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Journal of Pediatric and Neonatal Individualized Medicine 2012;1(1):43-48
doi: 10.7363/010110

Review

Gender differences: are there differences even in Pediatrics and Neonatology?

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Abstract

The approach to research on gender differences in an evolutionary context has always been complex. Many factors, from those initially linked to preliminary considerations about the differences between the sexes in different historical and cultural moments have often influenced studies of this type.

Gender Medicine, consolidated in the United States as a research field since the 1980s, studies the way in which membership in gender, male or female, affects the development and impact of disease and response to therapy. We can say that this is a new, transverse dimension of Medicine that assesses gender differences in physiology and pathophysiology of many clinical diseases, with the aim of reaching treatment decisions based on evidence in both men and women.

In an historical moment focused on the individualization/personalization of care, among the objectives that modern health care has been given, there is this research aimed at identifying as early as possible gender-related diseases with the aim of identifying causes and possible methods of intervention.

It leads to defining a kind of Medicine, a recent branch of biomedical science, that focuses on recognizing and analyzing the differences arising from the belonging to a gender, male or female, from several aspects: organic, functional, psychological, pharmacological, social and cultural.

A gender approach to Medicine can reduce the level of error in medical practice, promote therapeutic appropriateness, improve and customize therapies and generate savings for healthcare systems. These effects have been demonstrated for adults and need to be confirmed during infancy and childhood.

The purpose of this discipline is to innovate and guarantee everyone, man or woman, newborn and children, the best possible treatment based on scientific evidence.

Keywords

Gender Medicine, newborn, children, Neonatology, outcome, sex differences.

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How to cite

Tandoi F, Agosti M. Gender differences: are there differences even in Pediatrics and Neonatology? J Pediatr Neonat Individual Med. 2012;1(1):43-8. doi: 10.7363/010110.

Background

According to the principles of Gender Medicine men and women, for their biological diversity, also have different sensitivity to certain diseases and respond differently to certain treatments. It would seem a trivial consideration, but until now little attention has been devoted to these issues [1, 2]. Suffice it to say that no 'leaflet' of drugs includes different doses for males and females, while everyone knows that, for example, certain substances such as alcohol have a greater impact on women's metabolism than on men's (and it is not just a problem of weight) [3].

Studies to determine gender differences began years ago mainly on adults. The first systematic attempt to bring order into the chaos of research in this field was made in the subject of Psychology in 1974 by Maccoby and Jacklin. Summarising the results of over 1,400 empirical studies on 80 personality traits and cognitive abilities, the authors concluded that it was possible to see differences in a consistent way only in the following cognitive domains: language, in which women were considered to have greater competence, visual-spatial and mathematics, in which instead men were found to be more skilful [4, 5]. In terms of personality, men also appeared to be generally more aggressive than women, both physically and verbally [4, 5].

Subsequent studies have essentially confirmed these results by extending the analysis to more complex aspects such as attitudes, cognitive styles, interpersonal aspects etc. [6, 7]. However, these differences are not expressed exclusively in neurocognitive and psychological fields, but also in a broader context involving multiple organ systems in various organic and functional expressions. This diversity can be present in children even in the earliest stages of their life.

Moreover, the main scientific explanations of gender differences in a wider scope of psychological and somatic factors lead to biological factors: hormonal, genetic and evolutionary causes have been called into play to demonstrate that men and women are different in their structure not only the psychobiological basis of the Central Nervous System, but also in other parenchyma during the development and accretion phase, beyond the obvious physical and physiological differences [8].

This paper covers the main steps that led to defining the concept of "Gender Medicine" during adulthood and then extrapolate this concept also for newborn infants, children and adolescents, a field in which some issues are well known and others are being developed.

Over the years, medical research has identified an important group of diseases mainly of adulthood, and interesting several districts that have a higher expression in a gender rather than in the other. A short list of these diseases, an approach in which "gender" has meant a better understanding and better treatment, is described below.

Cardiovascular disease/infarction

Cardiovascular disease (atherosclerosis, infarction) has always frightened men more than women. But it is a mistake, since 38% of women who have a stroke die within a year, compared with 25% of men. Even in the case of stroke, the following 12 months are at greater risk for women (25%, versus 22% of men) [9].

The incidence of some diseases is also linked to ethnicity as well as gender and age and only complex analyses are able to evidence these points. In white populations for instance, age appears to modify the effect of sex on stroke risk, and compared with men, women are protected from stroke until approximately the age of 75 to 85 years, after which the protection is lost or reversed. Compared with non-Hispanic whites (NHWs), Mexican Americans (MAs) are at higher risk of stroke; however, age- and sex-specific stroke incidence data are currently not available for this population. This analysis found that among both NHWs and MAs aged 45 to 79 years, men were at higher risk of stroke than women. The magnitude of increased stroke risk in men compared with women diminished with age, and after age 79 years, no sex difference in stroke risk was observed [10].

Women appear to be less able than men in recognizing in time the main alarm bell of infarction, angina pectoris, since the symptoms present differently from in men. In manuals of Medicine it is typically described as chest pain at the sternum, oppressive, constrictive, of short duration, which may radiate to the left arm. According to the WISE (Women Ischemic Syndrome Evaluation study of the U.S. National Institute of Public Health), in women the symptoms that appear first are a pain radiating to the shoulders, back, neck, shortness of

breath, persistent nausea, sweats chills, vomiting, fatigue, anxiety and weakness. Operators who are not aware of these differences do not recognize these symptoms, or they trace it back to the flu or other gastrointestinal problems. Consequently admission is too late, or perhaps not treated in coronary care, making therapies less effective [9].

Atherosclerosis

Atherosclerosis in women has a different development. In men, the atherosclerotic plaques begin to form starting at the age of 30, while in women this usually occurs after menopause. During the childbearing years the female body is protected by estrogens, which act on the dilation of blood vessels, making them wider and more elastic and thus allowing the passage of blood even in the presence of plaques and facilitating redress for injury. With menopause, however, this hormonal protection wears off and the body is suddenly exposed to all risk factors [11].

Diabetes

This metabolic syndrome has a prevalence of 60% in women over 65 years of age. In general, women with diabetes have a poorer quality of life and a shorter life expectancy.

From the point of view of cardiovascular complications, diabetes can be considered the most dangerous: the risk of cardiovascular death is more than double for women than men. A fifty-year-old diabetic woman lives on average 8.2 years less than one of the same age without diabetes, compared with 7.5 years for men. Some forms of diabetes affect women in a "sensitive" phase of their lives such as pregnancy or menopause: in 50% of women with gestational diabetes this develops after 5-10 years as type 2 diabetes [12].

Asthma

The prevalence of this disease has a double trend: before puberty, men are affected two times more than women. After sexual development, this difference disappears; even among adult women asthma is more common than in men. The 'overtaking' is due to hormones: estrogens, in fact, regulate the release of several proinflammatory molecules (cytokines) involved in the outbreak of the asthmatic reaction. Menopause is also a risk period: when the ovaries begin to cease their functions, there is an increase in spontaneous production of cytokines, resulting in a worsening or even an onset of the disease [13].

Lung cancer

At the beginning of the last century, lung cancer was a rare disease in women. It began to spread among women since the 1960s, partly because of the spread of smoking. When compared with men, the lungs of women, even non-smokers, are more vulnerable to cancer. Even in the case of lung cancer, as well as in that of breast cancer, hormones – especially estrogens – play an important role. In more fertile women the disease is more aggressive; contrary to what occurs in the case of breast cancer, the number of pregnancies represents a negative factor: women who have had more children appear to be at higher risk of developing the disease [14].

Parkinson's disease

Parkinson's disease is 1.4 to 2 times more common in men than in women. A study conducted in 2003 by Kaiser Permanente in Oakland (CA, USA) shows an overall rate for males 91% higher than women: 19 cases per 100,000 men, against 9.9 cases per 100,000 women [15]. Although less affected, women complain in general about greater disability and a poorer quality of life. The disease has a similar course in both sexes and there are large differences in the duration. The extended incidence in males is probably due to genetic factors (a link has been shown between the disease and a mutation of certain genes on the X chromosome, of which men have only one copy), hormonal factors (estrogens may also protect women) and environmental factors (men are more exposed to toxic substances) [16].

Peptic ulcer

The two sexes appear to be affected by different forms: gastric ulcer is more common in women, while men suffer more from duodenal ulcer. Before the twentieth century, the disease was diagnosed mainly in males. But today we have moved to a substantive equality: a decline is especially the case in young males, but it increases in older women. One of the causes must be sought in an increase in smoking by the female population and the simultaneous decrease in the spread of cigarettes among teenagers. In addition, the growing use of nonsteroidal antiinflammatory drugs. of which

women are large consumers, may have contributed to this phenomenon. Finally, the change in social patterns, with an increasing number of working women, may have determined their increased stress, which is also an important factor in the development of the pathology. In women, however, peptic ulcer disease has a better course.

Moreover, young women have a better chance to heal than men of similar age. What gives women the advantage are, once again, hormones, as demonstrated by the fact that the incidence in duodenal ulcer, for example, increases considerably after menopause, when the protective action ceases, while it decreases in pregnancy, when hormones are maximally expressed [17].

Pain management

Another important chapter in Gender Medicine is the study of pain: chronic pain, in Italy, affects 26% of the population, of which 56% are women. Under 18 years of age 19.5% of boys are affected and girls as much as 30.4%. Apart from the numerical point of view, pain also assumes different characteristics in the two genders: migraine, headache, muscle tension are more frequent in females, while cluster headache is the most common form of chronic pain among men. Some experimental studies appear to link this different pain sensitivity to hormonal factors, and indeed results are obtained in animals by raising or lowering the threshold of pain by administration of estrogens (female hormone) and testosterone (male hormone) [18].

The role of women

The evidence shows that men and women fall ill in different ways and that the same disease may have a different impact on them. Women live longer, but they get sick more and use more health services. This is called the "woman's paradox": although women live longer than men, they bear the burden of more years of unhealthy life. Furthermore, compared to men, women are affected more frequently (1.5 to 1.7 times) and more heavily by the side effects of therapies. This depends on many factors, including the fact that drugs are rarely studied for women, although they are the largest consumers [7, 18].

Over the last sixty years, the role of women in the society has undergone profound changes, but this has unfortunately coincided with a deterioration of their health. In addition to diseases that affect women more classically and more frequently (osteoporosis, allergies, diabetes) those that once were considered typical of the male gender have increased. While having a longer life expectancy (the average lifespan is 84 years for women and 79 for men in Italy), women report worse health than men. According to the Italian National Institute of Statistics (ISTAT) data in 2008, 8.3% of women felt their health was poor, compared with 5.3% of men. To confirm this, women are the most avid consumers of drugs (20-30% more, mainly aged between 15 and 54 years), resulting in greater exposure to adverse reactions and side effects [19, 20].

Gender Medicine in children

Thus, dealing with Gender Medicine today, beginning particularly with children, means proposing the ambitious goal of predicting the risk of developing a given disease in one sex rather than the other by devising appropriate preventive strategies and treatment on the basis of a personalization of care, which will also impact favourably on the economic management of public health.

The concept of Gender Medicine in the neonatal age has been known for at least 40 years; it was introduced by Naeye under the name of "hypothesis of the male disadvantage" [21] which describes the increased perinatal mortality in males compared with females. Data on neonatal mortality are expressed from different sources. A recent report by the Center for Disease Control and Prevention (CDC) has highlighted the difference between male and female mortality at birth (7.44 vs. 8.6 per 1,000 live births out of a total of 2,104,663 male live births and 2,007,392 female live births) [22]. In any case, the "male disadvantage" can be defined, as already reported in literature, as the increased risk of males to be born prematurely and their greater ability to develop pathologies such as respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), chronic lung disease (CLD) and brain haemorrhage. In a recent analysis male sex was significantly associated with higher birth weight, death or oxygen dependency (72% vs. 61%, boys vs. girls), hospital stay (97 vs. 86 days), pulmonary haemorrhage (15% vs. 10%), postnatal steroids (37% vs. 21%), and major cranial ultrasound abnormality (20% vs. 12%) [23].

Other works underline gender-specific responses to perinatal and neonatal events and exposures explaining the male disadvantage in early childhood outcomes. According to the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, infants born 1/1/1997-12/31/2000, < 28 weeks, were evaluated with

a neurodevelopmental follow-up at 18-22 mo corrected age. Neurodevelopmental impairment (NDI) was one or more of the following: moderate-severe cerebral palsy (CP), Bayley Mental (MDI) or Psychomotor (PDI) Development Indices < 70, deafness or blindness. Boys (n = 1,216) were more likely than girls (n = 1,337) to have adverse outcomes (moderate-severe CP: 10.7% vs. 7.3%; MDI < 70: 41.9% vs. 27.1%; NDI: 48.1% vs. 34.1%). Major risk factors were also more common in boys. Independent multivariate associations of risk factors with outcome differed by gender, but not consistently in favour of girls. In multivariate models including both girls and boys, the male gender remained an independent risk factor for MDI < 70 (2.0, 95% CI 1.6-2.5) and NDI (1.8, 95% CI 1.5-2.2) [24].

These differences, in addition to being known for some time now, are still being revaluated and are not always are expressed in literature with the same homogeneity. Recently, a study conducted in the Austrian Tyrol in the period between 2003 and 2008 on 42,301 newborn infants, showed some differences between the sexes, although not always supported by statistical significance in favour of female sex (mortality, incidence of birth < 32 weeks gestational age) [25]. However, this study indicates greater statistical significance for the lower frequency of early sepsis and less need for steroid treatments for CLD in the female sex [25].

However, the most striking results are highlighted after discharge. An analysis of short-term morbidity, expressed as an index of rehospitalisation in the first two years of life, shows strong significance of readmissions of preterm males in the first year of life and in any case in favour of males on the whole sample. Girls were admitted less because of respiratory infections during the first two years of life, while males showed a greater number of admissions for surgery for inguinal hernia during the first year of life [25].

During the follow-up conducted in the first 24 months of life no particular disadvantage of males against females emerged for both aspects of neurobehavioural and sensory impairment (deafness and blindness), and cerebral palsy.

What is even more interesting in this article is that, not always in line with the current literature, some aspects of gender differences in favour of the female population are resized (Apgar scores, need for intubation/surfactant, incidence of PDA haemodynamically significant) or are not so apparent as before. The explanations may be the positive effects of antenatal steroids on neonatal outcome, gestational age at birth > 28 weeks, the type of study (prospective) and the relatively recent recruitment period in which it was made (in comparison to many studies, including recent periods for which recruitment is extended from 80 years to the year 2000) [25].

Similar studies, but in children, were also produced in Italy with a significant deterioration in the social and economic aspects. A recent analysis of the general data related to access to the emergency room of the Bambin Gesù Hospital in Rome showed that for the year 2010 the access of male patients was higher than female patients (25,366 against 19,959, + 27%), evenly spread over all ages. These data tend to show more attention to social/familial male child health, as taken from literature. The analysis of access to pathology showed a clear female prevalence for certain diseases (headaches, poor nutrition, chronic pain) than male, more affected by trauma (head injuries) [26].

As demonstrated for adults, a gender difference regarding the metabolism and side effects of certain drugs exists even in the developmental age, although at the moment such a difference is difficult and not always well demonstrated. It is clear that the approach appears to be influenced by a number of factors depending on age, type of drugs, the receptors and the type of tissue in which it is metabolised. However, there is also a strong impulse to further research [27-29]. An approach based on gender also includes the update of some essential tools for epidemiological studies in Neonatology. Currently, the Vermont Oxford Network does not provide a breakdown between the sexes and that, in view of this, it is desirable.

Conclusions

The development of knowledge employs many indicators to measure both process and outcome. The indicators should be used in programmes and policies, in the collection of epidemiological data and the demographic and statistical evaluation of results. Gender Medicine, also in children, can become an area where these tools can be validated and therefore easier to use. In the field of Neonatology however, based on recent estimates, the indicators used up to now are still unable to express unequivocal results.

The trend of a "weakness" intrinsic to the male remains, although it would appear redimensioned and otherwise related to geographic factors, antenatal care and gestational age at birth. The post-discharge period, however, remains a critical period in males, born preterm and at term, mostly in the first year of life when respiratory tract infections and trauma interfere with their health status.

Gender Medicine surely helps in looking ahead and planning major financial commitments in prevention. It also represents an efficient response to the needs of a healthcare system guaranteeing high standards of health care and meeting the needs and expectations of users, also determined by sex and gender. This was done for adults and it should also be valid starting from the earliest periods of life. At present, further studies are needed to determine appropriate interventions to gain an understanding of (and thus reduce) gender differences, thus integrating all the best resources for the health of citizens.

Declaration of interest

No conflicts of interest exist.

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