Gender bias in research: how does it affect evidence based medicine?

The evidence basis of medicine may be fundamentally flawed because there is an ongoing failure of research tools to include sex differences in study design and analysis. The reporting bias which this methodology maintains creates a situation where guidelines based on the study of one sex may be generalized and applied to both. In fact, study design in the 1970s in response to sex discrimination legislation made efforts to mix gender within study groups since this was considered the best approach to equality.

Although significant social progress has been made since then, the application of the principles behind the legislation to women's health and gender-based research have not been so positive. Those who research gender issues in clinical and laboratory medicine are aware of significant barriers both for researchers and for subjects entering studies. This is one illustration of continuing deep-seated patterns of disadvantage that triggered an equalities review by the UK Cabinet Office in November 2005. For example, research funding for coronary artery disease in men is far greater than for women, yet the at risk population of women, which is an older age group, suffers more morbidity and mortality. The lack of funding for women's disease in effect maintains women's lower economic status. It can also hinder research into gender medicine where significant advances in the diagnosis and management of coronary artery disease have built up from small differences into major gender medicine issues.[1] Clinical research also exhibits gender bias in other areas. One of these is in recruitment into clinical trials;[2] another is the reporting of gender-related data.[3] However, there is a dearth of gender-based clinical research from within the UK. Thus it is pertinent to use studies from North America and Europe where these issues have been investigated.

It was in 1994 that the US National Institutes of Health (NIH) issued a guideline for the study and evaluation of gender differences in clinical trials to ensure that the safety and efficacy of drugs would be adequately investigated in the full range of patients who would use the therapy.[4] Prior to this policy, women had been excluded from early studies of most drugs—mainly for safety reasons, but this prohibition meant there was little information about the effects of drugs in women. For example, women may have a different drug efficacy or side effect profile to men.[5] It was reported in 2005 that eight out of ten prescription drugs were withdrawn from the US market because of women's health issues.[6] This represents an enormous waste of research money as a consequence of neglecting gender research. The aims of the NIH guidance were to recruit enough women into studies to be able to allow valid analyses of differences in intervention effect, to evaluate the risks and benefits in women, and to provide opportunities for women to contribute to research through active participation in clinical trials while preventing exposure of a fetus to a toxic drug. Since then, in the USA, women can enter phase one, two and three clinical trials. Furthermore, training for and monitoring adherence to this policy has been undertaken by the NIH through the review process for research funding. However there has not been a dramatic recruitment of women's data into trial results.[7]

Monitoring for gender in NIH research has been reported from the US Congress Office. In 1997, 94% of grant proposals included women as research subjects.[8] This high figure, however, belies the underlying Society for Women's Health Research data that the richest charities (as distinct from government funded bodies) were not progressing with the inclusion of women as researchers and subjects and that only 3% of grant proposals measured sex differences.[6] One important methodological barrier appears to be that women using hormonal contraception must be considered as a separate group for purposes of analysis.[9] However, even the basic concept of including women, whatever their hormonal status, has been brought into focus by recent studies that identified significant barriers to the inclusion of women in clinical trials.

Questions concerning contraceptive use in clinical trials were investigated by an Institutional Board survey. These trials were mainly government sponsored in the years after gender discrimination was outlawed. It was found that certification of contraceptive use was required in 42% of protocols without explanation and in 36% of protocols because of the study drug used.[10] Almost 10% of protocols allowed no exclusions for contraceptive use (e.g. celibacy or sexual orientation). In addition, for the inclusion of women, up to four counter-signatures were required in some studies to confirm contraceptive use, whereas for men no signatures were required. The study concluded that access to studies by women created burdens that were disproportionate to men. Aspects of contraceptive requirements for studies that did not appear to have been considered by researchers or ethics committees included the risks of contraceptives, interference with drug metabolism by hormonal contraception,[11] that partners may be sterile, that fetal harm may also affect men, that the risk of fetal exposure to one dose of a drug was minimal and that women could make their own decisions.

A similar study in Sweden from 1997–1999 investigated why researchers excluded women from clinical trials.[2] The scientific reasons for excluding women were a lack of physiological data, repeat of studies that had previously used

only men so as to obtain comparable data, and the economic costs of research in women. This latter problem has been highlighted in a recent publication by the Society for Women's Health Research, where the guidelines advise that for research into sex differences the best standards for women are to use different hormonal states.[11] The economic costs of this 'gold standard' methodology have the potential to quadruple medical research grant costs.[12]

Another facet of gender bias in research is in the lack of incorporation of gender data into evidence-based medicine. For example, despite well recognized gender differences in coronary heart disease management in UK critical care units,[13] the UK NHS guidelines for management are not gender specific.[14] If research lacks or excludes female subjects then the guidelines should clearly state that the evidence has been obtained mainly from men. In addition, the context in which the evidence basis for medicine is drawn is also questionable because the factors that contribute to women's health (or lack of it) such as poverty and social deprivation will not be the same as for men. These differences need to be defined in order for guidance to reflect the social context of disease. Furthermore, the outputs of biased guidance can influence education, both in terms of what is taught (i.e. maintenance of the status quo) and who teaches it (e.g. gender bias in training) so that inequality is perpetuated.

In a recent NHS and Medical Research Council assessment of the causes and effects of socio-demographic exclusions of women from clinical trials, statins and non-steroidal anti-inflammatory drugs (NSAIDs) were investigated.[15] The two drugs demonstrated a dramatic difference in the gender of subjects included in trials. Whereas studies of NSAIDs reflected the population in which they were used, those for statins did not and only 16% of women were included in trials compared with 45% who were using statins. The authors of this study identified the neglect of gender issues in UK research and recommended facilitators to be identified to remove barriers to researchers and women. Including women in clinical studies recognizes that the population is not homogenous, research should benefit all people, protective policies may exclude the people most at risk and exclusion accords a lower status to women.

With the advent of gender medicine as a specialty that is developing across the world, a woman's reproductive status, menstrual cycle and contraceptive history has become significant in studying health, disease and pharmacology. In the UK we should seize the opportunity to implement best practices for health care research across genders and to establish gender specific evidence based guidance.

Competing interests AH is a researcher in gender-based research, is on the Medical Women's Fellowship Executive Committee and is the Deputy Chair of the British Medical Association Medical Academic Staff Committee.

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REFERENCES

1 Weisz D, Gusmano MK, Rodwin VG. Gender and the treatment of heart disease in older persons in the United States, France, and England: a comparative, population-based view of a clinical phenomenon. *Gend Med*. 2004;**1**:29–40

2 Soderstrom M. Why researchers excluded women from their trial populations. *Lakartidningen* 2001;**98**:1524–8

3 Rochon PA, Clark JP, Binns MA, Patel V, Gurwitz JH. Reporting of gender-related information in clinical trials of drug therapy for myocardial infarction. *CMAJ* 1998;**159**:321–7

4 NIH Guidelines on the inclusion of women and minorities as subjects in clinical research (1994) **59** Fed. Reg. 14508–14513

5 Light KP, Lovell AT, Butt H, Fauvel NJ, Holdcroft A. Adverse effects of neuromuscular blocking agents based on yellow card reporting in the UK: age and gender differences. *Pharmacoepidemiol Drug Saf* 2006;**15**:151–60

6 Simon V. Wanted: women in clinical trials. *Science* 2005;**308**:1517

7 Harris DJ, Douglas PS. Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *N Engl J Med* 2000;**343**:475–80

8 Marshall E. From dearth to deluge. *Science* 2005;**308**:1569–1572

9 Becker JB *et al*. Strategies and methods for research on sex differences in brain and behaviour. *Endocrinology* 2005;**146**:1650–73

10 Cain J, Lowell J, Thorndyke L, Localio AR. Contraceptive requirements for clinical research. *Obstet Gynecol* 2000;**95**:861–6

11 Anthony M, Berg MJ. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: part II. *J Health Gend Based Med* 2002;**11**:617–29

12 Brown BA, Long HL, Weitz TA, Milliken N. Challenges of recruitment: focus groups with research study recruiters. *Women & Health* 2000;**31**:153–66

13 Raine R, Goldfrad C, Rowan K, Black N. Influence of patient gender on admission to intensive care. *J Epidemiol Community Health* 2002;**56**:418–23

14 Doyle L, Payne S, Cameron A. Promoting gender equality in health. Equal Opportunities Commission 2003. http://www.eoc.org.uk/PDF/promoting_gender_equality_in_health.pdf (accessed 05/03/2006)

15 Bartlett C, Doyal I, Ebrahim S, *et al*. The causes and effects of socio-demographic exclusions from clinical trials. *Health Technology Assessment* 2005;**9**:Number 38