ABSTRACT

Hormone Therapy: Histories, Use, and Controversies Associated with Lower Urinary Tract Symptoms in Men and Menopause in Women

Grace Kohn

Director: Bill Neilson, M.D.

Research on hormone therapies has been evolving rapidly with controversy close behind. The first goal of this project was to investigate a controversy regarding testosterone replacement therapy treatment when associated with lower urinary tract symptoms. It was previously thought that testosterone replacement therapy would worsen lower urinary tract symptoms; however, it was found that mild or moderate symptoms were not worsened, measured using IPSS scores. It was discovered that there was a lack of data for severe symptoms and further research was recommended. The second goal of this project was to provide a clear and concise history of estrogen therapy for women in menopause. Controversies like the correlation of cancer and estrogen therapy were evaluated extensively. It was found that short-term use of estrogen therapy for post-menopausal women is best practice, while necessitating evaluation of risks and benefits with both physician and patient before initiation of treatment.

APPROVED BY DIRECTOR OF HONORS THESIS

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Dr. Bill Neilson, Honors College

APPROVED BY THE HONORS PROGRAM

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Dr. Elizabeth Corey, Director

DATE: _____

HORMONE THERAPY: HISTORIES, USE, AND CONTROVERSIES ASSOCIATED WITH LOWER URINARY TRACT SYMPTOMS IN MEN AND MENOPAUSE IN WOMEN

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Grace Kohn

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Fig. 1 Proposed management algorithm for a patient presenting with hypogonadism by severity of LUTS

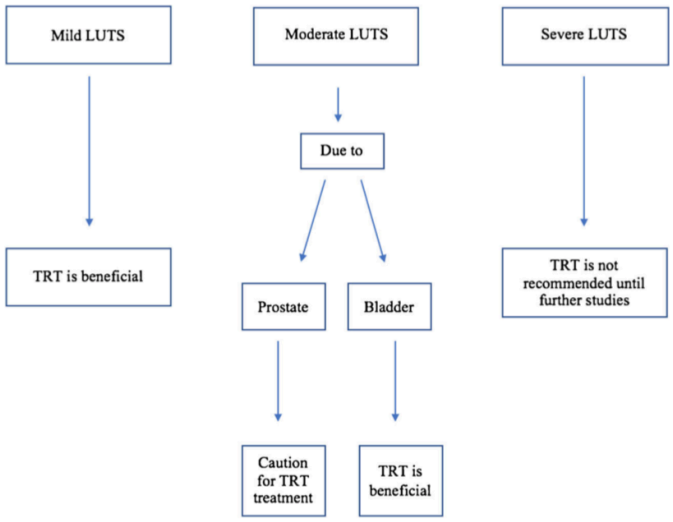

Table 1 and Figure 1 reprinted from Kohn, Grace E., Taylor P. Kohn, and Ranjith Ramasamy. “Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms.” Current Bladder Dysfunction Reports 12, no. 2 (June 1, 2017): 118–23. https://doi.org/10.1007/s11884-017-0419-2.

CHAPTER ONE

Introduction

Hormone therapies have become increasingly researched and have brought many controversies. In this paper, I hope to expand knowledge of hormone therapies and controversies associated. The organization of this paper will be as follows: a brief history of testosterone and estrogen therapy; controversies of hormone therapies; a paper published in June 2017 in *Current Bladder Dysfunction Reports* titled, '*Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms*;' a paper published in April 2019 in *Sexual Medicine Reviews* titled, '*The History of Estrogen Therapy;*' followed by a conclusion summarizing the conclusions of both papers.

A Brief History of Hormone Therapies

Throughout the 20th century the world saw a rise in hormone replacement therapies. Menopausal hormone therapy (MHT) and testosterone replacement therapy (TRT) are two of the largest uses of hormone replacement therapy. The expanded history of estrogen therapy, otherwise now known as MHT, will be expanded upon in the paper titled, '*The History of Estrogen Therapy*'.

The history of TRT is not wholly unlike that of MHT, each with early excitement, but later cast under doubt and critique. There are many references to castration throughout history. For example, in Ancient Greek myths, Aphrodite was created after Chronos cut off Uranus' testicles and threw them into the sea. In ancient China, castration

was a both a punishment for slaves but also done to preserve soprano voices of young boys, which was also done in Italy for Vatican choirs [1,2]. It is suggested that using testicles as a medicinal product began in ancient Rome and references have been found in Arabic medicine, China, and Germany [3].

In 1849, Arnold Berthold determined that a rooster's comb is dependent on androgens because when castrated they lose structure of the comb, aggressive behavior diminishes, and they lose sexual interest in hens. He realized that these behaviors and structures came back once the rooster was given an injection from the testes or given a testicle transplant [4]. Dr. Charles Edward Brown-Séquard injected himself in 1889 with testicular and ovular extracts, claiming they both rejuvenated him and suggested it may be the same in men and women, respectively [5,6].

Over the course of roughly the next 50 years, many studies were conducted to reveal the average value of testosterone levels in the male body. It was controversial whether or not pure testosterone was able to be synthesized from bovine testicles, as some researchers were able to extract enough testosterone to create a physiological effect, but some were not [7,8,9,10]. Drugs like Testifortan and Okasa produced in the 1920s both claimed to treat impotence, but it was later discovered that testicular organ therapy was entirely a placebo medication because the testosterone would be inactivated by the liver [1,11].

One of the most influential reports on testosterone therapy was in 1941 by Huggins and Hodges stated that testosterone aggravated prostate cancer [12]. This caused massive fear in the medical community which was ultimately felt for the next 70

years [4]. This fear of prostate cancer caused androgen deprivation therapy, most commonly in form of castration, to become the most common treatment for prostate cancer. In the 1970s, with the invention of immunoassays, doctors were able to clinically analyze levels of testosterone in the body. Accumulating evidence that TRT does not cause prostate cancer, along with the rise of the saturation model, which will be discussed later in the paper on TRT, provides key evidence for now increased use of TRT [3]. The Testosterone Trials in 2016 showed that TRT caused greater libido, erectile function, sexual activity, physical activity, mood, bone density, and resolution of anemia [13]. Although TRT is now a commonly used treatment, there are many controversies which have yet to be resolved.

Controversies in Hormone Therapy

For years there have been controversies surrounding estrogen therapy, as will be detailed further in the second paper titled, '*The History of Estrogen Therapy*', and there are similar concerns for testosterone therapy. This includes a risk for cardiovascular disease (CVD) when androgen deficiency is treated with testosterone therapy in both men and women. However, a literature review by Elagizi et al. showed that there is no conclusive evidence for or against as there are multiple comorbidities including poor general health, obesity, metabolic disease, and diabetes that may accompany hypogonadism – an indicator for testosterone deficiency in men – and CVD [14, 15].

Contrary to this, a review by Hwang et al. found that some studies showed that low testosterone levels and testosterone deficiency syndrome are related to a baseline

increased risk of cardiovascular (CV) events and that TRT can lower the risk [16,17]. Clearly this is an ongoing debate within the healthcare community, but no definitive results have been widely accepted or presented. Another review by Clavell-Hernández et al. in 2018 further confirmed that there is a lack of evidence to clearly delineate the exact association between the two. He suggests that clinicians continue to properly inform patients about CVD when prescribing testosterone therapy [15]. Hypogonadism and TRT will be further discussed in the first paper titled, '*Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms*.'

Other controversies include the use of hormone therapies and transgendered patients. Issues arising with menopausal hormone therapy (MHT) will be discussed in '*The History of Estrogen Therapy*' paper. However, it is recommended for both TRT and MHT that cross-sex therapies should elevate and maintain levels of hormones which are within the normal physiological ranges for the preferred sex, according to The Endocrine Society [18,19]. Transgendered men with an intact uterus, however, have increased risks for endometrial and ovarian cancers and should follow screening guidelines for cisgender females, which may lead to increased misunderstanding from healthcare professionals if not trained properly [18].

CHAPTER TWO

Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms[1]

Abstract

Purpose of Review

While early studies suggested that testosterone replacement therapy would enlarge the prostate and worsen lower urinary tract symptoms, this review seeks to examine the combined evidence of observational studies, randomized control trials, and meta-analyses published on the topic to determine if testosterone replacement therapy worsens lower urinary tract symptoms in hypogonadal men.

Recent Findings

The combined evidence of 15 randomized control trials and 2 meta-analyses has demonstrated emphatically that testosterone replacement therapy has no effect on lower urinary tract symptoms in hypogonadal men with mild and moderate symptoms.

Summary

No randomized control trial has sufficiently examined the effect of testosterone replacement therapy in men with severe lower urinary tract symptoms. While a few observational studies have seen no effect when hypogonadal men with severe lower urinary tract symptoms are treated with testosterone replacement therapy, future

[1]Kohn, Grace E., Taylor P. Kohn, and Ranjith Ramasamy. "Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms." *Current Bladder Dysfunction Reports* 12, no. 2 (June 1, 2017): 118–23. https://doi.org/10.1007/s11884-017-0419-2.

randomized controlled trials specifically studying the effect of testosterone on men with severe lower urinary tract symptoms are warranted. In summary, clinicians should rest assured that testosterone does not worsen lower urinary tract symptoms in hypogonadal men with mild or moderate lower urinary tract symptoms.

Keywords

Benign prostatic hyperplasia. Hypogonadism. Lower urinary tract symptoms. Prostate. Testosterone.

Introduction

Late-onset hypogonadism (LOH) is a "clinical and biochemical syndrome associated with advancing age and a deficiency in serum testosterone levels" [1]. Cross-sectional and longitudinal studies have demonstrated that a decline in total serum testosterone begins at 40 years of age [2, 3]. A decrease in serum testosterone can be accompanied by symptoms of LOH, which include decreased sexual desire, alterations in mood and cognitive function, erectile dysfunction, and fatigue [1]. These symptoms can be alleviated or reduced by supplementation with exogenous testosterone [4–8].

In addition, aging men can experience enlargement of the prostate (benign prostatic hypertrophy, BPH), resulting in lower urinary tract symptoms (LUTS) [9]. LUTS include increased urinary frequency and urgency, nocturia, incontinence, slow stream, intermittent stream, hesitancy (difficulty initiating urination), and the feeling of incomplete emptying [10]. Within LUTS, the symptoms can be divided into voiding

symptoms, which are related to prostate size, and storage symptoms, which are related to bladder function. LUTS that relate to the prostate include hesitancy, intermittency, and straining, while LUTS related to the bladder include nocturia, urinary frequency, and urgency. It is important to differentiate these symptoms into voiding and storage—as there is a consensus that storage symptoms will not be affected by testosterone use. The severity of LUTS is determined using the International Prostate Symptom Score (IPSS). IPSS is a validated, seven-question instrument that assesses hesitancy, intermittent stream, incomplete emptying, frequency, nocturia, weak stream, and urgency. An increasing IPSS score corresponds to an increase in severity of LUTS [11].

Early theories posited that testosterone replacement therapy (TRT) in men with LOH and BPH would exacerbate LUTS by inducing additional prostatic enlargement [12]. However, multiple randomized controlled trials and two meta-analyses have shown no evidence that TRT exacerbates LUTS [5, 6, 13••, 14, 15•, 16–18, 19••, 20–25].

Early research in prostate cancer found that androgen receptors were present on the prostate and responsible for prostate growth [26]. Using this knowledge, scientists developed androgen deprivation therapy and thus reduced prostatic volume in cancer patients. Based on this, it was theorized that the size of the prostate is related to the levels of androgens in the body. Further investigation on the mechanism of androgen deprivation on prostate size occurred with cultured human cells, as observations have shown that rodent and human prostates respond similarly to changes in hormone levels [27].

In the prostate, basal epithelial cells do not depend on androgen as they do not express androgen receptors. However, differentiated secretory cells in the prostate do express androgen receptors and are sensitive to the presence of androgen. Androgen and androgen receptors are required for the differentiation and survival of secretory cells. With androgen deprivation, apoptosis occurs in the secretory cells but not in the basal epithelial cells [27].

Some men have been previously denied TRT because the prostate can grow with androgen supplementation, and enlargement of the prostate can potentially worsen LUTS. The current Endocrine Society Clinical Practice Guidelines state that TRT is not recommended in men with severe LUTS [28]. However, this phenomenon of androgen-induced multiplication of differentiated epithelium is seen only at low testosterone levels. Clinical studies have demonstrated no relationship between testosterone level and prostate size after testosterone levels of 200–300 ng/dL and no relationship between TRT and LUTS [13••, 19••]. This finding is a crucial physiologic mechanism for the clinical data supporting no relationship between TRT and LUTS.

Clinical Research Studies Assessing LUTS and TRT

In 1943, Huggins et al. published a case series of 21 men which demonstrated that prostate volumes decreased with testosterone deprivation. While this study did not assess symptoms of BPH, many argued that this reduction in prostatic volume would inevitably lead to an improvement of the symptoms of BPH [12]. This theory was further strengthened when a randomized placebo-controlled trial by Holmang et al. 1993

demonstrated a 12% increase in prostate volume after 8 months in 23 eugonadal men treated with oral testosterone. While this did not observe any bladder obstructive symptoms in the men treated with testosterone, this study further implicated a possible relationship between testosterone and symptoms of BPH [29].

Yet over the last 20 years, growing evidence has suggested that there is no relationship between testosterone replacement therapy and LUTS. One of the first studies to formally assess this relationship between TRT and LUTS was Kenny et al. in 2001. In this RCT, 20 hypogonadal men were treated with TRT and an additional 24 hypogonadal men were given a placebo. After 1 year, the average IPSS scores had increased by 0.3 points while the average IPSS scores for the control group had increased by 1.8 points. This change was neither statistically nor clinically significant [18]. In 2010, Kenny et al. published another RCT which demonstrated a similar result in a larger population. Fifty-three hypogonadal men receiving transdermal TRT had an increase in average IPSS score of 0.1 points, while 46 hypogonadal men receiving a placebo had a decrease in average IPSS score by 0.1 points [5]. In a 2011 study, 46 hypogonadal men with mild BPH were assigned receive either testosterone enanthate every 4 weeks or a placebo; patients receiving testosterone had significantly reduced lower urinary tract symptoms, increased maximum flow rate, and increased voided volume compared to the placebo group [Shigehara et al. 2011].

More recently, three large RCTs have been published in the past 2 years examining the relationship between testosterone and LUTS. Paduch et al. evaluated 76 hypogonadal men with erectile dysfunction who received TRT and found a slight, but

non-statistically and non-clinically significant increase in IPSS for men on TRT (+0.6 IPSS points) compared to those without TRT (−1.2 IPSS points) [23]. Meuleman et al. examined 322 hypogonadal men and found a statistically significant decrease in IPSS for men on TRT (−1.33 IPSS points) compared to controls (+0.42 IPSS points) [22]. Finally, Konaka et al. found that in 334 hypogonadal men that there was a non-statistically significant decrease in IPSS for men on TRT (−0.56 IPSS points) when compared to controls (+0.88 IPSS points) [20].

One of the largest trials performed examining this relationship has yet to be published, but their results can be found at clinicaltrials.gov. In this RCT of 596 hypogonadal men, both the TRT group and control group had a decrease of 0.7 IPSS points after 36 weeks. This is the largest study to date evaluating the effect of TRT on LUTS, further demonstrating that testosterone has a minimal effect on LUTS [30].

A total of 15 randomized controlled trials (RCTs) have found that testosterone has no effect on LUTS as measured by IPSS. Eleven RCTs examined testosterone versus placebo over the short-term (<12 months) and four RCT studied testosterone with placebo over the long-term (12–36 months) (Table 1). In addition to using IPSS, four studies measured prostate growth in terms of prostate volume, PSA levels, and Q_{max} (maximum urine flow rate). While a clinically significant change in LUTS requires a change of three or more points on IPSS, no study reported an average worsening of more than 1.02 points on IPSS [13••, 15•, 19••]. No significant worsening of IPSS was seen in LUTS for either the short-term and long-term androgen replacement therapy trials using oral, transdermal, and injection routes.

Table 1 Table detailing randomized control trials assessing LUTS by IPSS

Author (randomized controlled trials)	Follow-up (weeks)	Sample size		Change in IPSS		Significant difference
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Kenny et al. [18]	52	20	24	0.3	1.8	No

Meta-analyses

Two recent meta-analyses on the topic have been published. Cui et al. and Kohn et al. found that neither short-term nor long-term administration of testosterone increased the risk of prostrate growth or worsening LUTS [13••, 19••]. The meta-analysis by Kohn et al. examined changes in IPSS after TRT for men with LOH with or without concomitant mild or moderate LUTS. This meta-analysis found no clinically significant change in IPSS for men who were treated with TRT compared to men who were not treated with TRT. This indicates that in men with LOH with non-existent, mild, or moderate LUTS, TRT does not worsen LUTS.

Cui et al. also evaluated safety of long-term TRT in 16 double-blinded RCTs. All RCTs involved rigorous monitoring of patients for prostate enlargement or significant

increase in PSA, and treatment was withdrawn if indications of prostate cancer or other complications arose.

For short-term testosterone replacement therapy, three RCTs showed similar changes in IPSS for injection, transdermal application, and placebo [19••]. Two RCTs found no clinically significant increase in IPSS score with oral administration of TRT [19••]. Four RCTs found no change in prostate volume with injection, transdermal application, and oral de- livery [13••]. Six RCTs demonstrated that transdermal androgen replacement therapy (TRT) increased PSA levels while injection, oral administration, and placebo did not affect PSA levels [13••]. Only two RCTs examined changes in Q_{max}, but found that it did not change when the patients were given injection or oral administration. No RCT explored the effect of transdermal androgen application on Q_{max} [13••].

For long-term testosterone replacement therapy, there was no change in PSA levels or prostate volume for any administration method according four RCTs [13••]. Six RCTs demonstrated that IPSS changes were nearly the same for TRT or placebo for all administration methods [19••]. Two RCTs measured change in Q_{max} for injection and oral administration, and found no reduction in Q_{max} compared to placebo [13••].

Men with Severe LUTS

The majority of papers do not discuss the impact of TRT on men with severe LUTS. Of the 14 trials analyzed by Kohn et al., five RCTs excluded men with IPSS ≥20,

several excluded men with IPSS >19, and one RCT excluded men with IPSS ≥14. Only two RCTs have been performed that included men with IPSS >19 [19].

Tan et al. included 17 men with severe LUTS in their study, but did not provide specific IPSS data for this group [25]. Pearl et al. found in a non-controlled trial of 120 men, the IPSS score decrease by an average of −7.42 after TRT. Compared to men with mild and medium IPSS scores, this decrease was determined to be significant. This study did not include how many participants had severe IPSS at baseline, whether patients taking medication for LUTS had been removed from the trial, and no control group was included [32]. Additional randomized controlled trials are necessary to provide more conclusive evidence on whether men with severe LUTS should be restricted from receiving TRT (Fig. 1).

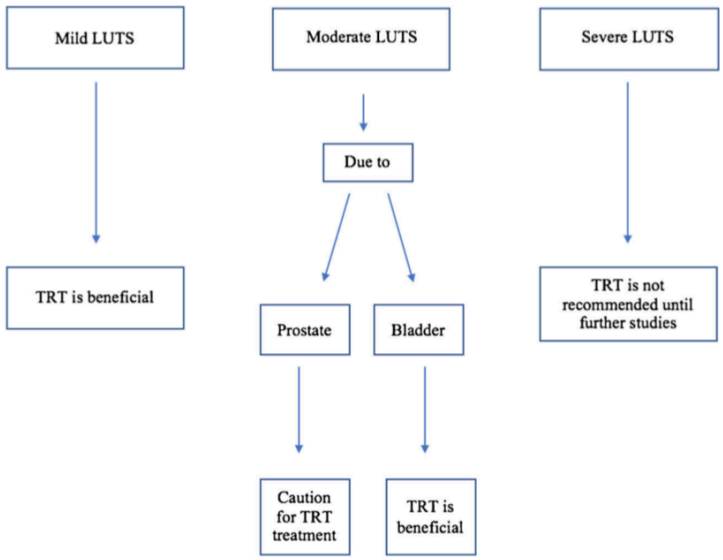

Fig. 1 Proposed management algorithm for a patient presenting with hypogonadism by severity of LUTS

Saturation Model for Effect of Testosterone on Prostate

It has long been believed that serum testosterone concentration in the body is linearly related to prostate growth, causing an increase in dysfunction as serum testosterone increases. Now, a model suggests that androgen receptors become saturated at a certain concentration of serum testosterone. The saturation curve demonstrates that serum testosterone will not have significant effect on prostate volume once the receptors have been saturated, namely above testosterone concentrations at or near castrate range [33]. This "saturation model" is based on basic biochemical principles and provides a better explanation for the clinically observed relationship between prostate volume and testosterone concentration [33]. Unfortunately, no clinical studies have demonstrated the serum testosterone level at which androgen receptors are saturated.

Conclusion

TRT has not been shown to exacerbate LUTS in men with mild or moderate symptoms. Additional studies are needed to examine men with severe LUTS as this population has not been adequately investigated. Future randomized controlled trials investigating testosterone treatment should include assessment of LUTS using IPSS as part of safety monitoring, but such studies should differentiate changes in LUTS by symptom severity. The sum of evidence suggests that physicians should feel comfortable prescribing testosterone therapy for hypogonadal men with mild and moderate LUTS, as TRT can significantly improve quality of life by alleviating symptoms of hypogonadism without worsening LUTS.

Compliance with Ethical Standards

Conflict of Interest Drs. Grace Kohn, Taylor Kohn, and Ranjith Ramasamy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

CHAPTER THREE

The History of Estrogen Therapy[2]

Abstract

Introduction

Menopausal hormone therapy (MHT) has proven an effective treatment for the amelioration of symptoms of menopause. The idea that a substance was the missing factor in a woman's body after menopause dates to the 1800's when cow ovarian tissue was injected into German women in a successful attempt to reverse the sexual symptoms of menopause. The early 1900's saw the rise of commercialized menopause "treatments" that ranged in substance, and even theoretical efficacy. The role of estrogen was first accurately described in Guinea pigs in 1917 by Dr. Papanicolaou.

Aim

To tell the detailed history of how estrogen was discovered and the controversy surrounding MHT.

Methods

A literature search was conducted using PubMed to identify relevant studies and historical documents regarding the history of estrogen therapy.

[2] Kohn, Grace E., Rodriguez, Katherine M., and Pastuszak, Alexander W.. "The History of Estrogen Therapy." *Sexual Medicine Reviews.* Accepted 2019. In Press.

Results

The history of estrogen supplementation and its controversies are interesting stories and relevant to today's ongoing investigation into hormone replacement.

Conclusion

The controversy of MHT remained until the first randomized trials examining MHT in the early 1990s that suggested MHT is cardioprotective in post-menopausal women, though this conclusion was contradicted in subsequent trials. In the present day, MHT is approved only for short term use for the symptomatic treatment of menopause.

Introduction

There is ongoing debate about the use of menopausal hormone therapy (MHT) in women, stemming from conflicting study findings and Food and Drug Administration (FDA) statements. The Women's Health Initiative was one such study which showed a relationship between MHT and cancer beginning in 1992.[1] The use of estrogen as effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause, testosterone to relieve symptoms of low sexual desire in women, and estrogen/testosterone use in transgender patients continues to be an evolving conversation. Women in whom MHT is indicated can experience improvements in quality of life and sexual symptoms, as well as an improvement in genitourinary symptoms, which include night sweats, hot flashes, flushes, and vulvovaginal atrophy. However, it is important to

note that there is an evolving understanding of the role of sex steroid hormones in genitourinary tissues as well as receptor types and signaling pathways. This exciting field will undoubtedly increase understanding and treatment options,[2] MHT is safest to initiate in women less than 60 years old or less than 10 years from onset of menopause. While modern debates regarding the safety and efficacy of MHT have become nuanced and complicated, the history of estrogen therapy is a story of scientific inquiry to improve symptoms of a non-life threatening medical condition that affects women, a novel idea for the time.

References to menopause date back to the 300s B.C., when Aristotle (384-322 B.C.) described the cessation of menstruation as occurring around the age of 40.[3] Discussions on the cessation of menstruation continue throughout literature, including mentions in the Bible. Although mentioned throughout literature, little is said about the actual experience of menopause. The term menopause, derived from the Greek words *men,* meaning month, and *pauses,* meaning stop, was not even used until the early 1800s, when it was coined by the French physician Gardanne[4]. This initiated the thinking that women's aging deserved medical attention.

Nineteenth Century Advancements in Female Hormone Therapy: The Start of an Era

The late 1800s and beginning of the 1900s saw the beginning of the Second Industrial Revolution, during which advancements in manufacturing and globalization were rapidly changing the world. Two studies in Germany published in March and April 1886, women who were either ovariectomized or experiencing menopausal symptoms with

injected ovarian tissue. F. Mainzer and R. Mond prescribed oral therapy of 5-20 g/day of bovine ovarian tissue. The patients experienced a dramatic reduction in sexual dysfunction. After switching to non-ovarian tissue, the treatment was ineffective. A third publication from Austria, in May 1896, showed that 0.2-0.8 g/day of dried ovarian tissue from reproductive age cows, resulted in symptomatic improvement in four of seven patients, six of whom were ovariectomized and one with physiological menopause. These studies were quickly followed by another by Mainzer, in June 1896, demonstrating that 1.0-7.5 g/day of dried bovine or porcine ovarian tissue was successful for reducing the symptoms of sexual dysfunction.[5]

Dr. Charles Edward Brown-Séquard, known as the "Father of Endocrinology," experimented on himself with an extract of guinea pig and dog testicles in 1889. This injection resulted in his claim that he had "rejuvenated himself," and suggested that these extracts may have the same effect on women. Ultimately, this was the seed for commercialization of sex hormone therapy. In the 1890s, Merck & Company produced Ovariin in both powder and pill form, a treatment for menopause made from powdered cow ovaries that successfully treated symptoms of menopause.[6]

Twentieth Century Leaps and Bounds

In 1917, near the conclusion of WWI, Stockard and Papanicolaou were the first to describe estrogen and the role of the hypothalamic-pituitary-adrenal (HPA) axis in guinea pigs.[7] By 1920, George Papanicolaou had turned his attention to the human reproductive system and was able to distinguish between normal and malignant cervical cells from cultured swabs.

He is best known for creating the Papanicolaou test, a revolutionary discovery that transformed the detection of cervical cancer in 1943.[8] Long and Evans, in 1922, defined the oestrous cycle in the rat, and were the first to discover and explain the tissue changes during the menstrual cycle its relationship to pregnancy.[9]

Although it was believed that hormones were present in ovarian preparations, as indicated by the maintenance of cyclic changes when ovaries were transplanted to other parts in the body, the actual hormones or their specific effects, as well as the efficacy of commercial extracts for clinical use, remained unknown.[10] This was further illustrated with two reviews by Frank and Novak in 1922, claiming distrust in the popular commercial preparations, given that there was no reliable test to measure the activity of the hormones (or extracts). Allen had discovered the oestrous (estrogen) cycle in rats and assumed that the corpus luteum and interstitial tissue would contain the "estrus hormone". In 1923, Allen and Doisy reported localizing, extracting, and partially purifying estrogen. They also determined some actions of estrogen in animal models.[10] This bioassay for detecting estrogenic activity would provide a basis for future hormone research, and facilitated the identification of estrogens in many different sources including mammalian tissues, excreta, and plants. Perhaps as significantly, the new assays facilitated estrogen synthesis. [11]

Although during the Great Depression in the United States, the first MHT product, Emmenin, was commercially produced and sold in 1933 in the United States by James Collip at Ayerst (Figure 1). [12]This was the first form of bio-identical hormone therapy and was derived from the urine of pregnant women. However, Emmenin was expensive to produce and was replaced in 1941 by Premarin, which was made from conjugated equine

estrogens.[13] The name Premarin derives from the pregnant mare urine from which these estrogens were derived.[14] Premarin was marketed to orally "replace" a woman's estrogen. Later, other routes of administration included an estrogen patch, produced by Searle in 1928, as well as oral ethinyl estradiol, produced by Schering in 1937.[15, 16] The synthetic estrogen, diethylstilbestrol (DES) was discovered in 1938, and was granted FDA approval in 1941. It was suggested that DES might stimulate bone growth.[16]

Several books and publications during the 1940s-1950s suggested use of estrogen therapy for "menopausal disorders" promoted steady increases in use of MHT, eventually doubling and tripling in use by the 1960s to mid-1970s. This trend was further encouraged by a book by Robert Wilson, called *Feminine Forever.* This book promoted the use of estrogen therapy as a way to eliminate emotional complaints and menopause, making a woman 'feminine forever.'[17] This created a market for drug companies and physicians to increase prescription and synthesis of estrogen therapy.[4] By 1975, estrogen was the fifth most prescribed drug in the United States.[18]

Controversy Arises

A sharp decline in the use of estrogen therapy occurred in the 1970s, when reports of a 4-14 times increased risk of endometrial cancers was linked to estrogen therapy. As a result, the FDA required a warning on all estrogen products that indicated a risk for blood clots and cancer.[19, 20] However, evidence in the mid-1980s stated that the addition of progestin would reverse endometrial hypertrophy associated with endometrial cancer by over 98%. This would counteract the estrogen-induced endometrial changes, initiating a

revival in MHT use.[16, 21] Estrogen use increased through the 1980s and 1990s among all women, with a corresponding increase in use of progestin by women with a uterus. Also, during this time, the link between decreasing rates of osteoporosis, coronary heart disease (CHD), and the use of estrogen therapy was being investigated.

The Coronary Drug Project began in 1966 and examined the effect of estrogen therapy on men with previous myocardial infarction. An increased risk of thromboembolic events and myocardial infarction was observed in men taking Premarin (5 mg and 2.5 mg).[16] The use of estrogen therapy for male to female transgendered patients is based on the recommendations for post-menopausal women, although no studies to date have compared the efficacy of different routes of administration. Interestingly, transgender women are at increased risk for bone loss, despite the use of estrogen therapy, in part likely due to concomitant anti-androgen therapy. The use of estrogen therapy in transgender women shows an trend toward increased risk of cardiovascular disease, although studies remain inconclusive. [22]

During the 1980s and 1990s, Albright et al. concluded that bone loss was linked to low ovarian hormone levels and that DES could represent a viable solution for improving bone density.[23] in 1972, the FDA stated that estrogen therapies were “probably effective” for the prevention of osteoporosis.[16] Evidence in the 1984 NIH Consensus Development Conference on Osteoporosis declared estrogens as the best way to prevent bone loss.[24] A Women’s Heath Initiative (WHI) trial in 1992 demonstrated that the use of estrogen for prevention of diseases is variably effective. This study was composed hormone therapy, dietary modification, or observational study if women did not qualify for the clinical trial

or did not want to participate. Within the hormone therapy component, women were randomized to combination estrogen and progestin therapy or estrogen only therapy. However, after one year, women were offered to begin calcium plus vitamin D.[25] Combination estrogen and progestin therapy was thought to decrease the risk of CHD and hip fracture, but increased the risk of endometrial and breast cancer with long-term use, up to 10% per year of use. Results from the estrogen-only group suggested a possible decrease in the risk of breast cancer. Bone density was shown to slightly, but significantly, increase in the calcium plus Vitamin D component of the study. [26] In the WHI studies, Prempro showed an increase in cardiovascular disease risk, which caused the studies to be terminated early. This may be because the WHI trials were composed of women with an average age of 63, of whom one-third had hypertension and one-half had a history of smoking. However, when a reanalysis of the data was performed, the estrogen therapy without progestin did not increase the risk of cardiovascular events. This suggests that progestins were possibly responsible for the adverse outcomes.[27]

The WHI hormone trials were intended to clearly define the effects of estrogen as a primary prevention measure for CHD. This study was led by cardiologists and the main outcome measure was cardiac in nature. The WHI trial and resulting follow up studies, were not meant to determine the efficacy of estrogen therapy in the setting of menopause. Rather, women who were selected for these investigations (50-97 years old) had higher risk for cardiovascular events, which would power the study with a smaller number of participants.[28] These were multicenter, parallel, randomized, controlled prevention trials which investigated the effects of hormone therapy in postmenopausal women with an intact

uterus on CHD risk. The study used Prempro, a daily estrogen (conjugated equine estrogen 0.625mg) and progesterone (medroxyprogesterone acetate 2.5mg) with a placebo to study cardiovascular disease.[1] Five years into the eight years of anticipated follow-up, the WHI study demonstrated an increase in breast cancer, stroke, pulmonary embolism, and myocardial infarction risk in women on hormone therapy who had a uterus, although a lower incidence of fracture due to osteoporosis was also observed.[29, 30] The group of women without a uterus, solely on estrogen (0.625 mg conjugated equine estrogen) was also terminated, as an increased risk of stroke was observed, although no increased risk of CHD was found.[30] Following the publication of these results, the use of HT decreased significantly, with concerns from patients and providers.

The WHI studies have been criticized, with critiques including concerns with the median age and range of ages of participants, overstatement of the conclusions, and the use of a single form and formulation of female hormone therapy. As women age, there is a natural increase in risk of myocardial infarction and thromboembolic events; therefore, it is difficult to determine the underlying cause of the increased risk observed in the WHI studies. Another critique is that the authors overstated the conclusions, excluding absolute risk and rather focusing on relative risk. The final major critique is that the estrogen-progesterone combination used for the trials was a single dose and single formulation, limiting the ability to make more global conclusions regarding female hormone therapy. [1, 30]

Following the publication of the WHI studies, estrogen therapy use declined by 45% and estrogen / progestin therapy use declined by 22%.[31] However, a study that

followed women after stopping treatment with estrogen or progestin therapy observed a 12% increased risk of malignancies for women who received conjugated equine estrogens (CEE) plus medroxyprogesterone (MPA).[32] Short term use of estrogen therapy has been approved by the FDA for menopausal symptoms, but not for prevention of CHD. Currently, estrogen therapy is used to reduce the frequency of hot flashes, insomnia, and vaginal discomfort, as well as potentially reducing stress incontinence and urinary symptoms using the lowest possible dose for relief.[33]

The FDA Generic Drugs Advisory Committee became aware of issues of safety and efficacy of generic conjugated estrogens in 1990 and proposed to remove all generic forms of estrogen from the market.[16] In 1995, Wyeth-Ayerst petitioned the FDA to include δ-dehydroestrone sulfate (DHES) as a required component for all conjugated estrogens. Prior to this, in 1970, the US Pharmacopeia (USP) conjugated estrogens contained sodium estrone sulfate and sodium equilin sulfate. This was only amended in 1992 to include three additional estrogens, as well as δ-dehydroestrone sulfate (DHES) in 1995.[34] However, in 1997, the FDA's Center for Drug Evaluation and Research indicated that it would not approve generic forms of Premarin that did not having the same active ingredients as the brand formulation because, without these, the drugs were unable to effectively treat menopausal symptoms and prevent osteoporosis. There were also concerns regarding the bioequivalence and safety and efficacy of the generic drugs [16] Premarin continued to rise in popularity, becoming the number one prescribed drug in 1992.[35]

Medical knowledge about the actual effects of estrogen therapy was varied, with some healthcare professionals indicating it was beneficial and some stating that it was not.[36] In 1993, the first large randomized control trial (RCT) for MHT began. The Heart and Estrogen/Progestin Replacement Study (HERS) examined the effects of estrogen-progestogen therapy on postmenopausal women with CHD. No significant differences in the progression of CHD were observed in women taking conjugated equine estrogen (CEE) (0.625mg) and medroxyprogesterone acetate (MPG) (2.5mg), and the placebo group. However, after the first year of the study the incidence of cardiac events in women in the treatment group was higher than that in women on placebo. This was, however, found to be negligible over the next three years, when the two groups were compared. Overall, no benefit was found in women with CHD taking hormone therapy. A second large RCT, HERS II, followed the participants for another 2.7 years, in which no significant benefits for CHD risk were identified. As a result, HT was recommended against for secondary prevention of CHD.[1] Despite this conclusion, in 1996, the United States Preventive Services Task Force (USPSTF) advised that all postmenopausal women consider using preventative hormone therapy.[37]

In 2005, the Kronos Early Estrogen Prevention Study (KEEPS) interventional clinical trial began in order to explore the correlation of early initiation of MHT, within 3 years post-menopause, to delay cardiovascular disease using low-dose oral Premarin (0.45 mg) or transdermal estrogen (50 μg), cyclic progesterone, or placebo. No significant differences in arterial wall thickness over the 4 years of study between the groups were observed, and coronary artery calcium, a marker for atherosclerotic plaque, was lower

among the hormone therapy groups. Although the differences were not significantly different, a trend towards significance was identified. Although blood pressure was increased in the WHI trials, due to lower dosage of estrogens in the KEEPS trials, neither the oral or transdermal patch significantly increased blood pressure. This study was unable to make definitive conclusions regarding the differences in breast cancer, endometrial cancer, myocardial infarction, transient ischemic attack, stroke, or venous thromboembolic disease between the three groups.[38]

The relationship between the effect of estrogen therapy and breast cancer led to the Gap Hypothesis, which posited that there is very little or no increased risk for breast cancer if hormone therapy was started at least five years after menopause occurred. This was investigated and supported by the data from the prospective, observational Million Women study in Britain. [39] However, the authors found a significant increase in risk of breast cancer in women who had begun therapy less than five years before menopause, regardless of type or length of therapy, or weight of women. In a study by Coombs et al., the risk of breast cancer in women using hormone therapy increased from a baseline 6.1% to 6.3% with use of estrogen therapy and 6.7% with use of estrogen-progestogen use, although the risk returned to baseline rapidly when therapy was stopped. Length of time on therapy was also important, as breast cancer risk increased 2.75% if hormone therapy had been used for more than five years and 1.85% if used two to five years.[29]

In 2016, it was still not known whether cardiovascular effects associated with MHT varied with time of initiation, between two to ten years after menopause. The Early versus Late Postmenopausal Treatment with Estradiol (ELITE) study, with support of the clinical

trials EPAT and WELL-HART, began to study the timing hypothesis. This indicates that the timing of initiation of hormone therapy will affect CHD and atherosclerosis. This study specifically looked at atherosclerosis with estradiol therapy with or without progesterone and found that progression of carotid-artery intima-media thickness was lower in the estradiol group, in comparison with placebo, for women who were less than 6 years post-menopause, but not those who were 10+ years post- menopause.[40]

Today, MHT in women is used to manage symptoms of menopause which impair quality of life. In 2017, The North American Menopause Society (NAMS) concluded that hormone therapy is still the most effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause as well as prevents bone loss and fracture, although risks depend on type, dose, duration of use, route of administration, and timing of initiation. For longer duration of hormone therapy, estrogen therapy is more favorable than estrogen-progesterone therapy. Women who are less than 60 years old or less than 10 years from onset of menopause have favorable outcomes of hormone therapy for symptoms of menopause. However, women who begin hormone therapy more than 10 years after menopause or are older than 60 years old at the time of initiation of hormone therapy, appear to have greater risks of CHD, stroke, venous thromboembolism, and dementia.[41]

Conclusion

The history of our understanding of menopause and estrogen supplementation is an interesting story that highlights many pitfalls of new therapies and evolving understanding of mechanisms of disease. From exciting claims that estrogen could be “the fountain of

youth", help with osteoporosis and reduce heart disease in women, to concerns of thromboembolic disease, breast and endometrialancer, it has been a highly debated topic in the last 50 years. While new research is emerging every day, oral estrogen use in post-menopausal women is currently limited to the short-term treatment of vasomotor flushing, and topical estrogen for vaginal atrophy. Overall, the risks and benefits of female hormone therapy should be considered by clinicians and patients, and treatment decisions made on an individual basis.

Figure 1 – Photograph of Emmenin, an early form of female hormone therapy

CHAPTER FOUR

Conclusion

Throughout the 20th century, there was a rise in hormone replacement therapies and research. Although controversies have followed both therapies, estrogen and testosterone replacement therapies are safe to use within certain guidelines. Ultimately, it is the duty of the physician to carefully consider risks and benefits of these therapies for patients. However, these review articles are meant to inform physicians about improving symptomology of LUTS and the history and controversies of estrogen therapies.

TRT does not increase symptomology of LUTS, therefore physicians should consider TRT as a treatment option for hypogonadal men with mild and moderate LUTS. And although TRT has not been shown to exacerbate LUTS in men with mild or moderate symptoms, there is a need for more studies in men with severe LUTS. Wider ranges of IPSS measurements are needed in future testing, but research should also categorize by severity of LUTS and associated changes in symptoms.

Estrogen therapy research is constantly being updated and improved; however, oral estrogen use in post-menopausal women is currently limited to the short-term treatment of vasomotor flushing, and topical estrogen for vaginal atrophy. I recommend future research in this field would consider increased research on transgendered women and the associated risks. Increased research on the specific mechanism of increased CVD and cancers associated with MHT is also needed.

BIBLIOGRAPHY FOR CHAPTER ONE

1. Nieschlag E, Nieschlag S. Testosterone deficiency: a historical perspective. Asian J Androl. 2014;16(2):161-168. doi:10.4103/1008-682X.122358

2. Melicow MM. Castrati singers and the lost “cords”. Bull N Y Acad Med. 1983;59(8):744-764.

3. Medvei VC. The History of Clinical Endocrinology: A Comprehensive Account of Endocrinology from Earliest Times to the Present Day. CRC Press; 1993.

4. Morgentaler A, Traish A. The History of Testosterone and the Evolution of its Therapeutic Potential. Sex Med Rev. April 2018. doi:10.1016/j.sxmr.2018.03.002

5. Rooke T, Rooke TW. The Quest for Cortisone. Michigan State University Press; 2012. https://muse.jhu.edu/book/14498.

6. Brown-Séquard EC. The effects produced in man by subcutaneous injections of a liquid obtained from the testicles of animals. 1889;134(3438):105-107.

7. Coviello AD, Bremner WJ, Matsumoto AM, et al. Intratesticular testosterone concentrations comparable with serum levels are not sufficient to maintain normal sperm production in men receiving a hormonal contraceptive regimen. J Androl. 2004;25(6):931-938.

8. Gallagher TF, Koch FC. The Testicular Hormone. J Biol Chem. 1929;84(2):495-500.

9. Moore CR, Hughes W, Gallagher TF. Rat seminal-vesicle cytology as a testis-hormone indicator and the prevention of castration changes by testis-extract injection. American Journal of Anatomy. 1930;45(1):109-135. doi:10.1002/aja.1000450105

10. Heller RE. Cowper’s gland and its reaction to castration and to different sex-hormone conditions. American Journal of Anatomy. 1932;50(1):73-95. doi:10.1002/aja.1000500104

11. Nieschlga E, Cüppers HJ, Wickings EJ. Influence of sex, testicular development and liver function on the bioavailability of oral testosterone. European Journal of Clinical Investigation. 1977;7(2):145-147. doi:10.1111/j.1365-2362.1977.tb01588.x

12. Huggins C, Hodges CV. Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. Cancer Res. 1941;1(4):293-297.

13. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of Testosterone Treatment in Older Men. New England Journal of Medicine. 2016;374(7):611-624. doi:10.1056/NEJMoa1506119

14. Elagizi A, Köhler TS, Lavie CJ. Testosterone and Cardiovascular Health. Mayo Clin Proc. 2018;93(1):83-100. doi:10.1016/j.mayocp.2017.11.006

15. Clavell-Hernández J, Wang R. Emerging Evidences in the Long Standing Controversy Regarding Testosterone Replacement Therapy and Cardiovascular Events. World J Mens Health. 2018;36(2):92-102. doi:10.5534/wjmh.17050

16. Hwang K, Miner M. Controversies in testosterone replacement therapy: testosterone and cardiovascular disease. Asian J Androl. 2015;17(2):187-191. doi:10.4103/1008-682X.146968

17. Surampudi V, Swerdloff RS. Testosterone replacement therapy: the controversies of cardiovascular risk. Cardiovascular Endocrinology & Metabolism. 2015;4(3):90. doi:10.1097/XCE.0000000000000058

18. Gupta S, Imborek KL, Krasowski MD. Challenges in Transgender Healthcare: The Pathology Perspective. Lab Med. 2016;47(3):180-188. doi:10.1093/labmed/lmw020

19. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine Treatment of Transsexual Persons:An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94(9):3132-3154. doi:10.1210/jc.2009-0345

REFERENCES FOR CHAPTER TWO

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Behre HM, Tammela TL, Arver S, Tolra JR, Bonifacio V, Lamche M, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of- life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. The aging male: the official journal of the International Society for the Study of the Aging Male. 2012;15(4):198–207. doi:10.3109/13685538.2012.699562.

2. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87(2):589–98. doi:10.1210/jcem.87.2.8201.

3. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001;86(2):724–31. doi:10.1210/jcem.86.2.7219.

4. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation- enhanced testosterone transdermal system in comparison with bi- weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab. 1999;84(10):3469– 78. doi:10.1210/jcem.84.10.6078.

5. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;58(6):1134–43. doi:10. 1111/j.1532-5415.2010.02865.x.

6. Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab. 2000;85(8):2670–7. doi:10.1210/jcem.85. 8.6731.

7. Wang C, Alexander G, Berman N, Salehian B, Davidson T, McDonald V, et al. Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. J Clin Endocrinol Metab.1996;81(10): 3578–83.

8. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab. 2000;85(8):2839–53.

9. Taylor BC, Wilt TJ, Fink HA, Lambert LC, Marshall LM, Hoffman AR, et al. Prevalence, severity, and health correlates of lower urinary tract symptoms among older men: the MrOS study. Urology. 2006;68(4):804–9. doi:10.1016/j.urology.2006.04.019.

10. Jones C, Hill J, Chapple C, Guideline Development Group. Management of lower urinary tract symptoms in men: summary of NICE guidance. BMJ. 2010;340:c2354. doi:10.1136/bmj.c2354

11. Barry MJ, Fowler Jr. FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148(5):1549–57.

12. Huggins C, Stevens Jr. RE, Hodges CV. Studies on prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg. 1941;43(2):209–23. doi:10.1001/archsurg.1941. 01210140043004.

13.•• Cui Y, Zhang Y. The effect of androgen-replacement therapy on prostate growth: a systematic review and meta-analysis. Eur Urol. 2013;64(5):811–22. doi:10.1016/j.eururo.2013.03.042. **This meta- analysis demonstrates that prostate size does not change in hypogonadal men undergoing androgen replacement therapy.**

14. Shigehara K, Sugimoto K, Konaka H, Iijima M, Fukushima M, Maeda Y, et al. Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study. The aging male : the official journal of the International Society for the Study of the Aging Male. 2011;14(1):53–8. doi:10.3109/13685538.2010.518178.

15.• Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, et al. Effects of testosterone administration for 3 years on sub- clinical atherosclerosis progression in older men with low or low- normal testosterone levels: a randomized clinical trial. JAMA. 2015;314(6):570–81. doi:10.1001/jama.2015.8881. **In this recently published randomized control trial of 248 hypogondal men, the authors demonstrate no clinically or statistically significant increase in lower urinary tract symptoms after 3 years of testosterone replacement therapy.**

16. Chiang HS, Hwang TI, Hsui YS, Lin YC, Chen HE, Chen GC, et al. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. Int J Impot Res. 2007;19(4):411–7. doi:10.1038/sj.ijir.3901562.

17. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol. 2010;73(5):602–12. doi: 10.1111/j.1365-2265.2010.03845.x.

18. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2001;56(5):M266–72.

19.•• Kohn TP, Mata DA, Ramasamy R, Lipshultz LI. Effects of testosterone replacement therapy on lower urinary tract symptoms: a systematic review and meta-analysis. Eur Urol. 2016; doi:10. 1016/j.eururo.2016.01.043. **This meta-analysis demonstrates that lower urinary tract symptoms are not worsened in hypogonadal men undergoing testosterone replacement therapy.**

20. Konaka H, Sugimoto K, Orikasa H, Iwamoto T, Takamura T, Takeda Y, et al. Effects of long-term androgen replacement therapy on the physical and mental statuses of aging males with late-onset hypogonadism: a multicenter randomized controlled trial in Japan (EARTH Study). Asian J Androl. 2015; doi:10.4103/ 1008-682x.148720.

21. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA. 2006;296(19):2351–61. doi:10.1001/jama.296.19.2351.

22. Meuleman EJH, Legros J-J, Bouloux PMG, et al. Effects of long-term oral testosterone undecanoate therapy on urinary symptoms: data from a 1-year, placebo-controlled, dose-ranging trial in aging men with symptomatic hypogonadism. Aging Male. 2015;18(3):157-163. doi:10.3109/13685538.2015.1032925

23. Paduch DA, Polzer PK, Ni X, Basaria S. Testosterone replacement in androgen-deficient men with ejaculatory dysfunction: a randomized controlled trial. J Clin Endocrinol Metab. 2015;100(8):2956– 62. doi:10.1210/jc.2014-4434.

24. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double- blind, placebo-controlled study. J Clin Endocrinol Metab. 2010;95(2):639–50. doi:10.1210/jc.2009-1251.

25. Tan WS, Low WY, Ng CJ, Tan WK, Tong SF, Ho C, et al. Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: a randomised controlled study. BJU Int. 2013;111(7): 1130–40. doi:10.1111/bju.12037.

26. Tammela T. Benign prostatic hyperplasia. Practical treatment guide- lines. Drugs Aging. 1997;10(5):349–66.

27. Peehl DM. Basic science of hormonal therapy for prostate cancer. Reviews in urology. 2001;3(Suppl 3):S15–22.

28. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guide- line. J Clin Endocrinol Metab. 2010;95(6):2536–59. doi:10.1210/ jc.2009-2354.

29. Holmäng S, Mårin P, Lindstedt G, Hedelin H. Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in eugonadal middle-aged men. Prostate. 1993;23(2):99–106. doi:10.1002/pros. 2990230203.

30. Brock G, Heiselman D, Maggi M, Kim SW, Rodriguez Vallejo JM, Behre HM, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo-controlled study. J Urol. 2016;195(3):699–705. doi:10. 1016/j.juro.2015.10.083.

31. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA. 2008;299:39.

32. Pearl JA, Berhanu D, François N, Masson P, Zargaroff S, Cashy J, et al. Testosterone supplementation does not worsen lower urinary tract symptoms. J Urol. 2013;190(5):1828–33. doi:10.1016/j.juro. 2013.05.111.

33. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol. 2009;55(2):310–20. doi: 10.1016/j.eururo.2008.09.024.

REFERENCES FOR CHAPTER THREE

1. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-333.

2. Traish, A.M., et al., Role of Androgens in Female Genitourinary Tissue Structure and Function: Implications in the Genitourinary Syndrome of Menopause. Sex Med Rev, 2018. 6(4): p. 558-571.

3. O'dowd, M.J. and E.E. Philipp, The history of obstetrics and gynaecology. 2000: CRC press.

4. Singh, A., S. Kaur, and I. Walia, A historical perspective on menopause and menopausal age. Bull Ind Hist Med, 2002. 32(2): p. 121-135.

5. Kopera, H., The dawn of hormone replacement therapy. 1991, Elsevier.

6. Rooke, T., The quest for cortisone. 2012: MSU Press.

7. Stockard, C.R. and G.N. Papanicolaou, The existence of a typical oestrous cycle in the guinea-pig—with a study of its histological and physiological changes. Developmental Dynamics, 1917. 22(2): p. 225-283.

8. Tan, S.Y. and Y. Tatsumura, George Papanicolaou (1883–1962): discoverer of the Pap smear. Singapore Med J, 2015. 56(10): p. 586.

9. Long, J.A. and H.M. Evans, The oestrous cycle in the rat and its associated phenomena. Vol. 6. 1922: University of California Press.

10. Allen, E. and E.A. Doisy, An ovarian hormone: Preliminary report on its localization, extraction and partial purification, and action in test animals. JAMA. 1923. 81(10): p. 819-821.

11. Lieberman, S., Are the differences between estradiol and other estrogens, naturally occurring or synthetic, merely semantical? J Clin Endocrinol Metab, 1996. 81(2): p. 850-851.

12. D'Souza, C., The Hot Topic: A life-changing look at the Change of Life. 2016.

13. Vance, D.A., Premarin: The intriguing history of a controversial drug. Intern J Pharm Compd, 2007. 11(4): p. 282.

14. Barrett-Connor, E., An epidemiologist looks at hormones and heart disease in women. J Clin Endocrinol Metab, 2003. 88(9): p. 4031-4042.

15. Stefanick, M.L., Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. Am J Med, 2005. 118(12): p. 64-73.

17. Wilson, M.D.R.A., Feminime Forever. 1968.

18. Bell, S.E., Sociological perspectives on the medicalization of menopause. Ann N Y Acad Sci, 1990. 592(1): p. 173-178.

19. Smith, D.C., et al., Association of exogenous estrogen and endometrial carcinoma. N Engl J Med, 1975. 293(23): p. 1164-1167.

20. Ziel, H.K. and W.D. Finkle, Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med, 1975. 293(23): p. 1167-1170.

21. Gambrell, R.D., Use of progestogen therapy. Am J Obstet Gynecol, 1987. 156(5): p. 1304-1313.

22. Unger, C.A., Hormone therapy for transgender patients. Transl Androl Urol, 2016. 5(6): p. 877-884.

23. Albright, F., P.H. Smith, and A.M. Richardson, Postmenopausal osteoporosis: its clinical features. JAMA, 1941. 116(22): p. 2465-2474.

24. Panel, N.I.o.H.C.D., National Institutes of Health Consensus Development Conference statement: adjuvant therapy for breast cancer, November 1–3, 2000. JNCI Monographs, 2001. 2001(30): p. 5-15.

25. Hays, J., et al., The women's health initiative recruitment methods and results. Ann Epidemiol, 2003. 13(9, Supplement): p. S18-S77.

26. Grady, D., et al., Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med, 1992. 117(12): p. 1016-1037.

27. Rossouw, J.E., et al., Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA, 2007. 297(13): p. 1465-77.

28. Utian, W.H., A decade post WHI, menopausal hormone therapy comes full circle--need for independent commission. Climacteric, 2012. 15(4): p. 320-5.

29. Alexander, I.M., The history of hormone therapy use and recent controversy related to heart disease and breast cancer arising from prevention trial outcomes. J Midwifery Womens Health, 2012. 57(6): p. 547-557.

30. Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: The Women's Health Initiative Randomized Controlled Trial. JAMA. 2004;291(14):1701-1712. doi:10.1001/jama.291.14.1701

31. Buist, D.S., et al., Hormone therapy prescribing patterns in the United States. Obstet Gynecol, 2004. 104(5, Part 1): p. 1042-1050.

32. Heiss, G., et al., Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA, 2008. 299(9): p. 1036-1045.

33. Hackley, B. and M.E. Rousseau, CEU Managing Menopausal Symptoms After the Women's Health Initiative. J Midwifery Womens Health, 2004. 49(2): p. 87-95.

34. Seaman, B., et al., The history of hormone replacement therapy: a timeline. Kleinman, Kinchy and Handelsman, 2005: p. 219-35.

35. Watkins, E.S., The Estrogen Elixir: A History of Hormone Replacement Therapy in America. 2010: The Johns Hopkins University Press.

36. Bush, T.L., M. Whiteman, and J.A. Flaws, Hormone replacement therapy and breast cancer: a qualitative review. Obstet Gynecol, 2001. 98(3): p. 498-508.

37. Force, U.P.T., Guide to clinical preventive services. 1996, Alexandria, VA: International Medical Publishing.

38. Brinton, E.A., et al., KEEPS: The Kronos Early Estrogen Prevention Study AU - Harman, SM. Climacteric, 2005. 8(1): p. 3-12.

39. Beral, V., et al., Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst, 2011. 103(4): p. 296-305.

40. Hodis, H.N., et al., Vascular effects of early versus late postmenopausal treatment with estradiol. NJEM, 2016. 374(13): p. 1221-1231.

41. Pinkerton, J.A.V., et al., The 2017 hormone therapy position statement of the North American Menopause Society. Menopause, 2017. 24(7): p. 728-753.