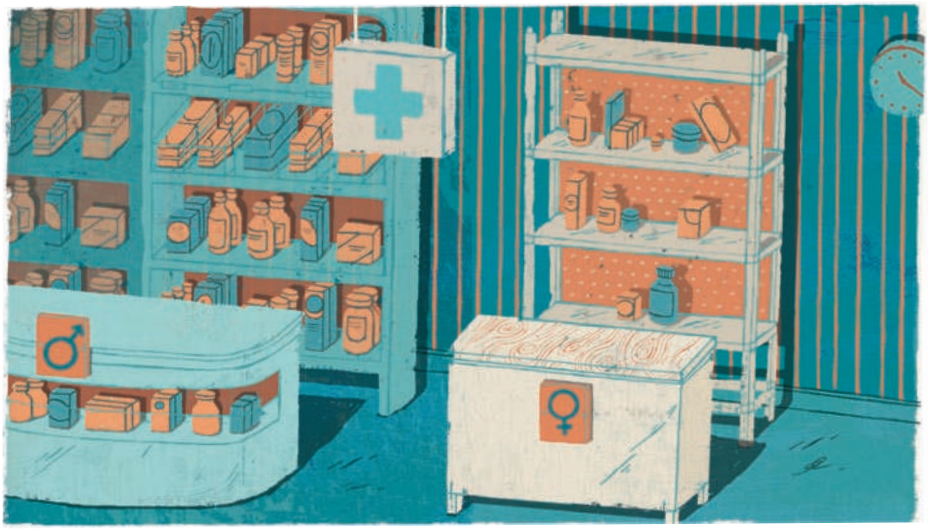
Sex bias in trials and treatment must end

Gender inequalities in biomedical research are undermining patient care. In the first of three related pieces, **Alison M. Kim**, **Candace M. Tingen** and **Teresa K. Woodruff** call on journals, funding agencies and researchers to give women parity with men, in studies and in the clinic.



E. BEE

It is 20 years since the US National Institutes of Health (NIH) set up its Office of Research on Women's Health (ORWH), and 17 years since Congress passed the NIH Revitalization Act to increase the representation of women and minorities in clinical trials. Some researchers and health officials seem convinced that women and men are now equally represented in biomedical research. A commentary in *Science* in 2008 even suggested that the bias had shifted against men and that women's health centres and initiatives aimed at recruiting women for clinical trials were no longer necessary[1].

The efforts of the ORWH and other centres have done much to increase female participation in clinical trials. Since 1993, more women than men have been enrolled in NIH-sponsored phase III trials. However, this is mainly attributable to a few large single-sex studies: cancer trials (breast, cervical or uterine), the Women's Health Study on the effect of aspirin and vitamin E on cardiovascular disease and cancer, and the Women's Health Initiative's long-term research into postmenopausal women.

Generally, women remain underrepresented in biomedical research. Studies published in 2000 and in 2008 concluded that women were still not included in mixed-sex cardiovascular trials in numbers that reflect the disease prevalence among the general population[2,3]. A survey of studies published in 2004 in nine influential medical journals found that only 37% of participants were women (24% when restricted to drug trials), and only 13% of studies analysed data by sex[4].

> "Good, well-promulgated research into sex differences will benefit everyone."

Parity of the sexes in biomedical research — or at least the inclusion of women in numbers that match the abundance in the general population of the condition being studied — is crucial, as is sex-specific analysis of results. Why? Because there are significant differences in the ways that men and women experience many diseases. Sex differences in incidence, prevalence, symptoms, age at onset and severity have been widely documented: in autoimmune diseases such as rheumatoid arthritis, lupus and multiple sclerosis; in some psychological disorders, including major depressive disorder, schizophrenia, autism, eating disorders and attention deficit hyperactivity disorder; and in chronic fatigue syndrome, asthma and several types of cancer.

Differences are particularly acute in cardiovascular disease, the leading cause of death for both men and women. Women in the early stages of coronary artery disease (CAD) often present symptoms such as unusual fatigue, abdominal discomfort and back, jaw or neck pain, which are all considered to be atypical because diagnostic standards were mainly established from research on men. As a result, women can be subject to potentially life-threatening delays before crucial diagnostic tests are administered. Furthermore, some of the tests used for diagnosis, such as exercise electrocardiography and radionuclide myocardial perfusion imaging, are unable to detect CAD with the same sensitivity in women as in men. This situation is likely to continue until the sex bias in clinical research is properly addressed. Until then, women will be forced to make do with therapies that may be of limited benefit to them.

All in the genes?

Sex disparities in the experience of disease are hardly surprising given the fundamental biological differences between men and women. A recent study of gene expression in mice showed that hundreds of genes in several tissues are expressed differently in males and females[5]. There are also hormonal differences and variations in imprinting, by which genes inherited from the father and mother are expressed in different ways.

Disease highlights these inherent variations. For example, genomic profiling of patients with non-small-cell lung cancer shows sex differences in the activation of signalling pathways[6]. This suggests that biomarkers, which indicate the presence or severity of disease, may have to be used selectively depending on the sex of the patient.

Biological differences also affect the way men and women respond to medications and therapeutics. For example, women wake faster from sedation with anaesthetics such as propofol and nitrous oxide, recover more slowly and develop more side effects such as headaches, nausea and vomiting. Anaesthesiologists have learnt that dosage calculations must take into account a patient's sex and, in the case of women, the stage of their menstrual cycle.

Despite the obvious physical and physiological differences between men and women and the abundance of literature on the way sex influences metabolic activity, drugs are rarely prescribed with such variations in mind. A 2005 study of 300 new drug applications between 1995 and 2000 found that even those drugs that showed substantial differences in how they were absorbed, metabolized and excreted by men and women had no sex-specific dosage recommendations on their labels[7]. This may be part of the reason why women are 1.5 times

more likely to develop an adverse reaction to prescription drugs than men[8].

Another problem is the lack of awareness among doctors about the importance of sex-specific differences. For example, a 2005 survey showed that only one in five physicians was aware that more women than men die from cardiovascular disease each year[9]. In 1996, the American Board of Internal Medicine recommended that "internists should be trained to provide comprehensive care to men and women based on an awareness of the influences of gender ... on an individual's health"[10]. Yet an independent survey conducted a decade later concluded that few US medical schools had fully incorporated sex-based education into their curricula, or offered courses or clerkships in women's health[11].

Time for change

It is time for the sex bias in basic research and clinical medicine to end. All those involved in scientific discovery and communication must do their part, from scholarly journals, regulatory bodies and funding agencies to researchers and clinicians. First, scientific journals should require authors to clearly label single-sex studies as such, and to address sex-based differences in their research designs and analyses, or to justify pursuing a single-sex study. Second, regulatory bodies and funding agencies should insist on the appropriate representation of both sexes in human and animal trials, and require researchers to consider sex differences during data analysis.

Third, and perhaps most challenging of all, it is vital that knowledge of sex differences gets from the lab to the clinic and becomes an essential consideration in physicians' interactions with patients. For instance, the US Food and Drug Administration (and analogous bodies outside the United States) should mandate that sex-specific reactions to medications be made clear to patients and clinicians. The need for continuing education in the clinical importance of sex differences is being addressed by organizations such as the Women and Heart Disease: Physician Education Initiative. Their recent pilot session with obstetricians and gynaecologists on sex differences in hypertension showed improved referral and counselling rates[12].

Fourth, health organizations should encourage more women to join clinical research studies and trials. A good model for this is the Illinois Women's Health Registry, set up by the Institute for Women's Health Research at Northwestern University[13]. Women who enrol in the registry are asked questions about their health and lifestyle, and in return are given information about and access to clinical studies that may help them and that they may be eligible to join.

Good, well-promulgated research into sex differences will benefit everyone: women and men. It is the next step on the path to truly personalized healthcare. ■

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Pregnant women deserve better

Clinical trials routinely exclude expectant mothers. This is unethical and unscientific, and regulators must mandate change, says **Françoise Baylis**, in the second of three related pieces on gender bias in biomedicine.

International ethical guidelines drawn up by the Council for International Organizations of Medical Sciences[1] clearly stipulate that pregnant women are eligible to participate in biomedical research. Yet they are routinely excluded from the vast majority of clinical trials of drugs, vaccines, nutraceuticals, natural health products and medical devices because of the harm the intervention might do to the developing fetus.

This is ethically and medically unacceptable for two reasons: pregnant women get sick, and sick women get pregnant. Patients who happen to be pregnant are as entitled as anyone else to safe and effective treatments, yet they are denied this and will be for as long as pregnant women are excluded from clinical studies. New drugs and devices are typically not approved for use in pregnant women as the many physiological changes that women experience during pregnancy — such as increased plasma volume, body weight, body fat, metabolism and hormone levels — make it impossible to calculate dose and safety information by extrapolating from data on men and non-pregnant women.

This means that when a pregnant woman has a health condition that requires treatment, her physician often has insufficient information to make an evidence-based recommendation. For example, some of the adjuvants in a recent H1N1 vaccine were tested extensively in clinical trials with different vaccines that excluded pregnant women.

There is an obvious alternative: small, well-designed trials for pregnant women, starting with phase I safety trials that would begin at the same time as phase III efficacy trials in the general population. With this staggered approach, pregnant women and fetuses would not be exposed to any compounds that failed in phase I and II trials. Another option would be to allow pregnant women to join phase III trials once a drug had passed safely through phases I and II. This would need to include enhanced safety monitoring for pregnant women, similar to that done in a stand-alone phase I trial. As researchers and sponsors are unlikely to make such changes of their own volition, regulators will need to make the inclusion of pregnant women in such trials mandatory, and oblige drug companies to conduct follow-up studies to identify any short- or long-term effects of the drugs.

Persuading pregnant women to take part in research can be difficult because of the perception that trials are riskier than taking prescribed medication. Trial organizers should take pains to demonstrate that this is often a false belief, and that it is generally safer for pregnant women to use drugs in a trial under controlled