

The paradigms of gender-specific research

Flavia Franconi¹

Abstract. In the opening section, the Author introduces the concepts of sex and gender, which have equal dignity and are considered as being associated in order to highlight their intricate, complex and long-lasting interactions: epigenetics would appear to have clarified the ways in which society modifies our biological body, removing the dichotomy between sex and gender. Starting from the fact that preclinical and clinical research was, in the past, primarily conducted on male subjects, some of the consequences of the absence of a gender perspective are analysed, such as a lesser appropriateness of treatment and a greater incidence of the adverse effects of medicinal products in women than in men. In addition to biological factors, environmental and socioeconomic factors are also considered: the example used is the role of caregiver, which is primarily covered by women, with heavy repercussions on their wellness. To conclude, the author discusses the hope that healthcare organisation assessment systems are developed using “gender-related” standards.

Gender-specific medicine is a new frontier that involves a new cultural and scientific awareness implicit to the term gender, because in addition to considering the person’s phenotypical similarities and differences, it considers his/her lifestyle, social, cultural and environmental context, occupational situation, etc., as these factors also significantly condition development, the evolution of disease and the possibility of access and response to treatment. It would also seem appropriate to point out that gender-specific medicine is recognised by the World Health Organisation, which, with the publication of its Equity Act (2002), highlights the importance of a gender-oriented approach to healthcare, before becoming a priority in 2013. Before going any further, it is appropriate to dedicate a little space to defining the terms “sex” and “gender”. The term “gender” indicates the influence of society and culture on a male or female body and is more extensively used than the term “sex” as it is considered to be more politically correct. On occasions the term “gender” was, and still is, used to indicate the female gender alone, which has produced, and continues to produce, a number of misunderstandings, however; it is now undeniable that gender-specific medicine considers

all genders, giving them equal dignity. Similarly the concept of “sex”, which refers to the biological differences between “male and female”, is not easy to define as studies on sexual determination and differentiation disorders show that male and female are a *continuum*¹. It is also important to realise that biological differences can be altered by gender and vice versa, which suggests that between sex and gender there are interactions that are both complex and constant, to the point that it becomes difficult to distinguish between their roles². The environment’s effect on genes, as shown by epigenetics, is sex-specific and varies during the course of life³. To conclude, epigenetics would appear to clarify the way in which society alters our biological body, removing the dichotomy between sex and gender that, in years gone by, caused lengthy discussions between the supporters of the supremacy of one or the other. Consequently, a number of authors, including that of this work, believe it is necessary to unite the two concepts using “sex-gender”⁴⁻⁶ to emphasise the intricate, complex and long-lasting interactions existing between sex and gender and in order to give the two concepts equal dignity. Precisely the superseding of this dichotomy has led to the need for complex new investigational paradigms making it possible to overcome reductionism in order to get close to the complexity of life.

Lastly, the many differences could be denied by the application of the principal of equality because, in line with the opinion of Nobel Prize-winner François Monod, the concept of equality in biology was “invented precisely because human beings are not identical”. Therefore, an abstract equalitarianism, that does not see the differences, can be translated as injustice. “Difference” is therefore a value to be conserved, so gender-specific medicine that exalts the differences is pervaded by the “equity” concept. It goes without say that the principle of equality is fundamental in the rights and opportunities field.

Gender-specific trials and therapy

Until just a few years ago, as far as medicine was concerned, the human race was composed more or less by just one gender, more precisely, the male gender. And

1. Head of the Social Policy Department, Basilicata Regional Authority; Department of Biomedical Science, Università degli Studi di Sassari.

yet epidemiology, the natural history of diseases, outcomes, etc. were, and still are, gender-specific^{4,6-9}. These differences are now starting to be noticed; however, in daily clinical practice women and children are still at a disadvantage, although with conditions such as osteoporosis, migraine and breast cancer, there are disadvantages for the male gender⁶. As already mentioned, the differences, or at least some of them, are known, but are often not translated into clinical practice, and therefore there is less appropriateness for women than for men. For instance, the differences in size and body composition (women are shorter and slimmer than men and have more adipose tissue, less muscular mass and a lower total water content than their male counterparts) have important consequences on the pharmacokinetic and toxicokinetic parameters of medicines and toxins^{6,10-12} and should, therefore, be considered when calculating the doses of medicinal products, whereas unfortunately, the mean dose is still calculated considering a Caucasian male weighing 70kg. The heart, kidneys, liver, brain, lungs, etc. are different in men and women⁶⁻⁷; these differences start in the uterus⁶ and vary with age. With this in mind, we wish to point out that antibiotic therapy during early infancy causes an increase in the body mass of boys, but not of girls¹³.

Besides biological factors, context also plays an important role in health and it is estimated that 24% of all illnesses are caused by unfavourable environmental exposure and social and economic factors, to the extent that it has been described as "status syndrome"¹⁴. More specifically, a lower financial and social status is associated with the onset of heart and metabolic diseases and this association is particularly significant for women¹⁵. Amongst the environmental factors that most affect women's health, we would like to recall the role of caregiver: a role that is primarily covered by women, which leads to a loss of wellness and a different response to medicines¹¹.

In order to adopt a gender-specific approach, it is necessary to also consider the investigator-research subject/doctor-patient relationship, because the gender of the investigator and/or physician also affects pharmacological response. For instance, diabetic women treated by female doctors are more likely to meet therapeutic targets than those followed by male doctors¹⁶. Treatment adherence is fundamental to pharmacological response and response to placebo, where gender would also appear to play a key role^{5,11}.

If we analyse what happened in an even very recent past, we see that preclinical and clinical research, with the exception of sex-gender-specific phenomena, was primarily, if not exclusively, conducted on male subjects¹². Indeed, preclinical research was conducted using primarily male animals and if we consider cell studies, we find that in 75% of cases their sex is unknown¹².

And yet, when they are studied, the differences are present, since cells can be different in various animal species, depending on the parameter that you study and on the cell and tissue examined¹⁷⁻¹⁸. Thorough analysis has shown that it is not sufficient to know the sex of animals or cells, because sex does not tell us anything about the environmental factors of the cell donor and the living conditions of animals¹². In other words, the concept of gender is not restricted to human beings, but must also be extended to the rest of the animal kingdom. Similar problems are present in clinical research, for example in trials for important cardiovascular medicines only 30% of the subjects enrolled are women¹⁹: and this is happening precisely in an era in which we talk of nothing but individualised medicine and evidence-based medicine.

This state of affairs may be responsible for the poorer safety profile of the medicinal products studied in women compared to their male counterparts^{10,11}. The greater incidence of adverse effects in women could be due to age, polytherapy - which is more frequent in women, because they prevail in the >65 years age range, overdose (as the mean dose is established considering a man weighing 70kg) and lack of clinical studies.

Women show a greater vulnerability towards certain adverse effects. For example, women are more prone to thiazolidinedione-induced bone fractures, lupus erythematosus induced by quinidine, hydralazine, etc., as well as long-QT syndrome induced by a great many drugs such as anti-arrhythmics, prokinetics, antipsychotics, antidepressants, antihistamines and antibacterials^{10,11,19} that can cause fatal arrhythmias because women, especially in the fertile age, have longer QT-intervals than men. The risk of adverse effects is also associated with depression, which affects females more than males⁶.

If environmental factors modify response to medicinal products, it goes without say that we need to implement protocols that take these aspects into consideration, as they play a central role in response to therapy. In order to develop these pathways, gender-specific research must consider the paradigms of intersectoriality, therefore adopting problem-solving strategies based on the ability to adapt, on pragmatism, on the adoption of the paradigm of complexity and, most importantly, on the operative definition of the concepts, factors and parameters attributed²⁰, therefore abandoning the dualistic or simplified use of sex and gender to avoid increasing the risk of confounding effects or reductionism²¹.

The application of a sex-gender oriented approach, in addition to contributing to appropriateness and the establishment of evidence-based medicine, may also help savings in the cost of treatment. Health expenditure is higher for women, even when we subtract the costs associated with pregnancy and childbirth²²⁻²³, which may be because they receive less appropriate treatments²⁴. Particularly important in this sense is the poorer safety

profile observed during pharmacological therapy. Indeed, adverse effects are, for both the individual and society, a loss of health that affects their quality of life, whereas for the community they represent a pointless waste of money. Therefore, the prevention of adverse effects in women is considered an instrument not merely of health, but also for money-saving that improves the sustainability of healthcare systems, without forgetting equity.

To conclude, we wish to point out that in order to produce health, to date the organisation of healthcare has been based on evidence-based medicine or on best practices; from now on it would appear appropriate for it to be based also on gender impact assessment in order to develop assessment systems using "gender-related" standards.

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Correspondence to:

Flavia Franconi

Dipartimento Scienze Biomediche,
Università degli Studi di Sassari
V.le San Pietro 43/C
07100 Sassari
email franconi@iol.it