Spheres of Influence

What's Good for the Gander May Not Be Good for the Goose

Statistically speaking, a woman is not as healthy as her male counterpart. She experiences more chronic health problems, more unique health problems, and reacts differently, even to a garden variety of ailments, over the course of her lifetime. Yet ask any reputable scientist to identify the best ways to determine causes, prevention, and treatment of illness in particular regard to women, and the likely response is a question mark. Women have traditionally borne the health consequences of being underrepresented or banned from clinical research simply on the basis of gender, but the tide is about to turn.

As Palma E. Formica, a member of the American Medical Association's Board of Trustees, recently observed, women are "different biological entities from men, with different hormones, patterns of disease, health, and responses to treatment." Researchers and physicians alike are beginning to notice. Progress is being made in closing the gap in so-called gender bias in clinical trials, with sweeping reforms being made by the legal, political, and medical systems. New federal studies, regulations, and ethical guidelines are in the works to encourage the use of females as research subjects in order for scientists to better understand and more effectively treat women.

According to an unpublished report by the NIEHS, women are more likely to develop or experience worse effects of a variety of environmentally linked health problems. The NIEHS study indicated that a woman's greater percentage of body fat, use of oral contraceptives and estrogen replacement therapy, and exposure to heavy metals and other toxins may raise her odds for cancer, endometriosis, fibroids, osteoporosis, and cardiovascular disease. Yet prompted by concerns that experimental procedures or treatments pose unacceptable risks for women of childbearing age, trials for cardiovascular disease, cancer, AIDS, and many other diseases have been conducted only on men or postmenopausal women or not separately measured, leaving fertile women without clinically proven safe and effective medical treatments.

Lack of hard evidence about the impact of too few or no female subjects in research has compelled researchers to play guessing games. "Because women have often been excluded. . . the medical community has had to assume, sometimes incorrectly, that what is good for men is also good for women," said former National Institutes of Health Director Bernadine Healy. "It's a case of wrong-headed expectations leading sometimes to the wrong treatment, delivered too late."

Healy's call to reconcile the imbalance between research and practice is showcased by the largest community-based clinical intervention and prevention trial ever conducted in the United States. At a press conference in March, Healy named 16 Van-guard centers to carry out clinical studies of the leading causes of death and disability in women, with 4 centers mainly targeting minority participants. Twenty-nine more centers will be announced by mid-1994.

More than 160,000 women, ages 50 to 79, will take part in the Women's Health Initiative, a $625-million, 15-year study of the causes and prevention of heart disease, cancer, and osteoporosis–the major causes of death and disability in women. According to Healy, by September each center will enroll about 3500 study participants beyond childbearing age in a series of clinical trials or observational studies. The objective is to test the effects of a low-fat diet, dietary supplements, exercise, hormone therapy, and smoking cessation in preventing colorectal and breast cancer and hip fractures.

On the environmental front, a series of upcoming workshops and studies on women and cancers caused by workplace exposures are on a growing roster of government-funded projects. "The environment affects us and we affect the environment, so it's a very symbiotic relationship . . . we as human beings must understand the interaction," said Judith H. LaRosa, deputy director of the Office of Research on Women's Health at the NIH, which is co-sponsoring a study with NIEHS to determine the epidemiology of lead, diet, and blood pressure, among other projects.

Researchers say females are usually excluded from animal studies unless their physiology is studied, while female clinical trial participants are not probed to see how or why they react variably largely because of their hormonal variations, need for contraception, contraception counseling, and potential for pregnancy. "This means pharmaceutical companies can market drugs with no information about their reproductive impact and. . .large-scale clinical trials with female subjects are never conducted," said Vanessa Merton, associate dean for Clinical Education and professor at Pace University School of Law.

Until now, the Food and Drug Administration's guidelines kept fertile women out of any clinical trial before its final stages and then only after generating animal data on a treatment's reproductive and teratogenic effects. This spring the FDA gave the green light for women of childbearing age to enroll in phase 1, 2, and large-scale phase 3 trials on new drug applications. "We are also requiring gender analysis which we had asked for but discovered was not being done as frequently as we would have liked," said Ruth Merkatz, special assistant on women's health issues to FDA Commissioner David Kessler. Gender analysis refers to monitoring and recording differences in clinical data between men and women.

Merkatz indicated that FDA plans to explore when and how pregnant women could participate in clinical trials, but gave no timetable or conditions. She said more active surveillance after marketing is crucial, as physicians now prescribe medications to an expectant mother with no specified data. "They have been flying by the seat of their pants–not knowing whether a dosage works or how because her hormonal milieu is so different," Merkatz said, pointing to FDA's directive last year against acetylcholinesterase inhibitors for pregnant women with high blood pressure after a series of babies died *in utero*. The Department of Health and Human Services' regulations also restrict the use of pregnant women to clinical trials where treatment is therapeutic with minimal risk to the fetus.

Some legal scholars argue such policies are discriminatory and unconstitutional. "After fully being informed of the risks, [a woman] is told she cannot be trusted to decide whether to participate in a protocol, while no restriction is placed on men whose offspring may be at equal risk," Merton said.

Heightened interest in women's health needs comes four decades after diethylstilbestrol (DES), a synthetic estrogen, was linked to various health problems. Researchers found that women who took the drug to prevent threatened miscarriages were more prone to breast cancer, and their daughters are now vulnerable to vaginal cancer. It is more than three decades since thalidomide, a sedative taken by expectant mothers, resulted in severely deformed babies.

Long cited by research sponsors as grounds to exclude women from research

studies, many critics now dub such catastrophies "red herrings." "Those tragedies were caused not by research studies but lack of testing and safeguards in postmarketing surveillance into the drugs' potential for harming pregnant women," says a congressional staffer.

A 1991 NIH memorandum said underrepresentation of women in clinical studies has caused significant gaps in medical knowledge. "Without adequate representation of women in study populations, we cannot truly know whether we are most effectively diagnosing, treating, and preventing illness in our women patients," said Jean Hamilton, a member of the American Medical Women's Association, who spoke before the NIH panel on women's recruitment and retention in research studies.

A 1992 General Accounting Office (GAO) study criticized the NIH's pace in honoring its commitment to recruit women as research subjects.

The report criticized the NIH for scanty representations of women and minority subjects in federally funded, industry-sponsored research trials submitted as evidence for all drugs approved by the FDA since 1988. The landmark study coincided with a flurry of legislation and regulations that would mandate equal access to clinical trials.

In response to criticism from the GAO and Congress, the NIH buoyed its policy on including women in study populations and developed an action plan for women's health. The Public Health Service established the Office of Women's Health. Meanwhile, in 1990 the Office of Research on Women's Health (ORWH) was set within the Office of the Director of the National Institutes of Health. This office is charged with coordinating research related to diseases, disorders, and conditions that affect women, assuring that women are well represented in research studies, and promoting the recruitment, retention, reentry, and advancement of women in biomedical careers.

The latest version of the Women's Health Equity Act, which is part of the NIH reauthorization bill, is in conference. The bill codifies the ORWH as part of the NIH statute, requires the inclusion of women and minorities in clinical trials, and expands research on specific women's health needs. According to a congressional staffer, some $470 million is authorized for the act, which is expected to be signed into law by President Clinton this spring.

Meanwhile, headway is being made to audit NIH grants by the Congressional Women's Caucus, an assembly of female members of Congress that is trying to determine how many grants received a waiver to exclude women from research studies and how many grants were for studies of one gender. "No one thought a couple of laws would be a magic wand," said Congresswoman Patricia Schroeder (D-Colorado), a member of the caucus. "We're making sure women figure into new research proposals coming up so there is solid information based on solid research."

Inclusion of women in research trials raises dozens of thorny questions, some of which were considered recently at a workshop by the National Academy of Science's Institute of Medicine Committee on Legal and Ethical Issues Relating to the Inclusion of Women in Clinical Studies. Testifying before the committee, R. Alta Charo, assistant professor at the University of Wisconsin Schools of Law and Medicine, argued that excluding women from government-funded research and potentially lifesaving treatments deprives a woman of her constitutional right to life and liberty and guarantees of equal protection under the law. Moreover, Charo contends that legally barring pregnant women from clinical trials seems to "elevate concerns for fetal well-being over concerns for maternal and female well-being."

Fetal well-being is indeed a concern and raises another facet of the issue, which was addressed by Michelle Oberman, a professor at DePaul University College of Law in Chicago, in testimony before an NIH panel on women's recruitment and retention in clinical trials: "The much greater perceived cost of including fertile women in clinical studies relates to the sponsors' fear that a woman will conceive while in the study, will choose to carry the pregnancy to term, and will give birth to a child with disabilities."

What is good for the proverbial goose may not be good for the gosling. "Unlike the adult subject in a clinical trial who knowingly consents to risk and thereby waives the right to sue for injuries, a child who is harmed while *in utero* through a clinical study may well have a cause of action against those who caused the injury," added Oberman, speaking on behalf of the Chicago Bar Association Alliance for Women, an advocacy group seeking legal reforms.

Clearly, there are significant disincentives to including fertile women in clinical studies, particularly in terms of increased concerns about costly lawsuits and medical treatment for injured subjects and their offspring. But because fertile women also need medical treatment there are costs of excluding them from trials that can show once and for all that the treatments they opt for are safe and effective. This is the dilemma that until now has limited or even precluded women from being included in clinical trials.

Researchers historically have used many justifications to exclude women from research studies. They argue that women are harder to recruit and retain; that male-only data are more homogenous and thus more useful; that inclusion of women is unduly costly; that government regulations require their exclusion; and that the threat to fetuses creates a legal and moral imperative to exclude all potentially pregnant women. Many participants at the Institute of Medicine meeting, such as Debra A. DeBruin, a professor in the Department of Philosophy at the University of Illinois at Chicago, believe that these criteria are flawed, unjust, and likely to be overturned. In regard to cost, DeBruin said that it is unethical to disperse resources on the basis of sex. "Surely, no one. . .would be willing to manage the costs of education by excluding children of color from our educational system," she said. "Likewise we must conclude that considerations of cost cannot justify excluding women from clinical studies."

Should legal and political roadblocks to inclusion of women in clinical trials be overcome, however, advocates believe the system must still work to accommodate and encourage female subjects deterred both by logistics such as child care, transportation, and cost (many third-party payers will not cover medical costs for clinical trials even when the standard treatment costs as much or more) as well as basic concerns about safety and credibility.

Despite the obstacles, evidence is mounting that given the chance, women want to participate. In one major nationwide clinical trial, many more of the 800 initial participants remained to complete the trial than sponsors expected. Speaking for the Society for the Advancement of Women's Health Research in Washington, DC, Maria Bustillo said the Postmenopausal Estrogen Progestin Interventions trial showed that self-interest and altruism are prime motivators. "Women expressed interest in knowing more about their own health and. . .in increasing knowledge about hormone replacement to benefit future generations."

For women, inclusion in clinical research trials means acquiring vital knowledge about their unique illnesses, physiologies, and responses to treatment in the hope that with such knowledge comes the power to ensure that they, like their male counterparts, receive the benefits of medical and scientific research. These benefits, due to women's unique capacity to bear children, may then be passed to society as a whole.

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