PODIUM #6

ANDROGEN VALUES IN PREMENOPAUSAL WOMEN WITHOUT SEXUAL DYSFUNCTION

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Introduction: A recent population study suggests that 43% of women aged 18-59, have female sexual dysfunction (FSD), and 32% of these have decreased libido. The role of androgens in female sexual function is uncertain. Androgen values are hampered by imprecise assays and the lack of a control range defining specific levels at specific ages in those without sexual dysfunction. The few control populations in the literature were not screened for sexual function. We wished to establish a control range of androgens in women age 20-49 years with normal sexual function.

Methods: Healthy pre-menopausal women (n=60) were recruited and screened for sexual dysfunction by interview and modified FSQ where principle component analysis revealed 4 domains in 15 questions: desire, central arousal, peripheral arousal and orgasm. No medications or oral contraceptives were used. Bloods were drawn (AM), at days 8-15 of the menstrual cycle, and analyzed at the same time in a steroid research laboratory.

Results: **MEAN HORMONE LEVELS (± SE) IN NORMAL CONTROLS (n=60)**

AGE:		**20-29** (n=17)	**30-39** (n=23)	**40-49** (n=20)
DHEA-S (ug/dL)		195.6 (±18.7)	154.9 (±15.9)	140.4 (±15.7)
Range (Mean ± SE)		176.9 – 214.3	139.0 – 170.8	124.7 – 156.1
SHBG (nmol/L)		51.1 (±7.5)	48.5 (±3.9)	52.7 (± 5.7)
Range (Mean ± SE)		43.6 – 58.6	44.6 – 52.4	47.0 – 58.4
Total testosterone (ng/dL)		51.5 (±6.0)	33.7 (±6.1)	32.8 (± 5.8)
Range (Mean ± SE)		45.5 – 57.5	27.6 – 39.8	27.0 – 38.6
Analog free testosterone (pg/ml)		1.51 (±0.12)	1.10 (±0.08)	1.02 (±0.12)
Range (Mean ± SE)		1.39 – 1.63	1.02 – 1.18	0.90 – 1.14
Free Androgen Index (FAI)		4.34 (±0.62)	2.5 (±0.46)	2.46 (± 0.48)
Range (Mean ± SE)		3.72 – 4.96	2.04 - 2.96	1.98 – 2.94

SHBG did not change with age (p=.67). Significant negative correlation was seen between age and: DHEA-S (r = -.35; p=.009); Total T (r = -.30; p=.02); analog free T (r = -.46; p<.001); FAI (r = -.35; p=.006).

Conclusions: In pre-menopausal women age 20 to 49 with normal sexual function androgen levels display an orderly decline. Androgen levels reported here are higher than previously published because only women with FSQ-verified normal sexual function were included. SHBG levels do not vary from age 20-49 so the waning FAI truly reflects the age-related decline in testosterone levels. Female androgen secretion may start to ebb at an earlier age than previously suspected. Further research concerning androgen insufficiency in younger women needs to be done and a larger population of control subjects needs to be obtained.

Laboratory Assays and Measurement Issues: Can Androgen Deficiency Be Reliably Addressed in Women?

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Dr. Bhasin is an internationally recognized expert on sex steroid metabolism and biology, and androgen effects on the muscle and prostate, and has published extensively on the effects of testosterone supplementation in androgen-deficiency states and in sarcopenia associated with chronic illness. He has published 83 peer-reviewed papers, 82 reviews and chapters, 150 abstracts and two books on androgen biology. He has served as an Associate Editor for the Journal of Andrology, a member of the editorial board of the Journal of Clinical Endocrinology and Metabolism, and a reviewer for JAMA, New England Journal of Medicine, Journal of Clinical Investigation, Endocrinology, Fertility and Sterility, and many other scientific journals.

Dr. Bhasin's current research efforts are supported by several NIH RO1 grants. Dr. Bhasin has received numerous teaching and research awards, and is a member of expert panels on Andropause, Androgen Deficiency in Men and Erectile Function in Men. He is the author of the American College of Physicians/American Society of Internal Medicine Disease Management Module on Androgen Deficiency in Men.

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That testosterone supplementation might improve some aspects of cognitive and sexual functions, muscle mass and strength, bone mineral density, and sense of well-being is not in question. It is, however, not known whether physiologic testosterone replacement can induce clinically meaningful improvements in health-related outcomes in older women without the limiting, virilizing side effects. It has been assumed that testosterone dose-response relationships are different in women than in men, and that clinically significant effects on psycho-sexual function, body composition, physical function, bone mineral density, and other health-related outcomes can be achieved at testosterone doses and concentrations that are substantially lower than those required to produce similar effects in men. Neither of these assumptions has been tested rigorously. Furthermore, the premise that the organ systems that are the targets of virilizing side effects, such as the skin, hair, vocal cords, and clitoris, differ in their testosterone sensitivity from muscle and bone remains unsubstantiated. The clinical applications of testosterone in women are critically predicated upon the postulate that by appropriate selection of testosterone dose, clinically beneficial effects can be dissociated from virilizing side effects. Inspite of growing media attention, the issue of androgen supplementation in women has remained controversial in the scientific community. Many uncertainties have contributed to a lack of consensus. The commercially available assays for total and free testosterone were developed for the measurements of much higher circulating concentrations in men; these assays have generally lacked the sensitivity and precision required to accurately measure the lower levels of testosterone in older women. There has been a paucity of normative data on testosterone levels in menstruating women, older women, and women with chronic illnesses; this has made it difficult to define androgen deficiency in women in precise quantitative terms. The available formulations for androgen administration were developed for the replacement of much higher doses required for the treatment of hypogonadal men. Very little pharmacokinetic data exist on the bioavailability and clearance of androgens delivered from the available formulations in women. Therefore, it is not surprising that many previous clinical studies in women used pharmacologic doses of testosterone in relatively unphysiological experimental paradigms. The objective of physiologic testosterone replacement is to restore serum total and free testosterone concentrations into a range that is mid-to high-normal for healhy, young women. Testosterone regimens that increase serum testosterone levels into the supraphysiological range should be viewed as pharmacologic.

Sexual dysfunction in women, a highly complex, multi-factorial syndrome, has become synonymous with androgen deficiency in the lay press. Observations that pharmacological doses of testosterone might improve sexual function in subsets of women with sexual dysfunction have been unjustifiably extrapolated to advocate testosterone replacement as a general treatment for sexual dysfunction in older women. It would be incorrect to assert that testosterone supplementation of older women has no role in clinical practice; on the other hand, the available data do not warrant a general recommendation for testosterone replacement for all post-menopausal women.

Androgens and Women's Sexuality: Scientific, Clinical and Regulatory Perspectives

Rosemary Basson, M.D.

Challenges for the Clinician

Whereas:

1. There are a number of theoretical androgen deficiency states[i] including hypopituitary states, adrenal disease, chronic cortisone administration, bilateral salpingo-oophorectomy, chemotherapy associated menopause, premature ovarian failure, GNRH therapy, oral contraceptive and oral estrogen replacement therapy.
2. There is scientific evidence (i.e. one study) of sexual benefit of replacing testosterone to high, but not mid normal premenopausal levels in a subgroup of women – women older than 47 years of age with previous bilateral salpingo-oophorectomy[ii], and one study of beneficial DHEA replacement in women with primary and secondary hypoadrenalism.[iii]
3. Time consuming but sensitive assays for testosterone at levels representative of the female range do exist,[iv]

In clinical practice:

1. The majority of women seeking our help for their lessened desire and lessened mental and physical sexual arousability do not fall into the above categories.
2. The accurate sensitive (equilibrium dialysis) assay for testosterone is not available.[v]

Moreover:

1. Uncertainty remains regarding androgen production by the postmenopausal ovary.[i,vi,vii]
2. Uncertainty remains regarding reduced SHBG with age in women (i.e. protecting against symptoms of androgen deficiency).[7,viii,ix]
3. There is uncertainty regarding the "normal range" of testosterone in sexually healthy women of different ages and different ethnicities and different body weights.[5]
4. There is no known threshold value below which sexual symptoms "usually" occur.[x]
5. There is a possibility that women become accustomed to higher testosterone levels and any increase in desire and responsivity is only temporary.[10]
6. Possibly the (unmeasurable) intracellular testosterone is more important (given the considerable proportion of testosterone activity that stems from the intracellular production from androgen precursors).[xi]
7. We have minimal longterm safety data. There is uncertainty regarding the relationship between increased insulin resistance and increased testosterone levels (as in polycystic ovary syndrome)[xii] – the insulin resistance is assumed but not proven to be the primary problem.
8. Replacing testosterone without estrogen is non physiological – the safety of systemic ERT beyond 3-4 years is in question.
9. Should testosterone be given premenopausally, there is the danger of masculinizing a female fetus, the risk of menstrual irregularity, insulin resistance, absence of safety data.

Finally, regarding the practicalities of replacement of testosterone:

1. We lack formulations of testosterone suitable (let alone approved) for women. Although methyl testosterone (+ CES) is prescribed off label, ie for sexual benefit, scientific evidence of benefit is seen only with doses that reduce HDL cholesterol,[xiii,xiv] plus there remains the l risk of liver toxicity that is seen with higher dosage in men.
2. The rapidly increasing but non-evidence based use of DHEA, of uncertain potency and purity can only be biochemically monitored in an imprecise manner as the testosterone produced in the cell is also metabolized in the cell.

<u>What is a reasonable, albeit imperfect, clinical approach in October 2002?</u>

1. Consider testosterone measurement and replacement only when a clear picture of the sexual consequences of androgen lack on ***response*** can be established:
   - reduced arousal to non-physical erotic stimuli, ***and***
   - reduced arousal to non-genital physical stimuli from self or partner, ***and***
   - reduced arousal to genital stimuli given in an appropriate erotic/intimate context, ***and***
   - reduced arousal from genital self-stimulation
   - orgasms are delayed, brief, of minimal intensity or not reached

Note the compounding effects of androgen lack on the intimacy based sex response cycle in addition to loss of any "spontaneous" desire. See figs 1,2,3.

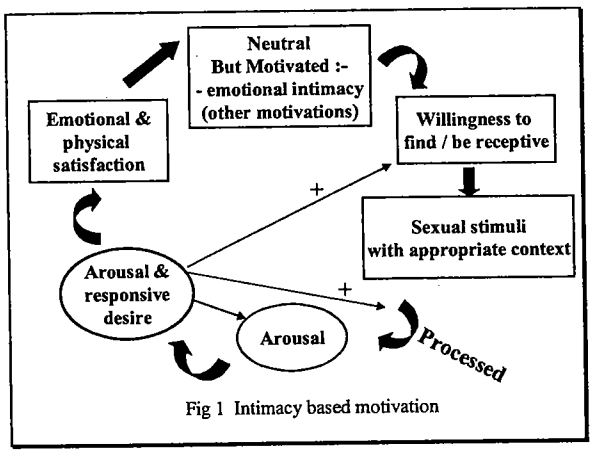

Fig 1 Intimacy based motivation

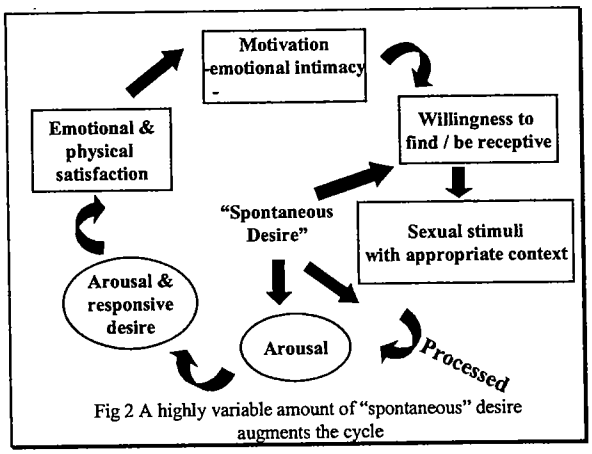

Fig 2 A highly variable amount of "spontaneous" desire augments the cycle

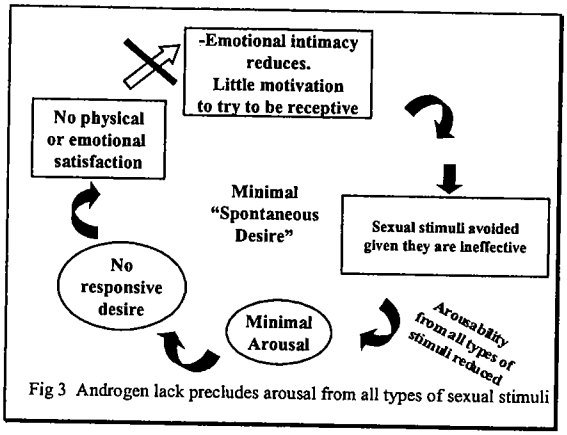

Fig 3 Androgen lack precludes arousal from all types of sexual stimuli

2. Consider testosterone replacement only after careful differential diagnosis:

- **depression** has been carefully excluded / treated
- **psychodynamic factors** reducing arousability and desire, either within the woman herself and/or between the two partners have been excluded

3. **There is no current indication for testosterone replacement *when symptoms are limited to minimal or absent innate, "spontaneous" sexual wanting.*** Shifren's study was of women with reduced desire *and reduced arousal, pleasure and orgasm.*[2] Lack of innate sexual neediness per se, but ability to access some feelings of desire and wish to continue a sexual experience once it has begun, i.e., experiencing sexual desire after and with arousal – appears to be normative for many women.[xv, xvi, xvii, xviii, xix] For some women this is lifelong, for others it becomes the norm as a relationship lengthens. Temporary cessation of sexual activity or physical separation of the partners tends to revive this apparently innate type of desire.

   A major difficulty has been the modeling of women's sexual response on that of the male such that the traditional definitions of hypoactive sexual desire disorder focus on the absence or paucity of sexual thoughts, fantasies, self-stimulation and conscious wanting of sex. Only recently, the concept of receptivity has been introduced[xx] to allow for the progression of motivation to be sexually active with the partner for a variety of reasons. A conscious decision to be receptive to stimuli potentially leads to arousal and subsequent desire. For the woman who can proceed in this way even though spontaneous wanting is absent, rather than considering supplementation of testosterone, the suggested clinical approach is to address the various motivations the woman might have to be sexual, why they may be currently problematic, address the adequacy of the stimuli, psychological factors affecting her arousability, and address any biological, sexual or psychological factors precluding a satisfactory outcome.[xxi]

4. When androgen deficiency has been diagnosed clinically, (see fig. 4), "confirm" if possible, ideally via equilibrium dialysis and in reality by the best available method (see previous article on testosterone assays).[4]

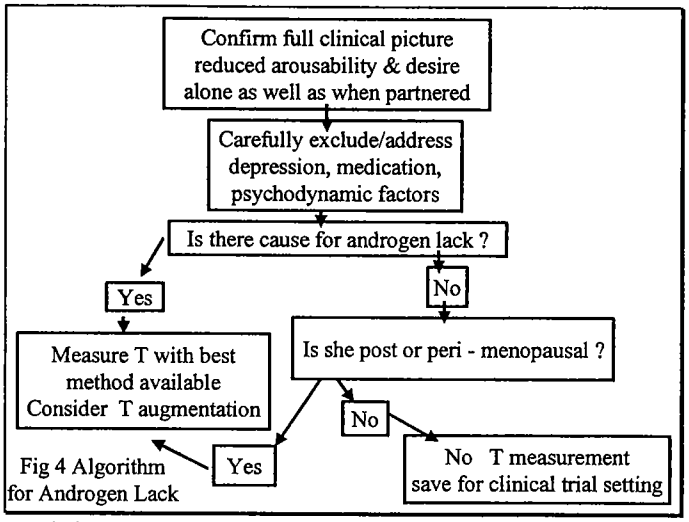

Fig 4 Algorithm for Androgen Lack

5. Augment androgen activity:
   - switch oral to transdermal estrogen (to decrease SHBG), possibly to minimize estrogen's ability to reduce ACTH[xxii]
   - switch from estrogen + progestin oral contraceptives (decreasing the reduction in LH, the reduction in ACTH and the increase in SHBG)
   - consider discontinuing systemic ERT and using a vaginal preparation[xxiii] (discontinuing the increased SHBG, the decreased LH, the decreased ACTH)
   - consider the investigational use of evolving transdermal testosterone preparations or oral testosterone undeconoate at suitable dosage – yet to be defined
   - If future studies suggest that at doses that do not reduce HDL cholesterol, there is benefit, consider the investigational use of methyl testosterone.

6. In the future, we may have access to
   - newer SERMS with different estrogen agonist and antagonist properties – some may not increase SHBG, some may not reduce LH and ACTH
   - "designer HRT" – this would be a molecule with *some* estrogen activity (on bones, urogenital tissues, the endothelium, lipids in a favourable manner, but not to stimulate the breast, endometrium or blood coagulation), and some androgenic action. Tibolone – partially fulfils these criteria. (It does not, for instance, increase HDL cholesterol, and it increases C reactive protein but it does reduce Lp(a) and promote fibrinolysis. It seems not to stimulate breast or endometrium but does increase bone density. It has positive effect on sexual response and desire compared to placebo). Unfortunately, this is not available in many countries.
   - selective androgen receptor molecules (SARMs) – ideally the molecule would be prosexual but without any increase in insulin resistance, minimal activity on the hair cell and the larynx and the sebaceous unit
   - molecules to mimic testosterone's action on the various neurotransmitters involved in sexual responsivity and desire – perhaps acting via certain dopamine, serotonin, and/or certain peptide receptors.