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THE CURRENT METHODS OF MEDICAL MANAGEMENT OF THREATENED ABORTION.

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THE CURRENT METHODS OF MEDICAL MANAGEMENT OF THREATENED ABORTION.

In order to form a background for this controversial subject - consider first the scope and etiology of threatened abortion.

Threatened abortion has been defined by Crowder, Bills, Broadbent (1) and Silbernagel (2) as the occurrence of uterine bleeding, with or without uterine cramps, in a uterine pregnancy of less than twenty weeks gestation. After twenty weeks gestation the condition is called premature labor rather than threatened abortion.

According to various authors threatened abortion occurs in from 10 to 20 per cent of all pregnancies with multiparas having a higher percentage of threatened abortions than do primiparas. The explanation here being that there are a greater number of multiparas than there are primiparas. Williams (3) places the incidence of threatened abortion at 20 per cent; Malins (4) and Taussig (5) at 10 per cent and Malpas (6) at 18 per cent.

Meyer (7) states that 22 per cent of fertilized ova actually do abort. Of all pregnant women 82 per cent can expect to carry their pregnancy to term. Malpas (6) shows that after one abortion, 87 per cent of these women have a normal pregnancy. After two successive abortions; 62 per cent have normal pregnancies. After three abortions 27 per cent have normal pregnancies and after four abortions only 6 per cent can be expected to carry pregnancy

to term. After three successive expulsions of fetuses of less than twenty weeks gestation, the term "habitual abortion" is applied.

Of the 18 per cent of pregnancies that are threatened with abortion only 28 per cent actually do expel the contents of pregnancy. Colvin, Bartholomew, Grimes and Fish (8) observed 1570 cases of threatened abortion. Without hormones and special vitamins, other than the usual multivitamins routinely administered during the antepartum care 1,098 or 69.9 per cent of the women continued to term; 440 or 28 per cent, aborted; and 32 or 2.1 per cent delivered prematurely, either spontaneously or following induction of labor because of pathologic conditions threatening the safety of the mother. In only 3.9 per cent of the abortions was the cause undetermined. As a result of these studies by Colvin et al (8) it can be stated, theoretically that only 3.9 per cent of the pregnancies studied would have been benefited or salvaged by specific hormone or vitamin therapy. This observation, when applied to all pregnancies, means that 0.7 per cent can be benefited by hormones and vitamins. Hertig (9) has shown 13 per cent of abortions may be benefited by therapy. This gives a variance of from 3.9 per cent to 13 per cent on the value of therapy.

The etiological factors of threatened abortion are numerous and interact on each other making classification difficult. Hertig (9) states that 90 per cent of spontaneously aborted products reveal pathologic conditions absolutely or relatively incompatible with further development of the ova.

In the absolutely incompatible group, consisting of blighted or pathologic ova, early death of the embryo occurs. In the relatively incompatible group, made up of monsters, hydrocephalics, etc., in spite of defects, the embryo continues to grow for a period before abortion is accomplished.

Hertig (9) found that 46 per cent of his series of abortions were due to blighted ova. Mall and Meyer (10) placed the figure at 48 per cent. Irving (11) reported that 70 per cent of abortuses were due to developmental defects, 52 per cent being due to defects of the ovum and 18 per cent to defects of all aborted products which fell into the relatively incompatible group.

Deficiencies in the endocrine balance play a major role also, but these effects are not thoroughly agreed upon by the various authors nor are their laboratory methods standardized to give like results.

During the first three months of pregnancy progesterone is secreted by the corpus luteum. On about the seventeenth day of pregnancy the syncytium of the chorionic villi begin to take over the secretion of progesterone and the corpus luteum degenerates. Theoretically during this period of change of its production site the progesterone level is lower than normal, thus, allowing uterine contractions and expulsion of the fetus.

The results of stilbesterol deficiencies have been studied by Smith, Smith and Schiller (12). They state that stilbesterol brings about increased production of progesterone

during pregnancy, in all probability by the placental gonadotropin; however, no direct relationship between stilbesterol deficiencies and threatened abortion has been shown.

Javert and Stander (13) found that of 79 women with symptoms of threatened abortions or histories of habitual abortions, 69 per cent revealed a deficiency of vitamin C. In 72 per cent there was a deficiency of vitamin K in the blood. They claimed success in 24 of 25 women found deficient in vitamins C and K by administering these vitamins along with minerals.

Vitamin C deficiency in the typical case of scurvy is not of interest here. It is the subclinical case which is a factor in threatened abortion. In subclinical deficiency the diagnosis cannot be made from the typical findings of scurvy but is discovered through a thorough history of eating habits, the "capillary fragility" test, and urinary excretion. The history of eating habits will probably show an intake of less than 100 milligrams of vitamin C each day. The capillary fragility test is not specific for vitamin C deficiency but, if abnormal, adds to the diagnostic evidence. Urinary excretion levels differ with various authors but the significance seems to be not in how much vitamin C is in the urine but whether there is or is not vitamin C present. Abt and Farmer (14) theorized that the presence of vitamin C in the urine indicated that the tissues of the body were saturated and that the body reserve was adequate. Blood studies are done for vitamin C determinations but the methods and values are not

standardised. It has been shown by Teel, Burke and Draper (15) that the vitamin C concentration of the blood is low in a considerable proportion of pregnant women and that the reduction is more conspicuous after the twenty-eighth week of gestation. Only about half of their subjects had normal values.

Bodansky and Bodansky (16) report that the blood level of vitamin C varies between the mother and fetus. They report a ratio of almost three to one higher concentration in the fetus. Walbock and Howe (17) have found the function of vitamin C in some way intimately concerned with the normal production of intercellular material. A deficiency of vitamin C is accompanied by loss of ability of supporting tissues to produce and maintain intercellular substances. Cementing and supporting materials are reabsorbed normally, hence, a deficiency of vitamin C leads to lack of new formation of intercellular material. This condition would then contribute to fetal abnormality which in turn may cause abortion.

Vitamin K deficiencies can give symptoms of threatened abortion. Here, rather than uterine contractions, we have bleeding that fails to stop. If permitted to continue the patient would become anemic, anoxic and shocky. Any one of the conditions could produce abortion.

For the diagnosis of vitamin K deficiency we have as an index the amount of prothrombin in plasma. Quick's (18) method of determination involves the determination, under standard conditions,

of the time required for clotting of recalcified plasma in the presence of an excess of added thromboplastin. By reference to a chart the prothrombin clotting time may be converted into prothrombin percentage of normal. Thus, a prothrombin time of twelve seconds corresponds to 100 per cent of the normal amount of prothrombin; a reading of twenty seconds corresponds to 30 to 40 per cent; forty seconds, to 10 per cent; seventy seconds to 5 per cent, etc. Prothrombin time of forty seconds according to Quick's method may be considered definitely abnormal, being accompanied by a propensity to hemorrhage.

Vitamin E has been studied in rats and rabbits and found to be essential for reproduction. This, however, is not true of the human being. Experimenters have determined values for vitamin E in human tissue but have been unable to prove that it has the same action as it does in rats. Clinically, blood determinations are not done because of the lack of knowledge of vitamin E and its action and because the methods of determination are complicated though their values are in close agreement. Treatment by vitamin E, therefore, is not based upon laboratory findings but upon therapeutic trial.

The function of the thyroid is greatly increased during pregnancy. The exact reason for this increase is not clearly understood. Bodansky and Bodansky (16) determined that the per cent of increase of the female body weight in pregnancy is much less in comparison with the increase of thyroid activity. It is

thought that an endocrine stimulation is produced by the anterior pituitary gland. If this increased activity of the thyroid is not present the progesterone level also is decreased thereby, permitting uterine contractions and expulsion of the fetus.

Some of the other causes of threatened abortion are: - amniotic adhesions, white infarct formation, placenta praevi, cord torsion or knots, congenital weakness, acute infections, excessive carbon dioxide content of the blood, acute or chronic decidual endometritis, retroverted uterus, anaesthesia, malnutrition, and salicylism.

Delee and Greenhill (19) state that a special predisposition must exist to explain those cases in which a slight jar, a misstep, a nervous shock, an automobile ride or other mild occurrences initiate abortion. At other times the severest injuries, mental and physical, are sometimes inflicted on the gravida without disturbing the uterus.

Operations imply trauma, but unless some predisposition exists they usually do not affect the pregnancy. Fibroids have been removed from the pregnant uterus and amputations of the cervix have been performed without inciting contractions. On the other hand, a slight operation on a distant organ may result in miscarriage. Ovarian tumors have repeatedly been extirpated safely, as have also breast and other tumors. Appendicitis is especially prone to cause abortion, probably because of infection. The removal of both ovaries during pregnancy has proved that the ovaries are not necessary for

the continuation of pregnancy after the third month nor are they necessary for labor. Overdoses of X-ray, antitoxic serums and vaccines have been known to cause abortion.

If a pregnancy is normal, uterine hemorrhage and uterine pains signify that interruption of gestation threatens. Early diagnosis of pregnancy is made difficult by a contracting uterus because other conditions may be simulated i.e. uterine fibroids. On bimanual examination, the large, contracting and relaxing uterus, the beginning softening and unfolding of the cervix and the bloody discharge show that some abnormal process is taking place. The rule is to treat every case of hemorrhage, after a period of amenorrhea in a woman capable of reproduction, as one of threatened abortion.

Colvin, Bartholomew, Grimes and Fish (8) found the type of bleeding to be of prognostic value. In those patients who had a brown bleeding initially, 55 per cent aborted and in half of these the product was of the blighted ovum type. In those patients who had bright red bleeding initially, often of considerable amount, occasionally tapering off to brown before recurring as bright red, only 10 per cent aborted and 87 per cent continued to term.

Although several methods for the detection of a viable embryo have been described, an entirely satisfactory procedure for detecting life or death of the embryo in cases of threatened abortion is not known.

Fletcher (20) studying vaginal smears, felt that the presence of basal-layer cells with their characteristic appearance

and staining qualities were indicative of exfoliation of mucosa associated with death of the ovum.

Frank and co-workers, (21) whose work was confirmed by Polonsky, (22) were the first to show that intrauterine death of the ovum is accompanied by a fall in the amount of "free" estrogen in the blood stream. Guterman (23) advocated a test for progesterone activity by estimating the level of pregnandiol excretion. This level provides a reliable index to progesterone metabolism. Rutherford (24) from a study of endometrial biopsies obtained from the lower uterine wall, was able correctly to determine life or death of the ovum in 90 per cent of cases of threatened abortion. Biological tests have proved unreliable, inasmuch as the result depends not upon life of the embryo but upon the viability of the chorionic villi. Single bimanual examinations early in pregnancy are notoriously unreliable. These methods of detecting viability of the embryo are time consuming and expensive; they require special assistance, and the results are limited in accuracy.

Colvin et al (8) found that a fairly high percentage of accuracy in determining the prognosis in such cases is possible by a careful consideration of the knowledge gained from an evaluation of symptoms and the height of the fundus over a period of time. The variable subjective symptoms of pregnancy may, or may not, be of prognostic value.

In the discussion of the treatment of threatened abortion, the diagnosis must first be established. If a period has been missed, a case of vaginal bleeding, with or without uterine cramps, in a woman of reproductive age must be considered threatened abortion until further diagnostic examination can be performed. Heuser, C. H. et al. (25) states that bleeding at about the time of the first missed period should not be considered threatened abortion, since endometrial bleeding at the site of implantation has been shown to occur normally and might well be sufficient to result in outside bleeding at this time. Many authors have thought to have prevented abortion in early pregnancies only to find on subsequent examination that the pregnancy did not exist.

DeLee (19) hospitalized his patients for examination. He does not do a bimanual examination of the pelvis but does use either a bivalve speculum or two retractors - with care of course - to expose the cervix. The legal aspect of doing a speculum examination should be covered by a signed written statement and the examination made in the presence of witnesses. When fetal products protrude through the cervix, the whole conceptus should be removed. If nothing is seen through the speculum or retractors, the diagnosis is threatened abortion. Patients are put on bed-rest with an ice bag on the abdomen and with the feet elevated twelve inches. The barbituates should be given to quiet the patient. The bowels are not disturbed for the first three days. On the fourth day liquid petrolatum is given and its action aided by an olive oil

enema, to avoid the patients straining to evacuate hard feces. If bleeding ceases the patient may be allowed more freedom in bed and after five days may get up, but should resume her duties slowly, returning to bed on the slightest show of blood. However, if the patient continues to bleed more than seven days, he sees no point in keeping her in bed any longer. She should be permitted to get up and move around, because almost certainly the ovum is abnormal and nature will expel it anyway. DeLee does not mention the type of barbituate he uses. However, Crowder et al (1) have found that demerol produces nausea and vomiting in a high percentage of cases but found pantapone to be more useful as a sedative. Some authors have used morphine. In small doses morphine stimulated uterine activity though in large doses uterine contractions may be inhibited.

In addition to the above procedures various practitioners continue their study of the patient along different channels. Colvin et al (8) did not believe the urinary pregnandiol test to be of any significance in treatment; however, as a prognostic aid they feel it is of value. Their studies were based upon signs and symptoms of a viable fetus rather than urinary pregnandiol excretion. Greenhill (26), Yanow, Soule, Meyerhardt (27), Davis, Fugo (28), Guterman, Tulskey (29), Browne, Henry and Venning (30) feel that the value of urinary pregnandiol excretion is more than of prognostic value. In cases of less than 10 mg. excretion in twenty-four hours by the Guterman method they feel the prognosis

is bad but feel that progesterone should be administered. Much work has been done with the use of pregesterone in the treatment of threatened abortion. Enthusiasts have recorded glowing reports of salvage percentage of threatened abortion cases. However, when these experiments are repeated by other workers the results cannot be duplicated. This is especially true where the dosage of pregesterone is 10 to 25 mg. per day by mouth. The prophylactic use of progesterone during pregnancy does not seem warranted because of the small percentage of patients who might possibly be helped and the expense to the patient. Davis, Fugo, Guterman and Tulskey feel that dosages of 50 to 120 mg. of progesterone daily may have some effect. They base their beliefs upon the observations of Davis and Fugo (28) who found the normally pregnant patient excretes 40 to 50 mg. of pregnandiol each day during mid pregnancy, it is likely that three to four times this amount is present in the body; therefore dosages of 25 mg. and less seem inadequate. The worth of massive doses of progesterone has not been proven although some encouraging reports have been made by enthusiasts.

One definite contra-indication to the use of progesterone according to Falls et al (31) is a woman expelling a pathologic ovum. Pathologic products should be allowed to be expelled from the uterus without delay. The treatment with progesterone of a pathologic ovum may produce a mole which must be surgically removed.

Karnaky (32), Rosenblum, Melinkoff(33) and Smith (34) believe the use of stilbesterol is of significance in the treatment

of threatened abortion. Smith (34) used a definite pattern in the treatment of her patients and reported 78 per cent of her patients carried pregnancy beyond twenty-eight weeks. Karnsky (32), Rosenblum and Melinkoff (33) did not use a schedule and gave large doses. Karnsky did not give any salvage percentages but he feels that regardless of the initial dose (500 mg.) or total dose (120,730 mg.) it is impossible to abort a woman. Rosenblum and Melinkoff using large doses of stilbesterol reported a salvage percentage of 86 per cent in eight-one cases.

The rationale for the use of stilbesterol or diethylstilbesterol for the treatment of threatened abortion as reported by the Smiths (12) is the stimulation of the production of progesterone. If such was the case then pregnandiol excretion levels should be elevated in patients receiving stilbesterol. Davis, Fugo (28) and others found no alteration in the normal level of pregnandiol excretion. If this is true there is no theoretical basis for the use of stilbesterol in the treatment of abortion. Smith (34) viewed her 78 per cent salvage as being of no significant advantage when compared to 70 per cent who would carry to term without any treatment. Crowder, Bills and Broadbent (1) observed one hundred patients. Thirty-seven were treated with bed rest and sedation and sixty-three were treated with bed rest, sedation and stilbesterol. The dosage of stilbesterol was 25 mg. every thirty minutes for six doses then 100 mg. daily until asymptomatic for

twenty-four hours, then 50 mg. daily to the twenty-eighth week of pregnancy. They found that 51 per cent treated with bed rest, sedation and stilbesterol and 57 per cent treated with bed rest and sedation retained the pregnancy to viability. In view of these reports it would seem that stilbesterol is of no value in treatment of threatened abortion.

Vitamin E was first used as a treatment for habitual abortion. Wheat germ oil is used as a treatment without specific purpose. Silbernagel (2) believes that the salvage of life be it pre- or post-natal is reason enough for treatment. He believes that our search for a method of stopping it after it has begun, should be changed to finding a method of preventing spontaneous abortion. Silbernagel has also found that vitamin E and wheat germ oil are not one and the same. Vitamin E is contained in wheat germ oil but so are many other substances. It is this observation that has lead to the difficulty in trying to repeat the observations of Currie (35) and Vogt-Moller (36). The vitamine E content of wheat germ oil has not been standardized. The possibility of wheat germ oil containing other substances may affect the results of these observations.

Silbernagel and Patterson (37) gave two three minum capsules of wheat germ oil concentrate throughout the entire pregnancy. Of the two hundred and forty-five patients observed under this treatment twenty-four or 9 per cent threatened to abort; ten patients of the twenty-four went on to pregnancy at term;

fourteen, or 5.8 per cent, aborted. No control was used in this experiment.

Silbernagel (2) reported that alpha tocopherol acetate, when given orally in a dosage of 12 to 24 mg. per day, was found to be effective in 16.7 per cent of the cases. The parenteral use of 200 mg. each day was effective in 20 per cent of the cases. When distilled tocopherols were given orally in a dosage of 150 to 200 mg. each day they were found to be effective in 42.8 per cent; 200 mg. of alpha tocopherol acetate administered parenterally, and 150 to 200 mg. of distilled tocopherols administered orally resulted in a continuation of pregnancy in 85.7 per cent of the patients studied. It must be remembered that while promising, the necessity of parenteral administration of any agent limits its value.

Paine (38) and Clayton (39) feel that the use of vitamin E or wheat germ oil concentrate is unnecessary. They cite cases of severe nausea and vomiting in which the patient shows many symptoms but does not abort spontaneously.

Thyroid deficiency of the pregnant mother could cause symptoms of threatened abortion. It is known that the anterior lobe of the pituitary gland is the master control of the other endocrine glands. However, there is so much inter-play by the actions of the glands that a hypothyroid condition would affect the pituitary by not secreting enough of a trophic hormone to the pituitary. By this system of relays the gonadotropins would be decreased. In this condition, as has already been proven, a

decreased progesterone level is not a good prognostic sign for the continuation of a pregnancy. A hypothyroid condition is not often found in pregnancy but is found more in sterility problems. However, to prove a hypothyroid condition it is possible to obtain a basal metabolic rate which is, at best, of questionable value in border-line cases. Blood cholesterol levels can also be obtained, but here again, in border-line cases the test is of little or no value. The sleeping pulse is of more value than either of the above tests, but here again the border-line situation requires a more accurate diagnostic method. The iodine pick-up test is relied on for accuracy. This per cent of pick-up when compared to a chart gives an index of the function of the thyroid. If the above tests and especially the iodine pick-up are low then thyroid extract is indicated. No set dosage is known but each case presents its own problem of control.

The use of vitamin C in threatened abortion has as a basis for such treatment the findings of Teel, Burke and Daper (15) who found that in more than half of their patients there were low blood levels of vitamin C. In support of this is the work of Javert and Stander (13) who found that in patients with vitamin deficiencies threatened abortion could be prevented by the administration of vitamins and minerals. Bodansky and Bodansky (16) have found that a deficiency of a vitamin interrupts much of the endocrine balance. Thus it would seem possible that determinations of blood ascorbic acid may be indicated in threatened abortion. In deficient

cases of vitamin C should be administered orally.

The same that is said of vitamin C can and should be said of vitamin K. Here the test for deficiency is more easily made and the availability of vitamin K is equal to that of vitamin C.

SUMMARY

It would seem that the treatment of threatened abortion is unsatisfactory and such appears to be the case. Experiments have been conducted many times with reports that show very significant beneficial results; however, others have not been able to obtain the same results and in many cases show no beneficial results. This same cycle has been going on for years and still the worth of advocated treatments have not been proven.

The only concrete information now available is that approximately 16 per cent of all pregnancies threaten to abort. Of those who threaten to abort about 70 per cent continued to term with normal pregnancies; about 3 per cent deliver prematurely. The remaining 28 per cent actually expel the contents of pregnancy. Of this 28 per cent only about 4 per cent could not be explained while the others have definite deformities not compatible to a successful gestation.

CONCLUSION

1. About 16 per cent of all pregnant patients are threatened with abortion. Seventy per cent of this 16 per cent will carry to term.
2. The most dangerous period for abortion is about the eighty-first day of pregnancy.
3. Only 4 per cent of the 16 per cent can not be explained and, therefore, could possibly be aided by therapy.
4. Bed rest and sedation is as good a treatment as is bed rest, sedation and progesterone, stilbesterol, vitamin C, K or E, or thyroid extract.
5. The random prophylactic administration of progesterone, stilbesterol, excess vitamins and thyroid extract does not seem warranted considering only about 0.7 per cent could possibly be benefited by this treatment.
6. This percentage of loss of life without an explanation and apparently no treatment demands further investigation.

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