Review Article

Multidisciplinary, Interdisciplinary and Transdisciplinary Approaches to Women's Health Research: A View from the Seattle Midlife Women's Health Study*

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여성건강연구에 대한 다학제간 접근법: 시애틀 중년여성건강연구 결과*

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Over the past decade, there has been increasing emphasis on interdisciplinary research efforts in the opportunities for research funding provided by the National Institutes of Health in the U.S. At the heart of the NIH Director's encouragement to move beyond the confines of one's own discipline and exploring the new organizational models for "team science" is the NIH Roadmap, a design for growing science over the next decade and beyond(NIH 2005). Development of the Roadmap occurred in a context in which the fruits of the human genome project, as well as the need for clinical research, have tested the capacity of "normal science" as it was conducted in the US and other parts of the world. Our old models of the single investigator, working on a single theme over the course of a single career from a single perspective has reached the point of waning effectiveness owing to the complexity of contemporary science. Although there may be some isolated opportunities for that kind of work for specific topics, the

mainstream scientific movement in the US emphasizes the importance of team science. Translational science is also commanding attention as the next direction for linking the bench or laboratory effort to the bedside for clinical application. These recent changes in the way scientific work is envisioned press for movement to interdisciplinary and transdisciplinary research.

Multidisciplinary efforts can be seen when scientists work from their discipline-specific bases in parallel efforts to solve common problems. Interdisciplinary efforts are evident in researchers working from discipline-specific perspectives in a joint effort to solve common problems. Transdisciplinarity can be seen in the efforts of scientists create new perspectives or frameworks that cross the traditional boundaries of the disciplines. True transdisciplinarity requires understanding the language of the relevant disciplines, integrating their individual perspectives to form a shared problem. This is a significant

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effort because how one names the problem may drive how it is studied. Coming to an understanding of what the problem is and carrying out the research to solve the problem jointly is a hallmark of transdiciplinarity(Nowotny 2005). There are few models of transdisciplinarity available to guide our efforts and that is not surprising, given the ways in which most of us have been educated. Moreover, Mitchell(2005) asks whether it matters to have multidisciplinary, interdisciplinary transdisciplinary work as long as the collaboration broadens the scope of the work, yields new perspectives and insights and gives birth to new hybrid disciplines that may offer more sophisticated analytic approaches.

Is this an important question within the discipline of nursing? In the US, the importance of this question lies in our approaches to supporting science through federal grants as well as developing the knowledge for practice. Given that most nursing services are delivered in a system in which many disciplines participate, it is significant that at the least we conduct research that shares a focus on a common problem from many perspectives – interdisciplinary efforts – instead of working in parallel. Perhaps transdisciplinary efforts are the evolutionary consequence once interdisciplinary relationships are well established. Could we forge a new field of women's health? Or will we merely reproduce what we already know from our own disciplinary perspectives?

Of importance is that nursing, as a discipline, is poised well for interdisciplinary if not transdisciplinary work. The origins of scientific effort in the US have their roots in a variety of academic disciplines and these roots have shaped the evolution of our contemporary nursing science. Some history about the evolution of nursing science in the US may help illustrate how deeply we are rooted in other disciplines. As nursing programs entered universities from hospitals in the 1950s, there were few opportunities for nursing faculty to pursue doctoral studies. At the time, the most common pathways toward the doctorate were through programs in Education, either the Ed D or the PhD. The second generation of nurses to earn doctorates in the US studied in related disciplines. During the late 1960s and 1970s many nurses earned the PhD in physiology, public health, sociology, psychology, and anthropology. During the 1970s many nurses studying for the PhD pursued the Nurse Scientist Programs funded by the Division of Nursing in what is now HRSA. These nurses completed a minor sequence of courses in nursing as well as the discipline in which they

earned their degrees(Stevenson and Woods, 1986). These graduates contributed significantly to the development of the new doctoral programs in nursing which appeared in the late 1970s and the 1980s and continue to develop in the US even in the 21st century as the need for nursing educators burgeons. The inherent interdiscipinarity of our faculty, given their educational pathways, has enriched doctoral study in the US and, I believe that because of this, we are poised for the next stage of our scientific development. With these definitions in mind, and with that history lesson about the development of the US brand of nursing science introduced, let me now turn to the central aims of this paper which are to:

- Describe the development of an interdisciplinary women's health research program in nursing
- Illustrate the necessity of interdisciplinarity in both vision and collaboration efforts
- Trace progress in the research program to interdisciplinary involvement
- Discuss impact of interdisciplinary collaboration on the research outcomes as the results are translated to practice.
- Imagine the future possibilities for this work in a truly transdisciplinary effort.

Background: Development of The Seattle Midlife Women's Health Study as an Interdisciplinary Research Program

In 2006, after 15 years in the field, Dr. Ellen Mitchell and I ceased data collection for a study of midlife women's health as they traversed the menopausal transition. The experiences of conducting that study and the study outcomes represent a truly interdisciplinary effort and one in which there was interprofessional collaboration. In the spirit of our focus on interdisciplinarity, I will use our experiences with the Seattle Midlife Women's Health Study as an exemplar because it is the one I know best.

In 1989, two years before the US Women's Health Research Agenda was formulated and published by the National Institutes of Health, the UW School of Nursing won a center grant award from the National Institute of Nursing Research to establish a Center for Women's Health Research at the U of W. The original aims of the center were to promote research about women's health across the lifespan, with a particular focus on midlife and older women(Woods and Shaver, 1992).

One of the two large studies that was a component of the Center was titled "Midlife Women: Health and Health Seeking-Behavior." The focus of that study was largely descriptive, and included testing a model that accounted for women's health and health-seeking behavior as measured by several indicators. The major concepts organizing this study included: menopausal transition, health and health status, health behaviors and health practices, health seeking behavior, stress and coping, and social support. In addition, we obtained physical measures, e.g. height and weight, and demographic data. The methods for that study included an in-person interview conducted in the homes of the participants or at a site that was comfortable for them. In addition, we asked women to keep a daily health diary in which they rated their symptoms for up to 90 days or for two menstrual cycles. We then asked the women to complete an annual health update and to return it by mail.

Midlife and Menopause

From this first study we learned a good deal, including how women viewed midlife and menopause. Based on earlier work by developmental psychologists, we asked women to describe what midlife and menopause meant to them. We found that the women in the Seattle Midlife Women's Health Study described midlife similarly to women from earlier birth cohorts with one important exception: the centrality of work and personal achievements in their lives. Not surprisingly, contemporary midlife women viewed midlife as a reflection of their roles in society(Woods and Mitchell, 1997). In addition, women informed us about their views of menopause which they saw as cessation of their periods, ending of their reproductive ability, a time of horonal changes, a change of life, a changing body, changing emotions and part of an aging process. Few of these women described menopause as a time of increased symptoms or disease risk or as a time for medical care. They also were uncertain about their expectations of their own menopause(Woods and Mitchell, 1999).

We focused our earliest analyses on health outcomes of importance to the women in our study by emphasizing symptoms women experienced and depressed mood. Using data from the health diaries that women kept, we attempted to characterize the symptom clusters that women experienced in the time period before they began the menopausal transition

and during the earliest years of the transition. Ellen Mitchell studied the symptom diaries women kept, in which she focused on 28 symptoms that were commonly reported as associated with menopause. Using factor analysis, she found five clusters of symptoms: dysphoric mood, vasomotor symptoms, somatic symptoms, neuromuscular symptoms, and sleep disruption. Of the five symptom patterns, vasomotor symptoms and somatic symptoms were the least stable, varying the most over time. In contrast, dysphoric mood, neuromuscular, and sleep disruption symptoms were the least variable over the three years of diary-keeping(Mitchell and Woods, 1996). We concluded that the stability of dysphoric mood over the three period reflected a chronic situation, perhaps due to high stress, overwork, or an ongoing mental health problem. In contrast, vasomotor symptoms were beginning to vary with progression through the menopausal transition. These symptom clusters provided a focal point for many further analyses throughout the course of the study.

Studies of symptoms by medical sociologists, as well as biomedical scientists, had preceded our work. Drawing from the research by Mechanic(1962), for our earlier work on perimenstrual symptoms, we were aware that women perceived perceived, evaluated, and acted upon symptoms. As we began studying women's experiences of dysphoric mood, in particular depressed mood, we hypothesized three different pathways to depressed for women at midlife: a menopausal transition pathway, a health status pathway and a socialization f or midlife and stressful life context pathway. Our data showed that for women who were in the early stage of the menopausal transition or who had not yet reached that point, the stressful life context pathway was most influential in accounting for depressed mood. Health status influenced depressed mood directly and also through its effect on stress. Menopausal transition changes, including vasomotor symptoms and bleeding changes had little effect on depressed mood (Woods and Mitchell, 1997). In a related set of analyses looking across one year of follow up data, we found the same results, but in these analyses, vasomotor symptoms as well as having a history of postpartum blues and premenstrual symptoms were related to having chronic depressed mood over time(Woods and Mitchell, 1996). These results prompted us to look at the longitudinal patterns of depressed mood over time in this study, including women in the analyses who had participated for up to 15 years. When we used multilevel hierarchical linear modeling to analyze our data, we found that depressed mood across the menopausal transition decreased with age, and increased with stressful events, hot flash activity, family history of depression, history of postpartum blues, sexual abuse history, BMI and use of antidepressants. Being in the late menopausal transition stage, within a few years of menopause, also was a time of vulnerability to depressed mood (Woods et al, in press). We did not see this effect in our earlier analyses because too few women had progressed to the late MT stage.

Biopsychosocial Dimensions of the Menopausal Transition

During the second phase of the Seattle Midlife Women's Health Study we focused specifically on biopsychosocial aspects of the menopausal transition. In order to achieve our aims, we assayed urine samples from monthly first morning voids collected on day 6 of the menstrual cycle for women still menstruating. We also focused on developing a system for staging the menopausal transition.

Until this stage of our study, we had not decided how to view the multiple repeated datapoints we were collecting. Nonetheless, Ellen Mitchell, who was a nurse practitioner with a busy women's health primary care practice, as well as a PhD-prepared nurse researcher, committed herself to thinking about how to develop a staging system similar to that used to stage adolescents' progression through the stages of puberty. She examined each of the menstrual calendars women provided, searching for a pattern that would allow us to say women were nearer to or farther away from the final menses. During this aspect of our work, Michael Soules, a reproductive endocrinologist and fertility expert met with us to discuss how we were proceeding and to exchange the findings from his work in which he was examining follicle counts in women's ovaries as a basis for estimating how soon they would reach menopause. His purposes were to help women achieve a pregnancy using assisted reproductive technologies. Ours was to help women identify where they were in the progression to menopause and to help their care providers better estimate appropriate symptom management strategies based on these data. Ellen led our team in publishing a proposed staging system(Mitchell, Woods, and Mariella 2000) that helped justify a meeting sponsored by NIH, the Staging Reproductive Aging

Workshop(STRAW)(Soules et al, 2001). The results of this workshop, which involved researchers as well as clinicians whose specialty was menopause from around the world, included a proposed staging system. In subsequent years, Ellen participated in a multi-site study to assess which of several staging systems provided the most accurate predictor of the final menstrual period and could be used to distinguish between late reproductive, early, and late menopausal transition stages. I am pleased to say the system that Ellen led us to develop was judged to be the most useful of all! In brief, the period prior to the menopausal transition was labeled late reproductive, the early menopausal transition was indicated by variability from one menstrual cycle to the next by a week or more, and the late menopausal transition stage by skipping periods or having twice or greater cycle length than during the prior stage. The final menstrual period was said to have occurred after a woman had no menses for one year. Bleeding patterns, not the hormone indicators or symptoms, because the indicator of choice. Rhythmicity of the menstrual cycle was the underlying factor which the bleeding patterns indicated.

Developing the proposed staging system at the STRAW workshop was transdisciplinary, I believe: we all struggled to develop a nomenclature about the menopausal transition that differed from the one that had been used in prior epidemiologic and medical studies. No single discipline's viewpoint prevailed. The terminology in the staging system required us to step outside our disciplinary boundaries and think of a language and indicators that could be used by women, themselves, as well as researchers and clinicians.

The staging system also provided a key that unlocked our analyses. Prior to our development of the rules for a staging system, we and other large multi-site studies were floundering in knowing how to structure data analysis. Age didn't seem to be the right factor to use in thinking about menopause, nor did years prior to the final menstrual period. Women vary highly in their ages at menopause as well as in their transition times. It was only when we began to use the staging system in our analyses that our findings became much more interesting!

Use of the staging system allowed us to see clear patterns in our data, including the stages during which women experienced symptoms most severely, depressed mood patterns, changes in their FSH and estrone levels, lipid levels, and

well-being. In brief, use of the staging system allowed us to discern that the late menopausal transition stage was a period of vulnerability for women. During this stage they experienced a significant increase in their hot flash severity(Smith Di Julio et al., in press). They also experienced a significant increase in depressed mood(Woods et al., in press). Our early analyses also indicated that during the late menopausal transition stage women experienced a significant rise in FSH and also to a lesser extent, estrone levels(Smith-Di Julio, in press). We have reported that the majority of women who progressed to the late menopausal transition stage also had a significant rise in urinary cortisol levels(Woods et al., 2005). Our collaboration with an endocrinologist whose interest was in metabolism in midilife women led her to discover a stage-wise change in lipid levels, including an increase in total cholesterol, LDL-C, apolipoprotein B, triglycerides, and very low density lipids(Carr et al., 2000). These changes are of potential significance given the relationship of metabolic syndrome to heart disease in women. Of interest is that well-being did NOT change across the menopausal transition stages (Smith Di Juilo, submitted).

We were also interested in studying the relationship between endocrine levels and symptoms in this study. We were able to focus some of our analyses on various stages of the menopausal transition as well as take a view across the entire transition. From the latter perspective we were able to learn that: hot flashes were related to both higher levels of FSH and estrone; lower sexual desire to lower estrone levels; vaginal dryness to FSH and T levels; forgetfulness to FSH; and difficulty concentrating to increased T levels. This set of analyses, done with data from women who had completed the transition to menopause and traversed from the menopausal transition stage through postmenopause, reveal other important relationships. Although hot flashes were implicated in depressed mood symptoms in previously published studies, we found that hot flashes influenced both early awakening and night-time awakening, and that these, in turn were related to depressed mood. Indeed, sleep is at the center of these relationships: the relationships of depressed mood, vasomotor symptoms, cognitive symptoms of difficulty concentrating and forgetfulness, as well as lower sexual desire and vaginal dryness, are related to sleep symptoms(Woods et al., 2007).

As we continue the data analyses of endocrine events across the menopausal transition, we are integrating a perspective of stress and stress reactivity. Our prior studies of women across the menstrual cycle indicated that understanding the biological rhythm of menstruation cannor occur unless one studies this phenomenon within the context of women's lives(Woods et al., 1997: Woods et al., 1998a, 1998b). We are applying what we have learned from our earlier work as well as the large and growing literature about stress, allostatic load, and the relationship between the HPA axis and autonomic responses to stress and the HPO axis hormones. For this work we are relying on collaborators from physiology and nursing as well as psychology to guide us. We have several questions remaining to be answered: does perceived stress change across the menoapausal transition? Is our finding of a rise in cortisol during the late MT stage persist as women make the transition to postmenopause? How are perceived stress levels related to cortisol and catecholamines? And how are these, in turn, related to symptoms women experience during the MT?

Gene Polymorphisms and the Menopausal Transition

A final area of interest that required interdisciplinary effort is our recent focus on gene polymorphisms in the estrogen synthesis, metabolism and receptor pathways and their relationship to progression through the MT and symptoms. In order to pursue this set of questions, we have collaborated with Dr. Fred Farrin, a pathologist, and the technicians in his laboratory. After we had several conversations with Dr. Farrin, we explored the gene polymorphisms in the CYP 450 genes that control estrogen metabolism, catalyzing the synthesis of estrogen from its precursors(androstenedione and testosterone), in the genes that control estrogen metabolism from estradiol to 2 hydroxyestrone and 16 a-hydroxyestrone, and the estrogen receptor genes. Much of the work focused on the relationship of these polymorphisms to health had focused on breast cancer and we were among the few investigators who were interested in their relationship to aspects of menopause, including symptoms and bleeding.

Dr. Farrin's collaboration with us provided the opportunity for us to immerse ourselves in a new discipline, genetics and genomics, complete with a new language. In the post-Human Genome era, the new genetics is not for the timid! Committed to genotyping buccal cells obtained from swabs (very easy sampling technique), meant a serious commitment to

learning which of the polymorphisms were relevant to our work. We, like the SWAN investigators began by looking for polymorphisms that had been related to estrogen levels and also to a health outcome, usually breast cancer. We reasoned that these polymorphisms would be those most likely to be related to symptoms. We were also aware of the ethnic specific nature of these relationships given that the geographic origins of some ethnic groups in the world would portend different genetic backgrounds.

The polymorphisms that were the focus of our analyses included:

- CYP 19 polymorphisms(catalyzes conversion of and rostenedione and testosterone to estrogens several polymorphisms, including CYP 19 11 r)
- 17 B HSD polymorphisms(catalyzes conversion of estrone to estadiol – rs 615942, rs592380 and rs 2830)
- CYP 1A1 and CYP 1B1(catalyze conversion of estrone to 2-hodroxyestrone and 16 a-hydroxyestrone – several polymorphisms)
- and
- ESR1 and ESR2(the estrogen receptor genes several polymorphisms).

The results of the genotyping are complex, but a single example will illustrate the importance of these questions. In our data, we found that women who had polymorphisms in the 17-HSD gene had more severe hot flashes. In addition, we found that women with a repeat polymorphism in the CYP 19 gene(11 r) had both more severe hot flashes and higher estrogen levels. In our study these were found during the late menopausal transition stage, a time when women experience the most severe hot flashes(Woods et al., 2006). What this may portend is that women who have both hot flashes AND higher estrogen levels may be at risk for treatment with exogenous estrogens for their hot flashes. This is an important finding which needs to be replicated as it suggests that this subset of women may be at risk of getting a treatment for their hot flashes that could put them at risk. We also found that women with the CYP 19 11r polymorphism were older at the onset of the late stage of the menopausal transition (50.7 vs 48.6 years)(Mitchell et al., in press). They also may be exposed to their own endogenous estrogen for a longer period of time than are women without this polymorphism. This finding and potential implications raise the importance of replication of these relationships in other populations. In the

future, patterns of these relationships may help us identify groups of women for whom certain therapies are risky or those for whom the therapies may be ineffective. In addition, ethical issues about communicating this information to women need to be weighed heavily as the evidence accumulates.

Translation to Clinical Practice

The translation to practice of some of our work has been gratifying. I was thrilled when we were asked to contribute a chapter to the book "Our Bodies, Ourselves", a book written for the general population of women in the US and translated in many languages. This invitation signified that our work has relevance in the lives of the women, the same women who have participated in our research over the years. It was also gratifying to see that many clinicians are adopting using the menstrual calendar that we have used in our research and are teaching women about staging the menopausal transition. In the future we are looking forward to the opportunity to add our findings to a growing body of evidence that is guiding practice with midlife women, particularly that aimed at health promotion for them as a means to healthy aging.

In related research, we have participated in a study that developed a web-based decision aid for women to use in deciding how to manage their symptoms and promote their health in midlife(Saver et al., 2007; Woods, Falk et al., 1997, 1998; Woods, Saver et al., 1998). The development of the Menopause and Beyond decision aid preceded the publication of findings of the Women's Health Initiative that caused women and health professionals alike to question the safety of prescribing hormone therapy for prevention of chronic disease among midlife and older women(Writing Group for the Women's Health Initiative Trial, 2002). Our recent publication of the clinical trial of the Menopause and Beyond decision aid points to effectiveness of providing information and support in decision-making at a point when women are experiencing symptoms and questioning how to manage them.

In addition, we are currently collaborating with another group of investigators to identify and test interventions for managing menopause-related symptoms such as hot flashes. As we embark on this next series of studies, we have benefited from many opportunities for interdisciplinary collaboration. We will bring together investigators trained in nursing, medical, epidemiologic, physiologic, and behavioral

sciences to study menopause. We will try to refocus the aims of the work from the traditional disease management approach to a vision of menopause as a normal biological transition occurring in a complex social context. We will try to envision menopause as part of lifespan health with a past and future linked to it instead of a medical problem to be solved at a single point in time. We will try to transform the focus on therapeutics to one on health promotion that encompasses self management, complementary and alternative therapies, and allopathic medicine.

I believe the transdisciplinarity of our work will continue to grow. As we contemplate the research to be done on symptom management, I believe we will have the opportunity to redefine menopause and re-envision the phenomena we are studying and think about them from a different perspective. The fusion of the knowledge we glean from many disciplines and different scientists into a science of women's health may be the most exciting outcome of all.

Summary and Future Plans

At this juncture, Ellen Mitchell and I are systematically analyzing the data we have accumulated over the past 15 years, looking forward to the next challenges! We are contemplating the next research focus. Ellen has just retired from her faculty appointment, but has been elected to emeritus status, so we plan to continue our collaboration after all these years. We also are looking forward with curiosity and excitement to the future interdisciplinary work we will enjoy. We are still collecting data, though the funding for this study has ended. We are determined to continue following ALL the women who are willing to keep their calendars until they have completed the menopausal transition and a few years beyond.

As global health issues come to the center of our attention, we have had the opportunity to begin contemplating the possibility for international collaborations in women's health research, as well as interdisciplinary ones. We welcome your interest in our work and look forward to possible collaborations with scientists around the world.

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