PROGESTERONE THERAPY IN UTERINE FIBROMYOMA

AUBREY L. GOODMAN, M.D.

From the Endocrine Clinic, Joanna McClelland Memorial Hospital, Waco, Texas

IN A STUDY on experimental fibromyomas and their prevention, Lipschütz and Inglesias (6) showed that subserous uterine fibromyomas and extragenital subserous fibromyomas in the abdominal cavity can be produced in guinea pigs subjected to prolonged treatment with estrogens. All estrogens, natural and artificial, free and esterified, were shown to be tumorigenic. Under certain conditions of treatment with estrogens a female guinea pig only rarely escaped the development of abdominal fibromyomas. Continuous action of the hormone was an essential factor. When a period of one week of injections was followed by a period of two weeks without injections no fibromyomas were produced even after a year of such treatment. On the other hand, minute quantities of free estradiol, insufficient to produce fibromyoma when given three times weekly by subcutaneous injection, proved highly active when absorbed from a subcutaneously implanted pellet. It was suggested that the tumorigenic action of estrogens in the normal organism is controlled by the sexual cycle with the alternation of high and low level phases of blood estrogen and by inactivation or elimination of the hormone.

Uterine and extra-uterine abdominal fibromyomas produced in the guinea pig by subcutaneous injection of follicular hormone develop in the non-castrated female with less constancy and in lesser degree than in the castrated female. This suggests that the luteal hormone may be responsible for the antitumorigenic influence of the ovary. This was corroborated in a later study by Lipschütz, et al., (9) who demonstrated that progesterone\(^1\) prevented tumor formation by estrogens.

They hypothesize (5) that the development of uterine fibromyomas in women is due to disturbance of the normal balance between follicular and luteal hormones and of their normal timing, and that progesterone may prove useful as a therapeutic agent against fibromyoma.

Postulating that progesterone produced in the body may react synergistically with estrogen on the uterine mucosa but also have an antagonistic action, Lipschütz and his coworkers (10) investigated the preventive action of several steroids, including progesterone, on such experimentally produced tumors. Three different synthetic steroids—progesterone, desoxy-

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corticosterone acetate, and testosterone propionate were shown to have the capacity of preventing abdominal fibroids elicited by estrogens. The antifibromatogenic threshold, or the minimal quantity of the steroid which must be released to inhibit fibroids, was lowest with progesterone; deoxycorticosterone acetate was next in order, and was followed by testosterone propionate which was still highly active. The question was raised whether the descending order of the antifibromatogenic faculty of different steroids was coincident with their anti-estrogenic activity. This was the case in the guinea pig but not in the rat. The progestational activity of the three compounds appears to decrease in the same order as the antitumorogenic effect although these quantitative data are by no means exact. It seems somewhat contradictory, according to Lipschütz (5), that the progestational and antifibromatogenic activities should be of the same magnitude, since progestational activity is associated with stimulation of the proliferation of epithelial cells, whereas antifibromatogenic activity indicates inhibition of the proliferation of those cells which give origin to fibroblasts and connective tissue fibers. However, it has been suggested that both stimulation and inhibition of proliferation may depend upon different quantitative levels of the antagonistic substances in play. These results are in accord with clinical observations that uterine fibromyoma are most frequent in virgin women, and that these tumors are more often present in nulliparas than in women who have given birth to children. Their frequency is also reported to be greater in women who became pregnant only at a more advanced age and had fewer pregnancies. It is assumed that the longer action of progesterone may exert a preventative influence in women with a greater number of pregnancies.

As experimental fibroids elicited by estrogens are structurally different from uterine fibroids in women, Lipschütz questions (5) whether the above findings can be applied to the treatment of fibromyomata in women. But attention is called to the fact that the fibromyoma in women, like the experimental fibroids of the guinea pig, regresses when production of estrogen is suspended or diminished, as after the menopause, and after castration or ovarian irradiation. As progesterone is the most potent antifibromatogenic steroid, he suggests its therapeutic use.

Realizing that the application of laboratory results to the human female should be made with caution, the author was stimulated by Lipschütz's extremely careful investigations to extend the studies into the clinical field with special reference to the therapeutic possibilities of progesterone.

It would have been highly desirable to have objective measurements of the tumors by making tracings of the uterine contour, injecting radio-opaque material into the uterus, sounding the uterus, etc., but such methods were difficult to employ with the facilities that were available.
All individuals in the series were charity patients of the clinic, and great difficulties were encountered in obtaining accurate data and regular attendance to the clinic. A clinical trial with progesterone in the following seven patients with uterine fibromyomata was undertaken:

**CASE HISTORIES**

**Case 1**

E. W., a white female, aged 31, was first seen on November 11, 1944, complaining of an increasing vaginal discharge of several months' duration. There was nothing unusual in her menstrual history. She started to menstruate at 13, periods occurred approximately every 28 days, lasting five days. No pregnancies.

**Physical examination** revealed nothing abnormal except in the pelvic examination. The introitus was patent and the perineum firm. When the cervix was exposed with a speculum, the lips appeared to be turned apart by what seemed to be a cervical fibromyoma approximately 3 cm. in diameter, extending through the external os and attached to the dorsal surface of the uterine canal which was otherwise normal.

**Diagnosis:** Fibromyoma of the uterus.

**Treatment:** On November 13, 1944, injections of progesterone in doses of 10 mg. three times weekly were begun. After three injections a definite change could be observed in the tumor. There was shrinkage, and slightly gray trabeculae were seen over the outer surface. The tumor gradually diminished in size, and by January 5, 1945, it had shrunk to about one fourth of the original size, allowing the cervical lips to approximate. Progesterone was discontinued for one month and then resumed. On March 1st there was a slight elevation of the lining of the canal with complete closure of the cervical lips. The original site of the tumor was firm, with gray trabeculae of fibrous tissue formation. The vaginal discharge ceased, and there was no change in the regularity of the menstrual cycle.

**Case 2**

W. W., a white female, aged 47, was first seen on January 30, 1945, complaining of heaviness of the lower abdomen, "bearing-down" sensation, pressure on the rectum, and an increase in frequency of urination of a year's duration. Except for the above, the past history was irrelevant. Menarche started at the age of 16 with regular periods every 28 days. She had one child at the age of 26; no miscarriages. About eight months previous to the first visit her periods started to lengthen, and for the past six months she had flowed constantly in varying amounts. With the change in periods there occurred hot flashes, a tight sensation at the base of the head and neck, a tingling of extremities and increased nervousness.

**Physical examination** revealed a short, obese, apprehensive female. The head, neck, heart, and lungs were normal. The abdomen was obese and pendulous. There was a large mass palpable over the pubis, halfway to the umbilicus, extending into both lower quadrants. The perineum was moderately relaxed, the cervix was enlarged and it pressed down into vagina but was not fixed. There was a slight endocervicitis. The uterus was enlarged, approximating the size of a three-months' pregnancy; it was movable, smooth, and very hard. There was tenderness along ligaments. The ovaries and tubes appeared to be normal. Moderate varicosities were present on both lower extremities.

**Diagnosis:** Uterine fibromyoma; slight endocervicitis; menopause.

**Treatment** was started on January 30, 1945 with injections of progesterone in doses
of 10 mg. six times weekly. By February 13th the tumor had decreased about 40 per cent in size; menstrual bleeding had ceased. On February 27th there occurred a normal period without discomfort. The patient's nervousness and hot flashes were markedly relieved. The uterus was no longer palpable by abdominal examination, and on vaginal examination it appeared to be the size of a lemon.

Case 3

F. W., a colored female, aged 24, was first seen on July 25, 1944, complaining of intermittent attacks of cramp-like, "bearing-down" pains across the lower abdomen and lumbar area of two weeks' duration. Menses had been irregular for the previous two months, with a profuse flow occurring daily with many large clots and usually lasting two weeks. One week prior to her visit a profuse, yellowish vaginal discharge was noted. The patient had had three pregnancies, the first occurring at the age of 14 years.

Physical examination was normal except for the pelvic examination which revealed moderate tenderness suprapubically. The cervix was indurated, indented and slightly enlarged. The uterus was hard, immobile, and was enlarged to the size of a large grapefruit.

Diagnosis: Fibromyoma of the uterus, degenerative type; cystocele.

Treatment: Patient was considered inoperable because of the fact that the uterus was bound down, firm, and immobile. Injections of progesterone, 10 mg. daily, were started on July 28, 1944. On August 2nd, she was improved, and was discharged from the hospital; there had been a decrease in the size of the uterus. On August 15th the uterine mass was considerably smaller, and the right adnexa were palpable. This was impossible at the start of the treatment. On August 22nd the uterine fibroid had decreased in size about 25 per cent. The patient failed to return for further treatment.

Case 4

O. J., a 24 year old colored female, was first seen in August, 1943, complaining of cramps with her menstrual periods. Examination showed the uterus in good position and of normal size. In April, 1944, she bled for two weeks and had cramp-like pains. Since July, 1944, she experienced upper abdominal pains, and on October 1st there occurred a normal menstrual period, but the abdominal pains persisted. Because of this she again sought medical advice on October 17th.

Physical examination revealed a small, deep suprapubic mass. The introitus was patent and the perineum relaxed. The cervix was slightly enlarged and had a mild endocervicitis. The uterus was hard and smooth, and was enlarged to the size of a two-months' pregnancy.

Diagnosis: Uterine fibromyoma; endocervicitis.

Treatment: Progesterone in doses of 10 mg. three times a week, was started on October 17, 1944. The patient was not seen again until December 5th, being on constant treatment. She reported two normal periods with flow lasting three days, and there was no distress of any kind during this time. The tumor mass had decreased by 40 per cent. Four weeks later the tumor was still of the same size, after which the patient failed to return for further treatment.

Case 5

L. L., a colored female, aged 52, was first seen on August 8, 1944, complaining of lower abdominal pain with pressure on the rectum and bladder, urinary frequency with nocturia. Her past history was negative until about two years ago when pains occurred. Her menstrual history in the lower abdomen with pressure on the rectum and bladder. Her menstrual history was normal until about one and a half years ago when she began to flow excessively dur-
ing her periods, only three occurring during the past year. For the past eight to ten months, she noticed urinary frequency with nocturia. Her first pregnancy was at the age of 14 years.

**Physical examination** showed a large mass extending four inches above the pubis and into both lower quadrants. The perineum was moderately relaxed; the cervix was enlarged, everted and infected. The uterus contained an irregular fibromyoma which filled two thirds of the pelvis.

**Diagnosis:** Large uterine fibromyoma; endocervicitis.

**Treatment:** The patient was given injections of progesterone, 10 mg. daily, and one week later the mass appeared to be undergoing involution. By September 12th, the fibroid had decreased one third in size. The patient failed to return to the clinic for further treatment.

**Case 6**

*B. C.*, a 34 year old colored female was seen on September 12, 1944, complaining of lower abdominal pain of five years’ duration. Menarche started at the age of 12, with regular periods every 28 to 30 days, lasting three days. Moderate cramps and backache occurred with each period.

**Physical examination** showed a small mass palpable just over the pubis, and there was tenderness on pressure over both lower quadrants. The pelvic examination revealed a slightly relaxed perineum and slight ectropion of the cervix with endocervicitis. The uterus was enlarged to at least twice normal size; it was movable, hard and smooth. Marked tenderness was present on pressure over the ligaments.

**Diagnosis:** Small uterine fibromyoma; endocervicitis.

**Treatment:** On September 12, 1944, injections of progesterone in doses of 10 mg. three times a week were started. On September 26th, the uterus had decreased 30 per cent in size. On October 25th, after the patient had received eighteen injections of progesterone (180 mg.), examination revealed a uterus only slightly larger than normal. The patient failed to return for further treatment.

**Case 7**

*B. E.*, a 26 year old colored female, presented herself on June 30, 1944, with a history of metrorrhagia. In March, 1942, she flowed excessively for three weeks, passing large clots. In August of the same year she had another similar experience. These recurred, and in July, 1943, a curettage was done. The following six periods were fairly normal, but in January, 1944, the excessive bleeding returned, and persisted. Her last menstrual period was said to have started June 18th, and stopped June 24th, only to start again the next day and persist to the date of her first visit. The patient had had a bilateral salpingectomy, and was being treated for syphilis. There was one miscarriage at the age of 14.

**Physical examination** showed a well healed midline scar, no abdominal masses, but there was tenderness on deep pressure both in the suprapubic region and to the right of the midline. Pelvic examination revealed a mass about the size of a small egg on the right upper half of the uterus, and there was tenderness on pressure on the ligaments.

**Diagnosis:** Small uterine fibromyoma.

**Treatment:** Injections of progesterone, in doses of 10 mg. three times a week, were started immediately, and on July 18th, after seven injections, the mass had decreased to about one third in size. Bleeding had stopped shortly after treatment was started, and a normal period occurred on July 14th. On August 1st the mass appeared to be com-
pletely gone; the uterus was small and slightly retroverted. The patient had received a total of twelve injections of progesterone, each 10 mg.

DISCUSSION

The reported cases have, in common, a degree of subsidence of the size of the uterus and a regulation of menstrual disorders in a period of time which, according to the author’s experience, is not conformable with the assumption of a spontaneous regression of the tumor. Whether we dealt with a true regression of fibrous tissue, as demonstrated in guinea pigs by Lipschütz and his coworkers, is also not revealed by these clinical observations. One has to consider a decrease in size of the uterus or a shrinkage by dehydration with the real tumor remaining essentially intact. Changes in size of the uterus, its vascularization and its water content under the influence of steroid hormones are so well established that one has to consider the possibility that simple clinical examination under not sufficiently controlled conditions may lead to misconceptions.

From such a small series of cases no valid conclusions of any kind should be drawn. No efforts have been made to support the diagnosis of uterine fibromyomata by histological evidence, although in all patients there was, clinically no doubt of the presence of a seemingly benign tumor. Dealing mainly with charity patients who would not return to the hospital after relief of symptoms made continued observation for a reasonable period of time impossible; thus, it should be emphasized that with this presentation, no claim for a final therapeutic effect of progesterone in fibromyomata is raised.

Progesterone is not offered as a substitute for the presently accepted methods of surgical or radiation therapy of fibromyoma. We believe, however, that the subject and the questions raised by our findings are of sufficient interest and practical significance to be studied by investigators whose facilities permit a careful investigation with all necessary laboratory support.

SUMMARY

On the basis of the work of Lipschütz and his coworkers, who reported that fibroids, produced in the guinea pig by continued estrogen administration, decrease and disappear under progesterone (and other steroid) therapy, seven patients having fibromata uteri, clinically diagnosed, were treated by injections of progesterone. An observed decrease in the size of the tumor or of the uterus in all cases was reported with the aim to encourage further investigation of the possible therapeutic value of this treatment in such conditions.
REFERENCES