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Review Article

Menopause and HRT Then and Now

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Abstract

Menopause is the onset of secondary amenorrhea that signifies the end of reproductive life. However, in addition to signifying the end of reproductive life and menstruation, it also signifies a key period of transition where women experience numerous disruptive effects of hormonal changes associated with menopause. Today these hormonal changes are increasingly well understood while improved healthcare standards and longer life expectancy means that women are spending a growing number of life years beyond this crucial transition event. Since its' invention, hormone replacement (HRT) has helped millions of women through this difficult transition and helped improve their quality of life beyond menopause. However, when evidence emerged in 2003 on the unacceptable increase in breast cancer resulting from hormone replacement, perception of hormone replacement changed dramatically. The use of HRT plummeted in most countries around the world as popular media gave widespread coverage to the new findings. As a result millions of women around either denied or were denied access to HRT. It was only recently that the claims linking HRT to significantly increased risk of breast cancer were re-examined. Results of this re-examination pointed to significant gaps in the original research and concluded that the claims of widely publicized 2003 study were in fact, unsubstantiated. With the publication of these findings, HRT has experienced a resurgence. Various organizations has since made contributions to the safe use of HRT, most significant of which include the "Global Consensus Statement on Menopausal Hormone Therapy" by the International Menopause Society.

Keywords: Hormone Replacement therapy; Menopause; Estrogen therapy; Premature menopause

Abbreviations

HRT: Hormone replacement therapy; FHS: Follicle-stimulating hormone; LH: Luteinizing hormone; REM: Rapid eye movement; UTI: Urinary tract infection: CVA: Cardiovascular accident

Introduction

Menopause is the term used to describe the end of menstrual cycles and by extension, the reproductive life of a woman.One of the earliest known references to menopause was made by Aristotle when he described the age of menopause as 40 years. However the term "Menopause" was coined much later by a French physician Dr. de Gardanne in 1821 [1]. During the early 19th century, the notion that menopause was a deficiency disease became popular. Various interesting remedies including testicular juices and crushed ovaries of animals were consequently tried as treatment for the condition. In the mid-19th century, the relationship between estrogen deficiency and menopause was established and interest grew in estrogen replacement as treatment for the condition. First synthetic estrogen was developed in 1938 [1]and the United States food and drug administration agency had approved estrogen for the treatment of hot flushes associated with menopause by the 1940s [2]. Interest in menopause has continued to grow in recent times at least partly fueled by an increase in literature regarding the topic. Menopause is a difficult experience and the concept of the seven dwarves of menopause, coined by American actress, businesswoman and author Suzanne Somers, in her book titled "The Sexy Years", gives a beautiful summary of the problems and complications of menopause. The dwarves are named itchy, bitchy, sweaty, sleepy, bloated, forgetful and all dried up [3] all readers, welcome to menopause!

What is Menopause?

Menopause is defined as at least twelve months of secondary amennorhoea. Menopause occurs with the last menstrual period, and event only recognized in retrospect. Perimenopause is the period in an around menopause, from the first signs and symptoms of menopause until after 12 months of onset of amennorhoea [4]. Climacteric in my words is undoubtedly a variable period including peri-menopause, which transforms a woman from reproductive to non-reproductive, a process that concludes withthe onset of menopause. Efforts have also been made to stage the process of reproductive ageing that result in menopause. In one study, the authors divided the period leading up to menopause in to three stage with the first and the earliest stage characterized by changes to flow and cycle length. The second stage was characterized by irregularity of cycles without skipping and the last stage by both irregularity and skipping [5]. Findings of the "Stages of Reproductive Ageing Workshop" (STRAW) further classifies this process of reproductive ageing in to stages that occur both before and after menopause [6]. In my own country, Sri Lanka, the mean age of menopause is 51 years [7]. In my personal opinion menopause is least influenced by nutrition and socio-economic status, but highly influenced by maternal age of menopause, smoking and autoimmune disorders. Last two factorscauses menopause to start at a younger age.

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The scientific basis of menopause

There are around 7 million primordial follicles in a female fetus at 4 to 5 months of intrauterine life [8]. These primordial follicles are responsible for the formulation and release of ova/eggs during the menstrual cycles of an adult female of reproductive age. The numbers of these follicles present in a female decreases with her age. At birth a female infant can have up to 1.5 million follicles while by the time she achieves puberty, this reduces to around 400 000 follicles. Only 400 to 450 of these follicles are used up through natural menstrual cycles [8,9], during the 35-40 year long reproductive life of an average female. Primordial follicles are also responsible for the production of a number of hormones that have profound effects on the female physiology. Developing follicles produce these hormones under the influence of FSH and LH, two pituitary hormones that are involved in the regulation of female reproductive system. FSH stimulates a group of cells known as granulosa cells to produce estradiol while LH stimulates theca cells to produce ovarian androgens [9]. Receptors for Estradiol are found in many organ systems including the skin [10] giving estradiol the ability to have widespread effects on physiologic functions of females.

Signs of menopause

The irritating and troublesome signs of menopause are well summarized by the seven dwarves concept. Change in the menstrual pattern is usually the first noticeable sign of menopause. During the peri-menopausal period frequency as well as the blood loss during periods can change from the usual set pattern for each woman. The first noticeable endocrine change of menopause is falling serum inhibin levels. Following this, due to reduced ovarian activity, the serum estradiol level fall with a resultant increase in FSH and LH to maintain the estrogen at its best physiological levels [11]. It's noteworthy that serum estradiol fall may take some time, hence raised FHS and LH levels are better early predicators of menopause. Rise in LH levels acting on the theca cells cause a rise in ovarian androgens which are subsequently converted to estrone E1 in peripheral fat tissues [12]. Frequently, the resultant changes in menstruation are irregular prolonged periods with variable amounts of bleeding.

Premature menopause

Any occurrence of menopause before 40 years of age is termed pre-mature menopause. This may result following surgical oophorectomy, autoimmune disorders, radiation, toxicity, chromosomal disorders and hypogonadism due to cranial pituitary causes. The resultant effects and complications are broadly similar to that of menopause [9]. However recent evidence suggests that due to early and prolonged loss of estradiol, the complications in these women can be much severe [13]. The use of hormone replacement therapy has been shown to improve at least some of these complications and hence, the use of HRT is recommended in premature menopause at least until the average age of menopause [14].

Symptomatology "the tip of an ice-berg"

It is our understanding that menopause leads to night-sweats and disturbances in the REM sleep cycle. Other commonly recognized symptoms of menopause include vasomotor symptoms like hot flushes, observed rise in body temperature and night sweats as well as psychological symptoms such as mood swings, irritability, anxiety, lack of concentration and lack of short term memory [9]. These symptoms ultimately culminate with the loss of self-confidence and finally depression leading to severe life-style, social, marital, psycho-sexual disturbances and low productivity as well as serious personality disturbances in modern women. To add to the misery, these women also suffer from urinary frequency, urgency, frequent UTI, vaginal dryness and vaginal discharge [9]. In addition to the aforesaid symptoms psycho-sexual problems are also aggravated by lack of libido. This dawns further problems of desperation, marital disharmony, marital conflicts, male extramarital relationships and finally divorce. However these problems are like that of the tip of an iceberg compared to the long-term increased risks of Alzheimer's, cardiovascular problems and osteoporosis leading to resultant chronic morbidity due to dementia and pathological fractures with resultant prolonged non-ambulatory status. With a life expectancy of 78 year [15] and an average age menopausal age of 51 years [7], the average Sri Lankan woman spends 27 years, more than 1/3 of her lifespan, after the onset of menopause. This illustrates the magnitude of the role hormone replacement (HRT) has toplayin the upgrading the lives of women as whole by easing the discomforts faced by them during the postmenopausal years.

HRT (Hormone replacement therapy) – what preparation?

It is our routine practice that estrogen alone is used for a women who had undergone hysterectomy and combined reparations are used in a women with an intact uterus to prevent any occurrence of endometrial hyperplasia, atypia and subsequent endometrial cancer. The HRT preparations can be single agent or combined, rooted orally, parentally in form of depot preparations, implants, local application and skin patches. It is our common understanding that local application is beneficial for genitourinary symptoms and avoids adverse outcomes of oral and parenteraladministration.

HRT now and then

With the invention of equine estrones and norethisterone, single and combined hormone replacement therapy was considered the wonder treatment of eternal youth, which was believed to be beneficial to almost all acute and chronic symptoms of menopause. This outlook changed significantly in 2003 when the landmark study on association of breast cancer and hormone replacement therapy [16] was published in Lancet. The paper claimed that the use of HRT by women aged 50 – 64 has resulted in 20000 extra breast cancers causing the Lancet editorial to recommend that HRT be discontinued as soon as possible in women aged 50-64. This message was soon picked up by media institutions worldwide resulting in widespread popularity of the idea that HRT was a threat to women's health. By 2010 the US market for HRT dropped to 21% of its original value in 2001 demonstrating the profound change in the use of HRT following this revelation [17]. Women were relieved from the fear of getting breast cancer after stopping HRT.

HRT boom

With the resultant widespread discontinuation of HRT, the suffering of the postmenopausal women once again took center stage in the scientific circles concerning menopause. Eventually the claim of the original Lancet study was re-examined by researchers to establish the validity of its conclusions and recommendation. Research findings on the validity of the Lancet article concluded that, while HRT may or may not increase the risk of breast cancer,

the "Million Women Study" (MWS) had not established a valid causative relationship between them [18]. This means that millions of women were denied of HRT on the basis of poor quality research. The revelation regarding the inaccuracies of the MWS was also taken up by media institutions which highlighted the plight of thousands of women forced in to needless suffering for a whole decade based on bad research [19-21].It must also be noted thatbreast cancer is regarded as the commonest cancer worldwide. In USA, 1:8 women will develop invasive breast cancer over their lifetime. Hence irrespective of the use of HRT, women areliable for this condition. Previous studies had already established that the increase in background risk of breast cancer in long term HRT users in comparison to those who didn't amounts to only a few cases of the actual disease. The same study also showed that HRT is associated with an increase in the mortality among the women who suffer acute/recent onset coronary arterial disease and CVA [22].

Current Recommendations

Current recommendations on breast cancer were collated by the International Menopause Society in 2013 to produce the "Global Consensus Statement on Menopausal Hormone Therapy" [23]. Following recommendations were made

- Menopausal Hormone Therapy (MHT) is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause.
- MHT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause.
- Randomized clinical trials and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone MHT may decrease coronary heart disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause. Data on estrogen plus progestogen MHT in this population show a similar trend for mortality but in most randomized clinical trials no significant increase or decrease in coronary heart disease has been found.
- Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse.
- Estrogen as a single systemic agent is appropriate in women after hysterectomy but additional progestogen is required in the presence of a uterus.
- The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause and the risk of venous thromboembolism, stroke, ischemic heart disease and breast cancer.
- The risk of venous thromboembolism and ischemic stroke increases with oral MHT but the absolute risk is rare below age 60 years. Observational studies point to a lower risk with transdermal therapy.
- The risk of breast cancer in women over 50 years associated with MHT is a complex issue. The increased risk of breast cancer is primarily associated with the addition of a progestogen to estrogen therapy and related to the duration of use. The risk of breast cancer attributable to MHT is small and the risk decreases after treatment is stopped.
- The dose and duration of MHT should be consistent with treatment goals and safety issues and should be individualized.
- In women with premature ovarian insufficiency, systemic MHT is recommended at least until the average age of the natural menopause.
- The use of custom-compounded bioidentical hormone therapy is not recommended.
- Current safety data do not support the use of MHT in breast cancer survivors.

HRT on Breast Cancer and BRCA Carriers

Rebbeck TR et al. in his article in 2005 indicated that HRT can be used in short courses of up to one year without significantly increasing the breast cancer risk in BRCA carriers [24]. However it is my understanding, longer the duration, higher the risk of breast CA.

Good governance (BMS Recommendation for optimizing mid-life health and beyond – advice to women)

2013 British Menopausal society had recommended that the decision to use HRT should be made by each women having been given adequate information by her health professional to make an informed decision. The HRT dosage, regime and duration should be individualized with annual evaluation of risk vs benefits. Arbitrary limits should not be mentioned for the use of HRT. Lifestyle modifications in terms of exercise and diet, weight control, control of diabetes and hypertension and cessation of smoking will further reduce the risk of coronary and cardiovascular risk, osteoporosis and breast cancer [25].

References

1. Singh A, Kaur S, Walia I. A historical perspective on menopause and menopausal age. Bull Indian InstHist Med Hyderabad. 2002; 32:121-135.
2. Nelson HD, Nygren P, Freeman M, Chan BKS. Drug Class Review on Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage. Portland, Oregon: Oregon Health & Science University. 2007.
3. Singer N, Wilson D. Menopause, as Brought to You by Big Pharma, the New York Times; 13th December. 2009.
4. Utian WH. The International Menopause menopause-related terminology definitions. Climacteric. 1999; 2: 284- 286.
5. Mitchell ES, Woods NF, Mariella A. Three stages of the menopausal transition from the Seattle Midlife Women's Health Study: toward a more precise definition. Menopause. 2000; 7: 334- 349.
6. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive Summary of STRAW+10: Addressing the Unfinished Agenda of Staging Reproductive Aging. Climacteric. 2012; 15:105-114.
7. Jayasekara R. Factors influencing the age at natural menopause in Sinhalese women. The Ceylon Journal of Medical Science. 1994; 37: 26.

8. Wallace WHB, Kelsey TW. Human Ovarian Reserve from Conception to the Menopause. PLoS One. Public Library of Science. 2010; 5: 8772.

9. Dodampahala SH. Text book for Obstetrics and Gynaecology - Essential Topics. Colombo: Samudra Publications; 2015.

10. Hasselquist MB, Goldberg N, Schroeter A, Spelsberg TC. Isolation and Characterization of the Estrogen Receptor in Human Skin. J ClinEndocrinolMetab. The Endocrine Society. 1980; 50: 76-82.

11. Buckler H. The menopause transition: endocrine changes and clinical symptoms. Br Menopause Soc J. 2005; 11: 61-65.

12. Lucisano A, Acampora MG, Russo N, Maniccia E, Montemurro A, Dell'Acqua S. Ovarian and peripheral plasma levels of progestogens, androgens and oestrogens in post-menopausal women. Maturitas.1984; 6: 45-53.

13. Scott EL, Zhang QG, Vadlamudi RK, Brann DW. Premature menopause and risk of neurological disease: basic mechanisms and clinical implications. Mol Cell Endocrinol. 2014; 389: 2-6.

14. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric. 2015; 18: 483-491.

15. World Health organization. Sri Lanka: WHO statistical profile. : World Health organization. 2015.

16. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003; 362: 419-427.

17. Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999-2010. Obs Gynecol. 2012; 120: 595-603.

18. Shapiro S, Farmer RDT, Stevenson JC, Burger HG, Mueck AO. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies: Part 4. The Million Women Study. J Fam Plan Reprod Heal Care. 2012: 38:102-109.

19. Smith R. HRT link to breast cancer 'flawed'', The Telegraph. 17th January. 2012.

20. Hope J. HRT breast cancer alert that led to thousands of women abandoning treatment was based on 'bad research'', Mail Online. 2012.

21. Lakhani N. HRT breast cancer link in doubt', The Independent. 2012.

22. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet.1997; 350:1047-1059.

23. De Villiers TJ, Gass ML, Haines CJ, Hall JE, Lobo RA, Pierroz DD, et al. Global consensus statement on menopausal hormone therapy. Climacteric. 2013; 16: 203-204.

24. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J ClinOncol. 2005; 23: 7804-7810.

25. Panay N, Hamoda H, Arya R, Savvas M. The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy. Menopause. 2013.

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