A series of review articles dealing with medical progress

Recent Advances in Medicine and Surgery

ROBERT TURELL, M.D., Editor

Endocrine Management of Transsexual

Hormonal profiles of serum prolactin, testosterone, and estradiol

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Transsexualism is an increasingly prevalent phenomenon to which the physician who deals with these patients must familiarize himself. The basic tenets of endocrine management of the transsexual follows to a great e nt the outline proposed by Benjamin in 1964.[1,2] The purpose of this communication is to propose an endocrine management of transsexuals before and after gender-reversal therapy employing radioimmunoassays of testosterone, estradiol, and prolactin as guides to such treatment.

The basis for this report is the experience of managing 51 male-to-female and 12 female-to-male transsexuals who were referred for initiation or modification of endocrine therapy over the past four years. All had been evaluated psychologically and found emotionally suitable for sex reassignment therapy. The values for serum testosterone, estradiol, prolactin, LH (luteinizing hormone) and FSH (follicle-stimulating hormone) were in the normal range for the 22 untreated male-to-female transsexuals tested. The clinical and endocrine data of 12 female-to-male transsexuals are presented in Table I; 6 of the 12 female transsexuals had associated endocrinopathies, that is, 2 had documented polycystic ovaries, 1 patient had primary amenorrhea with bilateral streak gonads, and 3 patients had varying degrees of hirsutism and laboratory data suggestive of polycystic ovarian disease. Two of the 6 female-to-male transsexuals had borderline elevated values of serum testosterone in association with regular menses. Serum prolactin levels were normal in the untreated male-to-female transsexuals, with a mean level of 9.3 ng. per milliliter, but rose significantly, that is, more than 25 ng. per milliliter, in 11 of the 23 patients tested during estrogen treatment (Fig. 1). One patient had a serum prolactin of 90 ng. per milliliter, which dropped to 16 ng. per milliliter three months after reduction of the dosage of estrogen employed.

Endocrine management of male transsexual

After assessing the patient's general medical history and clinical evaluation of the cardiovascular and endocrine status, it appears that the following should be noted to be absolute or relative contraindications to estrogen therapy:

1. Severe diastolic hypertension.
2. A past history of ischemic cardiac episodes or electrocardiographic evidence of significant cardiac dysfunction. A wide variety of cardiac diseases such as rheumatic heart disease, valvular defects, conduction disturbances, cardiomyopathies, or recent myocarditis should be included in this category.
3. A history of thrombophlebitis or thromboembolic disease.
4. A history of cerebrovascular disease.
5. Persistent hepatic dysfunction as evidenced by abnormal liver function study findings or a history of heavy alcohol intake.
6. Impairment of renal function.
7. Refractory migraine-type headaches, seizures, or retinal lesions.
8. Brittle or poorly controlled diabetes mellitus.
9. A strong family history of breast carcinoma or the presence of a suspicious breast mass.
10. Marked obesity with associated hyperlipoproteinemia.
11. Heavy cigarette consumption of over one to two packs daily.

A number of regimens in the initial management of the male-to-female transsexual may be attempted. The basic principle is that of "medical castration," that is, reduction of serum testosterone by suppression of the hypothalamic-pituitary unit and by the direct effect of estrogen on the testes. The feminization that follows allows the patient the option to

TABLE I. Clinical data on twelve female-to-male transsexuals

Patient Number	Age (Years)	Endocrine Status	Clinical Status	Specific Endocrine Studies
1	18	Regular menses minimal hirsutism	Normal	U*-serum testosterone,† 82 ng. per 100 ml.; U-serum estradiol,** 6.2 ng. per 100 ml.; U-serum prolactin, 2.6 ng. per milliliter
2	21	Regular menses	Normal	U-serum testosterone, 58 ng. per 100 ml.; U-serum estradiol, 16.3 ng. per 100 ml.; U-serum prolactin, 18 ng. per milliliter; U-serum LH,†† 34.3 mIU. per milliliter; U-serum FSH,*** 5.3 mIU. per milliliter
3	23	Regular menses	Normal	U-serum testosterone, 70 ng. per 100 ml.; U-serum estradiol, 2.7 ng. per 100 ml.; U-serum LH, 15.3 mIU. per milliliter
4	27	Regular menses	Normal	U-serum testosterone, 61 ng. per 100 ml.; U-serum estradiol, 12.0 ng. per 100 ml.; U-serum prolactin, 18.2 ng. per milliliter; U-serum LH, 22.5 mIU. per milliliter; U-serum FSH 4.1 mIU. per milliliter; U-progesterone,††† 8.1 ng. per milliliter
5	27	Regular menses; moderate hirsutism; acne	? PCOD****	U-serum testosterone, 41 ng. per 100 ml.; U-serum estradiol, 26.0 ng. per 100 ml.; U-serum prolactin, 26.7 ng. per milliliter; U-serum LH, 41.8 mIU. per milliliter; U-serum FSH, 20.4 mIU. per milliliter, U-serum DHA-S,†††† 220 micrograms per 100 ml.
6	32	Oligomenorrhea; very hirsute	? PCOD	U-serum testosterone, 77 ng. per 100 ml.; U-serum estradiol, 11.8 ng. per 100 ml.; U-serum prolactin, 5.0 ng. per milliliter; U-urinary 17KS,*****, 16.8 mg. per 24 hr.
7	33	Oligomenorrhea; galactorrhea; hyperthyroidism, age 30. Treatment: RAI††††††-131-followed by hypothyroidism, on sodium levothyroxine (Synthroid), 0.15 mg. daily	PCOD******	U-serum testosterone, 84 ng. per 100 ml.; U-serum estradiol, 10.7 ng. per 100 ml.; U-serum prolactin, 11.3 ng. per milliliter; U-serum LH, 24.2 mIU. per milliliter; U-serum FSH, 5 mIU. per milliliter; U-serum DHA-S, 112 micrograms per 100 ml.; U-serum Δ4-A,††††††† 320 ng. per 100 ml.
8	36	Primary amenorrhea	Gonadal dysgenesis. Laparotomy age 28, 60.5 in.; no anomalies	T*******-serum testosterone, 138 ng. per 100 ml.; T-serum prolactin, 12.1 ng. per milliliter
9	37	Regular menses	Normal; postcastration	. . .
10	40	Primary amenorrhea; hyperthyroidism age 25; Treatment: RAI-131	PCOD; wedge resection, age 34	. . .
11	41	Regular menses; moderate hirsutism	? PCOD	U-serum testosterone, 87 ng. per 100 ml.; U-serum estradiol, 14.3 ng. per 100 ml.; U-serum prolactin, 31.2 ng. per milliliter; U-serum LH, 30.2 mIU. per milliliter; U-serum FSH, 10.2 mIU. per milliliter
12	43	Regular menses	Normal, postcastration	T-serum testosterone, 917 ng. per 100 ml.; T-serum estradiol, 1.3 ng. per 100 ml.; T-serum prolactin, 17 ng. per milliliter; T-serum LH, 85.5 mIU. per milliliter; T-serum FSH 78 mIU. per milliliter; T-serum DHA-S, 112 micrograms per 100 ml.

* U = untreated.

† Normal adult male range = 300 to 800 ng. per 100 ml.; normal adult female range = 25 to 85 ng. per 100 ml.

** Normal adult male range = 1 to 5 ng. per 100 ml.; normal adult female range: follicular phase = 3 to 10 ng. per 100 ml.; luteal phase = 1.5 to 30 ng. per 100 ml.; ovulatory peaks may be 3 to 10 times level found in follicular or luteal phase of cycle.

†† Normal adult male range = 6 to 30 mIU. per milliliter; normal adult female range = 5 to 30 mIU. per milliliter; ovulatory peaks may be 3 to 10 times level found in follicular or luteal phase of cycle.

*** Normal adult male range = 5 to 25 mIU. per milliliter; normal adult female range = 5 to 20 mIU. per milliliter; ovulatory peaks may be 3 to 10 times level found in follicular or luteal phase of cycle.

††† Normal adult male range = <1.0 ng. per milliliter; normal adult female range, follicular phase = 0.1 to 1.1 ng. per milliliter; normal adult female range, luteal phase = 0.5 to 26.0 ng. per milliliter.

**** ? PCOD = possible polycystic ovarian disease (no documentation by laparotomy or evidence of enlarged ovaries; clinical diagnosis based on available clinical and laboratory data; an adrenal source of hirsutism cannot be excluded).

†††† Serum DHA-S = dehydroepiandrosterone sulfate. Normal adult male range = 158 to 400 micrograms per 100 ml.; normal adult female range = 76 to 340 micrograms per 100 ml.

***** Urinary 17KS = urinary 17-ketosteroids. Normal adult male range = 12 to 20 mg. per 24 hr.; normal adult female range = 8 to 14 mg. per 24 hr.

†††††† RAI = radioactive iodine.

****** PCOD = polycystic ovarian disease (as documented by laparotomy or sonography)

††††††† Serum Δ4-A = delta-4-androstenedione. Normal adult male range = 65 to 248 ng. per 100 ml.; normal adult female range = 85 to 290 ng. per 100 ml.

******* T = treated.

see if this is a suitable hormonal environment with which the individual is comfortable. As the patient continues treatment there is ample time for self-reassessment of the sex-reversal decision, along with an opportunity to cross-dress with its social implications.

One such regimen is the initiation of moderately large doses of a combination estrogen-progestin oral preparation such as norethynodrel and mestranol, 5 to 10 mg. and 75 to 150 micrograms daily, respectively. This may be used in certain instances with concomitant intramuscular injections of estradiol valerate, 20 to 40 mg. every two to four weeks, for the first three to six months of treatment. This is particularly useful in those instances where a rapid response is desirable emotionally and physically and when the patient is underweight. Fairly rapid diminution of scalp hair loss may be noted with reduction of acne and facilitation of facial electrolysis during the early months of treatment. One may, however, administer estrogens alone orally as ethinyl estradiol, 0.15 to 0.5 mg. daily, or as conjugated estrogens, 2.5 to 5.0 mg. daily, with or without the addition of monthly injections of 20 to 40 mg. estradiol valerate intramuscularly. This treatment has the theoretic disadvantage of unopposed effects of estrogens on the breast without the added beneficial effect of the progestin on a more full breast development.

The initiation of treatment by itself has an anxiety-allaying and calming effect on most patients. The gradual development of feminization includes varying degrees of breast development; reduced libido, desirable in most patients who feel guilty about masturbation, and so forth; decreased size and consistency of testes; and development of feminine contours with some suppression of facial hair regrowth following electrolysis. All these parameters of feminization are documented by the suppression of serum LH with reduction of serum testosterone to adult female levels below 85 ng. per 100 ml. Periodic measurements of serum testosterone provide a useful guide to adequacy of hormonal therapy with a view to achieving a testosterone level between 35 to 85 ng. per 100 ml.

Follow-up evaluations of the patient should be performed at monthly intervals with observations of weight, blood pressure, and clinical signs of feminization. Subareolar painful nodules are not uncommon during the initial phase of therapy. The breasts must be palpated at frequent intervals since the development of breast carcinoma in such patients has been documented.[3] Galactorrhea was present in three patients and commenced 10 to 24 months after initiation of estrogen therapy. All three were hyperprolactinemic with levels of 26, 44, and 90 ng. per milliliter. The latter patient's therapy was stopped, and galactorrhea ceased as the prolactin level returned to 16 ng. per milliliter three months later.

Interval studies of blood chemistries including glucose, liver enzymes, and triglycerides are also indicated at two- to three-month intervals. Minor degrees of fluid retention and hypertension may be minimized by using the smallest possible dose of hormonal therapy for each individual case and with judicious use of diuretics with salt restriction. This clinical and chemical monitoring is essential to avoid some of the problems related to estrogen therapy: namely, hypertension, fluid retention, carbohydrate intolerance, and cardiovascular and hepatic complications. Three to four weeks prior to sex-reversal surgery, all estrogens should be discontinued to avoid the theoretic dangers of hypercoagulability in the postoperative phase.

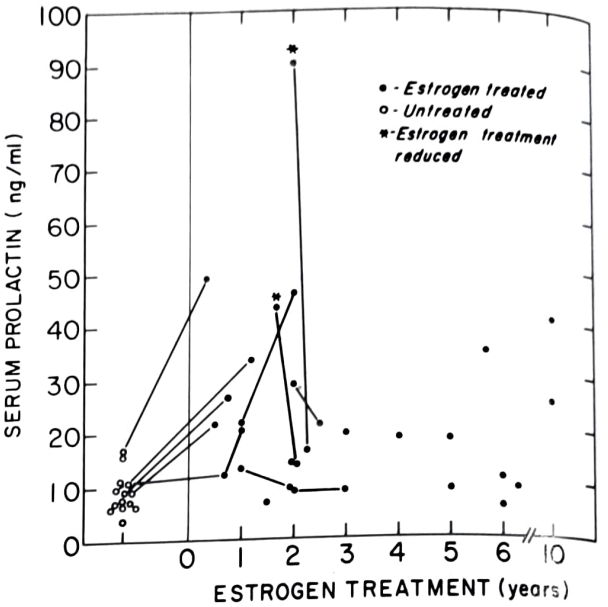

FIGURE 1. Serum prolactin concentrations of 13 untreated and 23 estrogen-treated transsexuals in relation to duration of hormonal treatment.

Several weeks after surgery the estrogen therapy can be modified to a regimen virtually similar to that of a hypogonadal woman. A combination estrogen-progestin preparation may be employed similar to the usual oral contraceptives. The advantage of using a progestin may be an enhancing effect on breast development in addition to providing some theoretical protection to unopposed effects of estrogens on the breast and/or hypothalamic pituitary system. One may use a combination of 30 micrograms of ethinyl estradiol combined with 1.5 mg. norethindrone acetate or with 0.3 mg. norgestrel daily.

Others have been maintained with 50 to 100 micrograms of ethinyl estradiol or 0.625 to 1.25 mg. conjugated estrogens orally daily. A progestin such as 10 mg. medroxyprogesterone acetate may be given for 7 to 10 days of the month together with the oral estrogen. Routine follow-up studies should be performed at three- to four-month intervals, including the recording of the blood pressure, fundi, legs for evidence of varicosities or phlebitis, breasts, and palpation of the liver.

Measurement of serum prolactin is also an important facet of patient management both pre- and postoperatively. This measurement indicates pituitary and/or hypothalamic hypersecretion in response to estrogen therapy. Most patients on estrogen therapy develop a mild elevation of serum prolactin. However, elevation of serum prolactin over 40 to 45 ng. per milliliter is an indication of an estrogen-induced hypothalamic suppression of prolactin inhibitory factor and/or lactotroph hyperplasia, possibly a forerunner of adenoma formation.[4-6] Following temporary cessation of the estrogen or reduction of the dosage, the prolactin level decreased in two patients, indicating a reversible state of hypothalamic-pituitary dysfunction (Fig. 1). Serum prolactin determinations should be performed at least every three months. Failure of hyperprolactinemia to decrease following cessation of the drug should be reinvestigated with thyroid function studies and polytomography of the sella turcica to exclude the rare possible development of a pituitary microadenoma. None of the hyperprolactinemic patients in our series were hypothyroid.

Liver scans should always be performed in the presence of a hepatic mass. Interval scans of the liver at three- to four-year intervals may also be indicated in view of the increased reported cases of hepatic cell adenomas and focal nodular hyperplasia in patients receiving estrogen therapy.[7,8]

Endocrine management of female transsexual

The percentage of female-to-male transsexuals is unknown, but it appears to range between 20 to 35 percent of all transsexuals.[9] As with the male transsexual, the patient is carefully screened and evaluated psychologically and medically to exclude cardiovascular, hepatic, renal, or lipid disturbances. In view of the erythropoetic effect of androgens, chronic respiratory disorders such as emphysema and bronchial asthma are relative contraindications to therapy, particularly in heavy smokers. Menstruation to the female transsexual constitutes a psychologic trauma, and to a great extent treatment is directed to suppress menstrual activity with androgens. Unlike the male transsexual, a gradual increased dosage of injectable androgen is indicated. Oral androgens are not used in view of possible cholestatic jaundice and associated liver enzyme abnormalities induced by the oral agents. One may initially administer 100 to 150 mg. testosterone enanthate or cypionate intramuscularly every two to three weeks, increasing the dosage to 200 mg. every two weeks until menses cease. In most instances, amenorrhea will ensue with this dosage regimen, but episodic bleeding may occur. When amenorrhea and virilization are achieved, serial measurements of LH and estradiol are useful in determing the adequacy of hypothalamic-pituitary suppression, as well as the proper dosage of the androgen. Increased libido, deepening of the voice, acne, increased masculinity, prominent facial hair growth, and cliteromegaly are clinical parameters of the efficacy of treatment. Severe scalp hair loss and acne, oiliness of skin, weight gain, and fluid retention may force modification of the dosage of testosterone that is to be administered. Following castration, the dosage of the injectable testosterone is reduced to 150 to 300 mg. of the ester every three to four weeks. This is sufficient to maintain virilization and prevent post castration vasomotor symptoms. As with estrogens, serial careful clinical monitoring should be performed pre- and postoperatively, including the use of liver scans when indicated. As with the use of estrogens, liver abnormalities such as peliosis hepatis, hepatic cell adenomas, and hepatocellular carcinomas have been described in patients on androgens.[10,11]

Conclusion

The literature relating to the endocrine treatment of the transsexual is sparse. The pioneering studies of Benjamin[1,2,12] and others,[9,13-16] have offered certain guidelines for diagnosis and treatment of transsexualism which are to a great extent valid today. The psychologic and surgical aspects of transsexualism were purposely avoided since a number of select articles are available to the interested physician.[15-19] The medical and endocrine treatment of the male or female transsexual is basically responsible medical care with an awareness of the potential risks of hormonal therapy. With the advent of radioimmunoassays in clinical practice, the physician can monitor the effects of such hormones on the hypothalamic-pituitary unit and utilize the levels of serum testosterone, estradiol, LH, and prolactin in judging proper hormonal therapy both pre- and postoperatively. The initial period of hormonal therapy is most important in that it allows time for the patient to reassess the medical and psychologic consequences of therapy and to prepare for possible sex reassignment surgery. In either case, the responsible physician has to assess the positive as well as negative aspects of treatment individually, offer encouragement when needed, and advise and guide the patient throughout a trying period of life.

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Acknowledgments. The author is grateful for the kind assistance and encouragement of Harry Benjamin, M.D., Mr. Garrett Oppenheim and the Confide organization. My thanks also to Leah Schaefer, Ph.D., David Wesser, M.D., Roberto Granato, M.D., Peter Fries, M.D., Charles Ihlenfeld, M.D., Nancy Sklar, M.A., and Mrs. Virginia Allen for the kind referral of their patients and their help in the understanding and care of these patients.

The typing of the manuscript by Miss Marva Moo Yin was most appreciated.

References

1. Benjamin, H.: Clinical aspects of transsexualism in the male and female, Am. J. Psychotherapy 18: 458 (1964).
2. Idem: For the practicing physician: suggestions and guidelines for the management of transsexuals, in Green, R., and

Money, J., Eds.: Transsexualism and Sex Reassignment, Baltimore, The Johns Hopkins University Press, 1969, appendix to chap. 20, p. 305.
3. Symmers, W. S.: Carcinoma of breast in transsexual individuals after surgical and hormonal interference with the primary and secondary sex characteristics, Brit. M. J. **2:** 82 (1968).
4. Yen, S. S. C., Ehara, Y., and Siler, T. M.: Augmentation of prolactin secretion by estrogen in hypogonadal women, J. Clin. Invest. **53:** 652 (1974).
5. Jacobi, J., Lloyd, H. M., and Meares, J. D.: Onset of oestrogen-induced prolactin secretion and DNA synthesis by the rat pituitary gland, J. Endocrinol. **72:** 35 (1977).
6. Fulling, K. H., Mills, B. K., Swarm, R. L., and McKeel, D. W., Jr.: Diffuse prolactin cell hyperplasia is the precursor lesion to estrogen-induced and spontaneous adenomatous neoplasia in rats, abstract 563, proceedings, 60th Annual Meeting, The Endocrine Society, Miami, Florida, June 14–16, 1978.
7. Edmondson, H. A., Henderson, B., and Benton, B.: Liver-cell adenomas associated with use of oral contraceptives, New England J. Med. **294:** 470 (1976).
8. Klatskin, G.: Hepatic tumors: possible relationship to use of oral contraceptives, Gastroenterology **73:** 386 (1977).
9. Pauly, I. B.: Female transsexualism: part I, Arch. Sex. Behav. **3:** 487 (1974).
10. Farrell, G. C., et al.: Androgen-induced hepatoma, Lancet **1:** 430 (1975).
11. Goodman, M. A., and Laden, A. M. J.: Hepatocellular carcinoma in association with androgen therapy, M. J. Australia **1:** 220 (1977).
12. Benjamin, H.: Nature and management of transsexualism, with a report on thirty-one operated cases, West. J. Surg. **72:** 105 (1964).
13. Money, J., and Primrose, C.: Sexual dimorphism and dissociation in the psychology of male transsexuals, in Green, R., and Money, J., Eds.: Transsexualism and Sex Reassignment, Baltimore, The Johns Hopkins University Press, 1969, p. 115.
14. Money, J., and Brennan, J. G.: Sexual dimorphism in the psychology of female transsexuals, in ibid., p. 137.
15. Pauly, I. B.: Female transsexualism: part II, Arch. Sex. Behav. **3:** 509 (1974).
16. Pomeroy, W.: The diagnosis and treatment of transvestites and transsexuals, J. Sex. Marital Therap. **1:** 215 (1975).
17. Jones H. W., Jr., Schirmer, H. K., and Hoopes, J. E.: A sex conversion operation for males with transsexualism, Am. J. Obst. & Gynec. **100:** 101 (1968).
18. Money, J., and Gaskin, R. J.: Sex reassignment, Internat. J. Psychiat. **9:** 249 (1970).
19. Laub, D. R., and Green, R., Eds.: The Fourth International Conference on Gender Identity Dedicated to Harry Benjamin, M.D.: selected proceedings, Arch. Sex. Behav. **7:** 243 (July) 1978.

New methods identify risk of birth defects among babies born to older mothers

Medical science has long been aware that birth defects occur more frequently among infants born to older women.

However, it is now possible to determine early in pregnancy if the infant is likely to suffer severe abnormalities, says a report in the November 23 *Journal of the American Medical Association.* Thus older women who choose to become pregnant can take advantage of recent advances in diagnosis that offer an opportunity to identify the risk of bearing a child with disorders or defects and consider elective abortion.

In an Atlanta, Ga., study, physicians found that, with the new techniques, women aged 35 to 44 years have no greater risk of bearing an infant with a detectable severe birth defect than do younger women.

The report is by Marshall F. Goldberg, M.D., of the Center for Disease Control in Atlanta.

In an accompanying editorial, Norman Fost, M.D., of the University of Wisconsin, Madison, points out that the new diagnostic techniques will by no means find all potential birth defects, but they can reduce the risk of bearing an affected infant.

Dr. Fost contends that prenatal diagnosis is ultimately a birth-facilitating rather than a birth-preventing service. More than 95 percent of the diagnoses in the womb disclose no abnormality of the fetus.

"For the older woman," says Dr. Fost, "the availability of such services makes conception acceptable where previously it was often avoided because of irrational fears or the rational desire to avoid even a small risk of having an affected child."