Treatment of Amenorrhea: When Pregnancy Is and Is Not Desired*

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We have had three discussions this afternoon concerning amenorrhea, and most of these have dealt with the diagnosis of causative conditions. I am going to discuss the treatment of these women.

Whether or not the woman wishes to conceive in the immediate future determines the plan of treatment in most cases. If conception is desired, I believe it should not be immediately assumed that the amenorrhea is the sole cause of the infertility. I would check patency of fallopian tubes and adequacy of the husband's sperm production before treating for conception. Regardless of the plans for pregnancy, however, it should be determined whether the woman is merely not ovulating with adequate endogenous ovarian estrogen production or whether the ovulatory failure is associated with lack of estrogen as well. The former might occur if pituitary gonadotropins were reduced and/or the preovulatory LH surge were absent. The latter condition may be due to failure of production of pituitary gonadotropins or to menopause with elevated levels of pituitary gonadotropins.

Several brief case reports of women with amenorrhea will follow. In some of these, there will be organic disease of the extragenital endocrine glands such as the thyroid gland, or the adrenal gland, or the pituitary gland. In others, there will be no identifiable extragenital endocrine disease; then the treatment would vary depending on whether or not the woman wishes to become pregnant.

Case 1. This patient was a 35-year-old gravida 1, para 1, aborta 0 who was seen after having amenorrhea for six months. She had noticed tachycardia, sweats, and weight loss. The radioactive iodine uptake was 80% in 24 hours; this is much higher than normal for this laboratory. A diagnosis of hyperthyroidism was made. The patient was treated with radioactive iodine and had resumption of regular menses after the second course of treatment. She is not presently trying to become pregnant.

In preparing for this talk, I was looking for instances of thyroid disease that caused amenorrhea, and I couldn't find any where hypothyroidism was the etiologic factor. I am as aware as you all are of the thousands of women who have taken thyroid medication as treatment for amenorrhea, but in the patients' charts to which I had access, I could not find one where this was the real etiologic factor. I did find the following case of hyperthyroidism.

Case 2. This was a 30-year-old gravida II, para I who had had amenorrhea for two years after a spontaneous abortion. She had moderate hirsutism, but no other virilizing signs. An endometrial biopsy showed "resting endometrium," that is, proliferative glands without mitotic activity. Thyroid studies were normal, and two urinary 17-ketosteroid determinations were moderately elevated; 16.1 and 18.1 mg/24 hours. It was decided that this was a case of adrenal androgenic hyperfunction. The patient was initially treated with dexamethasone 2 mg three times a day for 2 days, followed by 0.75 mg/day for maintenance. Ultimately, this was reduced to 0.5 mg/day. Under this treatment, the urinary 17-ketosteroids fell to 2.7 mg/24 hours. Ovulatory cycles began and conception occurred.

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Case 3. This was a 26-year-old gravida II, para 2 who was seen because of amenorrhea and galactorrhea since her last delivery two years earlier. This patient had been worked up about a year previously elsewhere and had had normal skull x-rays, normal visual fields, and normal EEG. The skull x-rays were repeated; this time a destructive lesion of the sella was seen, and the visual fields had a bilateral defect. A transsphenoidal removal of prolactin-producing pituitary adenoma was done leaving the remainder of the pituitary gland. Following this, spontaneous menses have returned and they are ovulatory. The visual fields have also returned to normal.

The first three cases dealt with patients who had organic diseases of extragenital endocrine glands. The remaining four cases have no identifiable extragenital endocrine disease.

Case 4. This was a 20-year-old gravida 0 whose menses began at age 13 and had occurred every 35 days lasting 7 days until two years earlier when amenorrhea had begun, coinciding with the first year of college. She had a history of having received thyroid medication in the past although she had received none for the preceding year. The free T_4 was 1.5 mg%, a normal value, and the maturation index was 0/65/35. Oral medroxyprogesterone was administered, and the patient had withdrawal bleeding after this. An extensive investigation was not done, but the medroxyprogesterone medication was continued for 3 months. After this, spontaneous cycles returned.

Patients who have endogenous estrogen can usually be treated with only a pure progestin given at monthly intervals. It is unlikely that they have anything seriously wrong with their hypothalamic-pituitary axis. When given an exogenous progestin at monthly intervals (we usually give medroxyprogesterone for 5 days beginning at cycle day 22), monthly bleeding episodes usually result. Some women who do not want to menstruate 13 times a year will be given the medication two to four times a year. I do not think it is good for endometrium to be continuously stimulated by estrogen, whether it is endogenous or exogenous, because of the possibility of endometrial hyperplasia, and I think that even if the woman is not enthusiastic about menstruating, she should be given this medication at least several times a year.

Case 5. This was an 18-year-old gravida 0 who had onset of menses at age 10 and who had had menses every 31 days lasting 5 days until she entered college. Prior to this, she had experienced amenorrhea in the summer when she had gone away to camp, but the amenorrhea had ceased when she returned home. She had very slight hirsutism, and there was no withdrawal bleeding after medroxyprogesterone. The serum FSH and LH were normal. Tests of thyroid function, skull x-rays, and urinary 17-ketosteroids were normal. The patient was treated with cyclic estrogens and progestins (conjugated estrogens 1.25 mg daily for 21 days with medroxyprogesterone 10 mg daily added on treatment days 17–21).

The failure of withdrawal bleeding after medroxyprogesterone alone in a patient who does have withdrawal bleeding after estrogen-priming before a progestin is given indicates lack of endogenous estrogen production. The group of patients without endogenous estrogen includes cases where the defect is ovarian (such as agenesis, castration, or premature menopause) as well as cases of pituitary failure (such as that secondary to defective releasing factors, ablation by surgery or radiation, and diseases such as Sheehan's syndrome). If this syndrome appears at a time when it is appropriate for a woman to stop menstruating, as would be the case if she were in her mid-40's, I don't think the condition necessarily needs to be treated. Certainly when it occurs in an 18-year-old girl, as this did, I believe that it is reasonable to treat with estrogen plus a progestin. This will result in regular episodes of withdrawal bleeding.

Case 6. This was a 27-year-old gravida I, para 1 who had become pregnant the first time without difficulty, but who had had amenorrhea for six years. She desired pregnancy. She weighed 208 pounds, had mild facial hirsutism, and normal adnexa. Urinary 17-ketosteroids were 4.4 mg/24 hours, a normal value. The maturation index was 0/86/14; a Rubin's test had shown tubal patency, and a postcoital test had shown abundant sperm. After medroxyprogesterone-induced withdrawal bleeding, this patient was given clomiphene 50 mg daily for 5 days, and she promptly became pregnant in the first month of treatment.

When clomiphene is used, the pregnancy rate will be around 30%. The incidence of ovulation is much greater than 30%, but every patient who shows evidence of ovulation does not always become pregnant. This may be due to the fact that we think the person is ovulating when she really is not. All of our

indices for detection of ovulation are based on the effects of progesterone, because we know that in normal women progesterone is present and exerts its effect primarily after ovulation, and we assume that this also happens in abnormal states. I am not absolutely sure that this is so, but I have no valid proof that it is not. Ovulation apparently is induced, or at least progesterone is produced, in about 70% of the women receiving clomiphene, but pregnancy occurs only in about 30%.

Sometimes couples will want to know when is the best time for exposure after clomiphene to achieve a pregnancy. It is my practice to tell the patients to begin having regular intercourse about four days after the last tablet and to continue this until the basal temperature has been up for three days. Clomiphene is not without side effects. Ovarian enlargement may occur in about 14% of patients, and sometimes the ovaries become quite large, but the problem is much less than with the agent that will be discussed shortly. Hot flashes are the common complaint that patients report. If patients are reassured about this and told that they are not menopausal, it does not seem to be a troublesome effect. The instance of multiple pregnancy is increased tenfold. Under normal circumstances, the incidence of multiple pregnancy is around 1 in 80; with clomiphene it will rise to around 1 in 10 or 1 in 12. Blurring of vision may occur in around 1% of patients, and when this occurs, it is an indication to discontinue the medication. Spontaneous abortion occurs at a higher rate than would be expected.

Case 7. This was a 29-year-old gravida 1, para 1, aborta 0 who desired pregnancy and who had had amenorrhea for nine months when she was first seen. She had been on oral contraceptive medication prior to her first pregnancy; this had been discontinued, and she had conceived promptly without difficulty. After that pregnancy, she took combination oral contraceptive tablets for several years. Her other workup had indicated that her thyroid function was normal, that the blood FSH and LH were normal, and that 17-ketosteroids were also normal. Tubal patency and sperm production were adequate. Attempts to induce ovulation with clomiphene began with a low dose of 50 mg daily for 5 days. This was raised gradually to 200 mg/day for 5 days, with chorionic gonadotropin added after this. This was not successful; then treatment with menopausal-chorionic gonadotropin was given according to the outline in Table 1.

TABLE 1
Outline of Gonadotropin Rx

Rx Day	Cervical Mucus	Plasma Estradiol	Rx
1	0		HMG 75-75 u.
2	0		HMG 150-150 u.
3	0		HMG 150-150 u.
4	1+		HMG 150-150 u.
5	1+	134 pg/ml	HMG 150-150 u.
6	2+	179 pg/ml	HMG 225-225 u.
7	2+	237 pg/ml	HMG 300-300 u.
8	3+	332 pg/ml	HMG 300-300 u.
9	3+	478 pg/ml	HMG 300-300 u.
10	4+	938 pg/ml	HMG 10,000 u.
11			
12	BBT down		
13	Sustained rise in BBT began, followed by menses.		

In such cases, one may get response to menopausal plus chorionic gonadotropin. The instance of pregnancy with this treatment is around 25%. This treatment is also associated with side effects. One has to be very careful in giving it. Ovarian enlargement may occur in up to 20% of the cases, and in extreme instances may be associated with acites and even plural effusions. The cysts may rupture, and there may be hemoperitoneum. The severe hyperstimulation syndrome is found to be associated with abdominal distention and hemoconcentration (because so much of the body's total fluid volume has gone into the abdominal cavity). The treatment is bedrest, intravenous fluids with close monitoring of electrolytes, and avoidance of pelvic examinations. This can become serious, can lead to thrombosis, and there have been several deaths. The instance of multiple pregnancy with menopausal-chorionic gonadotropin treatment is 20–37%, and the instance of abortion is around 28%; an incidence greater than would be expected with normal spontaneous ovulation. In one series, it was found that three-fourths of the multiple pregnancies were twins, and one-fourth of the multiple pregnancies were three or more.

There are several problems in treating women with gonadotropins. One wants to give enough medication to induce ovulation, but not so much that the hyperstimulation syndrome is produced. In this particular patient, the menopausal gonadotropin dosage was gradually increased until day 10 when good cervical mucus was seen, indicating that, more than likely, enough medication had been

given. Laboratory tests of estrogen production were done to determine that too much had not been given. In many institutions, the determination is of urinary estrogen, but at the Medical College of Virginia there is a technique whereby plasma estradiol can be measured in about six hours. The patients have blood drawn in the morning and return at 4:00 p.m., at which time the laboratory data is available. The aim is to reach a level of between 500 and 1000 pg/ml of estradiol. If the level stays under 1000 pg/ml, the incidence of hyperstimulation syndrome is much less than if the level is higher. If this patient had been given another day of treatment, a situation might have been created where hyperstimulation would have occurred. The patient did not become pregnant, although evidence for ovulation was obtained from basal temperature charts. I want to emphasize this because I think this is a way a physician can get in trouble. One can decide when he has given enough estrogen by the effect on cervical mucus, but one cannot tell when he has given too much. If estradiol levels are too high, one would not give chorionic gonadotropin, stop the treatment, and try again in a month or so, giving less medication. I think to avoid serious complications in treating a nonlethal condition, there has to be some way of assessing the estrogen production from the stimulated ovaries.

I have tried to illustrate the treatment for amenorrhea of different causes and to emphasize the fact that the treatment is different when the woman wishes or does not wish to become pregnant. I have also pointed out some of the hazards of the various methods of treatment of this condition.