Missed abortion following treatment of threatened abortion with progestational agents

Marlene E. Lengner

University of Nebraska Medical Center

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MISSCLE ABORTION, FOLLOWING TREATMENT OF THREATENED ABORTION WITH PROGESTATIONAL AGENTS

Marlene Lengner

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College of Medicine, University of Nebraska

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Omaha, Nebraska

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In 1921 Litzenberg applied the term missed abortion to all cases of death of the fetus in utero before viability with no effort at expulsion within the usual time of an ordinary abortion, the expulsion considered occurring up to 8 weeks after death.

Eastman, 1961, defines a missed abortion as the retention, two months or more after its death, of an early intra-uterine pregnancy.

Litzenberg states that in his cases hemorrhage was a prominent finding, giving the ovum a hemorrhagic appearance; but hemorrhage may be entirely absent. He noted that in the placenta infarcts were numerous, sometimes occupying nearly the whole organ, suggesting the probable cause of fetal death. One of the great dangers of missed abortion, he thought, was due to degeneration of the blood vessel walls which could be so completely destroyed that uncontrollable hemorrhage could occur. Disappearance or marked diminution of the amniotic fluid without rupture of the membrane was the rule.

He noticed the frequency of discrepancy between the size of the placenta and the fetus, the former being often as large as the placenta of a fetus a month or more older than the one found. This was considered to be due to connective tissue increase, hemorrhage into the placenta and a curious true growth of the placenta after the death of the fetus. He felt that when
the fetus died, especially in the early weeks, the chorion and decidua may go on growing because they are nourished by the maternal blood circulating in the intervillous spaces which may continue for a long time. LaVerge observed karyokinesis indicating cell multiplication rather than hypertrophy. He noticed that the inner layer of the villous epithelium, which is not in direct contact with maternal blood, is an early victim to coagulation necrosis; but the outer syncytial layer, bathed in maternal blood, is preserved much longer until thrombosis takes place shutting off the blood supply to the intervillous spaces. In the second half of pregnancy Von Franque asserted that this interesting phenomenon of continued growth after the death of the fetus did not occur. Microscopic studies showed all stages of necrosis of tissue, placenta, decidua, amnion, blood vessels, the fetus and even uterine walls. If the ovum remained in the uterus for a long time, drying out or mummification occurred.

By Litzenberg's definition, the symptoms of missed abortion are lack of increase in size of the uterus, cessation of fetal movements and other signs of pregnancy. Regression changes in the breasts also take place. Hemorrhage is a very inconstant accompaniment of missed abortion, but in some form or another it usually complicates the condition, sometimes constituting a great danger.

Eastman views the cases of missed abortion as follows. He states that in the typical instance, the first few months of
pregnancy are completely normal: amenorrhea, nausea and vomiting, breast changes, and growth of uterus. All goes well until the ovum dies, when there may or may not be vaginal bleeding or even symptoms denoting a threatened abortion, which subside. It is then noted that the uterus seems to remain stationary in size and the breasts regress. The patient is likely to lose a few pounds in weight. Careful palpation and measurement of the uterus reveal the fact that it has not only ceased to enlarge but is growing smaller, from the absorption of amniotic fluid and maceration of the fetus. Most patients are symptomless during this period, except for the persistence of amenorrhea. Some, however, complain of lassitude and depression. If the missed abortion terminates spontaneously, as most do, the process of expulsion is quite the same as in any ordinary abortion. The product, if retained several weeks after fetal death, is a shrivelled sac containing a highly macerated embryo, and if retained for months or years, it appears to be a mass of old tissue and blood with areas of dense calcification. He states that the cause of missed abortion is not known.

N. E. Borglin² (Sweden) stated in 1957, that there is nothing essential to distinguish missed abortion with a demonstrable embryo from an abortion occurring after more than 8 weeks in which the embryo has been absorbed. The duration of retention is often difficult to assess because it is not easy
and is often impossible to decide whether the embryo has died. The strikingly large number of ordinary abortions suggests that a missed abortion is only a variety of ordinary abortion. It is suggested that the term missed abortion be reserved for fetal death after the fourth month of pregnancy with retention of the dead fetus for at least six weeks. Many prefer conservative treatment, in other words, waiting for a spontaneous abortion, especially because of the risk of hemorrhage in surgical intervention, which is partly due to the frequently poor contractile power of the uterus in this condition. This inadequate power of contraction probably also causes retention of the dead ovum. Spontaneous abortion usually occurs with only slight loss of blood, because at this stage the vessels of the uterine endometrium have thrombosed and the uterus has recovered its power of contraction. The severe loss of blood on surgical evacuation of the uterine cavity and the copious bleeding sometimes accompanying spontaneous abortion, can occasionally be ascribed in part to hypofibrinogenemia.

The characteristic features of a missed abortion are considered as low spontaneous myometrial activity, low oxytocin sensitivity and danger of bleeding after surgical intervention mainly due to atony, but sometimes to afibrinogenemia. In view of the inactive state of the myometrium, which is often thin and fragile, and of the successful estrogen treatment of
a big group of missed abortions, it is felt that it is justified to conclude that lack of estrogen is an etiologic factor.

Cassmer has shown that when the fetus dies and the placenta is undamaged, the conditions predispose to missed abortion. On the basis of these findings, it was hypothesized that human spontaneous missed abortion is due to fetal death and the consequent changes in the hormone production of the relatively undamaged placenta. For a time after fetal death, the myometrium remains progesterone dominated (Stage 1), and effective activity cannot develop. Sooner or later, placental hormone production ceases; and being devoid of both hormones, the myometrium is "castrated" (or at least "non-pregnant") and unable to work (Stage 2). Estrogen domination will not occur until the myometrium is again stimulated by estrogen, either produced by the ovaries or given therapeutically. The etiology provides a clue to its treatment. In Stage 1, treatment with estrogen and oxytocin has no effect. Destruction of placental function alone (e.g. by intrauterine injection of hypertonic solution) removes the progesterone block. Estrogens may be useful, though they may not be necessary. Stage 2, estrogen alone usually starts the abortion and surgical intervention is rarely necessary.

The validity of this theory of the etiology and treatment of missed abortion was tested by these workers in thirteen consecutive patients. To accelerate abortion in seven of the thirteen patients, oxytocin was given as an I.V. drop. The purpose
of estrogen treatment in Stage 2 was to build up a potent myometrium from a "castrated" state and this necessarily takes several days. The estrogen, therefore, should be continued for 6 - 10 days. If abortion has not occurred after ten days, the hormonal state should be rechecked.

Their hypothesis of missed abortion was supported by the fact that two stages, characterized by different hormonal condition, could be distinguished and that selected treatment was successful on all patients.

Roland noticed that almost all patients who aborted had falling or low urinary hormone excretion before the onset of bleeding or other disturbances. When the preconceptional endometrium showed poor premenstrual secretory activity and urinary hormone excretions were correspondingly low, substitutional endocrine therapy during pregnancy appeared to salvage a sizable percentage of pregnancies. When the preconceptional endometrium showed poor secretory activity and normal levels of urinary hormone excretion, endocrine treatment during pregnancy had no effect. When urinary hormone excretion levels, particularly those of estrogen and pregnanediol were normal at onset of bleeding, percentage of pregnancies with a favourable outcome was much greater. Workers who feel that a considerable percentage of spontaneous abortion is due to maternal factors, have found hormone determinations of substantial importance.
Casamé reported in 1959 that in therapeutic abortions in mid-pregnancy he ruptured the membranes and pulled down the umbilical cord, which was ligated and cut. The foetus and the placenta were left in the uterus for three days and then they were removed through the cervix. In these cases with "isolated placentae" the urinary excretion of estrogens decreased rapidly. Three days after fetal death the urinary estrogens had fallen to 30% of their previous value, and the estrogens in the placenta had disappeared. Some workers believe that the fetus may be responsible for estrogen production. On the other hand, pregnanediol fell much less and after three days, the output was still 87% of the previous value. During these three days no uterine activity was observed. This indicates that if the foetus dies before the placenta, the production of estrogen ceases before that of progesterone. Because Casmer removed the whole conceptus after three days, we do not know from his studies how rapidly and to what levels the production of estrogen and progesterone may fall later.

When the fetus and placenta die simultaneously, as in saline-induced abortions, the placental production of estrogen and progesterone falls rapidly and simultaneously. The withdrawal of progesterone which affects only the excitability of the myometrium, acts more quickly than does the withdrawal of estrogens, which has the slower task of building up the
myometrium. Then, when placental function is abruptly destroyed, the effect of progesterone on the myometrium is dominated by estrogen for a time (Fig. 1).

Fig. 1

Under these conditions, contractions start and abortion is rapidly completed, thus, missed abortion does not develop. The mechanism must be similar in spontaneous abortions where fetal death is a consequence of placental death. On these findings was based the hypothesis that human spontaneous missed abortion is due to fetal death and the consequent changes in the hormone production of the relatively undamaged placenta. For a time after fetal death the myometrium remains progesterone dominated, and effective activity cannot develop. Sooner or later placental hormone production ceases; and, being devoid of both hormones, the myometrium is virtually "castrated" and unable to work.

Dr. M. Doyle states that daily determinations of the urinary excretion of pregnanediol and estriol before and after
intrauterine death in missed abortion showed that estriol excretion falls well before pregnandiol excretion. If the hypothesis is correct, two stages of missed abortion should be found:

Stage 1. with a progesterone dominated myometrium resulting from partial functioning of the placenta, and characterized by slight reduction of pregnandiol and greater reduction of estrogen excretion.

Stage 2. in which the myometrium is "castrated," characterized by severe reduction of both estrogen and pregnandiol excretion.

It is not known how long after fetal death, placental progesterone production can be maintained. The time after fetal death, therefore, does not necessarily indicate in which stage a case is.

The hormonal function of the placenta in missed abortion is not fully understood. Pregnancy tests, based on the chorionic gonadotrophins in the urine, are often negative but sometimes positive. The excretion of urinary pregnandiol is often low but occasionally normal or only slightly reduced. The urinary excretion of estrogen is very low, thus the hormonal function of the placenta, judged by the urinary excretion of these three hormones, is often severely impaired, though occasionally this impairment is only slight.

Stouffer and Aschworth believe that patients with intrauterine retention of a dead fetus are potential candidates for
development of hypofibrinogenemia. This disease results from a constant process of laying down of fibrin in the intervillous spaces of the placenta in the dead fetus syndrome and from local deposition of fibrin at the site of placental separation in cases of abruptio placenta.

Beginning with the third week after apparent fetal death, the concentration of fibrinogen in the plasma should be determined weekly. It is postulated that the fetus that is at least thirteen weeks old can develop the condition of hypofibrinogenemia. If the concentration of fibrinogen falls below 50 mg./100 ml., the uterus should be emptied promptly. At least 4 grams of human fibrinogen and several units of compatible whole blood should be immediately available. After emptying the uterus, close attention should be given to blood loss from the vagina. Present evidence, however, indicates that once the uterus is empty the process of defibrination ceases and hemostasis can be maintained without further administration of fibrinogen.

Zielinska (Poland, 1958) found four cases of hypofibrinogenemia in 20 pregnant women with a dead fetus. Fibrinolysins were also found. These usually appeared four weeks after the moment of death of the fetus. The behavior of fibrinogen and fibrinolyasin levels in these women is characteristic. The fibrinogen level may remain high despite the presence of
fibrinolysins. Thanks to which the hypofibrinogenemia does not appear as often. During labor a considerable decrease in fibrinogen level takes place. After three hours, the level increases and after 24 hours it returns to normal.
PROGESTERONE AND PROGESTATIONAL AGENTS

The main actions of progesterone are directed toward preparation of the uterus for reception of the fertilized ovum and maintenance of a favorable environment for its growth and development. Studying the biosynthesis and metabolism of progesterone and its interrelations with other steroid hormones, Plotz and Davis (Univ. of Chicago) found that cholesterol of two sources is available in an endocrine gland for synthesis of progesterone: (1) cholesterol synthesized within the endocrine gland and (2) plasma cholesterol, which is derived from dietary cholesterol and cholesterol synthesized in the liver, the rate of absorption of plasma cholesterol by the corpus luteum and placenta was found to be efficient and rapid. Progesterone itself is not excreted into the urine, but its principal metabolite, pregnanediol, appears in large and increasing amounts in the urine of pregnant women, reaching peak values of 70-90 mg./24 hours during the last part of the third trimester. Pregnanalone, another metabolite of progesterone, follows a similar excretion pattern. Progesterone secreted into the circulation from the glands disappears rapidly from the blood. Similarly, when progesterone is administered I.M. the hormone and/or its metabolites diffuse promptly from the blood circulation into the fat compartment of the body. These
findings explain (1) the failure of large doses of progesterone injected I.M. to raise the blood level of progesterone and the rapid disappearance of progesterone from the blood after I.V. injection and (2) the delayed excretion of progesterone metabolites after I.V. injection.

The sources of endogenous progesterone are as follows: The ovaries, the adrenals, and in pregnancy the placenta are the sites of progesterone production in the female.

The progesterone produced in the ovary comes primarily from the corpus luteum. The following biochemical results are presented as evidence (1) The relatively large amounts of progesterone in human corpora lutea of the menstrual cycle and of pregnancy, (2) The increased pregnanediol excretion after formation of the corpus luteum, as well as the drop in pregnanediol after physiological repression or removal of the corpus luteum.

Through the work of Hechter, it is known that progesterone occupies a key position in the biosynthesis of the adrenal cortical hormones. This does not necessarily mean that the adrenal cortex must secrete progesterone, however, indication that secretion of the hormones may occur has existed for some time. Clear cut evidence for the production of progesterone by human adrenal cortex was presented by Short, through the demonstration of progesterone in adrenocortical venous blood after ACTH stimulation.
There is no question now that the human placenta produces progesterone. With the growth of the placenta, the progesterone production increases. Experimental evidence is:

1. Presence of progesterone in placental tissue at all phases of gestation;
2. Increase in progesterone concentration in arm vein blood during pregnancy, with rapid decrease after removal of the placenta;
3. Increase in pregnanediol excretion during pregnancy. Rapid decrease follows removal of the placenta;
4. Increase in pregnanediol concentration in the arm vein blood during pregnancy;
5. Increased progesterone levels in fat tissue during pregnancy;
6. Maintenance of pregnancy with abnormal pregnanediol excretion after removal of the corpus luteum or of the ovaries in early pregnancy;
7. No initial change of pregnanediol excretion after operative removal of an abdominal pregnancy, the placenta being left in situ. After expulsion of the placenta in a normal delivery, pregnanediol excretion drops immediately;
8. No change of pregnanediol excretion after artificially induced fetal death with the placenta left in situ. Rapid decrease following removal of the placenta;
9. Normal pregnanediol excretion in Addison's disease or
following bilateral adrenalectomy; thus the adrenals are not the main source of progesterone.

(10) Higher levels of progesterone in the uterine venous blood than in peripheral venous blood at the end of pregnancy;

(11) Higher levels of progesterone in the umbilical venous blood than in the blood of the umbilical arteries;

(12) Presence of progesterone in a chorion epithelioma;

(13) Conversion of $\Delta^5$-pregnenolone to progesterone by placental tissue in vitro;

(14) Conversion of $\Delta^5$-pregnenolone and cholesterol to progesterone in placental perfusion experiments.

Effects of Progesterone on Endometrium

The withdrawal of progesterone near term has been thought by many workers to be a factor for the onset of labor. Although few dispute the relaxing effect of progesterone on the myometrium, the diminution either of progesterone in the blood or of its metabolic products in the urine near labor has never been well established. In vitro studies in human pregnant and non-pregnant myometrium have revealed that the inhibiting action of progesterone can be antagonized if enough oxytocin is added in the muscle bath. On the other hand oxytocin stimulated contractions can be abolished if enough progesterone is added.

Concerning the action of the progesterone on the endom-
etrium, Brux noted: (a) The appearance of glycogen in the basal part of the cells of the glands (lucid zone) later at the apical part; (b) The formation of connective spindles with cellular "puffs" which give a lacy aspect to the glands; (c) Cellular modification of the endometrial stroma, evidenced by a widening of the cytoplasm of the fibroblastic and reticular cells, especially in the superficial zone; (d) and, surrounding these, gradually formed coiled arteries.

These endometrial transformations appear progressively following ovulation, reaching their maximum at the 26th day of the cycle, with glycogen in pools in the lumen of the tubes and the appearance of a mucoid secretion in the cells. Hemorrhagic ruptures, marked edema and an invasion of polymorphonuclear leucocytes are the expression of the very near breaking down of the endometrium. Progesterone will produce certain morphologic changes in the endometrium only if there is adequate estrogen stimulation.

A group of workers in New York did cytological examinations of the smears of surgical castrates under estrogen and progesterone therapy. They found that the cell types are often more highly proliferated than usual in the luteal phase of the normal menstrual cycle. It was not an infrequent finding in patients under hormone therapy that some parts of the endometrium showed more marked secretory changes than others.

The endometrial specimens were taken two weeks after the
commencement of progesterone therapy, and the histological findings were classified into the following four groups.

(1) Proliferative changes only;

(2) Minimal evidence of secretory change. Several glands exhibited no evidence of secretory change, whereas some of the glands show subnuclear vacuolization with central position of nuclei;

(3) Early secretory changes (delayed for the time of administration of progestational agents - 14 days). Practically all glands show the following features: a. subnuclear vacuolization, b. central position of the nuclei, c. supranuclear vacuolization, d. minimal evidence of accumulated secretion, e. relatively sharp nuclear border at the gland lumen, and f. early tortuosity of the glands;

(4) Late secretory changes (compatible with the late luteal changes of the normal menstrual cycle). Practically all glands show the following features: a. basal position of the nuclei; b. supranuclear vacuolization of the cytoplasm; c. marked accumulation of glandular secretion; d. loss of sharp cellular borders with "melting" of the cytoplasm into the gland lumen and; e. well-developed tortuosity of the gland.

The 19-nor steroids have been widely used for ovulation inhibition. Twenty day courses of the 19-nor steroid combined with an estrogen are currently being employed. There have been several reports about the endometrial changes induced by the cyclic
administration of these compounds. With norethynodrel there is a very early appearance of glandular secretion similar to that seen in the early part of the normal luteal phase. However, after the appearance of intraepithelial vacuolization, the glands cease to progress and instead become small, involuted, and inactive in appearance. The stroma becomes markedly edematous, with variable degrees of pseudo-decidual reaction. Rice-Wray and others have studied the effects produced by the cyclic administration of norethindrone, and also emphasize the regressive changes and irregularity of glandular secretion. With both compounds advanced atrophy has been observed. Surprisingly, these endometria have a remarkable capacity to rebound immediately to functional and histologic normalcy once treatment is stopped.

Some of the events which take place during the normal cyclic evolution of the endometrium are as follows: glandular growth and tortuosity increase gradually reaching a maximum in the last quarter of the cycle. Secretory changes which begin on day 16, reach a peak on day 19 and 20, and then regress rapidly during the next two days. In the meantime stromal edema makes its appearance and pseudodecidual changes become apparent. The sequence of events during therapy with norethynodrel is glandular regression which seems to appear by day 14-16 and glandular regressive changes are far advanced by day 21. There is an almost complete disappearance of secretion by day 19-21.
except in an occasional isolated gland. Stromal edema is quite marked from the outset and becomes intense at day 19-21. Pseudodecidual change begins to appear about day 21, and remains patchy and low in its degree of development. This is a reaction markedly similar to that of progesterone.

Barnes states that such important differences between the myometrium of one area contrasted with the myometrium of another area indicates that the uterus throughout most of pregnancy cannot act as a unit. In contrast to the remainder of the myometrium, the muscle beneath the placenta apparently has a relative paralysis, a factor which may contribute to the fact that premature separation of the placenta is a comparatively rare accident rather than being a common place clinical phenomenon. In seeking an explanation for such differences, it would be quite logical to postulate that the placenta itself contributed the differentiating factor and that some placental ingredient permeated the myometrium locally and altered its chemical composition and hence its contractile ability.

Since it has been demonstrated in the estrogen treated animal that the administration of progesterone will elevate the resting membrane potential as well as the total tissue potassium of the myometrium, the postulate has been advanced that placentally produced or stored progesterone reaches the cells of the adjacent myometrium in greater concentration than it reaches the rest of the myometrium contributing to this relative paralysis. This
hypothesis gains support from the recent documentation of the effect of progesterone on other human smooth muscle. It has suffered, however, from the fact that endogenous progesterone has never been recovered from the myometrium by any of the previously available techniques. Zander makes the specific statement that "it has never been possible to demonstrate nonlabeled progesterone or either of the $\Delta^\beta$-3-ketopregneneol-one isomers in the target tissues, uterine muscles, and mucosa." Using labeled progesterone, Davis and Plotz and Zander indicated that only a very limited amount of administered hormone is present in the muscles (eleven to eighteen weeks of pregnancy).

Using gas-liquid phase chromatography, a technique has been developed for measuring tissue progesterone levels. Because this procedure requires fewer preliminary steps in purification and extraction, the placental levels found have been approximately twice those previously reported, and human myometrium from the term or near-term pregnant uterus has been found to have a concentration of progesterone varying from 0.05 to 0.63 micrograms per gram wet weight tissue.

Norethynodrel, a 19-nortestosterone derivative, has three main properties: (1) Progestational action when administered orally; (2) Inherent estrogenic effects and (3) Inhibition of the pituitary gland. It has a unique action on the endometrium. It has been thought to exert a progesterone effect
on the human endometrium without estrogenic priming, although it has been uncertain whether all components of the endometrium reacted similarly to the compound.

The following experiments were done on normally ovulating patients: Ten patients were given 10 mg. daily from the 4-24 day of the cycle. For the most part, the glands were arrested in the early follicular phase, with some showing slight dilatation in some patients with normal ovulatory cycles. The glands were lined with either high or low columnar epithelium, with a minimum amount of secretion. The cytoplasm stained poorly. The stroma was cellular, with some edema. There were some hemorrhagic areas. Five patients were given 10 mg. daily from 12-30 days of the cycle. The response of the endometrium was different when norethynodrel was started (at) near the mid-cycle. The glands, arrested at the late proliferative phase, became dilated and cystic. The epithelium was flattened because of the intraluminal pressure. The stroma was markedly edematous. There were no changes in the blood vessels.

Even though the endometrial glands are arrested in the early proliferative phase, treatment of patients with secondary amenorrhea will result in withdrawal bleeding in most cases. Norethynodrel appears, therefore, to exert estrogen and progesterone effects on the endometrium. This effect is limited to the stroma and less so to the epithelium.

Goldzieher says that perhaps the greatest clinical concern
about synthetic progestational steroids has been the possibility of masculinization of female fetuses in mothers treated early in pregnancy for threatened or habitual abortion. Unfortunately, the statistical bias inherent in the collection of "anecdotal" data makes it difficult to interpret the results. Any conclusion of the causal relationship between hormonal therapy and fetal masculinization based on this type of information may result in another example of post hoc fallacy. Several instances of clitoral hypertrophy have been observed by the author in newborn infants of mothers who received no hormone therapy. Other cases of masculinization have been reported in women who have received only stilbestrol, an estrogen which is not even a steroid. Such observations argue more for spontaneous occurrence than for any causal relationship. It therefore, seems not improbable that fetal anomalies in women treated with synthetic progestins reflect the current therapeutic vogue rather than any causal relationship between the steroid and the anomaly. To date, no case of human fetal masculinization in women treated with medroxyprogesterone has been reported despite the widespread use of this material.
REVIEW OF CASES OF POSSIBLE MISSED ABORTION FOLLOWING TREATMENT OF THREATENED ABORTION WITH PROGESTATIONAL AGENTS

In the treatment of threatened abortion with various progestational agents and progesterone some cases of what appear to be missed abortions have occurred. These patients, after being treated following an episode of vaginal bleeding and a period of lower abdominal cramping, have been observed to show discontinuation of increase in the size of the uterus and of the other signs of pregnancy that were present previously. It has been postulated that the treatment with progestational agents may in some unexplained manner lead to the death of the fetus in utero, or that the fetus is already dead and the agents affect the uterine motility. The fetus is retained like that of a missed abortion to be terminated by natural expulsion or dilatation and curettage. The following consists of a series of cases reported by various doctors in Omaha, Nebraska.

Case 1

A 30 year old Negro female, para 3-1-4-4, LMP about 4-2-62 was admitted to UNH on 7-5-62 with the chief complaint of vaginal bleeding, uterine cramping and possible passage of
tissue. She was treated with bedrest and Depo-Provera 75 mgm. I.M. She was given 100 mgm. of the Depo-Provera on the following day. The vaginal bleeding and cramping gradually subsided. A past history revealed menarche at 13 years old, regular 28 day menstrual cycle with no dysmenorrhea. In 1948 she had a term baby, 1953 - 8 month gestation, 1956 - term, 1957 - aborted at 6-7 weeks, 1959 - aborted at 3 months, 1960 - term, 1961 - aborted at 3 months. On 7-10-62 she again complained of crampy, aching pain below the umbilicus and extending laterally with lumbar region pain. She had a pinkish vaginal discharge. She began to flow again on 11-10-62 lasting three days and spotted until 12-5-62 at which time she was bleeding heavily. She was considered a missed abortion after being seen in the emergency room and a D and C was done. The pathological report showed a piece of cotyledon and hyalinized necrotic material

Case 2

A 30 year old para 3 gravida 7 abortions 3 with LMP on 8-21-62. She was first seen on 12-7-62 with an episode of profuse vaginal bleeding followed by spotting. She was given Provera. On 1-4-63 the uterus was the size of 3-4 months gestation. There was no quickening and occasional bleeding occurred. On 1-29-63 there still was no growth of the uterus. At this time Provera was stopped. She no longer felt pregnant. On 2-18-63 the uterus was still the 3-4 month gestation size. The fibrinogen
level was 250 mg.% on 2-14-63 and 350 mg.% on 2-27-63. A DandC was done on 3-2-63. Pathology report showed a macerated fetus, about 8 weeks gestation with a necrotic placenta.

Case 3

A 39 year old white female, para 0000, married 19 years, with LMP on 12-10-62. She has had a regular 28 day menstrual cycle with bleeding lasting three days since menarche. A frog test was positive in January. She began to spot in early February. About seven days later a flow like a normal menstrual period occurred and lasted three days. She was given a progestational agent and the bleeding stopped. In March there was no increase in uterine size, and the pregnancy test was negative. An abdominal hysterotomy was done on 3-12-63. The material removed was placental along with a 2 month gestation fetus - both atrophic and fibrous.

Case 4

A 43 year old white female became pregnant after a long history of infertility. She began to bleed vaginally and was placed on Depo-Provera 100 mgm. I.M. on August 31, at which time she was also taking sulfa. She received Depo-Provera again on November 17, November 24, and December 8. She had passage of bloody mucus on January 30, 1963. Last fetal movements were noted on January 29. On 4-5-63 a D and C was performed and ischemic necrosis in decidual tissue was found. Past history

Case 5

A 27 year old white female para 1011, LMP 12-62, EDC 9-15-63 with thrombocytopenic purpura and a history of a missed abortion in 1960 with a D and C following 5 weeks of bleeding. On 2-5 the fundus measured 8-10 cm, on 2-25 she was bleeding vaginally, the cervix was closed, fundus at 10 cm and she was placed on Depo-Provera 100 mgm. I.M. On 3-13 the fundus was 11cm and she was again given 100 mgm. of Depo-Provera. On 3-27 - fundus 12 cm. with one episode of spotting. She was given Depo-Provera 100 mgm. On 4-8 fundus 12 cm. - another 100 mgm. of Depo-Provera. On 4-22 there was questionable uterine enlargement. She was considered a missed abortion. The pregnancy test became negative on 4-30. A D and C was done on 5-3.

Case 6

A 27 year old, para 1001 - LMP 1-7-63. She was seen on 4-9-63 for vaginal spotting. On 4-23 she was treated with Ent CVP plus Provera. The uterus had not increased in size since the previous visit. She was also on Deluteval twice a week through May. On 5-30 she had an episode of severe vaginal bleeding with possible passage of tissue. The uterus was estimated to be the size compatible with two months gestation. A D and C was done and necrotic decidual and placental
tissue was found without a fetus.

Case 7

A 26 year old, para 1021, LMP December 1959, with a history of previous abortions in March 1959 and August 1959. In December she thought that she was pregnant and was given 15 shots of progesterone in an attempt to prevent another abortion. She had an episode of bleeding in April, but it did not seem like a period. She had complete amenorrhea since April 18, 1960. She didn't feel good and was given thyroid extract 1 grain for one year. She was considered a possible missed abortion because of the "shots." In October the frog test was negative. She was given progesterone and bled on the twelfth day after injection. On 10-27-60 she bled and passed tissue. A D and C was done. The pathology report indicated an incomplete abortion with fibrosis and degeneration in the placenta.

Case 8

A 22 year old white female, para 010, LMP 4-27-62, EDC 2-3-63. She was seen on 8-2-62 for pressure on the bladder, cramping and passing blood and a large clot. She was put on 40 mgm. orally of Provera the following day. She had some bleeding every day since then with occasional cramping. She stated that the time of bleeding coincided with the fourth period since her LMP. At the time of the second period she had
cramps but no bleeding. Pregnancy tests were negative on 8-13-62. A D and C was done on 8-17-62 and a macerated fetus and placenta were removed.

Case 9

A 26 year old white female, para 3002, LMP 9-5-62. She noticed spotting since 11-22-62. She was treated with 100 mgm. of Depo-Provera. She was seen on 1-5-63. The uterus which should have been the size of four months gestation was the size of a two month gestation. She no longer felt pregnant. She was diagnosed as a missed abortion. A D and C was done on 1-22-63 showing degenerated decidual tissue and chorionic villi.

The following cases are presented to illustrate the production of what appears to be a missed abortion after treatment of a threatened abortion with agents other than progestational agents.

Case 10

A 23 year old white female para 1011, LMP 11-14-57. She felt quickening on 3-2-58. On 3-9 she began spotting following voiding. She was placed on Lutrexin 2000 and 3-4 xd. The brownish spotting recurred on 4-4. On 5-9 there was no evidence of uterine growth since the previous month. On 5-29 a D and E was performed. There was escape of brownish amniotic fluid and minimal bleeding, no fetus and evidence of hydropic
degeneration. Microscopic examination showed placenta decidual and endometrium of early pregnancy with hydatiform deformity of villi.

Case 11

A 37 year old white female, para 7007, LMP 4-14-63, EDC 1-21-64, with a menstrual cycle of 20-23 days lasting four days. On 7-19-63 she was hospitalized as a threatened abortion. She was placed on Stilbestrol 25 mgm. three times a day, DUO-CVP twice a day. On 8-22-63 there was no bleeding or uterine enlargement. She was diagnosed as a missed abortion. A D and C was done on 8-30 and necrotic placental and decidual tissue was found.

Case 12

A 43 year old white female, para 2012, LMP 2-7-55. She was seen on 4-15-55 after spotting for one week. At this time the pregnancy test was positive. She was placed on 25 mg. Stilbestrol every four hours. On 6-13 the uterus was soft and irregular but not the size of a four month pregnancy. The pregnancy test was negative. She had spotting and cramping on 7-15 which lasted until 8-11. A D and C was done on 8-13 and it showed a placenta with necrosis, hemorrhage and acute inflammation and she was considered a missed abortion. Her past history included a cesarean section done for placenta previa in 1949, and a miscarriage in 1952, also, two possible miscarriages.
in March 1953 and July 1953. A D and C was done for a hydatidiform mole in August 1953.

The majority of cases were treated, at the time that spotting was noted, with a progestational agent in the attempt to salvage the pregnancy from aborting. The bleeding usually subsided within a short period of time. However, instead of proceeding on to a full term viable pregnancy the growth of the uterus and the other signs of pregnancy subsided and within four to ten weeks bleeding usually recurred and a dilatation and curettage was done on the basis of a diagnosed missed abortion. The ages and parities of the patients differed. Some of the patients had histories of previous abortions as well as missed abortions. Very few of them were on any other medication besides the progestational agents early in the pregnancy or at the time of treatment. According to the accepted definition of missed abortion, it is difficult to determine whether the treatment of a threatened abortion, as occurred in the above cases, with progesterone could cause a missed abortion to take place. The evidence seems to support the suspicion that it does possibly occur. Further research into the subject is necessary before any proof against the use of the progestational agents in such cases can be considered.
SUMMARY

The danger in the use of progestational agents in the treatment of threatened abortions is considered. A hypothesis is put forth that the type of treatment may in some way lead to the development of a missed abortion. Twelve cases are reviewed in which treatment with a progestational agent was begun when the patient began to spot early in the pregnancy. In each of these cases, in the ensuing weeks, a missed abortion developed and a D and C was necessary for removal of the necrotic products of gestation. No direct proof was set forth in the above thesis. This is considered only as a possibility to be considered in the use of progestational agents. As a preview to the case reports the various aspects of missed abortion were reviewed. A missed abortion was defined, according to Eastman, as the retention, two months or more after its death, of an early intra-uterine pregnancy. There were no decisions as to the etiology. The relationship between blood levels of progesterone and estrogen along, with the urinary excretion of pregnanediol and estriol before and after uterine death was examined. Several workers have noticed the fall in fibrinogen levels of women carrying dead fetuses. They have also noted that in spite of high levels of fibrinolysins the fibrinogen levels did not fall in direct proportion. The danger occurred during labor
when cases of severe bleeding did result.

The general properties and area of production in the body of progesterone was cited. The action of progesterone in pregnancy and its effects on the endometrium were discussed. The actions of norethynodrel were included here.
CONCLUSION

A hypothesis is presented in this thesis that the use of progestational agents in treating threatened abortions may be responsible for its developing into a missed abortion. These agents, in some way, may be the cause of death of the fetus and decrease in the size of the pregnant uterus. This is not to be used as proof in any way that this occurs, but is written to increase the index of suspicion when these drugs are used. Further extensive research, using controls, is necessary for proof that there is a direct relationship between the use of progesterone and the development of a missed abortion.
BIBLIOGRAPHY


