

MENOSOC Oration

Evolution of Menopausal Management: Embracing or Confronting Nature's Design?

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Good morning, ladies and gentlemen

It is my pleasure and privilege to be delivering the MENOSOC oration this year, at a time when the Menopause Society of Sri Lanka has the honor of hosting the 6th Biennial Conference of the South Asian Federation of Menopause Societies, with our own Dr. Rohana Haththotuwa inducted as its new president. Let me begin by humbly thanking Dr. Sanath Akmeemana for the kind introduction, and the Menopause Society of Sri Lanka for giving me the opportunity to deliver the prestigious MENOSOC oration this year.

To be born a woman is a blessing, as a woman is born not once, but many times, not just at birth, but at menarche, childbirth and then at menopause, each period of life being defined physiologically and embellished by fresh bodily changes, feelings, experiences and opportunities. Menopause is the final physiological milestone in this journey and heralds the beginning of a new chapter in the lives of women.

Natural menopause, which indicates the cessation of reproductive function, most often occurs in the fourth or fifth decade of a woman's life. The ovaries of women, which started producing fertilizable ova when a young girl attained menarche, exhaust their store of ovarian follicles at the onset of menopause, putting a stop to childbearing, menstruation and the production of the all-important female hormone estrogen.

Ovarian hormones are crucial to define the appearance and functioning of a woman. Estrogen is

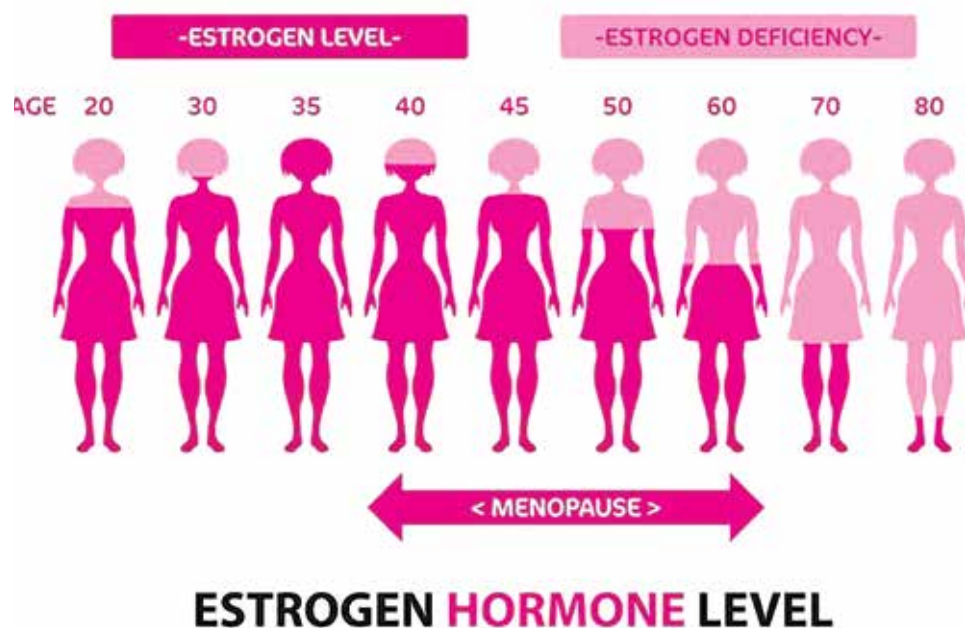


Figure 1: Variation in blood estrogen levels during a woman's lifecycle

mostly responsible for the secondary sexual characteristics and functioning of reproductive organs. It is needed for the menstrual cycle, pregnancy, breast feeding, libido, growth and a healthy cardiovascular function. Progesterone mostly influences pregnancy and breastfeeding. Androgens keep a woman healthy, and mainly aids having healthy muscle, bone, mood, cognition and libido. Together they achieve the role of a woman defined by nature. During the menopausal transition the blood levels of ovarian hormones gradually decline, and at menopause ovary stops producing estrogen and progesterone. This diagram shows how blood estrogen levels change during a woman's lifecycle, increasing from menarche to adulthood, and gradually declining up to menopause after which there is a steep drop (Figure 1) Estrogen deficiency is thus responsible for most health issues related to menopause.

Up to 80% of women experience menopause-related health issues that span physical symptoms, psychological problems, biochemical and systemic derangements. Physical symptoms mainly include vasomotor symptoms or hot flushes, menstrual irregularities, genitourinary syndrome of menopause and muscle and joint pain. Mood swings, irritability and loss of interest are the main psychological problems experienced. The health issues with more serious long-lasting complications are osteoporosis, obesity, dyslipidemia and cardiovascular disease. In women, the incidence of many non-communicable diseases increases after menopause. More women than men worldwide die of cardiovascular disease, with higher early mortality following myocardial infarction and worse long-term prognosis. One-third of women over the age of 50 are estimated to experience an osteoporosis-related fracture during their lifetime. Increase in dementia, sarcopenia, malignancies and diabetes are related to both ageing and menopause.

Let me now present the findings of a few studies we conducted. In a cross-sectional study we conducted among postmenopausal women attending a NCD clinic in Gampaha district, there was an overwhelming presence of modifiable cardiovascular risk factors in over half the women studied, namely obesity, high waist circumference, blood pressure, blood glucose, dyslipidaemia, with >70% having undesirable blood pressure, body mass index and waist circumference. We also conducted a similar study in Badulla. Here I compare the findings of the urbanized women in Gampaha district in blue with that of rural women in Badulla in orange. This shows alarming findings especially in rural women with about 50% or more having dyslipidemia, hypertension, visceral adiposity and high body mass index.

We also conducted studies on bone mineral density and osteoporosis in postmenopausal women in Sri Lanka. In this slide I describe the findings of bone mineral density on DEXA scanning in a study of women >35 years attending the healthy lifestyle clinic in Colombo. There was a significant increase in osteoporosis, especially of vertebra after menopause and the prevalence of osteopenia was high in both pre- and post-menopausal women. Negative T scores of vertebral and femoral neck bone mineral densities showed a significant positive correlation with both age and age at menopause. We also conducted osteoporosis screening among 305 women aged 27-81 years attending a health camp in Panadura base hospital, using heel bone densitometry. Here, we found lower T scores and >60% prevalence of osteopenia in postmenopausal women, though the prevalence of osteoporosis was <5%. The discrepancy in the prevalence of osteoporosis with other local studies is probably because of the method used to assess the bone density.

Let me now outline the historical perspectives of menopause and the evolution of its management.



The earliest known references to menopause have been very scarce, and one of the first documents describing menopause is by the ancient Greek physician Aristotle in the 4th century BC, in his work *Historium Animalum* he writes, “As for their end, the menstrual discharges ceases in most women about their fortieth year; but with those in whom it goes on longer it lasts even to the fiftieth year, and women of that age have been known to bear children. But beyond that age there is no case on record”.

There are records on menopause by physicians and scholars over the next few centuries, e.g., Pliny the Elder, Soranus the Greek gynaecologist and Paulus Aegineta, who identified the age of menopause as being between 35 to 60 years. In 1628 Robert Burton referred to hot flashes, other menopausal symptoms, and their therapy, in his book, *The Anatomy of Melancholy*. The English physician Thomas Sydenham was keen to point out that women were prone to “hysterick fits” between the ages of 45 and 50, and that restoring the menses in these hapless souls might be the solution. Medical interest in menopause increased considerably in mid 19th century. The 19th century, French physician De Gardanne studied at great length the symptoms experienced by women as they aged. He coined the term Menopause in 1821, which in Greek meant men or “month” and pausis or “cessation”, in his first ever article on the subject, now available on amazon. In 1845, the Frenchman Ponsan devoted an entire book to menopause, “the death of the womb.” His attitude on menopause was positive, and he stated “When the vital forces cease to conspire over the uterus, they will increase those of the spirit. The critical age passed, women have the hope of a longer life than men, and their thought acquires more precision, understanding and vivacity.”

In the late 19th century, the life expectancy of women started increasing worldwide, result-

ing in more women living beyond menopause, which led to recognizing of the need for a healthy postmenopausal period of a woman’s life. Soon, scientists began to identify hormones and their function in the human body. By the dawn of the 21st century, menopause was considered to be an important time of a woman’s life, and global interest in research and treatment of menopause had considerably increased, with numerous local and international bodies advocating and guiding the management of menopause related issues.

Now let me elaborate on the evolution of menopause management over the years. The current need for menopause remedies becomes glaringly obvious if you simply google menopause remedies. Though effective pharmacological treatment is available for most menopause related health issues, they seem to be inadequate to satisfy postmenopausal women. Thus, it is of no surprise that widely varied remedies have been practiced for menopausal problems since ancient times.

As there were no clear insights into its causation, the menopause was considered to be a disease, often referred to as “climacteric insanity”, possibly due to the lack of a working womb, and a mental illness to be cured. It was thought that when a woman’s menstruation ceased, toxins accumulate and cause disease leading to barrenness and wildness, sullenness and excitability, lethargy and hysteria, volubility and melancholy. Thus, diverse remedies mushroomed, claiming to cure this malady. Some remedies practiced were logical, though others could only be described as illogical, bizarre or even brutal. The nineteenth-century cures were mainly continued over from earlier times and included purgatives, bleeding and enemas. Some practitioners prescribed deadly-sounding douches containing a cocktail of acetate of lead, morphine and chloroform. Snake-oil too had its charm, and treatments such as opium, wine and cannabis may have certainly made women feel better, or at least



forget their complaints. Gruesome forms of surgical treatment such as ovariectomy and clitoridectomies were practiced as cures for menopause and hysteria. To add to the injustice, putting away symptomatic women for hysteria and general non-compliance was not uncommon in the 19th century.

Though the hormonal insufficiency in menopause was not overtly recognized, use of extracts from animal testes and ovaries, would have contributed to the replacement of reproductive hormones. Such practices dated from ancient times to the 20th century, with Brown-Séquard being coined the father of organ therapy. The modern therapeutic lifestyle changes were advocated by the 18th century gynecologist Dr. Samuel Ashwell who brought new insights into menopause. In his work, *Practical Treatise on the Diseases Peculiar to Women*, he recommended exercise, vegetarianism and the abstinence from alcohol for symptom relief

With the advent of the 20th century, many breakthroughs enhanced the understanding of menopause and its treatment. Estrogen was isolated by collaborative efforts of Allen and Doisy in 1929 and extracted from urine of pregnant mares in 1930 by Dr. Zondek. Within a decade after isolating estrogen, the first oestrogen replacement treatments were made available for treatment of menopausal symptoms. The FDA approved marketing of diethylstilbestrol in 1941 and conjugated equine estrogens (CEE) in 1942 for treatment of menopausal symptoms. Estrogen was clearly effective for ameliorating hot flashes and night sweats and the list of reasons why women should use estrogen began to grow. Hormone replacement therapy was considered the wonder drug for menopause, and medical industry contributed to persuading women that menopause was an illness in need of a cure. In 1966, Robert A. Wilson wrote the book *Feminine Forever*, which became a best seller with its claim that menopause is com-

pletely preventable. He traveled the country, lecturing on this topic, claiming that postmenopausal women who didn't receive estrogen treatment were no longer truly female, and with estrogen therapy, "Every woman alive today has the option to remain feminine forever." Thus, estrogen sales boomed, doubling and tripling in the mid-60s to mid-70s, truly medicalizing menopause.

Reports of increased endometrial cancer in estrogen users in mid 70s, led to a remarkable decline in its use. Evidence also surfaced that the incidence of breast cancer, strokes, and blood clots may increase with hormone treatment. But soon there was a rebound increase in estrogen sales with the discovery that adding a progestogen to estrogen reduced this risk, and that estrogen was beneficial for osteoporosis, coronary heart disease and blood lipids. This was despite evidence from major studies such as Heart and Estrogen/ Progestin Replacement Study (HERS) showing no benefit of estrogen on preventing coronary heart disease. At the beginning of the 21st century, there was a dramatic drop in estrogen sales, following the Women's Health Initiative (WHI) study in 2002 reporting greater harm than benefit of combined CEE plus a progestin.

It reported increases in breast cancer, ischaemic heart disease, strokes, and venous thromboembolism, though having beneficial effects on colorectal cancer and hip fractures. The trial was prematurely terminated and given wide publicity, causing panic among women causing a precipitous decrease in estrogen and progestin use. This led to a serious reevaluation of menopausal hormone therapy.

Current evidence confirms that HRT is associated with a reduction in atherosclerosis, coronary heart disease and associated mortality. It improves bone density and protects from osteoporosis, improves mood and sexual function and is unlikely



to increase the risk of dementia. Though HRT increases the risk of breast and endometrial cancer, venous thromboembolism and stroke, estrogen alone, vaginal or transdermal estrogen, and micronized progesterone preparations are associated with little or no increase of breast cancer, venous thromboembolism or stroke.

So where are we with HRT now? Many studies and reanalyses of WHI have revealed that HRT is highly beneficial when given to symptomatic women within 10 years of menopause or <60 years. Guidelines developed by professional bodies, advocate the use of HRT after individual risk benefit assessment to decide whether to use HRT and the dose, mode of administration and the duration of treatment. Multiple preparations are available, at lower doses, combinations and modes of administration allowing wide individual choices. All in all, used judiciously in individualized patients, the evidence shows that HRT is actually the wonder drug for menopause.

HRT is not the only treatment option for management of menopause related health issues. Lifestyle modification with healthy diet and regular exercise is vital for preventing non communicable diseases and improving physical and mental well-being. Calcium and vitamin D supplements, phytoestrogens, selective serotonin reuptake inhibitors, and several other pharmacological agents are effective for a range of problems. Surgical interventions play a role especially for genitourinary problems. Education of patients, healthcare workers and the public undoubtedly is of much value.

There are promising novel management options emerging. Neurokinin receptor blockers prevent hypothalamus-driven temperature fluctuations and appear to be effective for hot flushes. Experimental manipulation of DNA damage response (DDR) pathways in DDR-associated genes have shown to extend reproductive life in mice. Recent

identification of the *reprimo* gene thought to be responsible for menopausal weight gain, suggests prevention of weight gain via its genetic manipulation, a possible dream-come-true for women. Identification of genes linked to response to HRT (e.g., *SLCO1B1*) promises gene-targeted hormonal treatment. As variation in menopausal age is shown to be 30-85% determined by genetic variance, gene manipulation may be able to extend the age of menopause and lead to more exciting outcomes!

Let me now try to analyze the purpose behind the nature's design of menopause. Women experience menopause around the 50th year and typically live for decades afterwards. Among other mammalian females, only four species of toothed whales show a similar pattern of early reproductive cessation followed by a prolonged post-reproductive life. Other females generally breed till the end of their lives, so it is mooted why this uncoupling of somatic and reproductive ageing has taken place in women. The "grandmother hypothesis" is an explanation supporting the evolution of human menopause. This means that the older women's genes are propagated more effectively by promoting the survival of their grandchildren.

Another hypothesis is the need for prolonged care in a species as in humans, where offspring are dependent for an extended period, where the presence of non-reproductive older females will be able to provide the protection required by the young. Menopause could also very well be a by-product of an increased lifespan, where prolonged lifespan has let the post-reproductive phase to surface. As none of these are supported by concrete evidence, we will have to wait and see what future research will unfold regarding the origin of menopause.

Whatever the evolutionary reasons are behind menopause, the fact remains that the life expect-



tancy of women continues to increase, and most women will live over 1/3rd of their lives after menopause. Thus, it is vital to make this phase of life in women productive, healthy and happy. HRT, a result of the dedicated work of scientists over centuries, should be made use of to the maximum, with the other effective modes of management. This will enrich the quality of life of postmenopausal women and enhance their contribution to the society. So, it is up to us, the healthcare providers, to ensure that the management options are utilized wisely, and menopause becomes a positive period in a woman's life.

So, ladies and gentlemen, I wish to conclude the oration, and wish all menopausal women may live this physiological phase of their lives to the maximum. Ladies, let life begin again at menopause.

This is a proud and happy day for me, to deliver the oration of the menopause society of Sri Lanka, after a decade of being with the MENOSOC and contributing to most of its activities with dedication. There are many I am grateful, for my presence here today but I can only mention a few. My father Tikiri Banda Ratnayake, and my mother Mangalika Ratnayake enveloped us with love, instilled values and infused confidence and continue to do so. My father is 94 years and is not able to come but my mother is here with us right now. My teachers from kindergarten through Sirimavo Bandaranayeke Vidyalaya and Visakha Vidyalaya, were committed to our education and molded our attitudes and behavior. My university and postgraduate teachers and mentors continued to do the same.

My numerous friends and colleagues have always been my strength and joy, and I especially thank Dananja, Sudharshani and Dinithi from the bottom of my heart for always being there for me. The members of the Menopause Society of Sri Lanka have become my second family, and

we hope to work together to promote our cause. My family is so very special, and I could not do without my two sisters Pyara and Anokha brother Asanka, in-laws, nieces, nephews and extended family who continue to tolerate, criticize and give me joy. Finally, Harsha my husband has always been my strength, encouraging, supporting, caring and fun.

Thank you all for everything.