted with the unabsorbable fraction. (24) The final fraction is described by Evans and Bishop as follows: "The final yellow viscous oil does not develop crystals on long standing. It contains only a trace of ash and no nitrogen, sulfur, phosphorous, or halogens. It is remarkably potent. The exact chemical nature is still unknown."

Of greatest chemical interest was the biological activity of acetylated or benzoylated concentrates; the formation of such derivatives from vitamin E would signify the presence of one or more hydroxy groups. The antioxygenic action, which in these substances probably depends on a hydroxyl group, was destroyed by such esterification; biologic activity was not, hence, if vitamin E possesses a hydroxyl group, either it was resistant to esterification or the ester was physiologically utilizable. (17) By a group of interesting series of reactions, Olcott (19) demonstrated that vitamin E does contain a hydroxyl group which is easily esterified and whose esters with acetic acid or benzoic acid are utilizable (hydrolyzable) by the animal body while a urethane derivative formed with phenyl isocyanate, for example, is not.

Olcott found a band with a maximum at 2940 Angstrom units in the absorption spectra of the biologically active portion in purer concentrates of vitamin E prepared from cotton seed oils, and apparently is not connected with vitamin activity .

Olcott and Mattill (22) found that vitamin E is destroyed by bromination, but not by acetylation, benzoylation, mild oxidation with silver nitrate, or hydrogenation. The concentrate strongly resents saturation with hydrogen. Potassium permanganate destroys the activity of the vitamin. They also found that a concentrate of vitamin E is stable for as long as four weeks in a rancid food mixture.

Vitamin E is destroyed by ozone, perbenzoic acid, potassium amide, potassium ethylate and chlorine. (20)

Ferric salts also destroy the vitamin. (3)

O. H. Emerson, G. A. Emerson, A. Mohammad, H. M. Evans, (13) isolated alpha-tocopherol by means of the allophanate from cotton seed oil, lettuce leaves, and palm oil. From each of these sources, alpha-tocopherol has within the limits of accuracy of the test, the same vitamin E activity as that originally isolated from wheat germ oil.

Two additional tocopherols have also been isolated. Beta-tocopherol from wheat germ oil, was obtained by

the allophanate crystallizing in well formed needles melting at 144-146°, and gamma-tocopherol from cotton seed oil was obtained as the allophanate melting at 138-140°. These tocopherols appeared to be one-half to one-third as potent as alpha-tocopherol. The analysis of the allophanates of these tocopherols indicate that they may contain one CH<sub>2</sub> group less than alpha-tocopherol, though the possibility that all three are isomeric is by no means excluded.

Alpha-tocopherol yields a crystalline p-nitrophenylurethane and the allophanate indicates a provisional formula for alpha-tocopherol of C<sub>29</sub> H<sub>50</sub> O<sub>2</sub>. (12)

The word alpha-tocopherol was derived from the greek words tokos, meaning child birth, phero, meaning to bear, and ol, indicating alcohol.

## ABORTION

Abortion denotes the spontaneous, premature cessation of pregnancy at any stage in its course, excluding the delivery of a viable fetus.

Repeated spontaneous abortion, commonly referred to as habitual abortion, is a term applied to repeated or recurrent abortions in which there seems to be no recognizable cause.

The old accepted causes of this condition such as infection (of which lues is the most common), abnormal endometrium, sperm defect, defect in ova, heredity, and others have given way to two modern theories: namely, endocrine imbalance and hypo-vitaminosis. The first of these more recent theories presupposes that progesterin prepares the endometrium for the fertilized ovum and that while the corpus luteum is in ascendancy the pregnancy continues. At the same time pituitrin and estrin are inhibited. If estrin becomes dominant, the uterus is sensitized to pituitrin and labor ensues.

Little work was done on the treatment of abortion with vitamin E until 1931 when Vogt-Müller (30) presented two cases which he had successfully treated with such --

Case 1 - four previous abortions around three

months, treated with wheat germ oil, delivered a live, full term babe.

Case 11 - five pregnancies, aborted three to four months, treated with wheat germ oil, delivered a live, full term babe.

Vogt-Møller stated that the diets of these two Danish patients did not deviate from the ordinary food taken in Denmark. Therefore they could hardly have been poor in Vitamin E, but possibly the need for this vitamin might vary in different individuals, so that a hypo-vitaminosis E, could have been present in above cases.

Vogt-Møller (5) later reported favorable results due to the administration of wheat germ oil (vitamin E) in eighteen out of twenty one cases of habitual abortion. He suggested that this vitamin is needed because a hypo-vitaminosis exists during pregnancy, caused by the increase in maternal metabolism and the added requirements of the fetus. He further asserted that this may reflect back to thyroid imbalance, dental caries, anemia and other constitutional conditions which place an added burden upon the maternal reserve.

Shute (28) pointed out that the blood sera of seventy per cent or more of women aborting spontaneously displays a characteristic resistance to proteolysis when exposed to tryptic solutions. This appeared

to be an agent contained in the placenta and closely relating estrin - question of relation to vitamin E.

Shute (27) found that a preparation of vitamin E will remove temporarily the anti-proteolytic factor present in certain types of blood sera. Vitamin E should be administered until the anti-proteolytic factor has disappeared and then should continue with a dosage sufficient to keep the average serum normally digestible. If vitamin E can cause the anti-proteolytic factor present in the blood sera of aborting women to disappear, then such women on a summer diet (rich in vitamin E) would be unlikely to display marked anti-proteolytic power in their sera.

Malpas (15) reported nine cases which received vitamin E therapy. Successful results were obtained in two of seven cases, as in two cases wheat germ oil therapy was administered after bleeding had occurred. He believes that Shutes' hypophysis, the administration of wheat germ oil is successful in cases of repeated abortion because it lowers the resistance of the blood serum to trypsin digestion, stands or falls by the value of his test for the resistance to proteolysis of the blood serum. It would appear that while the experimental evidence for the role of vitamin E in the maintenance of pregnancy is impressive, the clinical results are far more convincing.

Malpas also believed that vitamin E is not the

only vitamin responsible for intra-uterine development. Mouriquand and his co-workers have demonstrated the importance of ascorbic acid in maintaining the viability of guinea pig embryo. The craving of most pregnant women during the early months for fresh fruits and vegetables may be the expression of the need for this vitamin.

Shute (29) observed a definite seasonal rhythm in the incidence of premature interruption of pregnancy, in abruptio placenta, and the conception of deformed fetuses. All of these phenomena appear to have some relation to deficiency of vitamin E in his experience. These pathological conditions appeared more frequently from January to June each year and more infrequently from July to December. This is due, in this latitude and country, to more available vitamin E in the green diets of summer and early autumn. It has been his annual experience that larger doses of wheat germ oil were required by women with precarious pregnancy in the months from January to June each year.

Experiments show, that where there is a large amount of vitamin E present in the dietary, fewer women have spontaneous abortion; and the sera of the women who fail to show a resistance to proteolysis detectable when treated with strong proteolytic solutions. It has been shown that vitamin E and estrin, or a substance

much like it, exists in a sort of equilibrium during pregnancy. If there is too much of the estrin like substance, the pregnancy is interrupted. An excess of vitamin E appears to have no effect on the pregnancy. There are also other factors such as anterior pituitary hormone, posterior pituitary oxytocic hormone, and progesterin also in equilibrium with estrin, and the balance of all these factors must be very complex and subtle.

Bishop (2) believes that progesterone renders the uterus quiescent, particularly during the early months of pregnancy before the placenta has reached full development, and that a lack of progesterone is a contributory factor in the production of habitual abortion. Experiments suggest that vitamin E helps maintain the normal activity of the corpus luteum during early pregnancy, not by direct action on the ovary, but by stimulation of the gonadotrophic function of the pituitary.

It has been shown by Rowlands and Singer (23) that the pituitaries of rats fed on a vitamin E free diet are markedly defective in the luteinizing or ovulation producing hormone as tested on estrus rabbits. At the same time neither anterior pituitary nor luteinizing pregnancy urine extracts are capable of preventing the resorption of the fetuses in a vitamin E free diet.

Watson (32) believed that possibly vitamin E supplements the work of the hormones. In this regard a relationship such as the following may be postulated. The hormones favor ovulation and implantation of the fertilized ovum in the uterus and they supervise the early stages of the development of the embryo. Vitamin E appears to act as an important adjunct in these functions by supplementing the hormonal activities during the embryonic phase of existence; but, more specifically it is a requisite for the further development of the fetus and the completion of pregnancy.

The developing fetus is, however, particularly susceptible to lack of vitamin E. According to Evans and Burr, probably all the fetal tissues require the factor but it appears that the middle germ layer and its products are especially sensitive to it.

Vitamin E plays an important part in reproduction. Either the amount of vitamin E which is stored in the maternal organism is insufficient to meet the demands imposed by pregnancy; or, for some unknown reason, there exists an inability to assimilate and utilize, in a normal manner, the vitamin E which is contained in ordinary food; or, inactivation of the factor occurs in some way.

Watson (32) reported his results with wheat

germ oil therapy:

Group I - a series of eleven patients who had sustained from three to fifteen spontaneous abortions prior to the exhibition of wheat germ oil. Of these eleven women, nine went to term and delivered healthy children. Six of the patients under this regime completed a pregnancy for the first time. No explanation was offered for the interruption of the other two cases.

Group II - a series of seventeen patients who had two abortions prior to the exhibition of wheat germ oil. Of these twelve gave birth to healthy living children after the use of the oil. In five cases the pregnancy was interrupted by spontaneously occurring abortions, and in one of these a definite toxic state existed, associated with marked albuminuria, which complication probably contributed to the otherwise unexpected cessation of the pregnancy. No explanation was offered for the interruption in the other four cases.

Group III - cases with one previous abortion. There were nine patients treated with wheat germ oil in this series. Of the nine treated, eight of these gave birth to healthy living children. In one, abortion took place a short time after the use of oil commenced. In several instances some of the patients

threatened to abort, but with the exception of the instances noted abortions did not follow.

Group IV - threatened abortion - fifteen patients were treated for the symptoms of threatened abortion, the majority after bleeding had begun. In eleven of these, the pregnancy continued uninterruptedly, terminating in natural deliveries. In four cases the abortion was inevitable.

Young (34) states that the administration of vitamin E during the earliest stages of pregnancy is capable of anticipating and preventing the fetal destruction which occurs in animals on a vitamin E free regime, but after the critical phase of placenta-tion, replacement of vitamin E is valueless. Congestion and hemorrhagic changes of a secondary nature occur in the placenta of such affected gestations, and this is associated with vaginal bleeding.

#### Deficiency of vitamin E

1. The general health remains normal.
2. Repeated and often rapidly succeeding matings and impregnation is the rule.
3. The successive pregnancies are blighted.
4. Administration of vitamin E at a sufficiently early stage breaks the sequence and, in a large proportion,

enables normal carrying of the pregnancy to full term.

Vitamin E possesses specific significance for the nutrition of the placenta, and that in some manner which is not clear, it operates through the activation of the luteinizing mechanism.

Watson and Tew (33) reported sixty five cases - classified and treated as follows: group -

1. Pregnancy women who had experienced two or more spontaneous abortions previous to receiving wheat germ oil therapy (habitual abortion).

2. Pregnant women who had experienced one spontaneous abortion previous to receiving wheat germ oil therapy.

3. Cases of threatened abortion.

Group	Present series treated with wheat germ oil.	No. Cases-Success-Failure		
1.		35	25	10
2.		11	9	2
3.		19	13	6

Juhasz-Schaffers in 1934 reported five cases of two or more previous abortions. Treatment with wheat germ oil resulted successfully in all five cases.

In many cases of threatened abortion the symptoms disappear spontaneously and the pregnancy subsequently progresses to a natural termination regardless of any special form of treatment.

Watson and Tew concluded that wheat germ oil appears to be of definite value and to have its greatest scope of usefulness in the prevention of repeated spontaneous abortions. Also the oil may be used to an advantage in threatened abortion if administered properly and in relatively large quantities.

Currie (6) reported results in patients with two or more previous habitual abortions. In some cases therapy was not instituted until after the twelfth week of pregnancy, that is, until after the placenta was fully formed, yet the results show sufficient success for some credit to be ascribed to the use of the vitamin, even after complete placentation.

Some authors believe the vitamin is to be of value only during the early months of pregnancy. Of the thirty seven patients treated, they had had one hundred and thirty pregnancies with sixteen viable children. Under treatment the results were: 25 full term, 1 died; 3 - 38 weeks; 1 - 39 weeks; 2 - 36 weeks, 1 died (twin); 1 - 34 weeks; 1 - 33 weeks; 2 - 32 weeks, 1 died (twin); 2 abortions.

Wheat germ oil has also been given, with success, in cases of threatened abortion. Fifteen of these have been treated and fourteen taken successfully to term. Along with administration of vitamin E other recognized methods of treatment were used.

Currie stated that vitamin E may be only essential during the early months of pregnancy, and by reason of the aid it gives in the formation of the placenta it provides for the supply of luteal hormone in the later months. He gave one capsule containing three minims of the oil extract daily from the attendance until the day of delivery. There is a question as to the amount of vitamin E to use and the length of time to be administered. At present it is safer to give not less than three minims of the oil extract throughout the pregnancy.

Cromer (5) reported a series of cases from his experience of wheat germ oil treatment of recurrent abortions and threatened abortions:

Group I - recurrent abortions -

Case	Age	Number abortion	Wheat germ therapy	Results	Remarks
1.	26	1	began before l.m.p., discon- tinued after 4th month.	Terminated at 8 mo., live child 6lbs. 4oz.	Abruptio placenta
2.	25	1.	Began before l.m.p., cont- inued through- out	Full term live child 6lbs. 4oz.	No abnor- mality.
3.	24	1	Began after 2 months, inter- mittently throughout	Spontaneous abortion after four months	Placenta infarcts
4.	32	2	Began at two months	Full term live child 7lbs. 2oz.	Small placenta

## Group II - threatened abortions -

Case	Age	Number abortion	Wheat germ therapy	Results	Remarks
1.	19	0	Began at 2 months, continued throughout	Term, 2 wks. early, live child, 6lbs. 12oz.	Small placenta
2.	20	0	Began at 4 months, intermittent throughout	Full term live child 7lbs. 5oz.	Large white scarred area at margin of placenta
3.	26	0	Began before l.m.p., continued throughout	Full term, live child 6lbs. 6oz.	Weight of placenta 480 grams, some scarring

Group I - those who have had one or more spontaneous abortions previous to this treatment.

Group II - those presenting the symptoms of threatened abortion.

Results: In the case, which terminated at eight months, the elevated blood pressure, uterine pain, backache, and the characteristic placenta, certainly place this patient in the category of abruptio placenta. This patient had begun therapy with wheat germ oil before becoming pregnant and had discontinued it voluntarily after the fourth month.

It has been shown by Shute and others that cases of abruptio placenta, real or impending, show an excess of estrogenic substance in the blood serum, and furthermore, that vitamin E is antagonistic to, or inhibits,

the formation of the excess estrogenic substance. Hence, it is quite possible that in this case abruptio placenta developed as a direct result of the withdrawal of vitamin E.

Case of abortion at four months - did not wish baby, rode, used douches and laxatives.

Cromer concluded that this is too small a series to allow for definite conclusions, but in general it can be said that vitamin E, when administered early and in sufficient quantities does have some value in recurrent and threatened abortion. The product must be started, when possible, before conception occurs and certainly as early as pregnancy is feasible, and continued to term. However, once a patient has started to bleed and have cramps and backaches, then one must have complete faith in an ever watchful providence to believe that wheat germ oil will stem the bloody tide.

## ABRUPTIO PLACENTA

Premature separation of the normally implanted placenta is one of the most common as well as the most perilous complication of pregnancy. It occurs in about one-half to one per cent of all pregnancies and carries a maternal mortality of approximately six per cent and a fetal death rate of more than sixty per cent.

This condition has been referred to as accidental hemorrhage, concealed hemorrhage, ablatio placenta, and premature separation of the placenta.

Some of the signs and symptoms of abruptio placenta are: uterine tenderness, low backache (sacral), followed by the occurrence of labor pains, violent fetal movements, uterine hemorrhage of varying grades of severity, nausea and vomiting, systemic signs of hemorrhage, shock, and definite changes in the blood pressure.

The placenta shows marginal lesions, which range from fresh clot through recently organized "cream cheese" clot of white infarcts on maternal aspect, they may extend to fetal aspect.

Shute (26) in testing the serology of pregnant women for evidence of imbalance between vitamin E and esterogenic substance, which characterizes most women who are aborting spontaneously, and found a

deficiency of vitamin E. Seventy-five per cent of these cases had an excess of blood estrogenic substance.

Duration of exp.	No. cases.	Per cent showing a relative deficiency of vitamin E and therefore an excess of blood estrogenic substance.
Jan. 1, 1934 --		
Jan. 31, 1935.	5	80%
Feb. 1, 1935 --		
May 31, 1936.	77	78%
29 months in all	82	78%

Of the above eighty two cases only thirty one were of the severe classical type described in standard works. Of these thirty one severe cases, eighty one per cent revealed vitamin E deficiency.

Shute (27) believes that a very important factor in the etiology of abruptio placenta is the appearance in the blood serum of an imbalance between vitamin E and an estrogenic substance. The effect of such an imbalance is to produce a relative excess of estrogenic substance. This develops weeks or months before the clinical signs and symptoms of abruptio placenta appear. Correction of such by administration of a potent vitamin E preparation is of great prophylactic value. Shute (29) found that in the treatment of these cases that vitamin E should be administered up to the onset of labor, because he feared the late development of abruptio placenta.

He observed that it did not unduly delay the onset of labor. The onset of labor at term is de-

terminated by many factors, of which the presence of an increase of blood estrogenic substance is only one, and this is by no means an essential nor invariable prerequisite. As vitamin E appears to act principally by neutralizing any excess of estrogenic substance in body economy, there would be no obvious reason why it should interfere with the onset or course of labor at term, and it does not do so. There is undoubtedly much more involved in the physiological onset of labor at term than just the balance between vitamin E and estrogenic substance in the body.

From January 1, 1934 to March 31, 1936, Shute (27) observed sixty five cases of abruptio placenta. In seventy five per cent of these he found a deficiency of vitamin E and an excess of estrogenic substance in the blood serum. In these cases vitamin E therapy was instituted, and it was found that in almost all the cases an adequate massive dose of a potent vitamin E preparation completely abolished, in twenty hours, the circumscribed area of tenderness. The accompanying sacral backache and uterine cramps subsided almost as rapidly. Uterine hemorrhage, when present, stopped promptly.

When such therapy was interrupted the uterine tenderness and bleeding often reappeared, only to disappear with characteristic rapidity on further

continuation of the vitamin. Shute (30) found that upon cessation of vitamin E therapy, the estrogenic substance increase usually reappears in the blood serum and coincidentally symptoms and signs of abruptio placenta reappear.

A definite seasonal rhythm has been observed in the incidence of premature interruption of pregnancy, and in abruptio placenta, and the conception of deformed fetuses in particular. These pathological conditions appeared more frequently from January to June each year and more infrequently from July to December. This is due to more available vitamin E in the green diets of summer and early autumn in this latitude and country. From experience, it has been found that larger doses of wheat germ oil are required by women with precarious pregnancies in the months from January to June each year.

Shute (26) found that with the administration of eight to twelve drams of bulk wheat germ oil, the uterine tenderness would be abolished, and, the rest of the characteristic signs and symptoms of abruptio placenta would disappear. The best results were obtained in women who presented no signs or symptoms of true toxemia of pregnancy.

## STERILITY

The condition of sterility signifies the inability to reproduce young.

Dr. Benedict and his associates in the nutrition laboratory of the Carnegie Institute in Boston in 1917 worked on human vitality and efficiency under prolonged restricted diet. He used two squads of twelve men each, one squad was subjected to such dietary restrictions that they lost twelve per cent of their weight. No attempt was made to alter the character of the food, merely the amount of such. The amount of protein was dropped from one hundred to sixty grams per day. These men were apparently normal throughout the experiment and were able to carry on their regular work and exercise. They were under careful observations at all time.

Profound results were noted, such as:

1. Blood pressure dropped from 115 to 90 systolic.
2. Flood pressure dropped from 80 to 63 diastolic.
3. Morning pulse rate dropped from 60 to 40-45.
4. Basal metabolism fell between fifteen to twenty per cent.

During the entire experiment there was an

accumulated loss of nitrogen of approximately one hundred and seventy five grams, which would correspond to about one thousand and one hundred grams of protein.

It was also noted that the reaction time for carrying out certain coordinated movements was definitely prolonged.

Nearly all subjects showed a slight but definite anemia, and toward the end began to develop mental irritability.

Certain observations were made in regard to the sex life of the men and it was found that without exception while on the diet, the occurrence of nocturnal emissions ceased altogether, as did all erection or other sex phenomena.

Gaspard reported that during the serious famine in France, in 1917, many women noted cessation of the menses. The number of conceptions during the famine was less than half of those occurring in corresponding months before or after that period.

Rubner is also quoted in regard to his report on undernutrition in Germany during the blockade. At that time the ration actually distributed contained only thirty one grams protein and thirteen hundred and forty four calories. There was a loss of twenty per cent in body weight and a great increase in the

number of deaths. This diet also caused a cessation of menses in many women and therefore increased sterility.

In 1922 Evans and his colleagues found that rats which were fed on a purified diet containing only vitamins ABCD, cease to reproduce after two or three generations. According to them the onset of sterility is not sudden but gradual, and is not entirely due to a failure of the male to produce spermatozoa or the female to produce ova. The egg may be fertilized and implantated in the uterus, but the fetus which results, sooner or later ceases to grow and diminishes until it has become completely absorbed. Evans put forth the view that the sterility was due to lack of an unknown factor which has been called vitamin E. (4)

It was found that tested individuals produced litters of healthy young when fresh green lettuce leaves had been added to their dietary. It was thus apparent that they were in the presence of a new member of the "vitamin" substances, specific in dietary needs, which they designated by the letter X or as the anti-sterility factor.

In all instances the occurrence of sexual congress has been confirmed by the detection of the plug (bouchon vaginale) and by the microscopic finding of residual sperm in the vaginal canal. Resorption

is best detected by isolation of the female and the institution of daily weighings for five days, between the twenty and twenty fifth day, and the finding of a more gradual decline in the mothers weight than is found in the precipitous drop at partuition.

Necropsies performed late in gestation show various stages in the resorption of the young. Studies of the uterine mucosa just before implantation (i.e., late in the fifth day after coitous or early in the sixth day) show that the "implantation bed" is abnormal, in that quite a massive extravasation of erythrocytes has occurred, presumably by diapedesis, infiltrating the connective tissue meshes of the endometrium. When placentas are established, they exhibit a similiar type of abnormality, for there are hemorrhages in them and other circulatory faults, chief of which is the occurrence of characteristic abnormally distended maternal venous sinusoids. (9)

It is difficult to show that the early reproductive steps are normal and only the placenta diseased. Clear indications that this is the truth are afforded by instances in which a change in dietary regimen effected after ovulation and fertilization had occurred, led to the birth of normal young. (10)

Sherman and Smith (24) found a high percentage

of fertility in the first gestation of such a group of rats, but second and subsequent gestations showed increasing sterility. Two factors were considered to be chiefly responsible for initial fertility on diets supposed to be free from vitamin E; the transmission of a part of the mothers store of vitamin E to her offspring during gestation and the inclusion unwittingly of vitamin E in the basal diets in traces which may vary seasonally.

It was found that the sterility in the female was only temporary and could always be cured, since only temporary tissues are damaged. In the female no degeneration of the ova can be demonstrated - indeed, it would appear that a deleterious influence of the lack of the vitamin is not shown by the ova or other ovarian tissue, but only by the developing embryo. When vitamin E is low or absent, the fetal, rather than the maternal tissue in the placenta, shows elective disorders. There are indications that the maternal mechanism is abnormal in a strange tendency of the uterus to form spontaneous nodular deciduomas when pseudopregnancy is provoked by copulation with a vasectomized male.

In the male sterility tends to go beyond recall through the breaking down of the permanent testicular tissues. (24)

It is especially interesting that the male germ cell exhibits this need and not the female germ cells. This may be due to the tissue growth. The male germ cells are, however, produced at rates exceeding that involved in blood cell formation and we noted no disturbance in hematopoiesis when vitamin E is absent. Furthermore, the remarkably rapid and entirely normal growth of the entire body that takes place when young animals are weaned and put on vitamin E free diets would indicate that only during a "critical" time in fetal life are the tissues dependent on the vitamin.

Vitamins are more important during pregnancy than at any other period of the life history of a woman, and they show a marked bearing on the vitality and chances of survival of the fetus. (18)

Sterility has been obtained on milk and other diets containing lard, but when the lard was removed there was invariable an increase in the fertility of the rats. The ease with which lard undergoes rancidity explained the instability of vitamin E in lard containing diets. (7)

When cod liver oil was added to the diets and the development of rancidity changes allowed, the diets were rendered inferior for reproduction. The logical explanation is that certain lards contain antioxygens, which prevent oxidative changes and conserve and vitamin E

which may happen to be in the diet.

The dependence of vitamin E for its preservation of the presence of an antioxygen results in the close association of vitamin E and antioxygen. This, like vitamin E, is found in the unsaponifiable portion of the fat.

Fertility is not merely a function of the generative organs, but of the whole organism.

Possible ways in which reproduction in the female can be affected by diet are; by a specific action on the ovary, a, by inhibiting the production of healthy ova; b, by causing atresia; c, by interfering with its endocrine functions; d, by causing an atonic condition of the uterus; e, by affecting implantation, or f, the placenta or fetus. (14)

Evans and Bishop(8) in 1922, found that rats fed on a purified diet, were for the most part sterile in the first gestation, and wholly so in the second. The failure to breed was due to a peculiar disease which affected the placenta and products of conception resulting in their death and resorption, with ovulation and fertilization not being affected.

Macomber (16) in 1929, showed that reproduction was normal in rats on diet of protein 2.4 grams, carbohydrate 6.72 grams, fat 214 grams, a total of fifty nine calories. When he reduced that diet thirty

three per cent to protein 1.6 grams, carbohydrate 4.48 grams, fat 1.6 grams, a total of thirty nine and seven tenth calories, the reproduction ceased altogether until the diet was restored to normal, though the weight and health of the animal was little affected.

Macomber cited four cases in which sterility and menstrual disorders had ensued with negative basal metabolic rates. With readjustment of the diet and exercise the patients menses became regular and then were able to become pregnant. He reviewed the diets of two hundred and six women which had consulted him for sterility. In some cases the trouble was with their husbands, some had closed tubes, etc. Comparing the diets of above patients with standards set by Langworth, he found them to be reduced by eighteen per cent in calories and ten per cent in protein. He concluded, that there was a large body of evidence, both experimentally and clinically, to show alterations in the diet actually do produce sterility. An analysis of the diets of the two hundred and six sterile women showed that they deviate in many important ways from normal. A large number showed evidence of nutritional disturbance. Of the two hundred and six, forty became pregnant. This result occurred, at least in part, as the result of changes in diet and such other means as

the increasing of exercise, the taking of endocrine medication or the treatment of anemia. It seems to Macomber therefore, that he has in diet a means of treating sterility which cannot afford to neglect.

Barrie,(1) working with twenty three female rats, examined the pituitary gland in which sterility had been produced by a diet deficient in vitamin E. Microscopic examination of the tissues showed hypoplasia of the thyroid and degranulation of the acidophils and basophils of the anterior pituitary gland. When given an adequate dose of vitamin E concentrate, however, such sterile animals produced and reared a litter of normal young.

In cases of vitamin E deficiency in the female rat, living litters were produced, however, they usually died within a few days. Examination of the pituitary showed degeneration changes suggestive of pituitary dwarfism with secondary cretinism.

Evans and Bishop (9) found striking results with lettuce, forty grams of green leaves being a curative dose. Whole wheat and oats also was found to be effective. Normal fertility animals in which sterility disease had been proven to exist was restored by 0.25 grams daily (250 mg.) of wheat germ embryo.

They were able to extract the curative principle

from curative food stuffs with wighty or ninety per cent ethyl alcohol and ether. This is singularly concentrated in the deep brown oil they obtained by ether from wheat embryo after preliminary treatment with hot eighty per cent alcohol. A daily dose of slightly more than one hundred millograms of this oil confers cures of the dietary sterility.

Vogt-Moller treated four cases of sterility with wheat germ oil and reported two cases which resulted in pregnancy, and two cases with unfavorable results.

Watson (32) reported thirteen cases of sterility treated with wheat germ oil in which he had no favorable results.

Watson and Tew (33) reported fifteen cases of sterility which were treated with wheat germ oil and recieved no favorable results.

From the above twenty eight cases cited by Watson, and he concluded that vitamin (wheat germ oil) therapy was of no value in the treatment of non-fertility.

## SUMMARY

Vitamin E was first discovered by Evans and his colleagues in 1921. It is a light yellow oil which is clear, solidifying about 0° centigrade, and does not develop crystals on long standing. The exact chemical nature of the vitamin is still unknown.

The greatest usefulness for the vitamin seems to be in recurrent and threatened abortions. There is an antiproteolytic factor present in the blood serum of aborting women which is responsible for the abortion syndrome. The use of vitamin E eliminates this factor and allows the pregnancy to continue to term. Approximately seventy five per cent favorable results have been recorded in the literature with the use of vitamin E in recurrent abortion, and a higher percentage in threatened abortion.

This syndrome was found to be more frequent from January to June of each year, due to a lowered percentage of vitamin E in the diet during this period.

In treating recurrent abortion with vitamin E, one should begin therapy as early in pregnancy as feasible and continue to term as it has no effect what so ever on labor. The dosage of such is still undetermined.

Shute, in testing the blood serum of eighty-two

cases of abruptio placentae, found that seventy-eight per cent had a deficiency in vitamin E and an excess of estrogenic substance. This condition was abolished within twenty hours following the administration of a potent vitamin E preparation. The best results were obtained when the patient presented no signs or symptoms of true toxemia of pregnancy.

The sterility which is produced with a diet deficient in vitamin E in the female can be cured because only temporary tissues are damaged, while in the male the resulting sterility is permanent. The early reproductive steps in the female are normal, and only the placenta diseased with resorption of the fetus. Experimental results in treating sterility with vitamin E have been very encouraging, while clinically the results have not been favorable.

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