Gender differences in rheumatology and the point of view of the Italian Society for Rheumatology (SIR)

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Introduction

Gender differences in the prevalence of rheumatic diseases (RDs) are well described. Data highlight the very high gender bias towards females for systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) (9 : 1 female/male ratio). Rheumatoid arthritis (RA) is also more common in women, who are two to three times more prone to develop the disease than men. For other RDs, such as ankylosing spondylitis (AS), the prevalence favors males. While the gender differences are well established, the origin of these differences is still not fully known. Differential immune regulation, X-chromosome gene dosage effects, sex hormones, and sex-specific exposure to environmental factors are all implicated to contribute to these sex differences[1]. A growing body of evidence shows that the clinical profiles of women and men with RDs are markedly different, suggesting a need to tailor disease assessment and treatment approach.

Reproductive issues

Moreover, most RDs mainly affect women during the reproductive years, therefore the discussion of reproductive issues with patients is a crucial point.

Fertility of women with RDs seems to be reduced compared to healthy women of a similar age. However, the underlying cause is not clear and seems to be multifactorial and related to disease activity, therapy, impaired sexual function and personal choices. Very limited information is available on fertility in male patients with RDs. Data on the effects of anti-rheumatic drugs on fertility are scarce in both women and men[2].

In female patients, special concerns include the effect of pregnancy on maternal disease, the impact of disease activity on fetal health and the safety of medications during pregnancy. Patients with RDs can experience a flare during pregnancy. However, the risk of flare in pregnancy and the flare rate differ among RDs and depend on type of disease. RA and chronic arthritis, such as polyarticular juvenile idiopathic arthritis (JIA), tend to improve spontaneously during pregnancy in the majority of patients, though less frequently than described in the past. Spondyloarthritis (SpA) tends to be stable or to get worse during pregnancy, even though the available literature is scarce. SLE can flare in up to 50% of pregnancies, including a major organ involvement in nearly 25% of the cases. The effect of other connective tissue diseases on pregnancy or *vice versa* has been less investigated. Pregnancy does not seem to worsen the activity of systemic vasculitis, but a disease flare during pregnancy can lead to severe complications. On the other hand, pregnancies in some RDs, such as SLE and anti-phospholipid syndrome, are characterized by an increased incidence of fetal loss, prematurity and intrauterine growth restriction. In addition, the presence of anti-Ro/SSA and anti-La/SSB antibodies can have harmful effects on the fetus. For these reasons, maternal counselling is a key point to ensure the optimal timing of pregnancy (remission or stable disease in the previous 6 months), complete autoantibody profile, comorbidity assessment and drug adjustments[3].

The effect of gender on clinical presentation and progression

As well as prevalence varying with gender, the severity of RDs, meaning the severity of symptoms and the degree of disability, may also differ between males and females. However, taking into account the low prevalence of each disease in the general population, this cannot be easily defined. According to the analysis of two independent cohorts of incident primary SS, a Swedish one and an Italian one, around half of the male patients presented with more than one extraglandular manifestation at diagnosis, supporting the conclusion that SS in men represents a more severe form of disease, regardless of the lower risk for men to develop it[4].

A meta-analysis investigating studies with a total of 11.934 SLE patients found renal involvement, serositis, pleurisy, thrombocytopenia, and high titer of anti-double stranded DNA antibodies to be more frequent in male patients[5]. Another large meta-analysis added an increased ratio of seizures in male patients as a result of neuropsychiatric involvement[6]. An American study demonstrated greater disease severity in male SLE patients. In particular, male patients were more likely to suffer renal and cardiovascular co-morbidities while female patients were more likely to suffer from urinary tract infections, hypothyroidism, depression, esophageal reflux, asthma, and fibromyalgia[7].

Increased mortality in a large multicentre international cohort of SLE patients was reported to be associated with female gender[8]. Similar observations were documented in a Spanish population[9]. Among chronic arthritis, RA seems to be more severe in women, who show higher baseline disease activity and disability scores and lower rates of remission, as described by several studies[10-14]. Despite overall higher disease activity, the majority of published studies did not report any difference in radiographic progression of RA by sex.

In axial SpA (axSpA), though the studies are limited, and some are inconclusive, the general trend shows gender differences in pain distribution. Among women, back, neck, knee, and hip pain appear to be more common, whereas foot and joint pain are more common among men[15,16]. Differences in extra-articular manifestations have also been reported; enthesitis and inflammatory bowel disease appear to be more prevalent in women and acute anterior uveitis is more prevalent in men. Furthermore, compared with men, disease burden is higher in women and the quality of life is significantly lower. However, radiographic progression appears to be more severe in men compared with women. Overall, women are reported to have greater disease activity and worse functional decline, despite fewer radiologic abnormalities compared with men[15, 16].

The effect of gender on comorbidities in rheumatic diseases

While data suggests that gender can influence the clinical profile and progression of RDs, it is important to note that comorbidities may significantly alter the course of disease. In the GENIRA study, a project aimed at studying gender differences in RA patients and how these differences impact on patient outcomes, seventy RA patients of each gender were evaluated cross-sectionally. Women with RA presented significantly worse disability and quality of life outcomes as compared to men. However, these differences could be explained by female gender-associated comorbidities such as depression and osteoporosis rather than gender *per se*[17]. In an American cohort of gout patients, women were older, had a greater burden of comorbidities and a different risk factor profile as compared to men (women more often taking diuretics, men more frequently had dietary triggers)[18]. A large Swedish population-based study showed that all patients with gout had a higher occurrence of comorbidities at the time of the first diagnosis, compared to matched controls from the general population. The majority of these comorbidities were more common in women than in men, and, in particular, diuretic use and obesity[19].

The effect of gender on the perception of disease

Perceived differences in severity appear to be a fertile area for behavioral differences as one of the causes of gender disparity in RDs. The different severity of disease activity in RDs could be related to a different perception of the disease. In fact, it has been described that women report more symptoms and poorer scores on most questionnaires[20], including scores for pain[21], depression, and other health-related items[22,23], potentially affecting disease activity measure and amplifying gender disparity in RD phenotype.

In a large international study in SLE patients, gender differences in disease-specific quality of life were evaluated. While men performed worse in the social support domain, women, especially those in the reproductive age group, scored worse on domains related to lupus symptoms and procreation[24].

The effect of gender on treatment

In contrast to the well-established gender differences in the prevalence of RDs, there is no evidence that men and women metabolize anti-rheumatic medications differently. Data from several European registers showed a lower percentage of response to tumor necrosis factor inhibitors (TNFi) and a greater discontinuation rate in female RA patients versus males[25-29]. Also in axSpA, the efficacy of TNFi has been reported to be significantly lower in women as compared to men[30]. Predictors of TNFi treatment response, including the presence of HLA-B27, the absence of enthesitis, short disease duration, and being naive to TNFi are negatively associated with female gender. The higher percentage of body fat in females and the influences of female hormones have also been thought to influence response to TNFi. Furthermore, compared with men, adherence to TNFi is lower and switching of TNFi is higher among women[30]. Despite the higher burden of axSpA in women, these differences may help to explain the reduced treatment response and poorer outcomes of women with axSpA.

There are, as of yet, no gender-specific treatments. On the other hand, there are special issues for female patients, because of the risk that drugs may have in terms of reproductive side effects and/or excretion into the breast milk with passage to the child during breastfeeding. Based on a systematic literature review and pregnancy exposure data from several registries, European League Against Rheumatism (EULAR) statements on the compatibility of anti-rheumatic drugs during pregnancy and lactation were recently issued[31].

The point of view of the Italian Society for Rheumatology (SIR)

In recent years, gender medicine has emerged as a new approach, aiming at recognizing and analyzing gender-based differences in several aspects: anatomical, physiological, biological, functional, social, and response to treatments[32].

In 2016, the "Gender Medicine" Study Group of the Italian Society for

Rheumatology (SIR) was established to study how RDs differ between men and women in terms of prevention, clinical signs, therapeutic approach, prognosis, psychological and social impact. Special attention has been focused on reproductive issues, such as pregnancy and breastfeeding. A leaflet for patients was created to point out some essential aspects of reproductive issues and pregnancy in women with RDs, to facilitate communication between the doctor and patient. The leaflet contains clear and simple information about reproductive health, fertility, contraception, conception, the growth of children, safety of drugs during pregnancy and lactation.

An Italian Registry of the Autoimmune Congenital Heart Block (the Lu.Ne Registry) – a rare syndrome caused by the transplacental transfer of maternal anti-Ro/SSA and anti-La/SSB autoantibodies to the fetus – is an ongoing project aiming at collecting all cases of congenital heart block referred to Italian Rheumatology Centers.

In May 2018 a multicenter, national-based, prospective cohort study on pregnancy in RDs (P-RHEUM.it) was started. The primary objective of the P-RHEUM.it study is to evaluate the safety and efficacy of anti-rheumatic treatments for RDs during pregnancy and puerperium in terms of incidence of adverse pregnancy outcomes, maternal rheumatic disease outcomes and children's outcomes.

A collaboration between the SIR and the Italian National Institute of Health (Istituto Superiore di Sanità-ISS) led to the development of an "implementation program". The program focuses on increasing the awareness among the general population about RDs in a gender perspective, focusing on the implications during pregnancy and on providing a certified source of information for citizens and patients who want to learn more about RDs in a simple and interactive way (e.g., social networks). In the context of this project, a video was created to raise awareness about the most common fears that women with RDs have about pregnancy. This video is available on the Facebook page of "IS-Salute"[33].The SIR and the ISS are working on a future project to create a link to the webpage of the P-RHEUM.it study on the web platform "ISSalute" so that patients with RDs can be reached throughout the country and become aware of the existence of Pregnancy Clinics where they can refer for follow-up and, if they wish, participate in the study.

Conclusion

Overall, the knowledge of gender-specific differences is rapidly increasing. Women and men differ at many levels, from the molecular, such as genes, to the societal, such as habits and exposures. No single explanation is available for the large differences in sex ratios that characterize RDs. All causes including genes, cells, organs, hormones, the whole body, and the environment remain possible. The influence that gender has on the disease itself, the medical treatments that can be used, and the way that treatment decisions are made for female and male patients are an important area of research. The goal for the near future is a better understanding of the disease mechanisms and more appropriate therapeutic approaches with better long-term prognosis for both female and male patients.

Acknowledgments

The authors thank the President of Italian Society of Rheumatology, prof. Mauro Galeazzi, for supporting studies of gender-related issues.

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