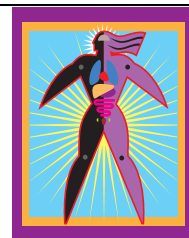


Expanding the frontiers of women's health research — US style

Sex analyses in studies can have clinical implications



IN THE PAST DECADE, biomedical and behavioural research has provided evidential credibility for the field popularly known as “women's health”.^{1, 2} During this time, heightened interest and increased resources were given to the study of “conditions unique to women”,³ and to sex and gender differences in health.⁴ These efforts have increased our understanding of the aetiology, prevention, management and health outcomes of many conditions that affect women.⁵ In doing so, this research has progressively widened its focus from reproductive conditions to concepts of health throughout women's lives. It has also influenced the culture of science and the paradigms by which scientific studies are now designed and conducted.^{1, 6}

Policies for research supported by the US National Institutes of Health (NIH) now mandate the involvement of sufficient numbers of women in studies to determine whether sex/gender differences exist. The US Institute of Medicine of the National Academy of Sciences has recommended that researchers should disclose the sex of origin of cell and tissue cultures used in research; and biomedical journals are beginning to recommend that investigators report analysis of data by sex.⁷

Research continues to document many sex/gender health differences (Box 1 and Box 2) and is beginning to define gender-specific preventive measures, risk factors, or treatments. For example, different clinical manifestations of heart disease in women have been noted,⁸ as have potentially fatal sex-based arrhythmias for women in response to some cardiac drugs.⁹ Another example of how results from sex analyses in studies can have clinical implications is the demonstration that women are more likely to have a lower threshold for pain and may be more responsive to some analgesics such as kappa-opioids.¹⁰

In the United States, the drive for dedicated women's health research came from public policy and grassroots activists.¹¹ In response, the NIH established the Office of Research on Women's Health (ORWH) within the Office of the NIH Director in 1990.^{12, 13} The ORWH advises the NIH Director and staff on women's health research matters; ensures that NIH-supported research adequately addresses women's health issues; ensures that women are appropriately represented in biomedical or behavioural research; and, develops opportunities for and supports the involvement and advancement of women in biomedical careers. Other agencies within the US Department of Health and Human Services address aspects of women's health that fall within their mission, including healthcare services, drug regulation, or health policy.¹⁴

It was subsequent to the initial research agenda on women's health in 1992,¹⁵ that the ORWH emphasised research that encompassed the totality of factors influencing women's health across the life span. Since 1999, with the eight-volume Agenda for research on women's health for the 21st century,¹⁶ increased emphasis is now given to interdisciplinary research, disease prevention, analysis of research

1: Definitions

Sex: refers to being male or female according to reproductive organs and functions assigned by chromosomal complement

Gender: refers to socially defined and derived expectations and roles rooted in biology and shaped by environment and experience

data by sex/gender and the inclusion of diverse populations of women in studies. This is to enable the exploration of factors that contribute to differences in health outcomes and in responses to therapeutic interventions. Research priorities are directed to: the relationships between early life activities and health or ill health in later life; the role of personal behaviours and lifestyle choices in the health and ageing processes (focusing on such issues as obesity, exercise, addiction, and smoking cessation); and many other delineated areas. These include multisystem disorders, mental health and addiction, complementary and alternative medicines, violence and quality of life.

A January 2003 workshop sponsored by the ORWH in Washington, DC, “Science meets reality: recruitment and retention of women in clinical studies and the critical role of relevance”, examined the lessons we have learned from the past decade such as:

- ways to recruit and retain women in clinical studies;
- the importance of community participation in the design and planning of a study to facilitate recruitment of participants from that community;
- how investigators can better communicate with potential volunteers, show respect for vulnerable people and avoid the use of coercive recruitment tactics; and
- the means to ensure that clinical research is relevant and targets questions important to public health.

The workshop also identified emerging ethical and policy issues including:

- the need to appreciate how sex differences should be taken into account in the design of clinical research;
- the shift from the ethics of protectionism (that often resulted in exclusion of women, especially pregnant women or women of childbearing age, from research to “protect” them from harm) to the ethics of inclusion (recognising the need to include women of all ages in studies as long as the potential results would not cause harm);
- concepts of justice in research, such that potentially beneficial research would not just be offered to one group of volunteers or patients, and that all populations subject to a disease or condition have the right to be studied — a concept embodied in the NIH policies requiring the inclusion of women (and minorities) in human subject research; and,
- the differences between clinical care and clinical research.

Finally, one of the most critically important issues is the translation of clinical research into practice, which becomes

2: Known sex/gender health differences

Heart disease: presentation, outcomes, and responses to intervention

HIV/AIDS: manifestations and progression

Pain: response to pain and pain therapies

Depression: clinical features and management

Diabetes: prevalence and care, especially type 2 diabetes

Musculoskeletal diseases: incidence and effect; eg, of osteoarthritis, osteoporosis and sports injuries

Autoimmune diseases: mortality

especially apparent when research outcomes contradict established clinical practice.¹⁷ This happened in 2002 when the outcomes of the oestrogen/progestin postmenopausal hormone therapy arm of the NIH-funded Women's Health Initiative randomised controlled trial became available.^{18,19} The study provided definitive evidence that long-term therapy with combination oestrogen and progestin does not reduce cardiovascular disease in postmenopausal women (as had long been thought), but rather had unexpected results — showing an increased risk for cardiovascular disease as well as an increase in risk for breast cancer. Such studies provide strong justification for continuing research to document risks versus benefits of common, but unproven, approaches to disease prevention and treatment of women. At present, efforts focusing on translating research findings into healthcare include the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health, an innovative initiative which supports both basic and clinical projects related to research priorities that can advance scientific discoveries from “bench to bedside”.²⁰

Research on women's health and sex and gender factors is providing the data with which to better arm the physician for possible variations in approaches, drug dosages, or diagnostic practices for not only women but also men. This new knowledge is creating new challenges to ensure that future physicians possess a full understanding of how to better provide gender-appropriate healthcare.²¹⁻²³

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