

## Gaps in Menopause Knowledge

Sun Kyoung Yum, Tak Kim

Department of Obstetrics & Gynecology, Korea University Anam Hospital, Seoul, Korea

The average middle aged woman goes through a volatile period of endocrine fluctuations as she passes through menopause and the stages that precede and follow it. Ovarian hormones are steroid hormones. They readily cross the cell and nuclear membranes and influence transcription of numerous genes. Such influences are tissue specific and state specific. In short, changes in ovarian hormones mean that a women will experience changes in her entire body systems. When an individual woman's constitutional factors, pathologic states, medications, environmental exposures are taken into consideration, the integrated changes become too complex to predict. Inter-study sampling differences with the complexities in the backdrop may have led to conflicting conclusions in menopause research. This paper reviews some of the controversies in the care of menopausal women. (**J Menopausal Med 2014;20:47-51**)

**Key Words:** Health knowledge attitudes practice, Hormones, Menopause, Women's health

### Effects of Sex Hormones

Women's hormones, also referred to as ovarian hormones, sex hormones, gonadal hormones, are steroid hormones. Steroids are lipids, thereby readily cross the cell membrane, and the nuclear membrane to interact with the blueprints of human body, the genes encoded in chromosomes. Women's hormones have wide and complex effects on gene expressions.<sup>1,2</sup> Moreover, modulation of expression of one gene will sequentially affect the expression of other genes. Therefore, changes or fluctuations in women's hormones will have implications well beyond reproductive functions and can affect all body systems. It is imaginable that the hormonal changes occurring around menopause will cause changes in a woman that will be as complex as the period of sexual maturation.

Attempts to replicate the dynamic changes in the hormonal milieu and the entire body systems through molecular and research and animal assays will be limited in its

relevance to the human condition. Even clinical trials aimed to answer specific questions are often too reductionistic to translate to the individual woman.

### Statin Example in Menopausal Women

As an example, let's examine a piece of information generated from a clinical trial that statins can reduce cholesterol levels in menopausal women.<sup>3</sup> Another piece of information suggests that the magnitude of effect is more pronounced in women than men.<sup>4</sup> It may have been that such trials have enriched their subject eligibility criteria for signal detection and such samples may be too artificial to be generalizable. Then, there are textbook knowledge that levels of cholesterol and different lipoproteins are associated with cardiovascular events and mortality. And there are guidelines that define a recommended level of cholesterol to

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Address for Correspondence: Tak Kim, Department of Obstetrics & Gynecology, Korea University Anam Hospital, 73 Incheon-ro, Seongbuk-gu, Seoul 136-705, Korea

Tel: +82-2-920-5310, Fax: +82-2-920-5357, E-mail: tkim@kumc.or.kr

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be maintained regardless of sex. If we add the information presented above, then we may deduce that statins may prevent cardiovascular events and mortality in menopausal women.

Then, there is another piece of information that in menopausal women, depression is very common, and maybe even more so than dyslipidemia.<sup>5</sup> Antidepressants and statins do not by themselves increase blood sugars in significant amounts. However, a particular combination of antidepressant and statin may significantly increase blood sugars.<sup>6</sup> Medical textbooks and guidelines give more weight to diabetes than dyslipidemia as a cardiovascular risk factor. Now, the deduced conclusion for a clinician may be that statins in certain contexts may actually negatively affect cardiovascular risk in menopausal women.

Even when the medical community was eager to embrace the statin prevention story, there were reports outside the mainstream that reported that in the elderly, reduced cholesterol levels may be associated with increased mortality.<sup>7</sup> Recent evidence suggest that in menopausal women, statins may precipitate diabetes<sup>8</sup> and the United States (US) Food and Drug Administration (FDA) has ordered such information to be specified in the prescribing information for statins.

What we can learn is that pieces of information generated in artificial or convenient samples may be incorrectly extrapolated to the menopausal women, leading to many years of wrong information guiding clinical practice. The first and second sets of information led to a different conclusions. If we collect more information, the conclusion may change again and again. We may need to deviate from the traditional reductionistic approaches of scientific research and take on more holistic approaches to understanding menopausal women, including more macroscopic and ecological examinations.

## The Public Question on Hormone Replacement Therapy (HRT)

For many years since its introduction, HRT was believed by many to be a 'really good thing'. Menopausal women kept returning to the clinic asking for prescription refills,

describing life with and without being dramatically different. Women reported having more energy, feeling the weight of age lifted, aches and pains alleviated, free from emotional fluctuations and easy irritability, greater satisfaction in sexual life, and less distress from urinary discomforts. Women were feeling happier and healthier. Physicians felt fulfilment in belief they were doing something good and prescribed HRT to their families and themselves.

Then, in the beginning of the 21<sup>st</sup> century, the public heard a massive government funded study in menopausal women had to be terminated prematurely based on detrimental results of the interim analysis. Many years passed and the public is again presented with research results showing the benefits of HRT. They simultaneously hear of conflicting findings from other results.

In the eyes of the public, the jury is still out on whether or not HRT is beneficial for the menopausal women. There have been so many conflicting results from different research and the conclusions presented to the public keeps changing. It seems now, many people have lost interest in following the developments in the field and have postponed decisions about whether they should or should not undergo HRT at an individual level.

The pitfalls of media coverage often lie in the lack of discrimination between associations, causality, risk factors, odds ratios, etc. The public is often presented with misleading or premature conclusions because all these concepts are used interchangeably and indiscriminately.

In order to avoid such fallacies, each piece of evidence should be carefully examined for accurate interpretations.

## Controversies about HRT - What Information Do We Have?

The Women's Health Initiative (WHI) was strategically planned and funded by a US government agency, the National Institute of Health (NIH). It was a mega study that examined menopausal women in an observational & clinical nested design. The results presented in 2002 raised concerns in the medical community and public fears of breast cancer risk associated with HRT.<sup>9</sup> In subsequent publications, physicians were presented with two surprises about the

effects of HRT. Firstly, the cardio-protection effect that everyone had taken for granted was not observed.<sup>10</sup> Secondly, thromboembolism risks that were thought to be acute risks and expected to be seen in only those with underlying risk factors, turned out to be a long term risk.<sup>11</sup>

The consequences of the presented results from the WHI went past the clinic. The HRT market that was about 3 billion dollars in size in 2001 was reduced to 1.8 billion by 2009. One day after the 2002 announcement of results, Wyeth stock plummeted by 24%.<sup>12</sup> By 2012, Pfizer, which bought Wyeth paid 900 million dollars in settlements related to Prempro litigations<sup>13</sup> and legal disputes are still in progress.

Subsequent analyses of the cardiovascular risk led to the understanding that multiple factors are inter-related in complex ways and that no simple conclusion can be drawn. One of the WHI ancillary studies performed by a subgroup of the investigative centers was the Coronary Artery Calcium Study (WHI-CACS). In this study, women between the ages 50–59 who received estrogen treatment had significantly less coronary calcification.<sup>14,15</sup> Coronary artery calcification is thought to be a surrogate marker for cardiovascular events and the WHI-CACS results were interpreted as HRT having cardio-protective effects in younger menopausal women. Secondary analyses of the WHI also led to similar conclusions. Association between HRT and cardiovascular risk differed by age group. HRT seemed to be cardio-protective in younger menopausal women and the effects were influenced by the time to treatment after menopause, cardiovascular risks increasing with delayed treatment.<sup>16</sup> The findings of the WHI may be limited in clinical utility in that the “younger” menopausal women did not constitute a significant portion of the study sample.

## Other Controversies in Menopause Research

There are many other clinical controversies in the menopausal population beyond cardiovascular risks. One controversy is the effect of HRT on senile ophthalmologic conditions. Macular degeneration, cataract, glaucoma are eye disorders that are closely related to aging and most

often observed in the elderly. In a WHI ancillary study, HRT was not associated with senile macular degeneration.<sup>17</sup> In a recent study, estrogen alone decreased the risk of glaucoma proportional to the duration of treatment; the risk decreased by upto 19% in 4 years.<sup>18</sup>

Another difficult question that needs to be answered soon is the one about Alzheimer’s and other dementias. In the WHI study, combination of estrogen and progesterone was reported to increase the risk of dementia.<sup>19,20</sup> For a long time, estrogen was believed to be neuroprotective and therefore preventative against dementia.<sup>21,22</sup> That is, although combination of estrogen and progesterone may be dementia-prone, estrogen alone has been understood as protective. According to a paper published early this year, in women over 65 years who received HRT, the relationship between serum estrogen levels and risk of dementia was observed to be a ‘J’ shaped curve. In this study, diabetic patients with high levels of estrogen showed a 14-fold increase in dementia.<sup>23</sup>

## Are We Adequately Prepared to Face the Aged Society?

Traditionally, menopause was synonymous with impending end to a woman’s life. Historically, women spent limited number of years beyond menopause. The modern woman, with increased longevity, has a very different experience in which about a third of their life is now post-menopausal.

Only humans and killer whales experience menopause. There may be evolutionary benefits in grandmothers raising grandchildren.<sup>24</sup> However, throughout evolution, females have been optimally selected for reproduction. Menopausal period did not determine evolutionary selection, so the modern women have not been selected for best quality of life post menopause.

Pollycove and colleagues<sup>25</sup> have proposed that in menopause, women’s systems return to simulate phases of lactation; similar hormone changes occur as well as similar changes throughout the body. The changes in the mother’s body during lactation have been optimized for survival of the offspring. During menopause and lactation, fat and calcium enter the blood stream in large amounts,

The fat and calcium are used for production of milk during lactation, but during menopause, they produce dyslipidemia and osteoporosis. Reduced elasticity of the vagina, vaginal dryness, dyspareunia restrict sex during lactation and may have species conservation purposes through focus on child rearing. The same changes during menopause cause marital disputes and depression. Increased temperature, hypervigilance and increased arousal which all protect the offspring during lactation lead to only discomforts in the menopausal women, including vasomotor symptoms, night sweats, chronic insomnia and consequent health risks.

Whether it is through understanding the evolutionary meaning or lack of meaning of menopause or through analogies with the period of lactation, there is increasing social need to understand the menopausal woman and to assist her in living a healthier and happier old age. Due to medical advances as well as many other social factors, human life expectancy continues to increase. According to the Organisation for Economic Co-operation and Development (OECD) Health Data<sup>26</sup> 2013, the average life expectancy of Korean women has reached 84.5 years. The average age at menopause in Korean women is estimated to be 49 years.<sup>27</sup> This means an average Korean woman spends more than 1/3 of her life and a little over 30 years in post-menopausal state.

As discussed throughout this paper, the hormonal changes occurring through menopause lead to complicated changes in a woman's entire body systems. The middle age woman undergoes physical and emotional changes that are as complex as an adolescent undergoing puberty. We need a lot more information about women undergoing (pre/peri-) menopause and the life beyond.

Obstetrics and Gynecology has always been an area that has tried to understand and assist the woman in her entirety. Traditionally, besides pathologic conditions, the field has focused much its research and clinical efforts to understand normal puberty and pregnancy. With the advent of the aged society, now the field needs to quickly make significant advances in its understanding of the normal elderly woman. The ultimate goal would be the promotion of health and happiness through specialized knowledge and management of women's hormones.

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