LETTERS TO THE EDITOR

The Endocrine Care of Transsexual People

To the editor:

I commend the authors and the journal for publishing Clinical Review 161 on the endocrine treatment of transsexual people (1). Despite the central role the endocrinologist plays in the management of these patients, there are few clinical studies or publications by the endocrine community focusing on this area. This is well reflected by the range of hormonal preparations and dosages used by different centers specializing in the treatment of transsexual people (1). Most of these clinical guidelines and protocols are empiric and have not been compared or tested in a controlled and rigorous manner. This leaves the clinical endocrinologist with the responsibility of integrating recommendations from the various centers. Moore et al. (1) embarked on this difficult task and have drawn general guidelines of their own but pointed to the need for randomized clinical trials. I would like to comment on some of the issues dealt with by the authors:

1) Asscheman et al. (2) have reported an incidence of thromboembolic episodes of 2.1% in male-to-female (M→F) patients less than 40 yr of age and in 12% of M→F patients above 40 yr of age under estrogen therapy. This led them to recommend transdermal estrogen administration to subjects over age 40 yr. In a subsequent analysis of 816 M→F transsexuals, the same group reported a substantial decrease in the incidence of thromboembolic events, which could be attributed to their change in clinical practice (3). Because the risk of this severe complication is also significant in younger patients, I would propose the use of transdermal preparations as the first-choice estrogen treatment for all age groups.

2) Hyperprolactinemia is a common finding in M→F transsexual patients, and its degree is positively correlated with the dosage of estrogen (3). Nevertheless, the incidence of prolactinoma is extremely low and probably does not warrant the routine performance of visual field assessment during follow-up, as recommended by the authors (1). Prolactin levels should, in my view, be measured at the initial visit before assessment during follow-up, as recommended by the authors (1). Progesterone should not be withheld during the use of estrogen therapy.

3) Maurice et al. (1) recommend assessment of bone mass in M→F transsexuals after surgical castration. Female-to-male (F→M) transsexuals are also at risk for osteoporosis. It has been shown that in the F→M population, estrogen treatment prevented bone loss after testosterone deprivation, whereas in the F→M group, testosterone treatment was in general unable to prevent the decrease in bone mass associated with the decline of serum estradiol levels (4). Furthermore, the change in bone mineral density correlated inversely with serum gonadotrophin levels. High LH levels appeared to be the best predictor of bone loss and reflected hormone undertreatment (4). Therefore, it would be wise to recommend performance of densitometry studies for F→M subjects as well and to incorporate measurements of LH to the other variables to be tested during the follow-up of these patients.

4) Endometrial hyperplasia is a serious concern in testosterone-treated F→M transsexuals. Consequently, periodic uterine sonohysterography, which can be performed through the abdominal wall if technically feasible, is advised until hysterectomy is performed. On the other hand, pelvic exams are very demanding for these patients from the psychological point of view. Because most of them do not have sexual contact that involves intercourse, the performance of routine Pap smears, as recommended, is probably not necessary, based on the recommendations of the U.S. Preventive Services Task Force for screening for cervical cancer (5).

5) Preservation of fertility is an important issue that should be discussed with patients. Freezing and storage of sperm should be proposed to M→F transsexuals before hormone therapy is initiated.

In conclusion, much improvement is needed in the quality of treatment that transsexual people receive, together with an empathic and supportive approach that these patients require.

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References


Authors’ Response: The Endocrine Care of Transsexual People

To the editor:

The Clinical Review by Moore et al. (1) on endocrine treatment in transsexual people in the August issue of JCEM is timely. We wish to offer some nuances to the recommendations made by Moore et al. (1).

The authors state that transition should be rapid and complete. However, cross-sex hormonal effects are, to an extent, irreversible. In our view, hormonal treatment should be embedded in the so-called “real-life test”. The real-life test is an extended period of full-time living as a member of the desired sex. The real-life test allows the subject and the attending professional to monitor the experience in the new sex status as she/he habituates her/his responses to other people. Without this test of how others react and how she/he reacts to others, the subject knows only her/his private convictions and fantasies of being a member of the opposite sex. The subject should have lived at least 2 yr full-time in the new sex before irreversible surgical reassignment is considered. The real-life test may be prolonged if too many hurdles present themselves during the test period. It is our belief that a slow transition phase of usually 2 yr, rather than a quick one, may be more advisable. Arguments include psychosocial reasons and, furthermore, a more gradual adaptation of the body to a changing hormonal milieu. In this regard, the dual-phase hormonal schedules may be recommendable. The first largely reversible phase includes antigonadotropes (e.g. cyproterone acetate 50–100 mg daily) in male-to-female transsexuals and progestins (e.g. lynestrenol 5 mg daily) in female-to-male transsexuals. This is an important phase of the real-life test, during which sex-specific features of the natal sex such as erections/ejaculations or menstrual bleeding are suppressed. This allows assessment of whether loss of characteristics of the natal sex alleviates the suffering of the candidate and whether induction

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of characteristics of the desired sex will further enhance well-being. If so, this is to be followed by administration of cross-sex hormones, with largely irreversible feminization and masculinization. Pharmacological ablation of endogenous sex steroid production before the initiation of exogenous cross-sex steroid treatment may allow a lower dosage of cross-sex hormones and reduce the risks of side effects and thus morbidity. This is worthy of research, but preliminary results in patients treated following this hormonal regimen, published in abstract form, indicate relatively few and minor morbidities that are mostly reversible with appropriate treatment (2). Unlike Moore et al. (1), we would no longer advise ethinylestradiol in the high dosage of 100 μg anymore because it is associated with an unacceptably high thrombotic risk (3). Moreover, we would like to argue that transdermal estrogens also can be advised under the age of 40, especially in smokers.

Moore et al. (1) argue that the Amsterdam group (4) reported a high incidence of depressive mood changes, hyperprolactinemia, and thromboembolic events, compared with a normal population. It is not unreasonable to assume that these effects are related to the dosage of administered hormones. Whether depression in transsexual people is due to hormonal changes is debatable. Transsexuals go through important life events during transition, both before and after sex reassignment surgery (SRS), with gains and losses. So, the question is not whether depression scores are worse in transsexual people than in a control group, but whether the score has improved after gender reassignment. Preliminary results of our follow-up study show that suicidal attempts had significantly diminished after SRS (5). Improved and consistent general well-being is one of the important reasons why we consider both hormonal treatment and SRS to be parts of a rehabilitation process wherein, gradually, bodily features are adjusted to gender identity. Usually, after 2 yr of cross-sex hormonal treatment, SRS is performed. Moore et al. (5) state in their recommendation table that endometrial ultrasounds should be performed every 2 yr in female-to-male transsexuals. In Europe, female-to-male transsexuals usually undergo hysterectomy and ovariectomy after approximately 2 yr of androgen administration. Long-term androgen administration induces polycystic changes of the ovaries indistinguishable from polycystic ovaries (6). Polycystic ovaries are more at risk of malignant development.

Finally, we feel that recommendations for the initial visit should include clinical examination assessing general health, hormonal status, and complication risk and karyotyping to diagnose intersex conditions.

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Authors’ Response: The Endocrine Care of Transsexual People

To the editor:

We thank Dr. Greenman (1) and Dr. T’Sjoen et al. (2) for their comments on our recent review article. They each add helpful additions to the recommendations presented in our review. We have a few comments to the issues raised. Both teams suggest the use of transdermal estrogen delivery for all age groups. This is reasonable and supported by the data as outlined. However, this may not offer a transition as immediate and dramatic as often desired by patients. We agree that visual field evaluation need not be done routinely because the development of a pro-lactinoma is rare. Certainly, freezing and storage of sperm or embryos could be recommended to individuals, although this is not a frequent request.

In regard to Greenman’s (1) comment on gynecological surveillance of female-to-male (F⇒M) transsexual people, vaginal ultrasound is a standard of care in following the endometrium in patients at increased risk for hyperplasia or carcinoma (3). However, a transabdominal pelvic ultrasound performed by an experienced technician may be a reasonable, although less ideal, alternative. Most importantly, a patient with new vaginal bleeding or a possible history of hyperplasia should receive prompt and thorough evaluation by endometrial biopsy and/or hysteroscopy. The recommendations from the National Institutes of Cancer and the U.S. Preventive Services Task Force (4) include routine pap smears for all sexually active women with a cervix. In postmenopausal women, the Task Force recommends ceasing cervical cancer screening after at least three negative pap smears as long as there are no abnormal pap smears in the last 10 yr. It is important to remember that individual F⇒M transsexual people may be at risk for human papillomavirus and cervical cancer through current or past vaginal intercourse. Additionally, it can take years for a cervical abnormality or cancer to develop. Stopping cervical cancer surveillance can be recommended only on a case-by-case basis.

Comments made by the Amsterdam group (2) are very helpful. The prevalence of an abnormal karyotype in this population is unknown, probably small, and probably irrelevant in the decision to treat. Therefore, we do not recommend routine chromosomal analysis unless the history or physical exam is suggestive of an abnormality. We do agree with their group that in many situations, particularly in adolescents or young adults, antiandrogens might be a better first step before using feminizing hormones. However, we also want to emphasize the importance of encouraging full transition. We strongly discourage incomplete treatment, whereby individuals have a mixture of female and male external sexual characteristics.

Developing guidelines in the face of limited data can be challenging. We appreciate the input from experienced clinicians, as above, to enhance the treatment transsexual people receive.

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The Effect of Octreotide on Parathyroid Carcinoma

To the editor:

In her excellent review of parathyroid carcinoma, Shane (1) states, "The long-acting somatostatin analog, octreotide, has also been reported to inhibit PTH secretion in a woman with parathyroid carcinoma metastatic to bone..." citing a case report by Koyano et al. (2). This encouraged us to try octreotide treatment in a 46-yr-old woman with parathyroid carcinoma metastatic to the right jugular fossa, positive on octreotide scan, causing local discomfort and hypercalcemia. We ordered a low starting dose of octreotide, 50 μg sc every 12 h; however, due to a clerical error, she received 500 μg every 12 h. Despite the high dose of octreotide, her serum calcium increased from 10.0 mg/dl before treatment to 11.1 mg/dl the next day, with no significant change in serum PTH levels (1422 pg/ml before treatment, 1543 pg/ml after). Octreotide was held temporarily and restarted 4 d later at a dose of 25 μg every 8 h. The dose was gradually increased to 50 μg every 8 h, but nausea and vomiting precluded increasing it further. After 5 d of octreotide treatment, despite aggressive hydration, her serum calcium rose to 14.5 mg/dl, and octreotide was discontinued.

Because of our disappointing experience, we reviewed the report of Koyano et al. (2) that was cited by Shane (1). They described a patient with parathyroid carcinoma metastatic to the lumbar spine and right iliac bone in whom a 200-μg dose of octreotide resulted in serum PTH "falling" from 919 pg/ml before dosing to 812 pg/ml 2 h later and "returning" to approximately 960 pg/ml 6 h later. About 2 wk later, a 7-d course of octreotide, 100 μg every 8 h, caused PTH to "fall" from 1447 pg/ml to 1164 pg/ml, but then it "rose" to 1733 pg/ml (higher than pretreatment levels) within 5 d after discontinuation. Their report does not permit judging whether these changes in serum PTH concentration might be due to random fluctuations or a true effect of octreotide.

Although Miller and Edmonds (3) reported a patient with primary hyperparathyroidism who seemed to respond to octreotide (initially 50 μg and subsequently 100 μg every 12 h) with modest decreases in serum PTH concentrations and normal levels of serum calcium, investigation of patients with primary and secondary hyperparathyroidism has not shown any effect of octreotide on serum PTH concentrations or calcium levels. Lucarotti et al. (4) studied 21 patients with primary hyperparathyroidism who were given octreotide 100 μg every 12 h for 6 d with no effect on serum PTH or calcium. Zielke et al. (5) randomized 40 patients with primary hyperparathyroidism and 40 patients with secondary hyperparathyroidism to receive a single dose of 200 μg octreotide or placebo and found no effect on serum PTH concentration or calcium levels 4 h later. Additionally, no somatostatin receptors were found in any of the parathyroid tissue from the 80 patients of Zielke et al. (5).

Octreotide appears to be effective in treating hypercalcemia due to neuroendocrine malignancies that produce PTH-related protein (6). Ridefelt et al. (7) further suggest that octreotide may be helpful in treating hypercalcemia of neuroendocrine origin, but not of parathyroid origin. In mouse pancreatic B cells, octreotide and somatostatin reliably decreased glucose-stimulated elevations in cytoplasmic calcium, whereas in normal bovine parathyroid cells and adenosomatous or hyperplastic human parathyroid cells, octreotide did not affect calcium or PTH release (7).

Side effects may limit treatment with octreotide. Zielke et al. (5) found that 45% of patients suffered adverse effects from a single 200-μg dose, including nausea, diarrhea, headaches, and dizziness.

Because there is no successful medical treatment of metastatic parathyroid carcinoma, a trial of octreotide therapy may be warranted. However, we see no evidence that octreotide is effective for treatment of hypercalcemia associated with parathyroid carcinoma, and it may be associated with side effects that preclude its long-term use.

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A response to this letter was invited, but the authors of the original article chose not to provide one.