Testosterone Therapy in Women with Gynecological and Sexual Disorders: A Triumph of Clinical Endocrinology from 1938 to 2008

Abdulmaged M. Traish, MBA, PhD,*† Robert J. Feeley, MA,† and Andre T. Guay, MD‡

*Boston University School of Medicine, Department of Biochemistry, Boston, MA, USA; †Boston University School of Medicine, Department of Urology, Boston, MA, USA; ‡Endocrinology, Lahey Clinic Northshore, Center for Sexual Function, Peabody, MA, USA

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ABSTRACT

Introduction. Although the term “medicalization” has been used by some to describe contemporary testosterone use in women with sexual disorders and testosterone deficiency syndrome, testosterone therapy for women with various gynecological and sexual disorders has been practiced since the late 1930s.

Aim. The study aimed to perform a historical review of testosterone use in women with sexual and gynecological disorders. This review is necessary to bridge important knowledge gaps in the clinical use of testosterone in women with sexual health concerns and to provoke new thoughts and understanding of the multidisciplinary role of testosterone in women’s overall health.

Methods. Review of medical literature on androgen therapy in women was carried out from 1938 through 2008.

Results. Approximately 70 years ago, clinicians from various disciplines relied on personal experience and clinical observations for outcome assessment of testosterone therapy in women. These early reports on testosterone use in women with sexual medical problems served as a foundation for the development of contemporary approaches and subsequent testosterone treatment regimens. Testosterone use was reported for sexual dysfunction, abnormal uterine bleeding, dysmenorrhea, menopausal symptoms, chronic mastitis and lactation, and benign and malignant tumors of the breast, uterus, and ovaries.

Conclusions. Health-care professionals engaged in the management of women’s health issues have observed the benefits of androgen therapy throughout much of the 20th century. Despite this clinical use of testosterone in women for more than seven decades, contemporary testosterone therapy in women is hotly debated, misunderstood, and often misrepresented in the medical community.


Key Words. Androgen Deficiency in Women’s Sexual Disorders; Testosterone; Androgen Therapy; Female Sexual Dysfunction

Testosterone Therapy in Patients with Gynecological and Sexual Disorder: An Overview

Testosterone therapy in women afflicted with various gynecological and sexual disorders was undertaken as early as 1938 [1,2]. Berlind noted the beneficial effects of androgens in ameliorating various gynecological disorders in women [3]. The author summarized data from 106 cases where effectiveness of the synthetic androgen, methyltestosterone (MT), in inhibiting lactation in puerperal women, reducing postpartum engorgement of breasts, alleviating dysmenorrhea, afterpains, premenstrual tension and mastalgia, menopause, and functional uterine bleeding. Over 75% of the patients in each gynecological group had significantly improved symptoms after MT treatment.

As early as 1941, it was shown that androgens are synthesized in the female and are the precursors of estrogen biosynthesis[4,5]. Salmon noted that:
Abel's rationale, in the 1940s, for androgen use in women with gynecological disorders was not rooted in mere speculation but grounded in an understanding of women's physiology.

Looking back, 70 years ago, clinicians practicing in the 1940s had to make important decisions in the absence of multi-institutional, placebo-controlled clinical trial data assessing long-term safety and in the absence of sensitive biochemical assays to determine plasma sex steroid hormone concentrations or activity. Such clinicians relied heavily on observations to guide their clinical decisions (Table 1). Clinicians noted many benefits of testosterone supplementation in defined patient cohorts and, therefore, cautiously proceeded with their patients' best interests in mind. Physicians had limited testosterone formulations available and therefore observed the responses with various formulations to assess more reliable clinical success. They noted that testosterone crystals suspended in water were at least half as potent as TP in oil and that use of the water-based solution could avoid local allergic reactions to the oil [11].

Also, TP pellet implantation was perceived as advantageous in that it “more nearly approached the endogenous mechanism of hormone secretion in the normal female organism.” [12]

By mid-1940s, use of androgen therapy in women with gynecological disorders was accepted in the medical community. A chapter authored by several well-renowned and established clinicians in the field and published in the well-respected series of “Vitamins & Hormones,” summarized the vast amount of clinical information generated during that era and provided a detailed discussion on the use of androgens in the management of women with various gynecological disorders [13]. The introduction to the chapter clearly reflects a growing awareness regarding androgen’s beneficial effects in women:

For approximately a decade androgens have been utilized as therapeutic agents in women. The too rigid early concept of androgens as male hormones seemed at first to lend merely an academic interest to their application to women; but with the growing awareness that they were capable of profoundly altering the sexual physiology of women their potential value as therapeutic agents...
began to be appreciated. In the intervening decade they have been widely used in the management of a variety of derangements of female sex physiology and more recently for numerous metabolic disorders. The literature which has accumulated is now sufficiently extensive to permit a tentative evaluation of the present status of androgens as therapeutic agents in women. [13]

Carter et al. provided a comprehensive discussion of the physiological effects of androgens in women and addressed the effects of androgens on the following: (i) the anterior pituitary; (ii) ovaries; (iii) endometrium; (iv) myometrium; (v) fallopian tubes; (vi) vaginal epithelium and secretions; (vii) menstruation; (viii) breasts; (ix) virilization; (x) urinary tract; and (xi) metabolic, vascular, and psychological effects [13].

Clearly, the advent of androgen use in women has prompted debate on the beneficial and adverse effects of this new therapy. Hamblen did not condone androgen therapy but suggested that two instances warrant androgen treatment: postmenopausal women with hormonal imbalances and women with certain hypermastias, where local androgen treatment could negate estrogenic effects [14,15]. In 1942, Hamblen wrote a provocative article denouncing androgen therapy in women and described it as a “fad” or “fashion,” arguing against the necessity of this treatment. He felt estrogen treatment alone was adequate to provide similar benefits without the potential for masculinization [16], a finding that echoed the sentiment of Korenchevsky [17]. Although differing opinions have existed over the last several decades, the majority of the well-documented studies seem to point toward androgen’s beneficial role in women. In the forthcoming sections, we discuss some of these studies and review the use of testosterone therapy in female sexual and gynecological disorders.

### Androgen Therapy of Sexual Dysfunction

The notion that androgens are integral to women’s sexual physiology was supported by studies demonstrating the effect of androgens on women’s libido and on sexual function for the past seven decades (Figure 1). Loeser found that patients (N = 10) given implantations of testosterone tablets (smallest dose, 300 mg) experienced an enlargement of the clitoris, an increase in libido, and a heightened sense of well-being [7]. It should be noted that 300 mg was a very high dose for pellet implantation of testosterone in a woman. Interestingly, however, during the same year, Rubinstein et al. found that smaller dosages (25 mg TP 3×/week) depressed sexual libido in five patients and hypothesized that this was the result of negative feedback on the anterior pituitary by TP [9]. This observation appeared to be the exception among many other studies that demonstrated androgen therapy to increase sexual libido. It should be emphasized that a dosing regimen of 25 mg of TP 3×/week for several weeks can amount to a considerably higher dosage than that of a 100 or 300 mg testosterone pellet implantation. Therefore, it makes sense that the lower total dosage of testosterone pellet implantation, as com-

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**Table 1 Clinical studies on androgen use in gynecological and sexual disorders in women**

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pared with the 3×weekly injection regimen, may increase libido because the dosage is not strong enough to inhibit the pituitary.

Salmon reported similar results to those observed by Loeser and noted clitoral enlargement in six of his patients and an increase in libido in response to androgen treatment [4,7]. He also observed that a number of young, married women who formerly considered themselves “frigid” were able to experience “a marked increase in coital gratification, culminating in an orgasm” after TP injections and that “in the majority of these cases, the effects wore off within several weeks after the discontinuation of the injections.”

Androgen therapy for the treatment of fibromyomas of the uterus increased libido and improved feeling of well-being in many patients [18]. This observation was confirmed by Abel [10]. Kennedy and Nathanson found that treatment of patients with breast cancer with androgens resulted in 37% of patients experiencing increased libido [19]. Interestingly, Studd et al. found that combining 100 mg of testosterone and 50 mg of estradiol produced greater improvement in libido than estradiol treatment alone and that libido did not correlate with plasma levels of follicle stimulating hormone (FSH) or luteinizing hormone (LH) [20]. Importantly, Greenblatt et al. noted that the female libido was a result not just of hormonal imbalances but also of “sentimental, psychological, and anatomical factors. . . .” [8] The authors also found that pellet implantation of 100 mg, as opposed to parenteral or oral administration, yielded the most consistent effect on increasing libido in their patients. The authors noted that these treatments had a large impact on individuals who were sexually frustrated or who were excessively sexual and could play a large role in improving relationships between sexual partners. In 1943, Greenblatt conducted another study and classified his patients into the following subgroups:

(a) 8 women who never had any libido or had very little of it; (b) 22 women who had once known libido but lost it; (c) 14 women who had a moderate amount of libido, and (d) 10 women in whom libido was good or very good. It was impossible to increase the libido of 2 psychologically frigid women who never had experienced sexual desire. On the other hand, restoration of the libido readily occurred following implantation in those women who at some time had known libido . . . Among those women who had a strong to moderate degree of sexual desire before implantation, all noted either no significant change or further increase in sexual pleasure. Two women with normal libido had a temporary decrease in sexual desire for several weeks immediately after pellet implantation and then a resurgence of the libido to a greater degree than that before the implantation . . . [12]

From the aforementioned description, it was obvious that women’s sexual libido is more complex than previously thought and is governed not only by hormone availability but also by women’s prior experience and memory of sexual libido. Salmon and Geist further postulated that androgens heighten response to psychosexual stimulation, cause the external genitalia to become more sensitive, and increase the intensity of sexual gratification [6].

Androgen therapy appears to increase libido through a variety of mechanisms. Increasing the
sensitivity and size of the clitoris might lead to more consistent sexual gratification. These clitoral changes “are accompanied by an awareness of sensations which are usually secondary to sexual stimulation and which may consequently initiate the sequence of events leading to increased libido and sexual responsiveness” [13]. A greater sense of well-being induced by androgen treatment may also contribute to sexual satisfaction.

Sherwin explored the role of androgens in female sexual health and suggested that androgens have more of an impact on sexual motivation [21]. In another study, Sherwin and Gelfand investigated three groups of women who underwent total abdominal hysterectomy and bilateral oophorectomy with one group receiving an estrogen-androgen preparation intramuscularly once a month, the second group receiving estrogen alone, and the third group remaining untreated [22]. Women receiving androgen and estrogen treatment reported higher rates of sexual desire, sexual arousal, and numbers of fantasies than those receiving estrogen alone or those kept untreated. Rates of intercourse and orgasm were higher in women treated with androgen and estrogens. Sherwin further suggested that, whereas exogenous estrogen is important for the integrity of genital tissues, testosterone is the hormone most critically implicated in the maintenance of libido or sexual desire in women [23]. A review of randomized controlled trials evaluating the efficacy of combined estrogen-androgen on sexual functioning in postmenopausal women demonstrated a high degree of agreement among the findings. Combined androgen and estrogen often increased the frequency of sexual intercourse and orgasm in naturally and surgically postmenopausal women [24].

Sarrel et al. investigated the efficacy of estrogens alone and in combination with testosterone on sexual function and menopausal symptoms in postmenopausal women [25]. Sexual desire, satisfaction, and frequency were significantly improved in women treated with combined estrogen–androgen therapy but not by estrogen alone or estrogen–progestin therapy. The authors concluded that androgens play a pivotal role in sexual function but that estrogens are not a significant factor in determining levels of sexual drive and enjoyment.

Arlt et al. investigated women with adrenal insufficiency and evaluated well-being and sexuality with the use of validated psychological questionnaires and visual-analog scales, respectively [26,27]. Treatment of women with the androgen dehydroepiandrosterone significantly improved overall well-being as well as scores for depression and anxiety and significantly increased the frequency of sexual thoughts sexual interest and satisfaction with both mental and physical aspects of sexuality. The authors concluded that DHEA improves well-being and sexuality in women with adrenal insufficiency. These observations are consistent with the findings of Waxenberg et al. in which women who underwent adrenalectomy for breast cancer reported complete loss of sexual function [28].

Several studies on androgen treatment of women have demonstrated that, in women who underwent oophorectomy and hysterectomy, transdermal testosterone improved sexual function and psychological well-being [29–46]. A number of these studies examined the efficacy and safety of a testosterone in surgically menopausal women with sexual desire disorder who underwent bilateral oophorectomy [30,34–46]. The data strongly suggested that testosterone improved sexual desire and other sexual function domains and reduced distress in surgically menopausal women.

Braunstein suggested that the major adverse reactions to testosterone are hirsutism and acne and no increase in cardiovascular risk factors [31,32]. The author pointed out to the limited data on endometrial safety, and most data supported a neutral or beneficial effect with regard to breast cancer. There were no signs of increased risk of hepatotoxicity. The author concluded that therapeutic administration of testosterone in physiologic doses is safe for up to several years.

Testosterone Therapy of Abnormal Uterine Bleeding

During the early 1900s, testosterone therapy in gynecology had become an accepted form of treatment based on its ability to “override” normal ovarian function. The notion that androgen treatment could override ovarian function through inhibition of the anterior pituitary suggested that the inhibition of estrogen production might help attenuate symptoms associated with abnormal uterine bleeding, including dysfunctional bleeding and bleeding from structural causes. Shorr et al. noted that vaginal smears and biopsies showed that TP could counteract the estradiol-induced cornification of the vaginal epithelium [1].

Loeser studied five women with menorrhagia associated with small intramural fibromyomas [2]. He treated all patients intramuscularly with 50 mg
of TP on alternate days for 2 weeks or more. Treatment with TP, totaling 500 mg or more, caused menstruation to cease. In the absence of menstruation and the concomitant absence of uterine stimulation by female hormones, Loeser observed a decrease in size of the fibromyomas in all five patients [2]. Despite these favorable results and the ability of physicians, like Loeser, to stratify patients into groups according to diagnostic criteria, the medical profession was “confronted with the problems of therapeutic indications, margin of safety, and optimal dosage” regarding androgen use in women [47,48]. Despite these valid and serious concerns, Mazer and Mazer did not use them as justification for withholding testosterone treatment [47,48]. Instead, they turned toward animal studies to gain a greater understanding of androgens’ effects in vivo [47,48]. One conclusion they drew from the literature was that TP inhibited the anterior pituitary of the rat [47,48]. Based on this finding, Mazer and Mazer hypothesized that TP could help with dysfunctional uterine bleeding—particularly that in menopausal age where a surplus of FSH causes an increase in estrogen production, leading to hyperplasia of the endometrium and uterine bleeding [47,48].

Indeed, they found that dysfunctional uterine bleeding was “cured” in the majority of their patients [47,48]. However, it was not a result of inhibition of the anterior pituitary by TP as they had initially hypothesized. They found that TP did not impact the timing of their patients’ menstrual cycles, suggesting that the low TP dosages used in this study had a direct effect on the uterus [47,48]. The dosage used was not potent enough to disturb the ovary–anterior pituitary feedback loop. A “cure” was defined as having occurred when “abnormal bleeding ceased during the period of treatment and did not recur for at least 4 months after cessation of treatment . . . Patients who were only improved are classified as ‘not cured.’ ” [47,48] Out of the 38 patients (68%), 26 were “cured,” while 12 patients (32%) had either temporarily or not at all improved [47,48]. The authors noted that they achieved the same effects with 30–120 mg of TP in 30 days as studies that used 450–1,000 mg in 30 days [47,48]. In the latter regimen, the menstrual rhythm and endometrial pattern were typically altered. By not affecting these two factors, Mazer and Mazer concluded that the smaller TP dosages have a direct effect on the uterus, not on the anterior pituitary [47,48].

Interestingly, the authors also determined to what degree curettage prior to TP treatment helped to “cure” their patients [47,48]. They found that 17 out of the 23 patients that received curettage were cured, while 9 out of 15 patients given TP without curettage were cured [47,48]. The authors, though, did not correlate the “cure” rate with those with metrorrhagia or menorrhagia. Also, the authors did not provide a dose-response curve to show which of the 2.5, 5, 10, or 25 mg dose had the greatest effect. In addition, there was no mention of which group (those with menorrhagia versus those with metrorrhagia) received which of the aforementioned dosages.

Loeser noted that the implantation of testosterone pellets successfully controlled serious menorrhagia caused by fibroids [7]. Berlind found that, in 11 cases involving functional uterine bleeding, MT treatment at dosages ranging from 30, 40, or 50 mg daily, depending on the severity, was successful in all 11 cases [3]. During this same year, Salmon et al. and Geist and Salmon published seminal articles and stated that, although helpful, animal studies were not necessary for the justification of treating women with testosterone [5,49];

It seems to us to be both illogical and unnecessary to seek, in animal experiments, a rationale for the use of androgens in the treatment of abnormal uterine bleeding, when a physiologic basis for their use can be found in the biologic effect which testosterone evokes in human females. Thus it has been shown that testosterone propionate, if given in sufficient amounts to women, inhibits the secretion of gonadotropic hormone by the hypophysis, suppresses ovulation and menstruation and abolishes temporarily the normal proliferative and secretory phenomena of the endometrium, reducing the latter to a state of involution. In cyclical women, in contrast to rodents, the action of testosterone propionate appears to be monophasic, viz., antigynecogenic. It was felt, therefore, since testosterone inhibits both the gonadotropic activity of the pituitary (which appears to be the primary factor in the cycle of events which culminates in uterine bleeding) and the endometrium (which is the end organ involved in the bleeding process) that possibly abnormal uterine bleeding could be controlled by utilizing this antigynecogenic property of testosterone. [5]

This study was significant not just because it further verified the logic of treating women with androgens but also because it attempted to distinguish the effects that androgen therapy had on functional versus dysfunctional bleeding. Salmon et al. examined patients with functional menometrorrhagia and those with meno-metrorrhagia associated with uterine fibroids [5]. In 44 out of the 45 patients in the functional group, excessive bleeding was effectively and quickly controlled with TP. Posttreatment follow-up of up to 32 months revealed lasting beneficial effects of TP. TP in patients with uterine fibroids was less effective than in the functional group, with posttreat-
ment recurrence of symptoms occurring in 60% of the patients. A wide range of TP doses was used in this study, and the authors found that smaller doses were just as effective as large ones and that the smaller doses did not suppress menstruation or induce estrogen deficiency. Patients in both groups also reported a feeling of invigoration, an improved appetite, weight gain, and an increase in libido after injection. In this study, Salmon et al. used endometrial biopsies and vaginal smears to determine effective TP dosages for their patients [5]. As testosterone has a characteristic effect on the endometrium, the smear and biopsy techniques served as objective measures of testosterone activity. In fact, the authors observed that regressive changes in the endometrium and vaginal mucosa preceded defeminization. Therefore, they were able to avoid masculinization phenomena by paying close attention to whether TP treatment was causing morphological regression in the smear or biopsy.

**Androgen Therapy of Dysmenorrhea**

Rubinstein et al. showed that TP improved the management of patients with dysmenorrhea—a condition frequently associated with menometrorrhagia [50]. The authors believed that pain associated with dysmenorrhea was the result of an endocrine imbalance, with either excess estrogen or reduced progesterone levels, leading to excessive contractions of the myometrium. Contractility of the myometrium is diminished by progesterone, and the authors hypothesized that TP may relieve patients of pain associated with dysmenorrhea because testosterone possesses structural and chemical properties that may be similar to progesterone. This study employed several TP dosing regimens such as multiple injections of TP each week before menses or TP treatment once menstrual pain began. Out of 26 patients, 16 patients in this study were completely relieved of pain associated with dysmenorrhea and associated symptoms (15 out of the 16 had a functional uterine bleeding). A total of 4 out of 26 were partially relieved (2 of which had infantile uteri, the other 2 had retroverted uteri), while 4 out of 26 failed to respond to therapy. In 2 out of 26, pre-existing symptoms were aggravated. TP reduced dysmenorrhea, premenstrual tension, and profuse bleeding in the majority of these subjects. TP had the greatest benefit in those with functional (or “essential”) dysmenorrhea, suggesting that the etiology of dysmenorrhea is endocrinological.

Rubinstein et al. provided vivid descriptions of how TP treatment improved management of patients with dysmenorrhea [50]. The following is an example of the symptoms that one patient had prior to treatment:

... severe dysmenorrhea had been present from the onset of her first menstrual period. The pain which appeared with the flow was so severe that bed rest was required for twenty-four to forty-eight hours. Although she was then able to return to work, marked discomfort persisted throughout the period. Nausea, occasional vomiting, insomnia, and feelings of depression and anxiety accompanied the pain during the first one or two days. [50]

After treatment of the patient with TP, it was noted that

menses began on the twenty-fifth day and were practically free of all discomfort. She lost no time from work during this period, since she was free from digestive upsets, sleep disturbances, and the usual feelings of depression. [50]

In another case study, it seemed as though TP exerted a priming effect:

Treatment consisted of two injections of testosterone propionate in 5 mg doses administered s.c. on the twenty-fifth and twenty-third days of her menstrual cycle. Menses began on the twenty-fifth day and were practically free of all discomfort... During the next cycle the same treatment was repeated on the twenty-third and twenty-fifth days. Menses began on the twenty-sixth day again free from all discomfort. During the third cycle it was decided to note the effect of the 10 mg administered as a single dose. This was given on the twenty-fifth day and was followed the next day by menstruation which was accompanied by marked abdominal pain, nausea, and vomiting. [50]

Thus, it may be that the timing, rather than the total dosage of TP, is more important in determining the therapeutic value of TP for dysmenorrhea.

In 1942, Cinberg proposed a theory that dysmenorrhea resulted from the excitation of the autonomic nervous system resulting from vascular pelvic engorgement, causing normal uterine luteal phase contractions to be perceived as painful [51]. He believed that, by reducing menstrual flow, androgens alleviated the excitation of the autonomic nervous system, thereby attenuating symptoms associated with dysmenorrhea. No evidence was presented to support this contention. Thus, it remains in the realm of speculation.

**Androgen Therapy of Menopause**

Studies showing the beneficial effects of androgen therapy on menopausal symptoms also date back to the mid-1900s. Although it has been known for over 20 years that MT can cause hepatotoxicity and cardiotoxicity in men, leading to its removal...
from the market in treatment of men, it has still been widely used in conjunction with estrogens for treatment of menopause and other conditions in women since 1941. Androgen therapy developed, in part, as a result of inadequacies of estrogen treatment for menopausal symptoms in some cases. There is no denying that the beneficial effects of estrogen on menopausal symptoms have been well established. However, Gusberg reported that use of stilbestrol was beneficial in menopausal patients with cancer of the reproductive organs and was as effective as in menopausal women who suffered from abnormal uterine bleeding [52].

Gusberg stated:

Suffice it to say that in the human species whose genetic pattern is so complex, we think it unwise to subject susceptible tissue to a stimulating substance; those individuals who have already demonstrated the responsiveness of one of the reproductive organs to whatever abnormal stimulus develops carcinoma would seem especially unfavorable subjects in whom to administer a cell-proliferating substance like estrogen. We have also become impressed with the fundamental error in continuing estrogenic therapy in any postmenopausal individual for long periods of time for it creates a habit which is difficult to break; we have sought a method to remedy this condition. These considerations, together with the occasional production of abnormal endometrial patterns in patients who have developed stilbestrol bleeding led us to the use of androgen therapy for this selected group of menopausal patients. [52]

Gusberg found that MT had a beneficial effect in improving menopausal symptoms in his patients and that androgens were of greater benefit than estrogens. He also recommended that patients with specific conditions, such as cancer of the reproductive tract or breast, abnormal uterine bleeding, bleeding due to treatment with estrogenic substances, be treated with androgens only. Although some believed that androgens were the superior agents of treatment for menopausal symptoms, others believed that a combination therapy of androgens and estrogens would be more effective than androgens alone. Greenblatt et al. evaluated 102 patients with symptoms of menopause who were given diethylstilbestrol alone (0.25 mg), a combination of MT (5.0 mg) and diethylstilbestrol (0.25 mg), MT alone (5.0 mg), or a placebo [53]. The authors found the following: (i) estrogen treatment alone resulted in 96.9% improvement in their patients with hot flashes and other symptoms and that the vaginal smear showed constant maturation of cells; (ii) combination treatment of “androgens and estrogens resulted in 89.6% improvement” in their patients and found that “improvement in the hypoestrogenic vaginal smear was a constant finding”; (iii) androgen treatment alone resulted in satisfactory relief for 23.5% of their patients, but “a moderate degree of amelioration of symptoms was reported by approximately half(52.9%) of the patients”; and (iv) of those given placebo, 83.8% reported no improvement.

Although estrogens, based on the above percentages, seemed to be of greatest benefit to those with menopausal symptoms, patients also reported that estrogen treatment caused the most side effects: 30.5% and 34.2% of patients on estrogen treatment alone experienced nausea and uterine bleeding, respectively; 4% and 30.5% of patients on the combined androgen and estrogen treatment experienced nausea and uterine bleeding, respectively; 5.2% of patients receiving androgen treatment alone experienced nausea, while less than 1% of patients reported uterine bleeding; lastly, patients receiving placebo did not experience symptoms. So, taking into consideration both the benefits and the risks of developing side effects, the combination treatment may have been the best compromise for this set of patients. Another study conducted by Glass and Shapiro examined the effects of a mixture of estrogen and testosterone on 92 patients with menopausal symptoms [54]. They found that this combination therapy was more effective than either treatment alone and that 72% of patients preferred this treatment. Although many studies did find androgens to be helpful either alone or in conjunction with estrogen, Walter recommended against androgen therapy as only 27% of his patients benefitted and 32% of the 52 patients experienced some type of masculinization phenomena [55].

In addition to ameliorating menopausal symptoms, androgens had also been used in the treatment of psychosexual problems in postmenopausal women [20]. The authors had found that the combination of testosterone and estradiol was superior to estradiol alone in improving patients’ sexual response and libido. Sherwin et al. further elucidated the beneficial effect that androgens have on specific aspects of sexual behavior in 53 surgically menopausal women and found that androgen was responsible for an increase in “sexual motivation” but not “sexual activity.” [21].

Androgen Therapy of Chronic Mastitis and Lactation

Chronic mastitis was another condition that physicians attempted to treat with androgens [56]. It was hypothesized that excess estrogen stimulation might have also caused breast pain or enlargement.
Loeser (1938) reported that two of his patients had chronic mastitis and that they both benefitted from TP treatment (12 × 50 mg or 6 × 100 mg in a 3- to 4-week period) [2]. In fact, in one patient, palpable lumps in the breast had completely disappeared. While treating these patients, curettage was performed at various points to assess the endometrial state. Menstruation had been inhibited and the endometrium became atrophic. The implicit hypothesis was that, in inhibiting estrogen production, chronic mastitis would improve. Spence studied a group of 24 patients with chronic mastitis, 16 of which received TP treatment [57,58]. Spence’s case studies demonstrated that mammary pain can either be continuous or episodic throughout the menstrual cycle, that either one or both breasts can hurt, that palpable lumps can be present, and that the menstrual cycle can be normal or abnormal [57]. Spence first treated all patients with sterile olive oil to measure the placebo effect. He found that 13 patients (over half) dramatically improved. Of the 13 patients that dramatically improved, 8 of these patients (with no lumps) were not further treated with testosterone as their chronic mastitis had been relieved. However, the remaining 16 patients were treated intramuscularly with TP (either 25, 50, or 100 mg 2x/week for several months). Out of the 16 patients, 14 were relieved of pain. Spence noted that in 12 patients treated there were lumps in the breast; in 3 the lumps disappeared, but in 2 of these spontaneous disappearance could not be excluded, and in 1 2925 mg in five months was required, resulting in hypertrophy of the clitoris and extreme atrophy of the endometrium. In 5 patients there was some reduction in the size of the nodules. In 2 patients who were not improved fresh nodules appeared in the breast during treatment. Menstruation was suppressed in 7 patients receiving the larger doses. Increased growth of hair developed in 5 of the younger patients, in 4 with comparatively small doses, but this was not observed in older patients receiving much larger doses. It is emphasized that because of this complication and the undesirability of prolonged atrophy of the endometrium, testosterone propionate should be used with caution in women. [57]

Spence, in 1940, assessed the local inunction of testosterone ointment in chronic mastitis [58]. Nonmedicated ointment was first given as a control and 2 out of 8 patients were relieved from mammary pain. Subsequent daily inunction of 3–10 mg of testosterone or TP ointment helped to relieve pain associated with chronic mastitis in 6 out of 8 patients. Spence, in comparison to his study in 1939, did not notice any masculinization phenomena or menstrual cycle suppression and advocated using inunction over intramuscular injection of TP [58]. That same year, Atkins found a significant psychological component when treating chronic mastitis [59], consistent with the placebo effect observed by Spence [57], an improvement in symptoms associated with chronic mastitis through androgen therapy, and an exacerbation of symptoms with large doses of estrogens. In 1942, an article published in the New England Journal of Medicine authored by Nathanson et al. reported on the effects of TP administration in 30 patients “with severe mammary pain and secretion” [60]. The authors reported that TP was found to be an effective agent in the relief of the syndromes in a high percentage of cases. It appears to be more efficacious than the estrogenic hormone in the treatment of the same lesions. Recurrence of symptoms and signs is the rule, usually within six months after medication is discontinued. Prolonged and continuous treatment, especially with large doses, is to be discouraged. As much can be accomplished by planned periods of treatment followed by adequate rest intervals. Many patients present a predominant psychogenic element, and others have spontaneous remissions; therefore, care should prevail in the selection of the case for this or any similar type of therapy. [60]

The premise that caution should be exercised with regard to androgen therapy was a recurring theme in the literature. Yet physicians did not believe caution to be synonymous with restraint. Physicians were not blind to the beneficial effects of androgen therapy on their patients. Part of the benefit was derived from the physician’s ability to approach patients in a flexible manner and to tailor androgen therapy to their patients’ needs.

Androgen Therapy of Benign and Malignant Tumors

A study conducted in 1941 by Greenblatt et al. presented evidence that MT and TP were useful in management of women with small uterine tumors and associated bleeding [18]. The first set of six patients assessed by Greenblatt et al. presented with uterine tumors and symptoms such as severe hypermenorrhea, intermenstrual bleeding, and abdominal pain. TP (465 mg over the course of 13 months) followed by MT (20 mg over the course of 1 month) therapies reduced these complications, and the authors noted that TP and MT increased “their sexual libido and feeling of well-being,” and that “no virilizing symptoms developed in the dosages used in this series” [18]. The authors also found that small doses of TP or MT did not interfere with ovulation, a finding consistent with Hamblen et al.’s [15] and that these doses reduced intermenstrual length. The second set of 10 patients assessed by Greenblatt et al. presented

The notion that a tumor may regress in response to androgen treatment was further supported by observations made by Perloff [61]. Their rationale for treating uterine fibroids with TP was based on a previous study, which involved placing pellets of estradiol benzoate in the guinea pig uterus [62]. They observed that, in 75% of the cases, fibromyomatous tumors were formed. They also found that concomitant androgen treatment was able to limit the estrogen-induced production of these tumors. Based on these findings, they examined the role of androgens in treating uterine fibroids in women. Perloff described three case studies where he administered TP, in dosages as low as 30 mg/week, and observed a significant reduction in uterine tumor size [61]. In case studies involving 50 mg/week, uterine tumor size diminished, at the expense of somewhat irregular menses and slight virilization. TP’s beneficial effects on menstrual flow and tumor size diminished once treatment was terminated (in 2 out of 3 patients). Not all studies during this period found that testosterone reduced tumor size. It is possible that this relationship may be governed by tumor stage and responsiveness to treatment.

The following year, Beecham et al. hypothesized that patients with ovarian carcinoma might benefit from testosterone treatment [63]. Each of the 6 patients treated suffered from adenocarcinoma of the ovary or cervix and was given TP. After treatment, 5 out of 6 patients experienced an almost complete and prompt cessation of pain associated with the tumor and reported an increase in appetite, feeling of well-being, and an increase in strength. Despite these improvements, tumor size did not decrease. At the time, it “was difficult for the authors to make sense of such a dramatic improvement in the clinical profile” as “pain was so promptly and effectively relieved.” Despite these beneficial effects of TP, they felt that “until more evidence is accumulated, the treatment must be considered empirical.” However, they felt that “…this should not be misinterpreted as implying that the therapy is not of value. We believe that it is, and would be interested in an extension of its use.”

Physicians believed that androgen treatment held promise for patients with ovarian and cervical malignancy and that further testing was necessary to validate TP’s effects. Wyatt also found that TP did not help reduce ovarian carcinoma size in two case studies, although TP had a beneficial effect on patient “well-being” [64]. Greenblatt and Kupperman assessed the effects of different steroid hormones on the endometrium and found that the combination of 25 mg of TP combined with 10 mg of progesterone on a daily basis for 4–5 days results in the rapid cessation of bleeding in patients with menorrhagia [65]. Graham and Graham discovered another valuable property of androgen therapy [66]. The authors demonstrated that testosterone had a beneficial effect on patients with cancer of the uterine cervix by enhancing the effectiveness of radiotherapy. The authors discuss testosterone as being the most effective agent in increasing total-body sensitivity to radiation in mice and discuss their rationale for testosterone use in humans:

In each of five case studies described by Graham and Graham, the patients initially noted a poor response to the test doses of radiation [66]. However, upon treatment with TP, the radiation effect increased substantially, usually 1–3 days posttreatment, with as much as 52% of cells becoming radiated after 72 hours. Administration of α-tocopherol also had a beneficial impact on cellular-induced radiation changes. Of the four patients who received testosterone, none had any masculinizing effects, despite receiving a total of 250–1,000 mg TP (25 mg i.m. every other day.) While the mechanism of testosterone action was
unknown, testosterone favorably influenced cell response to radiation, and the authors acknowledged that a much larger sample size is needed to confirm the notion that testosterone could improve the survival rate of initial poor responders to radiation therapy with cervical cancer.

While TP therapy was beneficial in the majority of the subjects in this study, it is clear from the above description that there were side effects. It is important to note, however, that from a patient’s perspective, receiving large doses of TP to potentially diminish the size of a lump (that may be malignant) may be welcomed and override any fear of developing masculinizing symptoms. However, as Spence noted, caution is paramount when dealing with an agent that has a specific therapeutic window and the potential to have undesirable adverse effects on other organs [57].

Some patients clearly did not benefit from androgen therapy [67]. Farrow and Woodward found that patients with skeletal metastases, resulting from breast cancer, did not respond well to large doses of TP. Although TP reduced breast pain, larger doses of TP for treatment of skeletal metastases induced hypercalcemia and increased metastases growth. However, a series of studies have shown that patients with breast cancer and without skeletal metastases respond more favorably to TP treatment. Fels reported that, in his patient with breast cancer, TP reduced breast pain and vomiting and eliminated palpable nodules [68]. Based on a biopsy taken from a patient whose palpable nodules had disappeared, Fels hypothesized that TP did not act directly on the carcinomatous cells but rather on the fibrous tissue surrounding them, causing this tissue to proliferate and block the migration of neoplastic cells [68].

Prudente assessed the postoperative prophylaxis of recurrent mammary cancer with TP [69]. He noted that TP in the prophylaxis of mammary cancer after operation made sense biologically, as estrogens influence the formation of the tumor and androgens antagonize estrogens. Prudente also noted that

the results obtained in this indication as gauged by the survivals after 3, 4, and 5 years are about 100 per cent better than those observed after operation only. This fact indicates that testosterone propionate exercises a protective or prophylactic action against recurrences of surgically treated mammary cancer. [69]

Prudente recommended that the grade of histological malignancy should determine the dosage of TP administered and that up to 175 mg of TP per week should be used after mammary cancer operations. He also believed that virilization symptoms were secondary to the lifesaving benefits of TP treatment on the cancer. It should be noted that 175 mg of TP is the same dose as used in male testosterone replacement therapy and is likely to mainly act by suppressing the pituitary.

Another report found that use of large doses of TP in the treatment of advanced carcinoma of the breast was very effective in 4 out of 11 patients [70]. Over a period of 3 months, each of the patients received several thousand milligrams of TP, and no adverse effects were reported. Although, the authors attested to the fact that this sample size was small and the beneficial effects of TP, including their duration, could not be predicted. In 1949, the Council on Pharmacy and Chemistry wrote a report regarding estrogens and androgens in mammary cancer [71]. They found that, of 285 patients (77 with only soft tissue lesions, 82 with only osseous lesions, and 126 with both types) treated with TP for metastases,

approximately 62 per cent of these patients experienced subjective . . . relief of pain, feeling of well-being and increased appetite . . . Objective improvement in soft tissue lesions was seen in approximately 1 out of 5 patients, while objective improvement in osseous lesions was slightly less frequent, only 18 per cent of patients showing favorable response. [71]

Interestingly, the authors also reported on the effectiveness of estrogen in the treatment of 144 patients with metastases, 92 of which received diethylstilbestrol, while the rest received 1 of 5 other forms of estrogen. The council stated that “the majority of patients were treated for soft tissue metastases” and that

approximately 60 per cent of patients treated with estrogens showed some degree of subjective relief of symptoms. About half the patients with soft tissue lesions showed objective improvement after estrogen therapy. [71]

This is a striking result, especially as it had been believed at the time that estrogens, in part, were responsible for influencing tumor development in the breast. Unfortunately, the council did not draw any correlation between the different estrogen treatments and benefits. Although androgens and estrogens were used in management of patients with mammary cancer, the council urged that surgical treatment and irradiation should be given priority. The council also felt that future studies were needed to build upon this report and better understand the effects of steroids on mammary cancer. In 1953, Kennedy and Nathanson reported on the effects of intensive sex steroid hormone
therapy in advanced breast cancer [19]. The report focused largely on the description of systemic and local reactions that resulted from the high doses of steroids administered, which were the result not of the steroid interacting with the tumor but of the inherent properties of the hormone itself.

While TP was shown to be effective in cases involving chronic mastitis and mammary cancer, studies in the early 1900s also showed TP inhibiting lactation during the puerperium. At the time, it was understood that, by not treating this condition or by relying on existing methods of treatment, “pain, tenderness, engorgement and lumpiness of the breasts” would often result [72]. Kurzrok and O’Connell found that, of the 21 women who received 50–150 mg of TP over the course of 2 days, 19 experienced virtually complete relief [72]. Abarbanel found that, of 49 patients treated with 10 mg of testosterone, 82% were relieved of after pains [73]. He also reported that, of the 50 cases given 5 mg of TP (i.m.) followed an hour later by 5 mg of TP (s.c.), 92% experienced almost complete relief from severe painful breast engorgement.

Discussion

Health-care professionals specializing in the evaluation, diagnosis, and treatment of women’s health issues have observed the benefits of androgen therapy for a wide array of clinical symptoms and conditions not only in recent years but also throughout much of the 20th century (Table 1; Figure 1). Over the last seven decades, androgen therapy has been employed in the treatment of women experiencing symptoms associated with sexual desire disorder, dysfunctional uterine bleeding, dysmenorrhea, menopause, and mammary cancer (Table 1). Clearly, these historical studies provided the foundation for the advanced clinical studies reported over the past decade.

Surgical or natural menopause is associated with changes in the hormonal milieu and sexual function [74,75]. In addition, management of patients with breast cancer with chemotherapy also produces changes in the hormonal milieu and contributes to sexual dysfunction in women [76] Changes in sexual dysfunction in menopausal women are correlated with estradiol levels but not with testosterone levels [75]. This would suggest that postmenopausal women complaining of sexual dysfunction could benefit from treatment with estradiol alone and would experience improvement in sexual function. However, this is not the case in the experience of many clinicians. Estrogen treatment alone of postmenopausal women does not produce improvement in sexual desire or other domains of sexual function. Thus, the attempts to link estrogen levels to sexual function, especially sexual desire, without testosterone, have not been documented. Recent reviews on this topic have suggested that surgically menopausal women treated with testosterone experience significant increases in satisfying sexual activity and significant improvement in all domains of sexual function, and decreases in personal distress, with a favorable safety profile indicating that testosterone deficiency contributes to hypoactive sexual desire disorder [77,78].

Recently, several well-designed, randomized, placebo-controlled clinical trials focused the spotlight on the efficacy and safety of androgen therapy. Simon conducted a large, placebo-controlled clinical trial and found that surgically post-menopausal women with hypoactive sexual desire disorder, receiving testosterone patch treatment with concomitant estrogen therapy after 24 weeks, experienced greater total satisfying sexual activity, sexual desire, and less personal distress [46]. Additionally, the authors reported that women receiving transdermal testosterone scored significantly higher for arousal, orgasm, pleasure, and responsiveness in comparison to placebo, with no major safety concerns over the course of 24 weeks. Buster et al. also reported similar findings in a study using a testosterone patch for low sexual desire in surgically menopausal women [34]. Bolour and Braunstein described several clinical trials that highlighted testosterone’s beneficial impact on treating post-menopausal women with sexual dysfunction, displaying symptoms of androgen deficiency [33]. In fact, both Bolour and Braunstein and Braunstein reported that testosterone administration to post-menopausal women for up to 2 years was well tolerated without any major adverse reactions [30–33]. Kingsberg et al. suggested that women were able to competently judge their perceived benefits and measures of sexual function [39]. The Sexual Activity Log, Profile of Female Sexual Function, and the Personal Distress Scale can independently identify and verify patients who benefitted from testosterone treatment [39].

The Endocrine Society Guidelines on Androgen Therapy in Women [79] recommended that physicians do not diagnose or treat women with androgen deficiency. Some of the Endocrine Society Panel members do not practice in the field of sexual medicine and lack experience with diagnosis of androgen deficiency and androgen therapy in
women. For these reasons, we believe the conclusions made by the Endocrine Society Guidelines on Androgen Therapy in Women were not based on the breadth of existing clinical and scientific knowledge attained by many physicians in the field but rather on the panel members’ lack of experience with androgen deficiency and sexual dysfunction in women [79]. A comprehensive commentary challenging the conclusions made by the Panel of the Endocrine Society Guidelines on Androgen Therapy in women has been published [80] and cited herein. This commentary was endorsed by more than 25 nationally and internationally recognized clinicians and scientists who are experts in the field of sexual medicine.

Although both contemporary and historical studies have shown the benefits of androgen therapy in select female populations, it is important that the limitations of this type of treatment are not overlooked. For example, many studies have reported on the adverse effects of MT. Specifically, the US Food and Drug Administration (FDA) had recommended against using methyl testosterone as a treatment in women and men because of hepatotoxicity effects [81–83].

That we must proceed with caution is not a new concept in the practice of medicine but one that had been echoed by many of the historical clinical studies cited in this report. However, “caution” must not take the form of denying patients a valuable treatment option, especially in light of the accumulated data spanning approximately the past 70 years (Table 1, Figure 1). In Figure 1, it is interesting to note the dip to zero publications in the 1960s as well as the 10-fold change in scale of axes between left and right panels. In addition, these graphs illustrate the varying trends in medical treatment in female testosterone replacement therapy and the interest in basic and clinical research in this field of female sexual function. There has been a remarkable interest in understanding the role of androgens in the physiology of sexual function in women, as reflected by the increased research activity into the basic and clinical levels (Table 2). This increased research activity points to the potential usefulness of androgen therapy in women’s sexual function. A compilation of studies reported between 1995 and 2008 is shown in Table 2. Clearly, this area of investigation is gaining momentum and recognition as a major component of women’s overall and sexual health.

The studies discussed in this report suggest that androgens are important in maintaining sexual function in women and have important physiological function in women’s health. Over the course of the past 70 years, use of androgen in women was not associated with serious adverse effects, and this has been supported in recent studies cited in Table 2. Indeed, virilization, acne, and hirsutism are among the most noted side effects. However, with androgen doses aimed at restoring the physiological circulating concentrations, these adverse effects were found to be minimal, at best. The concerns regarding the safety of androgen therapy in women have been addressed by Braunstein and his colleagues [30–33]. We believe that careful and diligent monitoring of the clinical profile of each patient treated with testosterone is important. We must focus on the evaluation of long-term safety data and the identification of patients who may benefit from testosterone therapy.

It should be noted that in the mid-20th century, MT was used therapeutically in men and women. However, MT was shown to produce hepatic toxicity in animal studies [84–86] and in humans [82,87–90]. Interestingly, even with the current knowledge that MT may produce hepatotoxicity, some investigators continue to use MT [91–102]. In fact, Gitlin et al. suggested that combined esterified estrogen-MT therapy (in doses of 0.625 mg esterified estrogen + 1.25 mg MT or 1.25 mg esterified estrogen + 2.5 mg MT) was found to be safe regarding hepatic function in postmenopausal women during the course of 24 months in eight controlled clinical trials [100]. Nevertheless, considerable evidence exists in the literature to suggest that use of MT may be associated with liver damage and that use of MT is discontinued in men, and that its use in women is discouraged.

Current testosterone assays lack precision and are fraught with inconsistencies and inaccuracies. There is much criticism for the accuracy and precision of current clinical assays for total and free testosterone, especially in women [103]. Several studies have suggested that modern technologies such as liquid chromatography/mass spectrometry may provide better assays for testosterone measurements [104–111]. The criteria by which testosterone assays could be judged and the need for standardizations have recently been discussed [103]. It was suggested that normative values for total and free testosterone must be established for men, women, and children, and we must pay attention to the many variables that influence serum testosterone concentrations. Indeed, efforts need to be focused on developing assays that are sensitive, reliable, accurate, and with fewer confounding factors.
The medical and scientific community must continue the development of treatment guidelines that accurately reflect the rich expertise of the practicing physicians who manage women with various disorders and most take into account the wealth of accumulated evidence of the role of androgens in treating these women. We will provide better health care for patients if we utilize the lessons of history in our efforts to develop a better understanding of androgen use in women’s health.

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Corresponding Author: Abdulmaged M. Traish, MBA, PhD, Boston University School of Medicine, Department of Biochemistry, Boston, MA, USA. Tel: 617-638-4578; Fax: 617-638-5412; E-mail: atraish@bu.edu

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Statement of Authorship

Category I

(a) Conception and Design
Abdulmaged M. Traish; Robert J. Feeley; Andre T. Guay

(b) Acquisition of Data
Abdulmaged M. Traish; Robert J. Feeley; Andre T. Guay

(c) Analysis and Interpretation of Data
Abdulmaged M. Traish; Robert J. Feeley; Andre T. Guay

Category 2
(a) Drafting the Article
Abdulmaged M. Traish; Robert J. Feeley; Andre T. Guay
(b) Revising It for Intellectual Content
Abdulmaged M. Traish; Robert J. Feeley; Andre T. Guay

Category 3
(a) Final Approval of the Completed Article
Abdulmaged M. Traish; Robert J. Feeley; Andre T. Guay

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