EGM/ST/2010/EP.12
September 2010
ENGLISH ONLY

United Nations Division for the Advancement of Women (DAW, part of UN Women)
United Nations Educational, Scientific and Cultural Organization (UNESCO)

Expert group meeting
Gender, science and technology

Paris, France
28 September - 1 October 2010

Sex and Gender Analysis in Medical and Pharmacological Research

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Gender is an essential determinant of social outcomes, including health. Besides, gender can be separated neither from biology nor from other social identifiers as ethnicity, culture, age or social economic class (United Nations,1995). The concepts of '*sex*' and '*gender*' are a face of the nature–culture debate, with the presumption that sex is unchangeable, whereas gender is constructed and can change. Recently, evolutionary psychologists have proposed biological explanations of behaviour by arguing that social constructions may have a biological origin (Taylor et al, 2000). The phenotype is the result of complex interactions between genotype and environment, leading to a lifelong remodelling of our epigenomes, and numerous dimorphic genes expression might be under the control of sex-specific epigenetic marks (Gabory et al, 2009).

Environmental factors (social behaviour, nutrition or chemical compounds including drugs), especially during crucial windows of life, can influence health and diseases, in a sex/gender-related manner. Thus, developmental programs, for each sex, may be more sensitive to specific environmental challenges either during developmental programming and gametogenesis or throughout the individual's life, as well as under the influence of sex steroid hormones and/or sex chromosomes. Variation in programming could thus lead to various defects and different susceptibility to diseases between males and females. Importantly, recent findings suggest that this epigenetic programming could be sometimes transmitted to subsequent generations in a sex-specific manner and lead to transgenerational effects (Gabory et al, 2009).

* The views expressed in this paper are those of the author and do not necessarily represent those of the United Nations.

Historically, *men have been the investigators*[1] *of and the participants*[2] *in health research*. Data arising from these studies, mainly conducted on men have been extrapolated to represent the experiences of both sexes (Uhl K et al, 2007; Franconi, 2007; Schiebinger, 2003). Nevertheless, it is indisputable that there are substantial biological and social differences in the lives of females and males. Despite the multitude of health inequity problems, little systematic research has been done on the social causes of ill-health.

Indeed, research has overwhelmingly focused on biomedical research at the level of individuals. Researchers focused on the health of groups and the determinants of health inequities that are outside individual control have received a smaller share of research resources and attention. Östlin and Paraje (unpublished data, 2004) scrutinized worldwide health-related scientific literature using the ISI database[3] for the period 1992–2001. They found that only 0.2% of the total of 3,361,298 health-related articles dealt with health and social connections. *Ignoring factors such as, race and gender leads to biases in both the content and process of research.*

The recognition of the differences and similarities between men and women can impact on the prevention, diagnosis, development of diseases and outcomes, and on the efficacy and safety of treatments (Legato, 2004; Franconi et al, 2007). Thus there is a need to put on a gender lens and to adopt a gender approach in experimental and clinical studies. The design and analysis must include a gender perspective in order to go beyond a rough evaluation of differences and similarities, and must take into account the fact that females are not a homogenous population and the relationship between gender and age. The design and analysis should also consider what happens to and around us. Thus, social relationships (Fig. 1) should be examined because *phenotype inevitably depends on the interaction of the individual with the environment* (stress response) (Kandel E et al, 1991; Kajantieand, Phillips, 2006).

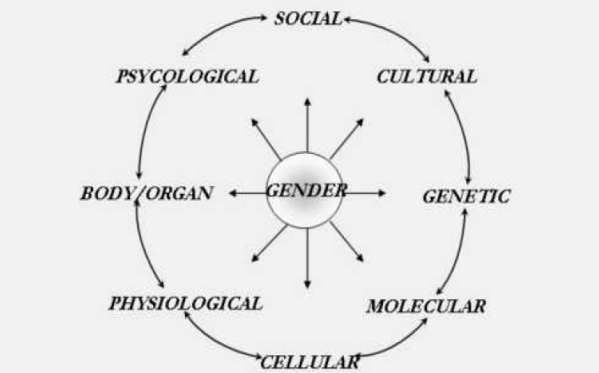

Fig. 1 Generators of sex-gender differences

Figure 1

For example, rat mothers behave differently versus female and male pups (Moore et al, 1986; Moore, 1992). Females synchronize estrous cycle when they live together, or when they smell male urine (McClintock MK, 1984; Novotny et al, 1999). Therefore, to assess which of the health disparities between sexes reflect inequities, research needs to analyse the complex ways in which biological and social factors interact. Research must also investigate the different experiences, behaviours, social norms and status of men and women that underpin health status, health-seeking behaviour and access to resources. Prevention, treatment, rehabilitation and care delivery need to be adapted and to take these factors into account. If they are not taken into account, they may adversely impact the health of both women and men, all the more so as there is, as already mentioned, *emerging and growing evidence that sex* (biology) *and gender*

[1] The fact that men have traditionally been the investigators has consequences because the gender of the researchers affects further issues such as research goals, experimental design, and interpretation of results which perpetuates gender biases. Men and women prefer maleness and masculinity, femaleness and femininity, respectively. While the number of women in research has increased, they still hold lower academic positions. It is important that the research team include both women and men, including in leadership positions, in order to reduce or to avoid inappropriate conclusions.

[2] The reason often given for excluding female participants in experiments is that the menstrual cycle introduces a potentially confounding variable into the study. There are also fears that experimental treatments or drugs may affect female fertility and expose fetuses to unknown risks.

[3] http://www.isinet.com/

(the social construction of masculinity and femininity) *interact constantly*, and that their interaction could be more complex than previously believed.

Publication bias

Publication in medical journals is an important measure of academic productivity. It is a criterion for academic promotion, and it represents an important communication process for the academic and scientific community. Additionally, it is also a means to get resources to produce and implement new research.

Rank bias

Recently, several journals have published special issues emphasizing the scientific, methodological, and ethical rationales for including sex/gender in research (Courtenay, 2001; Macintyre et al, 1996; Lawrence, Rieder et al, 2007; Prins et al, 2007), and new journals focused on sex/gender have emerged. However, these specific journals are poorly ranked (measured through bibliometric indexes such as impact factor), and therefore have little appeal for researchers, as publishing in lowly-ranked journals lessens their probability of obtaining academic promotions and research grants. Positive changes could occur when high quality and high impact journals are available in the field of gender research (Klinge, 2008).

Gender bias in authorship

Although women have made substantial strides in the past four decades, a gender gap remains among the authors of original articles in prestigious academic medical journals. The values that influence decisions about the selection of content for medical journals are largely determined by priorities in science, public health and commerce, but the composition of editorial boards is also important because it sends a signal to authors and readers about a journal's interests. It has been noted that editorial boards are mainly constituted by men (Kennedy et al, 2001; Keiser et al, 2003) which is substantiated by a survey showing that men occupy more than 80% of top leadership positions on these boards (Morton and Sonnad, 2007). This gender gap in authorship is particularly relevant among senior authors and editorial commentators. In the last years, however, an increase in women authorship has been observed (Jagsi et al, 2006).

Gender bias in selection: the chance of success

The existence of gender bias has been experimentally shown: changing the submitter's first name results in significant difference in the quality scores assigned to identical documents (Paludi et al, 1983. Steinpreis et al, 1999). Sex/gender differences are discipline-dependent. Women are in fact favoured in the exact sciences but disadvantaged in the biological and earth sciences, where women are more numerous.

Gender bias in funding

Women and men are, in fact, equally successful in acquiring grants (Gordon et al, 2009). However, there is significant gender difference in grant application behaviour at lower academic ranks (Waisbren et al, 2008). Although the number of women among students and faculty members has strongly increased, their representation on decision-making bodies, such as research granting agency committees or advisory boards, has not increased accordingly. However, increasing the proportion of female scientific advisers on decision-making bodies is not a guarantee that sex/gender will be included in mainstream health research. There is growing evidence of differential treatment of female scientists in terms of career opportunities, salary and as applicants for research funds and postdoctoral fellowships (Wennerås and Wold, 1997; Park, 2002).

Gender bias in education

Sex/gender awareness among doctors contributes to equity and equality in health, and helps achieve better health for both sexes/genders. Nevertheless, the gender determinant has been widely neglected by medical care providers. It is obvious that educating medical care providers plays a key role in overcoming the gender bias, yet gender issues do not enter into education and practice spontaneously. Neither research on women's issues nor the increase in the number of female students have resulted in transforming curricula (Verdonk et al 2009). Education influences gender bias because it can create an atmosphere of respect (or disrespect) towards women and minorities.

Gender bias in text books

Analyses of medical textbooks, education material, and examination questions have revealed stereotypical sex/gender patterns and even openly patriarchal views (Phillips, 1997; Lent and Bishop 1998; Alexanderson et al, 1998). Teachers have a responsibility to select appropriate literature and, if necessary, to offer complementary teaching material and methods. Sex/gender awareness in medical care providers contributes to equity and equality in health and aims towards a better health for men and women. Therefore, it is necessary to re-examine text books with a gender lens.

Gender bias in curricula

Medical schools and many other schools of care providers have been urged to revise their curricula to be more inclusive of sex/gender aspects of health. Both the *Report of a Survey and Recommendations on Women's Health in the Medical School Curriculum* (Women's Health in the Medical Curriculum, 1997) and the *Fifth Report of the Council of Graduate Medical Education (COGME) on Women and Medicine (*Council on Graduate Medical Education. Fifth Report, 1995*)* have highlighted the need for women's health to be integrated into medical education. The American Board of Internal Medicine has released a set of recommendations for medical educators based on "*the belief 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*" (Day et al, 1996, p. 375).

However, a successive survey revealed that few medical schools have fully incorporated sex/gender-sensitive education into their curricula (Henrich and Viscoli 2006). A survey on medical students' perceptions of the adequacy of women's health and sex/gender-specific teaching evidenced that curricula provided moderate coverage of the topic (Henrich et al, 2008). However to introduce sex/gender issues is necessary to overcome resistance created by the political-ideological connotations, to integrate many discipline going from molecular to the social aspects. Thus, *health care provider curricula should change to overcome gender inequalities in health and gender bias in medicine* by integrating sex/gender competencies. This would lead to gender-sensitive health services and equity in health.

Gender bias in research

Research team

The research team should include men and women. A heterogeneous composition could increase research quality by incorporating the different perspectives and approaches of men and women (Palich and Livingstone, 2003; Barjak and Robinson, 2008; Van den Brink, 2009; Cisco Systems, 2009, Evans et al, 2007).

In vitro studies: source of biological material

All somatic cells contain all chromosomes, including the sexual ones. Receptors for sexual hormones are present on a wide variety of cells. Thus, cells also have a sex. Although it is hard to examine the sex of cells, organelles, and cellular fragments, sex differences have been found in animal and human materials (Berkley, 1997).

Animal studies

Female mammals have long been neglected in biomedical research. As a consequence, our understanding of female biology is compromised. A recent survey shows that male bias is present in eight biomedical disciplines, with single-sex studies of male animals outnumbering those of females 5.5 to 1. (Beery and Zucker, 2010). The exclusion of females in much of non-human animal research limits our knowledge and the value of research. In consequence, it is crucial to change this situation.

It is important that international organizations such as the United Nations, the World Health Organization (WHO), regulatory agencies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and granting agencies adopt initiatives, similar to that of the National Institute of Health of the United States of America (NIH) which mandates enrolment of women in human clinical trials, and which recommends the inclusion of females in preclinical research. Sex-specific factors such as estrous cycle should also be considered (Becker et al, 2005; Johnson et al, 2009); so should the use of oral contraceptives, in view of their large human use. A female experimental group should always be treated with the association of estrogen and progestin drugs. The presence of different associations on the market could implicate that more than one specific association could be used. This point is particularly relevant considering the influence of hormones on drugs, on xenobiotic metabolism, and on same receptors (Franconi et al, 2007). Administration routes, dosing, and other pharmacotoxico-kinetic considerations should be taken into account because they can be sex-dependent (Franconi et al, 2007).

Little attention has been paid to how and when environmental and handling factors can influence experimental outcomes (Holdcroft, 2007) and even less attention has focused on sexual differences in these phenomena (Weedand and Raber, 2005). Significant changes in physiologic parameters related to stress and to the hypothalamic-pituitary-adrenal and the sympatho-adrenomedullary systems diverge by sex, as recently reviewed (Kajantie, Phillips, 2006). Further, complications arise from the fact that stress effects may diverge depending on the species, on the strain of animals, and on the kind of stressors (Kajantie and, Phillips, 2006). Thus, animal studies should take into account the potential role of environmental stress and gender differences, and include different species and the importance of diet.

Clinical research

Considerable sex and gender bias has been recognized within the field of medicine (Sims et al, 2010; Doyal, 2001, Phillips, 2006) encompassing many, if not all, diseases (Daly et al, 2006; Jindal et al, 2005; Raine, 2000; Herold et al, 1997; Chapman et al, 2001; Hariz et al, 2003; Nyberg et al, 2008). Despite the obvious relevance of sex differences to experimental outcomes, male research subjects continue to dominate biomedical studies as stated by the Nature editorial "Putting gender on the agenda" (2010). In most cases the bias is against women, but there are also reports about gender bias against men e.g. within research on depression and migraine (Olfson et a, 2001; Kempner, 2006). 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 (Kim et al, 2010). Given that evidence-based medicine is largely guided by the results of randomized clinical trials, the fact that clinical trial results are generalized to both women and men means that less evidenced-based medicine is applied to women (Lee et al,

2001; Gijsbergs van Wijk et al, 1996). It is, however, not sufficient to include both sexes in the sample; a gender analysis also needs to be carried out.

Regarding pharmacological treatments, a 2005 study of 300 new drug applications between 1995 and 2000 found that even those drugs that showed substantial differences in how they are absorbed, metabolized and excreted by men and women had no sex-specific dosage recommendations on their labels (Kim et al, 2010). This may be part of the reason why women are 1.5 -1.7 times more likely to develop an adverse reaction to prescription drugs than men (Franconi et al, 2007). However, it is unlikely that these drugs will be studied again. As many drugs are now generic (without patents), there is little economic incentive for studying them. To overcome this lack of knowledge, alternative strategies could be adopted, such as revising the original studies by retrospectively applying a sex/gender-based analysis (Johnson et al, 2009). The advantage of this approach is that it could be performed without lengthy time investments. It is important to recall that a sex/gender-based analysis is generally not applied in Cochrane systematic reviews on cardiovascular diseases (Doull et al, 2010). Moreover, a secondary analysis of data could be done when a gender analysis was not originally considered (Burns and Grove, 2001). The optimum would be the incorporation of sex/gender analysis at the beginning of a study, which would comprise both male and female animals.

Pregnancy

Although the Council for International Organizations of Medical Sciences clearly stipulates that pregnant women are eligible to participate in biomedical research, they are routinely excluded because of possible harm to the fetus.[4] This is ethically and medically unacceptable because pregnant women use many drugs, and they have the right to receive safe and effective care. Drugs should be studied in pregnancy, because the physiological changes induced by pregnancy make it impossible to calculate the appropriate dose and develop safety information by extrapolation from data on men and non-pregnant women. Thus, pregnant women often do not receive evidence-based medicine due to lack of information. Persuading pregnant women to take part in research can be difficult because of the perception that trials are riskier than taking prescribed medication (Baylis and Kaposy, 2010). *Correcting the current situation should become a priority.*

Gender bias in translational medicine

Translational medicine, which is currently defined as the translation of basic research into practical clinical applications, has great potential to develop and deliver new tools that may assist prevention, diagnosis, and treatment of disease. Before clinical trials are carried out, the safety and effectiveness of new drugs are usually tested in animal models (Sibbald, 2000).

The usefulness of animal testing has, however, been questioned because animal models are dissimilar to humans in numerous ways, which limits the generalizability of results to human biological systems (Croce, 1999). Discordance between animal and human studies could arise a) from the fact that many animal studies are of low quality (poor blinding, small groups with inadequate power, simplistic statistical analysis, selection of a variety of outcome measures, which may be disease surrogates or precursors and which are of uncertain relevance to the human clinical

[4] Thalidomide's teratogenic effects in the 1960s led the United States Food and Drug Administration (FDA) to examine the inclusion of females of childbearing potential in clinical trials. In 1977, the FDA issued the guidance ''General Considerations for the Clinical Evaluation of Drugs,'' which prohibited the participation of females of childbearing potential in Phase I and early Phase II trials (FDA, 1977). Females of childbearing potential could be included only after results from the preclinical and early Phase II trials showed the effectiveness of a drug on men, older women, or both (Sherman, Temple, & Merkatz, 1995). Although the 1993 study and evaluation of gender differences in the clinical evaluation of drugs (FDA, 1993) reversed the 1977 policy, women are not included in early phase trials in sufficient numbers.

condition etc; Horn et al, 2001), or b) from the failure of animal models to mimic clinical disease adequately (Franconi et al, 2008).

It is clear that there is a gender bias in preclinical test because male animals dominate the samples. There are, however, more subtle gender biases, such as the selection of disease models. For example, in humans, many gender differences have been described in diabetes mellitus. Diabetic women have a higher cardiovascular morbidity and mortality (Legato, 2004), whereas in rodent models, females became less diabetic than male (Franconi et al, 2008). It is extremely important to identify suitable animal models for studying gender differences in diseases.

Harmonization

Animal studies vary in methodological quality and sample sizes, rather than providing a single, definitive high-quality experiment for each intervention. For example, randomization and blinding are rarely reported. Methodological issues are important, given concerns about the differences between promising animal studies and negative clinical trials across a range of interventions. Animal experiments are part of the evidence used to decide which interventions are taken forward in clinical trials. Efforts to avoid bias are as important when reviewing the results of animal models as when reviewing the results of clinical trials. Klinge (2007) suggested to harmonize national statistics on animal use patterns so that rational priorities for reduction and refinement research can be identified internationally. National agencies in charge of drug registrations could apply such a regulation with regard to the conduct of animal and in vitro studies.

The harmonization of different regulatory tasks and different normative rules among countries appears to be necessary.

Future directions

Considering that sex is not a confounder but a basic biological variable, and that gender is a fundamental determinant in human health and diseases, there is a need to start considering sex/gender in all research phases. Sex/gender-based medicine could be the first step in offering true, personalized medicine that would consider individual differences.

Journals' duty to overcome the gender bias

a) Efforts should be made to attain parity of women leaders on the boards because a predominantly-male board would be focused on different goals and interprets the same results differently (Lawton et al 1997; Pierotti et al 1997; Robinson and Wise, 2003). Thus, *the presence of women should contribute to giving more attention to sex/gender aspects* because men and women mainly focus on males and females, respectively (Holmesand and Hitchcock,1997).

b) This could be of relevance in the choice of manuscripts that are published. The journal editors and reviewers should require specification of the numbers and ratio between the males and females studied. Generalizations from single-sex studies should be restricted to the sex investigated. Although adopting sex specification as part of journals' policy has been suggested in the past, few editors have responded to these exhortations. *Journal editors should adopt a mandatory policy for non-human animal research similar to that described in the instructions to authors of the Journal of the National Cancer Institute and Journal of Neurochemistry* (Wald and Wu, 2010).

c) *It would be useful for prominent medical and biomedical journals to dedicate a specific section to gender issues.* This could also help to overcome the chronic systematic imbalance between men's and women's problems observed in medical journals (Östlin et al, 2004). The slow recognition of women's health problems, the partial approaches to understanding women's and men's health, and

the dearth of information on how gender interacts with other social determinants continue to limit the content of health research.

Implementation in education
Until now sex/gender has not been well incorporated in health care provider curricula. As our understanding of sex/gender differences continues to expand, sex/gender-based medicine should become a primary consideration for all health care providers. Thus, curricula should change to overcome gender inequalities in health and gender bias in medicine through an integration of gender competencies, which would lead to gender-sensitive health services and equity in health.

Elimination of bias or ambiguity in selection criteria, and of barriers to returning to work after a break
This could help attain a critical mass of women in research, which in turn may increase the probability that existing research cultures will be transformed, and thus create a more conducive environment for sex/gender issues to be addressed in research.

Integrating women's input to research and policies, especially at high level
This could lead to the selection of different themes in research and to the adoption of different experimental design that may help to resolve gender bias, considering that women often have different priorities, needs, interests and resources (United Nations, 2002).

Overcoming potential pitfalls.
Gender research is complex, requires long-lasting evidence, and is full of potential pitfalls because there is not enough data and/or scholarly techniques to arrive at any conclusion. It is emerging that, in order to have results that can been extrapolated to humans and compare males and females, it is important to determine the age at which testing will occur, the time of the day, and the appropriate method of measurement of the trait. One must also know the diet or the housing condition before the testing. For female gestation, lactation and parity, the use of oral contraceptives should also be considered. Descriptive studies should be complemented with studies that try to elucidate the underlying pathways leading to observed health outcomes for both genders. When differences are found, further analyses should be required to explore the contributing factors. Detection of modest differences may require studies with more complex experimental designs, more complex model systems and more subjects to achieve statistical power, and thus may require additional financial resources.

It appears that the quickest action may come from the academic journals, which are moving toward adopting a common set of guidelines for studies using animals, which would require scientists submitting manuscripts to provide details including the sex of the animals, estrous phase, etc. Weighting data obtained from female animals and systematic reviews of animal experiments could be useful to determine similarities between animal models. It is accepted that systematic reviews of animal experiments could facilitate the translation of research findings from animals to humans (Macleod and Sandercock, 2005).

In summary, there is an urgent need for recommendations on the inclusion of female animals in experiments, and for guidelines on experimental designs that include a gender approach.

Identifying and understanding sex-based characteristics, particularly in the diseased state
This remains a great need in research at all levels, from the single cell to animal models to human subjects (Wald and Wu , 2010; Franconi et al, 2007).

Translation to the clinical practice

The usefulness of identifying and understanding sex/gender-related characteristics is undermined if the results of these endeavours are not translated to clinical practice.

Integrating social and biomedical sciences
The scientific community has evidenced numerous physiological and behavioral disparities between the sexes/genders, and they deserve to be integrated into research selection and design. In male and female mice, hundreds of genes have different expressions (Yang et al, 2006), suggesting that there is an inherent difference at the very basic level of our biological makeup. Moreover, these differences are influenced by sexual hormones, but they extend beyond sex hormones and involve imprinting (Tilghman, 1999), and developmental plasticity (Loizzo et al, 2010). The understanding of epigenetic factors in sex/gender differences should be enhanced in order to understand the degree of sex and gender interactions, and how they influence health and diseases.

Establishing sex/gender differences research centres
Sex/gender specific centres that encourage balanced representation of both sexes in preclinical and clinical studies are still critically needed. The centres should be characterized by an integration of different disciplines.

Implementing gender diverse research teams through a number of incentives
Diversity is linearly related to research quality. Because men and women have a different perspective and apply different approaches and questions into research, they can also be more creative.

Implementing gender-related research grants
This would be useful to encourage the scientific community to increase its efforts in understanding pathogenetic mechanisms of diseases, and to bolster gender-sensitive therapies.

Harmonizing normative issues among countries

Sensitizing the general public about gender issues
Gender blindness is pervasive among the general population, and is a barrier to overcoming gender bias. Gender issues should be taught from primary school, and should also include an emphasis on "great women", who tend to be neglected.

Acknowledgments. I wish to thank Drs. Walter Malorni, Anna Maria Moretti, Elisabetta Straface, Antonio Sassu for fruitful discussions and GISeG (Gruppo Italiano Salute e Genere) and SIF (Italian Society for Pharmacology) for their effort to implement a gender culture. I wish to thank the Ministry of Health "Ricerca Finalizzata 2007- Women Health " to Flavia Franconi.

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