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State of the art and prospects of gender medicine during the Covid-19 pandemic

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During the last conference of the Italian Epidemiology Association, held from 2 to 6 November 2020, the working group on Gender Health and Medicine, formed in those days, in collaboration with the national Center for Gender-Specific Medicine of the Italian National Institute of Health, organized a webinar on the state of the art and the prospects of gender medicine during the Covid-19 pandemic.

Gender medicine represents an interdisciplinary dimension of medicine, drawing attention to the study of the influence of sex and gender on human physiology, pathophysiology and pathology. With the approval of the Plan for the application and dissemination of gender medicine, in June 2019, the concept of 'gender' in medicine was introduced for the first time in Italy, as an assurance of appropriate and personalized treatments to be consistently provided nationwide. The Covid-19 pandemic affected the population in a different way depending on gender, and during the webinar the main gender differences found were presented, from biological mechanisms to epidemiological data.

The following experts gave their contribution to the webinar: Alessandra Carè and Elena Ortona, from the national Center for Gender-Specific Medicine of the Italian National Institute of Health in Rome; Eliana Ferroni, from the Veneto Regional Epidemiological Service, Azienda Zero; Patrizio Pezzotti, from the Department of Infectious Diseases of the Italian National Institute of Health; Isabella Tarissi de Jacobis, from the Bambino Gesù Pediatric Hospital in Rome; Cristina Mangia, from the CNR Institute of Atmospheric and Climate Sciences; Emilio Gianicolo, from the Universitätsmedizin in Mainz, Germany.

With gender medicine, the concept of "patient centrality and care personalization" is strengthened. Starting from this important point, Alessandra Carè began her introductory report on gender health and medicine, underlining the importance of taking into account gender differences at all levels of medicine, from the experimental stage to preclinical and clinical studies. Although the need to include balanced numbers of subjects from both sexes in clinical studies has been stressed, women remain underrepresented, particularly in the early phases of clinical trials, despite their bodies reacting differently than their male counterparts in many cases.

Indeed, women have a higher life expectancy at birth, although years gained are often lived with disability. Furthermore, due to their lower body weight, higher percentage of fat mass and reduced plasma volume, women have a different profile of absorption, distribution, metabolism and elimination of drugs, which determines a different response to therapies.

In addition, most of the clinical conditions show a different incidence in males and females, as well as the course of the disease. In some cases, symptoms are different, such as in myocardial infarction. Cancer generally affects men more than women, showing also a different location, as in the case of the colorectal tumor, often affecting the distal tract in women, but the proximal one in men. This difference may influence the validity of the standard screening by the fecal occult blood test: in this test, distal tumors could in fact give false negatives more frequently than the proximal ones, causing a diagnostic delay, and a worse prognosis.

These important differences between men and women show a different impact on the healthcare system, in terms of complexity of care and burden of disease. Eliana Ferroni, in her lecture on gender differences in epidemiology, showed how for some chronic conditions the disease burden is different according to gender. Chronic obstructive pulmonary disease (COPD) and diabetes are more frequent in men, and so the impact on the use of healthcare services is mainly driven by men. Women instead consume more healthcare resources for being cared for heart failure and dementia. A stratification by gender should be carried out in any epidemiological analysis, in order to highlight any differences that, otherwise, could not emerge. Currently, two of the main outcome assessment programs in Italy, such as the *Programma Nazionale Esiti* and the *Progetto Bersaglio* present indicators' data without carrying out any gender analysis. In the international context, the issue of gender differences is very relevant, and in many countries, epidemiological data are usually presented stratified by gender. In 2010, an EU agency – the European Institute of Gender Equality (EIGE) – was established, with the aim to eliminate gender inequalities in all sectors, including health, education, and work.

Data disaggregated by gender are important, because they allow developing tailored health policies, meeting the health needs of the population. For this reason, achieving 'gender equality' in epidemiology is a critical goal.

The Italian National Institute of Health, as part of the reporting activity of the Covid-19 integrated surveillance system, routinely carries out epidemiological analyses from a gender perspective. In his report, Patrizio Pezzotti presented a series of analyses of the incidence, hospitalization and mortality data for Covid-19 stratified by sex, highlighting some important gender differences. At the start of the first wave of the epidemic, the weekly trend in the number of cases showed a greater number of positive cases diagnosed in women than in men, due to the presence of more women in nursing homes. This gender difference then gradually disappeared, and from June onwards the weekly trend in the number of cases was similar in both sexes.

The number of diagnoses in women in Italy is slightly higher than in men. This difference, although mini-

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mal, still increases slightly in a model which, starting from the expected fatality rate, estimates the number of infections that have occurred. Even the estimated incidence rate of infections is in any case higher in women than in men. In addition, women with infection have a higher median age than men, which also reflects the higher percentage of females among the elderly.

In comparison with the resident immigrant population, it emerged that the percentage of positive cases is higher in women from some specific Countries, a phenomenon that could be explained by professional exposure (eg., caregivers and health care workers). In general, regardless of the Country of origin, men are increasingly at risk of hospitalization, present a higher number of accesses to intensive care, and have a higher mortality, particularly in the population over the age of 50.

Finally, an interesting analysis that evaluated the association between deprivation index and Covid-19 infection showed how in this second wave the incidence and mortality are higher in the most deprived areas; the deprivation index being the same, no gender differences are observed.

In her report on the differences between women and men in Covid-19 in relation to biological mechanisms, Elena Ortona focused on the biological mechanisms that could partly explain the sex differences observed in the Covid-19 data. The biological differences may be related to the expression of the ACE2 receptor and the TMPRSS2 co-receptor, which are affected by hormonal factors and by mechanisms of genetic and epigenetic regulation. SARS-COV-2 enters cells by binding to the ACE2 enzyme, which is expressed on several types of human cells, including lung epithelial cells. In the lungs, ACE2 plays a protective function from the damage caused by inflammation, fibrosis and oxidative stress. When the virus binds to ACE2 and enters the cell, it 'engages' it, thus limiting its protective function. Since estrogens induce an increase in the expression of ACE2 and the specific gene for this receptor is expressed on the X chromosome, it is possible to hypothesize a higher expression of ACE2 in the pulmonary epithelium of women, who would therefore be more protected from acute respiratory syndrome. TMPRSS2 expression is also modulated by sex hormones. Other factors that regulate the expression of ACE2 and TMPRSS2 are some microRNAs, whose expression in many cases is regulated by sex hormones. Another relevant aspect that can contribute to sex differences is the stronger immune response in women than in men. Finally, several studies have highlighted hypovitaminosis D as a risk factor for Covid-19. However, the anti-inflammatory effect of vitamin D is different in the two sexes, with it being more effective in women, due to estrogens. In conclusion, the study of the molecular mechanisms underlying the sex differences in Covid-19 will allow to identify new prognostic and predictive markers and new sex-specific therapeutic targets.

Isabella Tarisi De Jacobis, in the report on gender differences of Covid-19 in pediatric age, underlined how the available studies have shown that children get sick less frequently, contract the disease in a milder form and have a better prognosis than adults. In children, there are more symptomatic and/or paucisymptomatic forms and symptoms – when present – are comparable to those in adults for the respiratory picture, but show more frequently the involvement of the gastro-intestinal system. Pediatric Covid-19 occurs predominantly in males. The hypothesis about the best prognosis in boys and girls appears to be related to their immune systems. Children exhibit a different adaptive immune response. The reduced maturity and function of ACE2 and its lower expression in the nasal epithelium could explain the reduced susceptibility to Covid-19. In a retrospective study of a population admitted to the Bambino Gesù Hospital, it was found that females were hospitalized for longer periods and treated with more drugs than males. Males had higher inflammatory marker values and were more susceptible to thrombocytosis.

In her lecture 'Sex/gender and Covid-19: what data say and do not say', Cristina Mangia and Emilio Gianicolo presented Covid-19 data by sex and age in Italy, Germany, Spain and Sweden, Countries that have implemented different containment policies. Women are most vulnerable to infections between the ages of 30 and 60. Lethality is higher in men than in women. The ratio increases in the lower age groups, in support of the hypothesis suggesting the presence of hormonal protection mechanisms in women of childbearing age. The general mortality data observed/expected in Italy in the period March-May 2020 compared to 2015-2019 shows a comparable excess between the two genders, with a standardized mortality ratio of 132 among men and 127 among women. These differences highlight the need to better understand the interaction between gender and age both for epidemiological surveillance and for a better gender appropriateness of the current prophylactic and therapeutic treatments. However, surveillance is only possible if all indicators (symptoms, past conditions, primary and hospital healthcare, hospitalization) are published by age and sex. The analysis of the specific causes of death could help explain the increased mortality among women, who seem to be characterized by a lower lethality from Covid-19.