

more likely to develop an adverse reaction to prescription drugs than men<sup>8</sup>.

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<sup>9</sup>. 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”<sup>10</sup>. 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<sup>11</sup>.

### 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<sup>12</sup>.

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<sup>13</sup>. 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. ■

**Alison M. Kim, Candace M. Tingen and Teresa K. Woodruff** are in the Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, USA. Teresa K. Woodruff is also in the Department of Biochemistry, Molecular Biology and Cell Biology.  
e-mail: tkw@northwestern.edu

1. Holden, C. *Science* **322**, 219 (2008).
2. Harris, D. J. & Douglas, P. S. *N. Engl. J. Med.* **343**, 475–480 (2000).
3. Kim E. S., Carrigan, T. P. & Menon, V. *J. Am. Coll. Cardiol.* **52**, 672–673 (2008).
4. Geller, S. E., Adams, M. G. & Carnes, M. J. *Womens Health (Larchmt)* **15**, 1123–1131 (2006).
5. Yang, X. et al. *Genome Res.* **16**, 995–1004 (2006).
6. Mostertz, W. et al. *JAMA* **303**, 535–543 (2010).
7. Anderson, G. D. J. *Womens Health (Larchmt)* **14**, 19–29 (2005).
8. Zopf, Y. et al. *Eur. J. Clin. Pharmacol.* **64**, 999–1004 (2008).
9. Mosca, L. et al. *Circulation* **111**, 499–510 (2005).
10. Day, S. C., Cassel, C. K. & Kimball, H. R. *Am. J. Med.* **100**, 375–379 (1996).
11. Henrich, J. B. & Viscoli, C. M. *Acad. Med.* **81**, 476–482 (2006).
12. Lewis, V., Barnhart, J., Houghton, J. L. & Charney, P. *Int. J. Cardiol.* **139**, 204–206 (2010).
13. Bristol-Gould, S., Desjardins, M. & Woodruff, T. K. *Womens Health (Lond Engl)* **6**, 183–196 (2010).

See Editorial page 666, and comment online at [go.nature.com/4NSpck](http://go.nature.com/4NSpck).

# 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<sup>1</sup> 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

conditions with proper follow-up than to take drugs that are prescribed 'off label'.

The benefits of having reliable evidence-based data that clinicians could use to provide safe treatments are immeasurable. The current situation, in which pregnant women suffer either by not receiving treatment or because they are prescribed analgesics, psychoactive medications,

antimicrobials, diuretics, vaccines or other treatments that could harm them or their fetus, is unjust<sup>2,3</sup>. Correcting it should be a priority. ■

**Françoise Baylis** is in the departments of bioethics, philosophy and obstetrics and gynaecology, Dalhousie University, Halifax, Nova Scotia B3H 3P7, Canada.  
e-mail: francoise.baylis@dal.ca

1. CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*; available at [http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm)
2. Baylis, F. & Kaposy, C. J. *Obstet. Gynaecol. Can.* **32**, 473–476 (2010).
3. Lyerly, A. D., Little, M. O. & Faden, R. *Int. J. Fem. Approaches Bioeth.* **1**, 5–22 (2008).

See Editorial page 666, and comment online at [go.nature.com/LqKQy2](http://go.nature.com/LqKQy2).

# Males still dominate animal studies

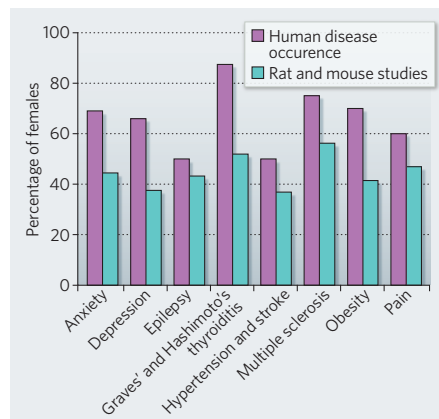
Many researchers avoid using female animals. Stringent measures should consign this prejudice to the past, argue **Irving Zucker** and **Annaliese K. Beery**, in the third piece of three on gender bias in biomedicine.

In the 1990s, several surveys showed a significant sex bias in animal experiments in many biological disciplines, with researchers using a disproportionately high number of male animals. Given that animal models underpin the development of treatments for numerous diseases, this has serious implications for health-care in women. So, to test whether or not the situation has improved, we recently conducted our own survey of almost 2,000 animal studies that were published in 2009 (ref. 1).

We found a male bias in 8 out of 10 biological disciplines, most pronounced in neuroscience (5.5 males to 1 female), pharmacology (5 males to 1 female) and physiology (3.7 males to 1 female). Although we identified a female bias in studies on reproduction and in the few immunology reports that indicated the animals' sex, 75% of studies in three highly cited immunology journals did not specify whether the animals used were male or female.

We also sampled the Thomson Reuters Web of Science database for 2009 to investigate the use of female mammals in animal studies for particular diseases, and then compared the results with the prevalence of those diseases in women worldwide (see graphic).

This revealed several alarming things. For example, diagnoses for anxiety and depression are more than twice as common in women than in men, but fewer than 45% of animal studies into these disorders apparently used females. Women have more strokes than men, with poorer functional outcomes, but only 38% of animal studies into strokes used females. Some thyroid diseases are seven to ten times more common in women, but only 52% of animal models used females. Other researchers have found that rodent studies into the effects of drugs on behaviour use males nearly exclusively, despite there being well-established differences in the ways men and women absorb and excrete drugs<sup>2</sup>.



**Gender gap.** The percentage of women in the total population presenting with a disease (purple; see ref. 1) outstrips the percentage of females in rat and mouse models of that disease (green; data from Web of Science). Only studies with 'female' or 'male' as keywords were captured, so the chart underestimates male bias relative to a survey of individual articles by field.

The prejudice against using female animals may be partly due to concerns that they are intrinsically more variable than males because of cyclical reproductive hormones, making them unsuitable for use as baseline models. For instance, a 1923 study that showed marked oestrous-linked variations in movement-related activity in female rats<sup>3</sup> may have discouraged the routine use of females in animal research. Yet there is little evidence to suggest that such variations make female animals inappropriate models. A 2005 meta-analysis found that female mice from many different strains were no more variable than males in the way they experienced pain. The researchers concluded that their findings "should force a reappraisal of the long-held assumption" that the oestrous cycle of female mice leads to greater variability in data<sup>4</sup>. Furthermore, hundreds of studies have shown that research using female animals

is valid and reliable for numerous traits<sup>5,6</sup>. In research on human diseases such as epilepsy and multiple sclerosis, in which symptoms have long been known to be influenced by ovarian steroids, female animal models are de rigueur.

To correct the sex bias in animal research we need stringent, strictly enforced measures, not voluntary appeals. Journal editors and reviewers should require authors of research studies that use only male or only female animals to state this in the title of their papers. This would highlight sex biases and spur researchers to balance the numbers of males and females that they use. Funding agencies should refuse to consider grant proposals that do not properly acknowledge the sex of the animals to be used, and favour those that include males and females and plan to analyse data by sex.

We hope that changes such as these will make sex parity in animal research the norm. There are already some encouraging signs, such as the recent formation of the Organization for the Study of Sex Differences in Washington DC, and the announcement of a new journal, *Biology of Sex Differences*. It is time for researchers, editors and funding bodies to consign sex-biased animal studies to medical history. ■

**Irving Zucker** is in the Departments of Psychology and Integrative Biology, and the Helen Wills Neuroscience Institute, University of California, Berkeley, California 94720, USA.

**Annaliese K. Beery** is at the Center for Health and Community, University of California, San Francisco, California 94143-0844, USA.

e-mail: [irvzuck@berkeley.edu](mailto:irvzuck@berkeley.edu)

1. Beery, A. K. & Zucker, I. Sex bias in neuroscience and biomedical research. *Neurosci. Biobehav. Rev.* (in the press).
2. Hughes, R. N. *Behav. Pharmacol.* **18**, 583–589 (2007).
3. Wang, G. H. *Comp. Psychol. Monog.* **6**, 1–27 (1923).
4. Mogil, J. S. & Chanda, M. L. *Pain* **117**, 1–5 (2005).
5. Velísková, J. *Neuroscientist* **13**, 77–88 (2007).
6. Gold, S. M. & Voskuhl, R. R. *J. Neurol. Sci.* **286**, 99–103 (2009).

See Editorial page 666, and comment online at [go.nature.com/NJkvuJ](http://go.nature.com/NJkvuJ).