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Testosterone implants in women: Pharmacological dosing for a physiologic effect

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ABSTRACT

Objectives: The objectives of this study were to determine therapeutic serum testosterone (T) levels/ranges and inter-individual variance in women treated with subcutaneous T implants.
Study design: In study group 1, T levels were measured at two separate time intervals in pre- and postmenopausal women treated with subcutaneous T for symptoms of androgen deficiency: (i) four weeks after pellet insertion, and (ii) when symptoms of androgen deficiency returned.

In a separate pharmacokinetic study (study group 2), 12 previously untreated postmenopausal women each received a 100 mg T implant. Serum T levels were measured at baseline, 4 weeks and 16 weeks following T pellet implantation.

In study 'group' 3, serial T levels were measured throughout a 26 h period in a treated patient.
Results: In study group 1, serum T levels measured at 'week 4' (299.36 ± 107.34 ng/dl, $n = 154$), and when symptoms returned (171.43 ± 73.01 ng/dl, $n = 261$), were several-fold higher compared to levels of endogenous T. There was significant inter-individual variance in T levels at 'week 4' (CV 35.9%) and when symptoms returned (CV 42.6%). Even with identical dosing (study group 2), there was significant inter-individual variance in T levels at 'week 4' (CV 41.9%) and 'week 16' (CV 41.6%). In addition, there was significant intra-individual circadian variation (CV 25%).
Conclusions: Pharmacologic dosing of subcutaneous T, as evidenced by serum levels on therapy, is needed to produce a physiologic effect in female patients. Safety, tolerability and clinical response should guide therapy rather than a single T measurement, which is extremely variable and inherently unreliable.

1. Introduction

Testosterone (T) is becoming increasingly recognized as a vital hormone in women. T elicits a physiologic effect via functional androgen receptors (ARs), which are located in almost all tissues including the breast, heart, blood vessels, gastrointestinal tract, lung, brain, spinal cord, peripheral nerves, bladder, uterus, ovaries, endocrine glands, vaginal tissue, skin, bone, bone marrow, synovium, muscle and adipose tissue [1,2]. T is also the major substrate for estrogen in both men and women and thus has an indirect effect via the estrogen receptor. Until recently, outside of its role in sex drive and libido, T has been virtually ignored as an essential hormone in female physiology and erroneously labeled as a 'male hormone'. Healthy pre-menopausal women have 15–20-fold higher levels of T than estradiol. In addition, there are exponentially higher levels of androgen precursors, including dihydroepiandrosterone sulfate (DHEAS) and androstenedione, producing an immeasurable amount of T locally, at the cellular level, which is able to bind to the AR. Unlike the acute decline of estrogen at menopause, T and its prohormones decline gradually with age [3,4].

Pre- and post-menopausal patients may experience symptoms of androgen deficiency including sexual dysfunction, dysphoric mood (anxiety, irritability and depression), lack of well-being, physical fatigue, changes in cognition, memory loss, insomnia, hot flashes, rheumatoid complaints, pain, vaginal dryness, urinary complaints and incontinence, which are becoming increasingly recognized and treated [5,6]. There is a paucity of data guiding T replacement therapy in women. Although some authors recommend following T levels and adjusting doses based on these levels, there is no evidence supporting that a single testosterone

Abbreviations: T, testosterone; CV, coefficient of variation; IRB, Institutional Review Board; BMI, body mass index; PK, pharmacokinetic; DHEAS, dihydroepiandrosterone sulfate; AR, androgen receptor.

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measurement is accurate, nor that it correlates with physiologic effect. More importantly, there is no evidence to support that testosterone levels on therapy should remain within ranges for endogenous production. This paper investigates the inherent variability of single measurement of testosterone and supports that pharmacologic dosing of subcutaneous T implants is both safe, and necessary, to produce a physiologic effect.

2. Methods

2.1. Study group 1: serum T levels (ranges) on therapy, 'week 4' and prior to re-implantation, 'end'

All patients in this group are part of an ongoing, 10 year, prospective IRB approved trial on the effect of subcutaneous T implants on the incidence of breast cancer [5]. Pre- and post-menopausal patients participating in the trial were either self-referred or referred by their physician to this private clinical practice (RG) for symptoms of relative androgen deficiency including; hot flashes, sweating, sleep disturbance, heart discomfort, depressive mood, irritability, anxiety, pre-menstrual syndrome, fatigue, memory loss, menstrual or migraine headaches, vaginal dryness, sexual problems, urinary symptoms, pain and bone loss. As reported elsewhere, no patient was excluded from therapy based on baseline serum hormone levels (we previously reported that there was no correlation between baseline hormone levels (estradiol, free T, total T) and incidence/severity of presenting symptoms as reported on the validated Menopause Rating Scale; and that all symptoms improved on subcutaneous T therapy alone, independent of baseline hormone levels [5]). Written informed consent was obtained on all patients.

285 patients treated with testosterone implant therapy for at least one year (mean 28.1 ± 10.4 months), seen at the clinic between February and April 2010, were included in a follow-up clinical, questionnaire study. 3.1 mm (diameter) T implants were compounded by a pharmacy in Cincinnati, OH. The mean testosterone implant dose in this cohort of patients was 133.3 ± 26.8 mg, range 55–240 mg. Dosing was based on weight and adjusted based on clinical response to therapy. Testosterone implants had been inserted, on average, every 13.8 ± 3.8 weeks. All patients were offered, but not required to have, blood testing. 154 of these patients had serum testosterone levels drawn 4 weeks after their testosterone pellets were inserted.

In addition, 'end' serum testosterone levels were collected on a separate cohort of 261 patients treated at the clinic between November 2011 and March 2012. Depending on the laboratory used and insurance coverage, free T levels were also performed on 153 of these patients. Patients were instructed to have serum T levels drawn when their symptoms of androgen deficiency returned, prior to their subsequent T pellet implant. Only serum T levels obtained within 2 weeks of the patient becoming symptomatic (i.e., 'end' levels) were included in this analysis.

2.2. Study group 2: pharmacokinetic study, inter-individual variation in T levels

In a separate IRB approved trial (Miami Valley Hospital, Premier Health Partners, MVH Study # 06-0090;6859), pharmacokinetic (PK) studies were performed in 12 previously untreated, postmenopausal women receiving identical doses (100 mg) of T as a subcutaneous implant. Serum T levels were measured at baseline (prior to therapy), 4 weeks and 16 weeks after T pellet insertion. BMI was calculated and correlated with serum T levels at baseline and on therapy. Written informed consent was obtained on all patients.

2.3. Study 'group' 3: circadian (intra-individual) variation in T levels

A 26 h PK pilot study was performed on a female patient treated with a 112.5 mg T implant. Venous bloodspot specimens were collected every 2 h during waking hours, throughout a 26 h period, 6 weeks after T pellet implantation.

3. Methodologies

3.1. Serum testosterone testing

In group 1, total testosterone levels were measured using liquid chromatography tandem mass spectrometry, LCMS (intra-assay CV 9%) or by immune-assay using Bayer Advia Centaur immunoassay (intra-assay CV 11.8%). The methodology used (IA vs. LCMS) depended on the lab, which was determined by insurance coverage.

Free testosterone was performed by tracer equilibrium dialysis calculation (intra-assay CV 11.3%).

In the 12 patients from group 2, total testosterone was measured by immune-assay using Bayer Advia Centaur immunoassay. A duplicate specimen was sent to a second lab (LC) for comparison. T was measured using ammonium sulfate precipitation radioassay (intra-assay CV 12%).

3.2. Venous bloodspot

Drops of venous blood from a forearm venipuncture were dropped onto specialized filter paper (Schleicher and Schuell 903; Bioscience, Keene, NH) and allowed to dry. Samples were stored at room temperature. Standard and control, 6.4 mm discs were punched from dried blood spot samples using the Wallac Multipuncher Dried Bloodspot Puncher (Perkin Elmer-Wallac). The samples, along with standards, were added to a 96 deep-well (2 ml per well) plates and re-hydrated in 200 ml per disk of assay buffer containing phosphate-buffered saline (Diamedix, Miami, FL), 0.025% Tween 20, and 0.01% ProClin 950 antimicrobial (Sigma–Aldrich, St. Louis, MO). From this point the standard procedure for serum testing using enzyme immunoassay for testosterone (DRG) was followed and results given in ng/dl (ZRT lab, Beaverton, OR).

3.3. Statistical analysis

The statistical program R (R Development Core Team, 2012) was used for all data analysis [7]. The Spearman's rank correlation coefficient, Spearman's rho (ρ), analysis was used to screen relationships between individual variables (T dose, BMI, T level). Coefficient of variation (CV) was calculated and expressed as a percentage.

4. Results

4.1. Testosterone dose and week 4 T levels (study group 1)

The mean serum testosterone level, 4 weeks after T implantation, was 299.36 ± 107.34 ng/dl (range 101–633, $n = 154$, CV 35.9%). This mean value is 4–6 times the upper limit of normal for endogenous production (i.e., 42–72 ng/dl).

As expected with weight based dosing, there was a positive correlation between the patients BMI and their testosterone implant dose (0.566, $P < 0.0001$). Conversely, there was no correlation between serum T levels at week 4 and BMI ($\rho = -0.043$, $P = 0.59$) (Fig. 1).

In this group of patients, treated with testosterone therapy for over one year, there were no reported adverse drug events. As

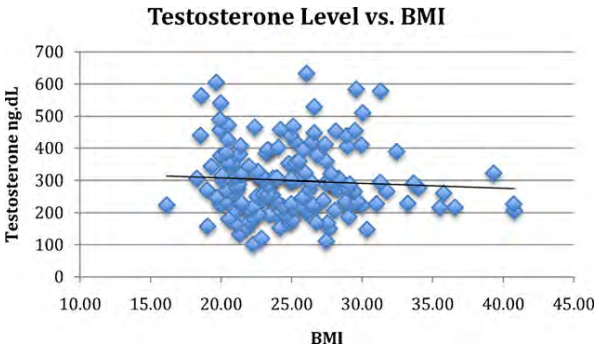

Fig. 1. There was no correlation between serum testosterone levels 4 weeks after T pellet implant and patients BMI ($\rho = -0.043$, $P = 0.59$, $n = 154$).

previously published, 85.7% of patients reported a mild to moderate increase in facial hair while 6.4% of patients reported a severe increase [8]. 32 of 285 (11.2%) patients reported a moderate increase in acne, half of who had a prior history of adult acne. One patient, with a history of adult cystic acne, reported severe acne on therapy. 50% of patients reported skin improvement on therapy (e.g., moister skin, softer skin and fewer wrinkles). Although occasionally reported in clinical practice, no one in this cohort reported clitoromegaly. Three patients (1%) reported perceived voice changes: (i) voice cracking, (ii) raspy voice and (iii) deeper voice.

4.2. 'End' serum testosterone levels: levels drawn when patient's symptoms returned prior to re-implantation (study group 1)

261 women in study group 1 had testosterone levels measured when their symptoms of androgen deficiency returned, prior to T pellet re-implantation. The mean testosterone level for this cohort was 171.43 ± 73.01 ng/dl (range 22–461, CV 42.6%).

153 of these 261 patients had both free and total testosterone performed by a single lab (Quest) at the 'end' of their pellet implantation. The mean total T in this group was 184.72 ± 74.6 ng/dl (range 47–461, CV 40.4%), over 4 times the upper limit of normal for endogenous production (reference range total T: 2–45 ng/dl). The mean free T level was 18.82 ± 11.51 pg/ml (range 1.1–74.8, CV 61.2%). The average free T prior to re-implantation was over 3 times the upper limits of normal for endogenous production (reference range free T: 0.1–6.4 pg/ml). There was a positive correlation between total T and free T ($\rho = 0.66$, $P < 0.001$).

4.3. Inter-individual variation (group 2)

Baseline serum testosterone level in the 12 post-menopausal patients, prior to T implant therapy, varied significantly, 23.9 ± 20.1 ng/dl (range 1–52, CV 84%).

The mean serum T level measured 4 weeks after insertion of a 100 mg T implant, was 190.8 ± 80 ng/dl (range 83–368, CV 41.9%) (Fig. 2). There was over a 4-fold difference between the lowest and highest testosterone level despite identical dosing. None of the patients had symptoms of androgen excess.

This significant variation in serum T levels persisted through week 16, past the time when symptoms normally return. Mean testosterone level 16 weeks after T pellet implantation was 74.9 ± 31.2 ng/dl (range 44–136, CV 41.6%).

For quality control, duplicate serum specimens in these 12 patients had been sent to a second lab at each time interval (baseline, week 4, week 16). There was no correlation in serum T levels, between the two labs (both using immune-assay) at low baseline T levels ($\rho = 0.4542$, $P = 0.138$). However, there was a strong correlation in serum T levels between the two labs at week 4 ($\rho = 0.9021$, $P < 0.01$) and week 16 ($\rho = 0.8231$, $P < 0.01$) when measuring higher serum T levels on therapy.

Interestingly, although all patients received a 100 mg T implant (non weight-based dosing), there was no correlation between BMI (24.5 ± 3.9, range 20.1–32.4) and serum T levels measured at either week 4 ($\rho = -0.1821$, $P = 0.571$) or week 16 ($\rho = 0.0841$, $P = 0.0795$).

There was no correlation between baseline T levels, and T levels at week 4 ($\rho = 0.3410$, $P = 0.278$) or week 16 ($\rho = 0.3269$, $P = 0.300$). However, there was a positive correlation between T levels measured at week 4 and week 16 ($\rho = 0.62949$, $P = 0.0324$).

4.4. Intra-individual (circadian) variation, 26 h study

Venous blood spot testosterone levels were measured every 2 h (while awake) over a 26 h period in a female patient 6 weeks after receiving a 112.5 mg testosterone implant. The mean testosterone level was 268.4 ± 67.1 ng/dl (range 176–383, CV 25%) (Fig. 3). Notably, levels fluctuated significantly throughout the day, similar to the circadian release of endogenous hormones [9].

5. Discussion

Testosterone therapy is becoming increasingly used in pre- and post-menopausal women to treat symptoms associated with hormone/androgen deficiency. We have previously reported that subcutaneous T alone (no estrogen) effectively treats many symptoms previously considered due to estrogen deficiency [5]. T exerts a direct effect by binding to ARs, which are located in almost all organs and tissues in both men and women. In addition, T is aromatized to estradiol in the ovary, adrenal gland and peripheral tissues; and has a secondary effect via the estrogen receptor. T has also been shown to effectively treat 'hormone deficiency symptoms' when used in combination with an aromatase inhibitor, supporting that testosterones biologic effect is primarily via its cognate AR [10,11].

Subcutaneous testosterone implants have been used in women since 1938 in doses of 50–225 mg. Long-term data exists on the safety, tolerability and efficacy of these doses in up to 40 years of therapy [12–18]. In addition, significantly higher doses of T, used to treat breast cancer patients and 'female to male' transgender patients have been studied and found to be safe [16,19–21].

Long acting, sustained release T implant dosing is weight based. As previously published, the T doses used in this current study (55–240 mg), are both clinically effective and well tolerated [5,8,10,11,25,27]. Higher T doses have been shown to correlate with greater improvement in quality of life as evidenced by the 'Menopause Rating Scale' total score and somatic, psychological and urogenital sub-scores [5]. This is consistent with other studies reporting that T effect is dose dependent [18,22–24].

In addition, these T implant doses have been shown to increase scalp hair growth and were not associated with androgenic alopecia [8]. As expected, there was a concomitant increased facial hair growth in the majority of patients. However, no patient discontinued therapy because of increased hair growth. Similar dosing (100–180 mg) effectively treats migraine headaches in both pre and postmenopausal women [25] and has safely been used (with an aromatase inhibitor) in breast cancer survivors to treat symptoms of androgen deficiency [10]. There have been no adverse drug events related to subcutaneous T therapy; and other than increased facial hair and mild to moderate acne, side effects have been minimal at these doses.

It has been documented in the past that serum T levels on subcutaneous implant therapy are higher than endogenous ranges [8,10,12,13,25] and that 'more consistent benefit is seen with testosterone levels that exceed the normal range' [26]. Higher

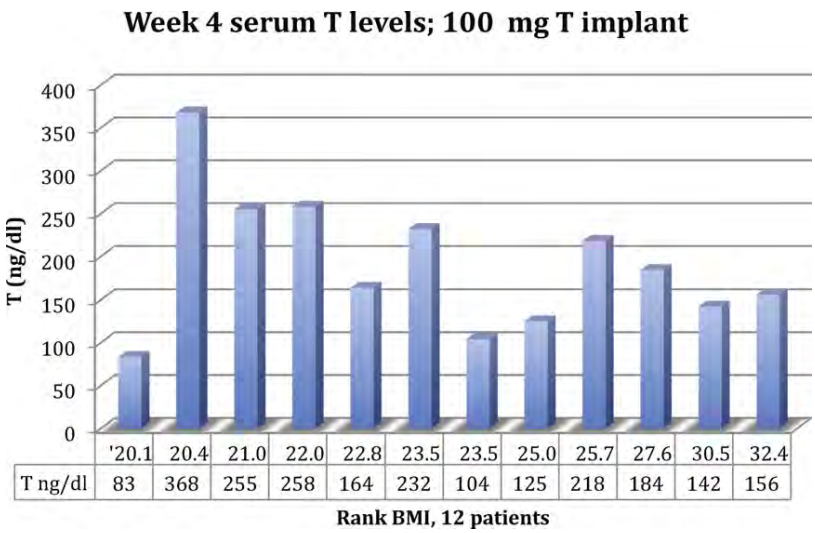

Fig. 2. Serum testosterone levels in 12 female patients, 4 weeks after therapy with a 100 mg T implant. Mean T level was 190.8 ± 80 ng/dl (range 83–368, CV 41.9%). There was no correlation between serum T levels and BMI ($\rho = -0.1821$, $P = 0.571$).

serum levels of T have been shown to correlate with greater clinical effect including a beneficial effect on lipids; higher HDL, lower VLDL and lower TG [18,27].

Contrarily, there is no clinical evidence supporting the recommendation that 'serum levels of T on therapy should remain within the upper limits of endogenous production for a young healthy female'. This theoretical 'physiologic dosing' of T in women has been shown to be clinically ineffective [18,24,28]. The simplistic concept of using a single serum T level to guide therapy ignores the complexity of physiologic events from production/release to biological effect; and totally disregards the significant contribution of local production, as well as, age related changes.

We have demonstrated that serum T levels, on the 'biologically effective' doses used in this study, were 4–6-fold higher on than endogenous T ranges at both 'week 4' (299.36 ± 107.34 ng/dl) and prior to re-implantation (171.43 ± 73.01 ng/dl). However, the majority of the circulating level of T measured in serum is tightly bound to SHBG, unable to bind to the AR and therefore, unable to elicit a biologic/clinical response. The relatively small proportion of T available to bind to the AR is a complex combination of unbound T, a portion of albumin bound T (i.e., low affinity binding protein compared to SHBG), and most importantly, the unquantifiable amount of testosterone produced locally at the cellular level from the androgen precursors, DHEAS and androstenedione.

Similar to T's decline with age, DHEAS and androstenediones production also decreases with age [3]. This decline in proandrogens markedly reduces the amount of T available at the cellular level. While androstenedione is found in 5–10-fold higher concentrations than T in serum, DHEAS levels may be thousands of times higher than T levels [4]. Thus, in comparison to T, the contribution of these prohormones to bioavailable T at the AR exponentially declines with age. With this marked decline in local production, increasing amounts of T (i.e., from replacement therapy) would be needed to supply a greater portion of bioavailable T to the AR.

There is also concern of AR 'resistance' [29]. Theoretically, with aging the AR, similar to the insulin receptor, may become resistant to T and require higher levels to elicit the same response.

This study has shown that a single serum T level on therapy is extremely variable and inherently unreliable. There was significant variation between individuals (CV > 40%) in both groups of patients tested, independent of dosing and BMI. In addition, the broad range in T levels reflects significant inter-subject variability in pharmacodynamic response to these serum T concentrations.

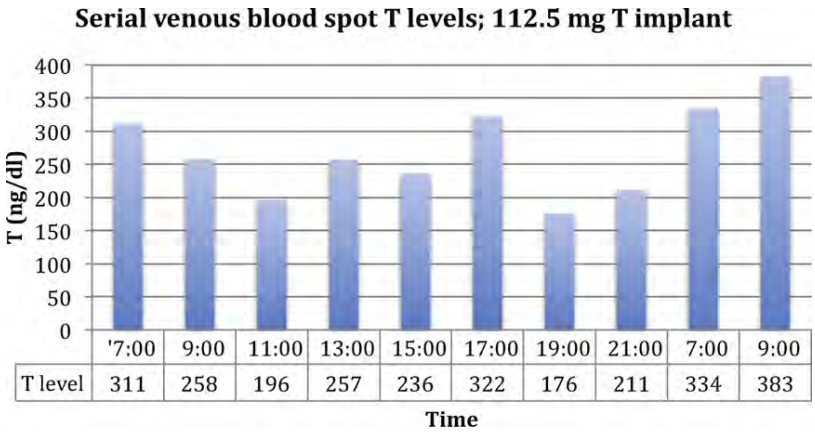

Fig. 3. Serial venous blood spot testosterone levels were measured every 2 h (while awake) over a 26 h period in a female patient treated with a 112.5 mg testosterone implant. Mean T level, 268.4 ± 67.1 ng/dl (range 176–383, CV 25%).

Our case presentation demonstrated significant circadian variation in a female patient over a 26 h period (CV 25%). A similar circadian variation (CV 21%) was also seen in a male patient treated with 1200 mg of subcutaneous T (data not shown). In addition, we have seen a variation in T levels in a female patient who inadvertently had consecutive serum samples analyzed (231 ng/dl vs. 310 ng/dl, CV 21%). Although these case findings are of limited value, in light of the significant inter-individual variation, we suggests that routinely monitoring T levels in clinical practice, and adjusting therapy based on a single value, should be viewed with skepticism; as well as clinical guidelines founded solely on serum levels on therapy.

We propose that T dosing should be based on adequate clinical efficacy, similar to insulin dosing, where individual biologic effect and tolerability determines dosing rather than serum levels based on endogenous production. We no longer routinely monitor serum T levels in all patients. However, because of aromatization and the adverse effects of excess estrogen in men and some women, we do measure estradiol and testosterone levels in subgroups of patients. Patients are treated with aromatase inhibitors, combined in the pellet implant based on history (e.g., breast cancer, endometriosis, fibroids etc.), symptoms (e.g., fluid retention, weight gain, anxiety etc.) and serum levels [11].

In this clinical practice (RG), in the past 7 years, over 16,000 T pellet insertions have been performed in over 1300 female patients on protocol. We have previously reported on the benefits and safety of T delivered by sustained release implants with an average starting dose of 2 mg/kg [5,8,25,27]. We have observed, that some symptoms (e.g., bone pain, memory loss, neurological complaints and tremor) and some diseases (e.g., multiple sclerosis, Parkinson's disease and Alzheimer's disease) require higher dosing (4 mg/kg) for optimal clinical effect. There have been no reported adverse drug events attributed to T therapy other than expected androgenic side effects, which are reversible with lowering T dose. Many patients prefer the clinical benefits of higher doses/levels of T and choose to take care of the side effects of therapy. We have also combined finasteride, a 5 alpha reductase inhibitor, with testosterone in a pellet implant (60 mg T + 6 mg of finasteride), which has markedly reduced the incidence of acne. Considering long term data on the use of testosterone in female to male transgender patients, excluding aromatization as mentioned above, there does not appear to be a 'maximum' dose based on safety [16,19,20].

A weakness of this study was that serum T levels were performed at different laboratories, by different methodologies (group 1). This was unavoidable as this is a private clinical practice and the study was not funded. We did demonstrate a strong correlation between methodologies ($P < 0.01$) at the 'higher' T levels on therapy. In addition, findings were similar when evaluating results from a large subgroup of patients who had T levels drawn at a single laboratory and measured by the same methodology. Perhaps future studies, without insurance limitations, could include more consistent measurement profiles including SHBG.

6. Conclusion

T therapy delivered by subcutaneous implant, has been shown to be both safe and effective in pharmacologic doses. Although various authors have suggested 'physiologic' dosing of T, we have found that 'pharmacologic' dosing (based on serum levels on therapy) is necessary to provide adequate amounts of bioavailable T to the AR. We have shown that a single T measurement is extremely variable. In addition, there is inter-subject variability in pharmacodynamic response. As with any medication, clinical response to therapy (i.e., physiologic effect), safety and tolerability should determine dosing.

Contributors

R.G. and C.D. contributed equally to the research, design of the study, analyzing the data, writing and editing the ms. R.G. recruited participants. S.K. contributed to writing and editing the ms. All authors approved the final manuscript.

Competing interest

None of the authors (R.G., S.K. and C.D.) have any competing interests.

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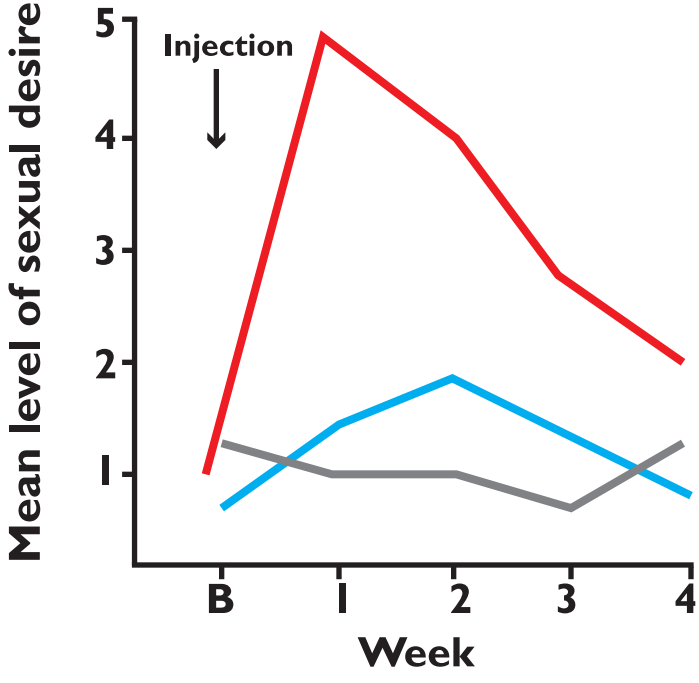

Sexual Desire

Estrogen + Testosterone

Control

Estrogen

ROUNDTABLE

Testosterone supplementation in women: When, why, and how

Although there is no commercially available FDA-approved testosterone preparation for use in women, clinicians have been providing testosterone supplementation to women for decades, with clinical improvement. How do these experts use testosterone in their practice?

Expert panel featuring Mickey Karram, MD; Rebecca Glaser, MD; James Simon, MD, CCP, NCMP, IF; and Lauren Streicher, MD

IN THIS ARTICLE

There are no currently US Food and Drug Administration (FDA)-approved therapies for testosterone use in women. Its use by clinicians is through dose modification of FDA-approved therapies for men, or preparations created by compounding pharmacies. Recently, several professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), North American Menopause Society, International Society for the Study of Women's Sexual Health, and the International Society for Sexual Medicine, convened an expert panel to develop a global position statement on testosterone therapy for women.[1] In this roundtable for OBG MANAGEMENT, moderated by Mickey Karram, MD, several experts discuss this position statement as well as the overall clinical advantages and drawbacks of using testosterone in women.

Testosterone indications

Mickey Karram, MD: For which indications do you prescribe testosterone supplementation in women?

Lauren Streicher, MD: I offer systemic testosterone therapy to postmenopausal women who have hypoactive sexual desire disorder (HSDD) and low serum testosterone levels, with one caveat—it is important that the patient's reported distressing lack of libido is not explained by another condition or circumstance. Many women present reporting low libido but, on further questioning, it is typically revealed that dyspareunia precipitated their loss of interest in sex. It is normal to not want to do something that is painful. In addition, low libido can often be explained by chronic disease, such as diabetes, cancer, or clinical depression.

Some medications, including selective serotonin reuptake inhibitors (SSRIs), frequently cause a decline in sexual interest. Finally, psychosocial and partner issues may be the culprit.

James Simon, MD, CCP, NCMP, IF: Much of the beneficial data for testosterone's use is for sexual function in postmenopausal women.[2] Female sexual dysfunction is highly prevalent among women during the postmenopause.[3] Androgen levels progressively decrease throughout adult life in all women, so the postmenopausal additional lack of estrogen has a recognized effect on genitourinary health. There is evidence that the insufficiency of androgens as well as estrogens after menopause can lead to genitourinary symptoms of menopause (GSM).[4]

Testosterone also is used for increasing strength, lean muscle mass, bone mineral density, and sense of well-being.[5]

Rebecca Glaser, MD: I consider testosterone supplementation in my clinical practice in both premenopausal and postmenopausal women for symptoms of androgen/hormone deficiency, including diminished sense of well-being; dysphoric mood; anxiety; irritability; fatigue; decreased libido, sexual activity, or pleasure; vasomotor instability; bone loss; decreased muscle strength; insomnia; changes in cognition; memory loss; urinary symptoms; incontinence; vaginal atrophy and dryness; and joint and muscular pain. We also have shown through preliminary and short-term data and case studies that testosterone therapy has a potential beneficial effect on migraine headaches, as well as active breast cancers in both premenopausal and postmenopausal women.[6-10]

What is appropriate bloodwork?

Dr. Karram: Do you obtain blood work before initiating testosterone treatment? If so, what tests do you order and what testosterone levels are considered to be normal for premenopausal and postmenopausal women?

Dr. Streicher: Unlike estrogen, which is predictably low in a postmenopausal woman, serum testosterone (T) levels are highly variable because of the adrenal component. Ovarian testosterone production does not cease at the same time as estrogen production. So I do obtain total and free T levels, prior to initiating treatment. Having said that, it has been well established that T levels correlate poorly with level of sexual interest, and there is no specific blood level that can be used to differentiate women with and without sexual dysfunction. We all have patients who have nonexistent T levels and have a very healthy libido, and other women with sky-high levels who have no libido. But it is useful to know levels prior to initiating therapy to be able to monitor levels throughout treatment. Also, if levels are in the premenopausal physiologic range, not only is she unlikely to respond but she is also at risk for developing androgenic adverse effects, such as acne and hair growth. In general, a low free T level (even if it is in the normal postmenopausal range) in a clinical setting of HSDD supports supplementation.

The assessment and interpretation of T levels can be challenging, particularly as the majority of testosterone is protein-bound and biologically inactive. Free T levels (the biologically active testosterone) in many labs are unreliable and need to be calculated.

In addition to total and free T, I check levels of sex hormone-binding globulin (SHBG), the protein that binds testosterone and renders it biologically inactive. If someone has high SHBG levels and is taking an oral estrogen, simply switching to a transdermal estrogen will result in decreased SHBG and increased free T.

CONTINUED ON PAGE 34

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Dr. Streicher reports stock holdings for InControl Medical and Sermonix.

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CONTINUED FROM PAGE 33

Levels of total and free T vary from lab to lab, so it is best to be familiar with those ranges and then be consistent in which lab you choose.

Dr. Glaser: Although I personally do order blood work on most patients (T, free T, estradiol, complete blood count, thyroid-stimulating hormone, and follicle-stimulating hormone), after 15 years of research and publishing data on testosterone implants, I do not believe that T levels are absolutely necessary or even beneficial in most cases. It rarely changes management in my patients.

As Lauren said, it is well known that T levels do not correlate with androgen deficiency symptoms or clinical conditions caused by androgen deficiency. If a patient has symptoms of androgen deficiency, a trial of testosterone therapy should be given.

T levels are not a valid marker of tissue exposure in women, reflecting less than 20% of total androgen activity. The major source of testosterone in pre and postmenopausal women is the local intracrine production of testosterone from the adrenal precursor steroids dehydroepiandrosterone (DHEA) and androstenedione, which would not be reflected in T levels.

In our study involving 300 women, we found no relationship between baseline T levels, presenting symptoms, or response to therapy.[6] Premenopausal and postmenopausal women had similar baseline T levels and similar response to therapy. Even women with baseline T levels in the mid-range responded to therapy.

> "Some of the most controversial topics in treating women with testosterone are related to dosing and T levels throughout therapy."
>
> —*Rebecca Glaser, MD*

Some of the most controversial topics in treating women with testosterone are related to dosing and T levels throughout therapy. Guideline authors often use the terms 'physiologic dosing' and 'physiologic ranges' when making recommendations for therapy. Although "physiologic" sounds appropriate/scientific, these rigid opinions/recommendations are not evidence based. There are no data supporting the use of endogenous T ranges to guide dosing or monitor testosterone therapy.

The decision to initiate testosterone therapy is a clinical decision between the doctor and the patient based on the patient's symptomatology, which is the therapeutic endpoint. Testosterone therapy must be done with adequate doses determined by clinical effect (benefits) versus side effects or adverse events (risks). T levels may be helpful, along with clinical evaluation when troubleshooting.

Utilizing data from thousands of patients, we have developed serum ranges for testosterone implants.[11] Even so, no two patients are the same, nor do they respond to therapy the same. It is always a clinical decision.

Dr. Simon: In the recent global consensus statement on testosterone use,[1] the experts were in agreement that "no cut-off blood level can be used for any measured circulating androgen to differentiate women with and without sexual dysfunction." They give their recommendation a C, and I agree that testosterone supplementation, with specific dosage levels, are a clinical decision.

Before initiating testosterone therapy, it is recommended that liver function and fasting lipids are assessed, as liver disease and hyperlipidemia are contraindications to treatment. These levels should be monitored twice in the first year and annually thereafter while the patient is taking testosterone. Breast and pelvic examinations, mammography, and evaluation for abnormal bleeding should be performed as well as the blood tests.[12] These recommendations are focused on safety not efficacy.

Administration route

Dr. Karram: How do you administer testosterone, and why?

Dr. Streicher: As there are no FDA approved testosterone products for women, clinicians must determine the dosage and route of delivery based on published clinical trials.

Dr. Glaser: I treat patients with subcutaneous pellet implants. The implants provide consistent and continuous delivery of therapeutic amounts of testosterone. There is a reason testosterone pellets have been used for more than 80 years and are more popular now than ever—they work. The insertion

procedure is simple and takes about 2 minutes. The treatment is cost-effective, avoids first pass, has no adverse effect on the liver or clotting factors, and there is no transference. Decades of data support both the efficacy and safety of testosterone implants.[6] However, testosterone implants are not regulated by the FDA and all patients are required to sign a consent informing them of off-label use, benefits, and risks of testosterone implant therapy.

Dr. Simon: I think the consent is important, as there is no package labeling to warn of possible side effects.

Dr. Streicher: Oral testosterone therapy, because of its first pass through the liver and association with adverse lipid profiles with negative effects on high- and low-density lipoprotein cholesterol levels, is not recommended. I prefer a transdermal approach. Pellets, implants, and injections have the potential to result in supraphysiologic blood concentrations. It must be emphasized that the goal of treatment is to approximate premenopausal physiologic levels. More is not better; excessive levels do not demonstrate a greater sexual response and are in fact more likely to have a negative impact due to androgenic side effects.

In most clinical trials, a 300 mg/d testosterone patch was effective, but these patches are not commercially available so I rely on transdermal gel from a compounding pharmacy. The typical dose needed to raise levels into the high to normal range for most women is 2.5 mg up to 5 mg per day of testosterone 1%, which translates to roughly 1 mL. Many pharmacies provide a dispenser, which allots the appropriate dose. Alternatively, I instruct the patient to place a dollop on her thigh (roughly in size of a single M&M candy).

I always tell my patients that the response is not immediate, typically taking 8 to 12 weeks for the effect to become clinically significant. I generally see a patient back 8 weeks after initiation of treatment to check T levels and evaluate response.

Dr. Simon: There are some data demonstrating that intravaginal testosterone can be a potential treatment for GSM. Intravaginal testosterone coupled with aromatase inhibitor therapy used for breast cancer treatment resulted in supraphysiologic T levels and reportedly improved vaginal maturation index and reduced dyspareunia. More study is needed.[13]

Dr. Streicher: Agreed. The lower third of the vagina and the vestibule is rich in testosterone receptors. Like Dr. Simon, in some cases of vaginal atrophy I prescribe a compounded local vaginal testosterone.

Testosterone and premenopausal women

Dr. Karram: Is there a role for testosterone supplementation in premenopausal women with normal estrogen production?

Dr. Glaser: Yes. In fact, in our study, more than one-third of the patients were premenopausal, which makes sense.[6] There is a marked decline of T levels and the adrenal precursor steroids (DHEA and androstenedione) in women between the ages of 20–30 years and around age 50. As we said, symptoms of androgen deficiency often occur prior to menopause and are not related to estrogen levels. In our study, testosterone implant therapy relieved symptoms of hormone (androgen) deficiency, including vasomotor symptoms, sleep problems, depressive mood, irritability, anxiety, physical and mental exhaustion (fatigue, memory issues), sexual problems, bladder problems (incontinence, frequency), vaginal dryness, and joint and muscular pain. Premenopausal and postmenopausal patients reported similar hormone deficiency symptoms. Premenopausal women did report a higher incidence of psychological complaints (depressive mood, anxiety, and irritability), while postmenopausal women reported more hot flashes, vaginal dryness, and urologic symptoms. Both groups demonstrated similar improvement in symptoms.

In addition, we have seen relief of severe migraine headache in premenopausal (as well as postmenopausal) women treated with testosterone implant therapy.[6,7]

Dr. Streicher: The goal of testosterone supplementation is to approximate physiological

> “There are some data demonstrating that intravaginal testosterone can be a potential treatment for GSM.”
>
> —*James Simon, MD, CCP, NCMP, IF*

Is testosterone appropriate for this patient?

Dr. Karram: How would you treat the following patient? She is 56, postmenopausal, and taking estrogen. She reports decreased libido, fatigue, lack of sleep, and lack of focus. Would you consider testosterone supplementation?
Dr. Simon: For her libido, yes. I would not give it to her for the fatigue if it were simply lack of sleep and without an associated medical condition. For her lack of focus, the testosterone could be beneficial. The central nervous system effects of testosterone are thought to be related to the conversion of testosterone to estrogen in the brain; if a person's getting enough estrogen, they shouldn't have lack of focus. Since some women may not want more estrogen, administering a little testosterone for libido also offers focus because it adds to the estrogen in the brain. If after giving her adequate amounts of testosterone her libido is not better in 8 weeks, it wasn't a testosterone problem. If she does report improvement, however, I would keep her on the agent as long as she is healthy. But most 56-year-old women who already met the criteria for going on estrogen should be fine with testosterone.

If this same patient were not reporting low libido but did report lack of strength, energy, or well-being I also would say, "Sure, give testosterone a try."
Dr. Glaser: I also would treat her with testosterone—with pellet implants. The dose would depend on her body weight. I usually start with an approximate dose of 1 mg of testosterone per pound of body weight. This amount of testosterone delivered continuously from the implant also supplies estradiol (via aromatization) locally at the cellular level.

I would treat her for as long as she chooses to continue testosterone therapy. There is no end- or stop-date where a person no longer benefits from therapy or adverse events occur. Testosterone does not increase the risk of breast cancer and it has a positive effect on many of the adverse signs and symptoms of aging, including mental and physical deterioration.

testosterone concentrations for premenopausal women. While testosterone may improve well-being and sexual function in premenopausal women, the data are limited and really inconclusive. More study is needed given that there is likely a wide therapeutic range with many variables. Having said that, there are some data that indicate that testosterone in premenopausal women may enhance general sense of well-being.[14]

Why is there no FDA-approved agent?

Dr. Karram: Why do you think the FDA has been reluctant to approve a testosterone agent for women?
Dr. Simon: Three potential testosterone drugs for use in women have been unsuccessfully brought to market after the FDA did not approve them. There are 31 approved products for men, each of which were approved because they safely restored normal testosterone concentrations in men with reduced levels and an associated medical condition. Unlike this scenario for men, for women, the FDA has required products to show clinical effectiveness in trials. For instance, Estratest, a combination estrogen-testosterone product, was in use in the 1960s—approved for women with estrogen-resistant hot flushes, and used in practice for sexual dysfunction. After the FDA implemented its Drug Efficacy Study and Implementation regulation system after 2000, which required safety and efficacy trial(s) before drug approval, the manufacturer removed the drug from market when presented efficacy study data for the added testosterone in the drug were deemed inadequate.[15]
Dr. Streicher: We have yet another example of the disparity between the FDA approval processes for sexual function drugs for men versus women. Take Intrinsia as another example. It was a 300-mg testosterone patch that underwent clinical trials in women who were post-oophorectomy with HSDD. The patch had demonstrated efficacy with minimal adverse effects and no statistically significant dangerous effects. However, the FDA declined approval, citing "safety considerations" and requested longer-term clinical

trials to evaluate potential cardiovascular or breast problems. Given that Intrinsia supplementation simply restored normal physiologic testosterone levels, and there was no such requirement in men who received supplementation post-orchiectomy, this requirement was nonsensical and unjustified.

Compounded formulations

Dr. Karram: Are compounding pharmacies appropriately regulated, and how can you be assured that the source of your testosterone is appropriate?

Dr. Glaser: Compounding pharmacies are regulated by the State Boards of Pharmacy, Drug Enforcement Agency, Occupational Safety and Health Administration, National Institute for Occupational Safety and Health, State Bureaus of Narcotics and Dangerous Drugs, and Departments of Health (in some states).

Compounding is a highly regulated profession that is constantly under scrutiny by agencies, patients, and physicians. Any additional regulations could adversely impact the accessibility of patients to individually compounded medications including intravenous and oncology medications. Over the past 20 years, I have treated hundreds of patients with breast cancer with compounded vaginal testosterone (with or without estriol) and subcutaneous testosterone (with or without anastrozole), greatly improving quality of life in women suffering from severe symptoms. Without the availability of compounded medications, there would have been no or limited alternatives for adequate and much needed therapy. Notably, there have been no adverse events or safety-related issues in more than 20 years.

Regarding whether or not "the source of your testosterone is appropriate," pharmacists can only use United States Pharmacopeia (USP) grades of testosterone. Testosterone used in compounding is required by the FDA to be of USP grade from an FDA registered and compliant facility. In addition, compounding support companies run additional USP tests to confirm their products meet USP standards prior to being delivered to individual compounding pharmacies.

Dr. Streicher: However, there potentially can be substantial variability between formulations and batches. Product purity can also be an issue. It is reassuring if the compounding pharmacy is compliant with purity of Active Pharmaceutical Ingredients and Good Manufacturing Practice rules and guidelines that assure the minimum requirements to assure high quality and batch-to-batch consistency. I find it helpful to always work with the same pharmacy once you have established uniformity and reliability. If there is concern, it is appropriate to check a patient's serum level 2 weeks after initiation of therapy.

Dr. Simon: I think the problem with some compounding pharmacies is that there may be incentives back and forth with the clinician to use a certain outlet, whereby the patient's best interest may not be served. I do believe that there is a role for compounding pharmacies, however. We also use them because some women may have strange reactions or be allergic to the preservatives, formulating agents, or even lactose, in various pills and patches, gels, and creams.

Testosterone for aging and cognition?

Dr. Karram: Do you think that testosterone supplementation in the elderly can have a positive impact on aging, Alzheimer disease, and dementia?

Dr. Streicher: The jury is still out on the cognitive effects of postmenopausal androgen supplementation. There is currently insufficient evidence to support the use of testosterone to enhance cognitive performance, or to delay cognitive decline. I prescribe testosterone only to treat HSDD, but I do tell my patient that she may possibly also benefit in terms of cognitive function, musculoskeletal parameters, and well-being. Large RCTs are needed in those areas to justify prescribing for those benefits alone.

Dr. Simon: I would say this is the place for future development, but where there is very likely to be a benefit is on sarcopenia.

> "There is currently insufficient evidence to support the use of testosterone to enhance cognitive performance, or to delay cognitive decline."
>
> —*Lauren Streicher, MD*

Dr. Glaser: There is evidence some that testosterone is neuroprotective.[16] In my clinical practice I have seen "self-reported" memory issues improved on therapy, often returning toward the end of the testosterone implant cycle. Adequate amounts of bioavailable testosterone at the androgen receptor are critical for optimal health, immune function, and disease prevention.

Dr. Karram: In conclusion, this expert panel agrees that testosterone supplementation is beneficial for sexual dysfunction in postmenopausal women, with also many other potential benefits that require further investigation. Route of administration preferred by Dr. Simon and Dr. Streicher is transdermal or a transvaginal cream. Dr. Glaser uses a subcutaneous pellet approach. Thank you all for an engaging and informative discussion. ●

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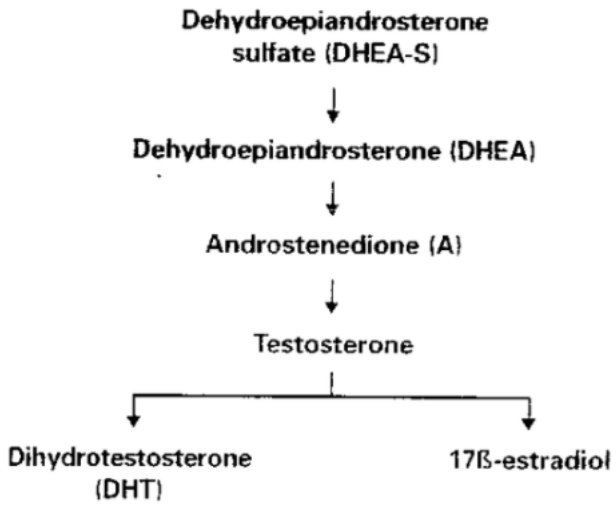
FIGURE 1

Biochemical synthesis of testosterone from precursors



Your Guide to Menopause

(https://www.everydayhealth.com/menopause/guide-hormones-hot-flashes-painful-sex-more/)

MENOPAUSE (/MENOPAUSE/)

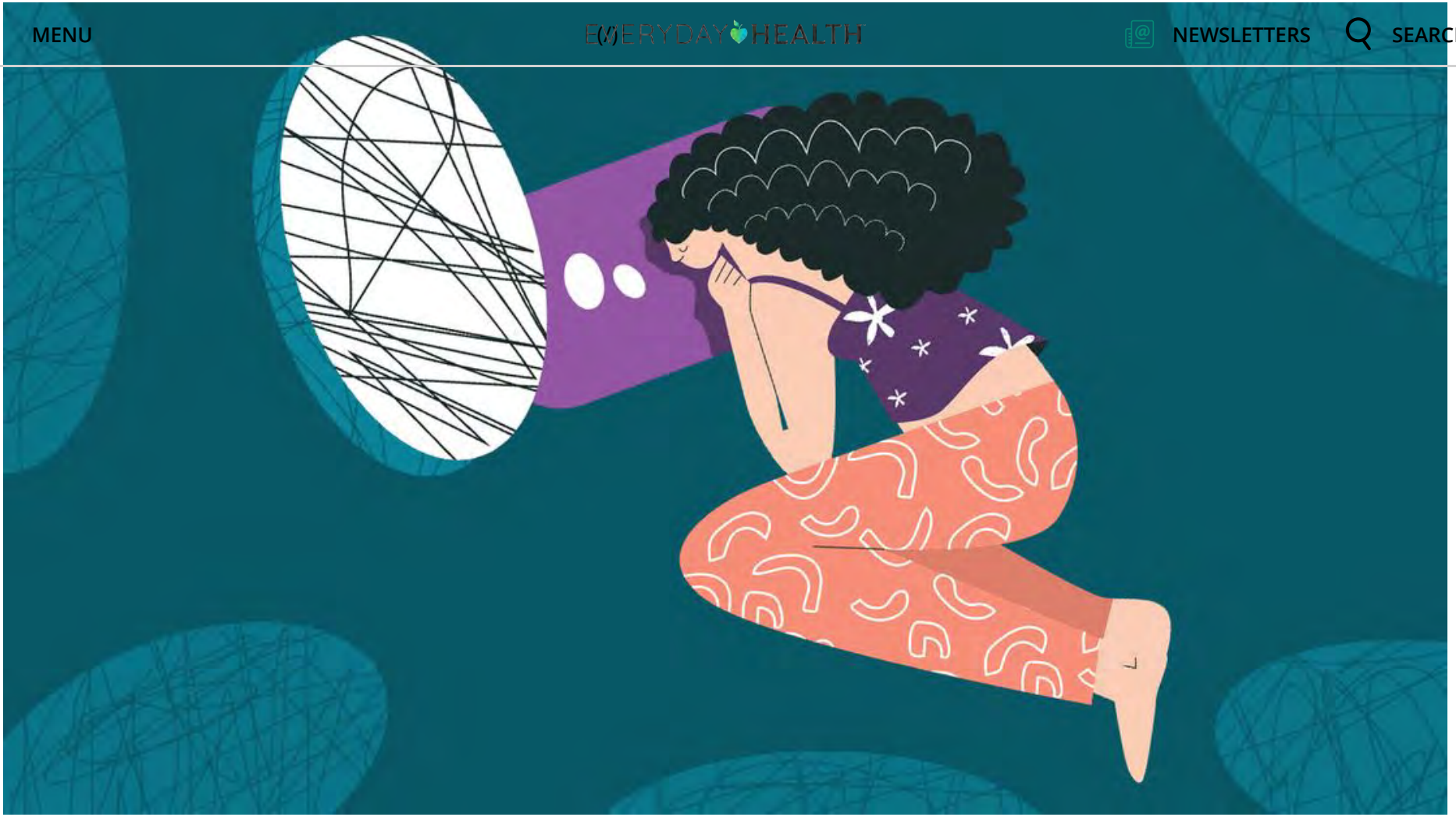
Sex After Menopause: The Psychological Factor

After menopause, sex can... well... hurt. So it's no wonder that sex can cause anxiety for many women. Here's how to overcome those emotions and make sex less painful.

By Andrea Peirce (/authors/andrea-peirce/) Medically Reviewed by Kacy Church, MD (/authors/kacy-church/)

February 17, 2021

Medically Reviewed



If sex has become painful, you may experience some anxiety before penetration. Maria Petrishina/Getty Images

Ask a woman in her 50s what some of the most uncomfortable symptoms of menopause are, and she'll likely say hot flashes or night sweats. While this may be true, there are other, less commonly discussed symptoms that tend to be even more bothersome, not to mention permanent.

Some of these potentially life-altering symptoms can include intense vaginal dryness (/vaginal-dryness/guide/) and pain with penetration, urgency and pain with urination, and overall feelings of genitourinary burning and irritation.

Called genitourinary syndrome of menopause (GSM) (https://www.everydayhealth.com/menopause/treatment-of-menopausal-symptoms-experts-issue-new-guidance/), this constellation of symptoms affects as many as 27 to 84 percent of post-menopausal women and can "significantly impair health, sexual function, and quality of life," according to a study published in September 2020 in the journal *Menopause* from The North American Menopause Society (https://pubmed.ncbi.nlm.nih.gov/32852449/) (NAMS).

During menopause, estrogen (/estrogen/guide/) and other hormones that were once supplied by the ovaries plummet. When that occurs, vaginal tissue becomes thin and drier; the vaginal wall shortens and narrows; and the vulva's larger, outer folds (labia majora) and inner folds (labia minora) shrink. Penetration can become painful as a result, and the vaginal muscles learn to reflexively tighten up with anxiety before sex.

In other words, "The vagina (/vaginal-health/guide/) becomes smarter than the owner," says Sheryl Kingsberg, PhD (https://www.uhhospitals.org/doctors/Kingsberg-Sheryl-1861418675?utm_campaign=Kingsberg_Sheryl_11100_Euclid_Ave&utm_source=yext&utm_medium=locallisting&utm_content=website_url), a psychologist at University Hospitals Cleveland Medical Center.

But there are ways to overcome this anxiety and ease the pain.

Painful Sex After Menopause: A Conspiracy of Silence

When Dr. Kingsberg shows women illustrations of what's happening to their vaginas without estrogen, they say things like "Holy cow! No wonder it hurts when I'm trying to have sex!"

Problem is, many women don't realize that vaginal dryness and pain during penetration can be caused by menopause or changes in hormones, says Kingsberg.

In something of a "conspiracy of silence," says Kingsberg, doctors assume their patients will tell them if they're in pain, whereas patients assume their doctors would ask about such serious symptoms. Because of this, "Women don't know that they are entitled to ask for help to treat it," she says.

This miscommunication often makes many women feel alone, says Lauren Streicher, MD (https://www.drstreicher.com/), medical director of Chicago's Northwestern Medicine Center for Menopause. "They're thinking that there's no solution and that what they're experiencing is simply the way it's going to be for the rest of their lives," she says. "But I tell them, 'Number one, you are not alone. And number two, this is fixable.'"

Treating the Emotional and Physical Symptoms of Painful Sex During Menopause

While GSM tends to get worse if it's left untreated, there are ways to reverse some of the symptoms. Ideally, say Kingsberg and Dr. Streicher, you should have multiple doctors working together, including:

A gynecologist or women's health nurse practitioner, who can assess the problem, determine which treatments might be best, make referrals, and write prescriptions if needed.

A psychologist who specializes in behavioral medicine or sexual medicine, who can help you "trust your vagina again," says Kingsberg. Streicher notes that some women — namely, those who think their only problem is a "vagina that's like the Sahara Desert" — may initially resist seeing a therapist, certain that there's no psychological issue at play. But ultimately, a psychologist can make a big difference in helping you overcome this issue, says Kingsberg, to allow for pain-free penetration.

A pelvic floor physical therapist, who can show you how to isolate and strengthen key vaginal muscles while relaxing others. (Not everyone will need a pelvic floor specialist.)

To find specialists, you can search the provider directory at NAMS (https://portal.menopause.org/NAMS/NAMS/Directory/Menopause-Practitioner.aspx). Many are more accessible than ever, thanks to telehealth.

Other treatments for painful sex after menopause may include:

Non-hormonal vaginal lubricants and moisturizers

For mild pain and discomfort, these over-the-counter treatments (https://www.menopause.org/docs/default-source/for-women/mndryness.pdf?sfvrsn=f093c698_8) may do the trick. You can apply the moisturizer daily (https://www.everydayhealth.com/womens-health/menopause/low-libido-heres-how-have-great-sex-after-menopause/) (as you would your face) or whenever you feel dry. An important caveat: These products can help keep vaginal tissue lubricated, but they can't treat the underlying GSM, says Kingsberg.

Prescription medications

Prescription low-dose vaginal estrogen can be taken to replace the hormones lost during menopause, says Kingsberg. It can be applied directly to the vaginal area, where it has "minimal, if any, systemic absorption" into the rest of your body, she emphasizes, adding that absorption of the hormone over the course of a year is equivalent to about one to two birth control pills (/sexual-health/birth-control/).

Other treatments for GSM include vaginal dehydroepiandrosterone (DHEA) and the estrogen agonist/antagonist pill ospemifene.

Relaxation techniques

Practicing relaxation strategies can help you remain calm as well as heighten your awareness of which pelvic (and other) muscles might be seizing up at the thought of sexual activity. A pelvic floor therapist is specially trained to help you zero in on relaxing these regions.

Vaginal dilators

These devices help stretch and enlarge the vagina, but they must be used carefully , often alongside relaxation techniques. It's very important to start slowly, with extremely gradual — and wanted — exposure to a graded or expandable dilator.

At first, the "device" may be your own pinkie, which you would place at the entrance of your vagina every day for short periods of time to get used to it being there, says Kingsberg. Using half-inch increments at most, you can advance your finger or the dilator into your vagina, but only once you — and your vagina — have learned that there's no sneak attack involved. "My rule [when using dilators] is, No pain!" she says.

Talk therapy

When it comes to sex after menopause, "A little psychological help can go a long way," says Kingsberg. Some of the many topics she discusses with her patients include a drop in libido (slow or low arousal) and partner expectations.

With relationships, the "age of the relationship" matters even more than the age of the person, she says. "Smart couples know that limerence — that excited and passionate phase of a relationship — only lasts a couple of years," she says. After that, couples need to schedule sex around their other commitments, such as work and childcare.

Long-term relationships aren't without their challenges, either, she says. For example, some people may need to work on nurturing the romance, as they can take their partners for granted.

Once past middle age, people tend to have more privacy and free time, which allows them to spend more time enhancing their sexual life. Sometimes physical limitations, such as erectile dysfunction (/erectile-dysfunction/), end up being a good thing, because they prompt couples to experiment with new things, says Kingsberg.

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