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Sex and Management of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease more common in women than men (3:1). Although sex-based differences may play a complex role in promoting an autoimmune dysfunction, to date the comprehensive knowledge of the link between sex and RA is still partially lacking. Furthermore, males and females have been demonstrated to differently deal with their chronic pathologies, modifying the perceived sex-based burden of disease. Gender medicine is a newly approach focusing on the impact of gender differences on human physiology, pathophysiology, and clinical features of diseases, analyzing the complex interrelation and integration of sex and psychological and cultural behavior. A better comprehension of possible factors influencing sexual dimorphism in RA susceptibility, pattern of presentation, disease activity, and outcome could contribute to a tailored approach, in order to limit the morbidity of the disease. RA disease activity seems to be higher in women, whereas the response rate to synthetic and biologic disease-modifying therapies appears to be better in males. Moreover, the common strategies for RA management may be affected by concomitant pregnancy or childbearing desire, with particular regard to treatments with potential teratogenic effects or impact on fertility. Finally, comorbidities, such as fibromyalgia, major depression, and osteoporosis, are more frequent in females, while the impact of sex on cardiovascular risk is still controversial. Moving from the role of sex in influencing RA pathogenesis, epidemiology, and disease characteristics, this review explores the evidence on how sex can have an impact on strategies for managing patients with RA.

Keywords Sex · Rheumatoid arthritis · Gender medicine · Treatments · Pregnancy · Lactation

Introduction

Several data showed that autoimmune diseases are more prevalent in females, representing the fourth cause of disability for women [1, 2]. Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease, characterized by a chronic inflammation leading to tissue damage, functional impairment, severe disability, and premature mortality [3]. As part of the autoimmune disorders, RA is more common in women, which are two to three times more prone to develop the disease than men, with data suggesting a progressive increase in the incidence of RA in females during the last decades [4]. Despite this ascertained epidemiologic data, the comprehensive knowledge of the link between sex and RA is still lacking. Sex-based differences in immune response contribute to the diversities in pathogenesis of infectious disease and response to vaccinations between males and females [5, 6]. From a pathogenic point of view, the same hormonal differences along with genetic and environmental factors may play a complex role in promoting an immune system dysfunction toward an autoimmune process, confirmed by autoimmune disease onset and fluctuation when hormonal changes occur, as observed during puberty, pregnancy, hormone replacement therapy (HRT), and menopause [7]. Furthermore, males and females have been demonstrated to differently deal with their chronic pathologies, potentially modifying the perceived burden of disease between sexes [8]. During the last years, gender medicine has emerged as a new approach, aiming to recognize and analyze the gender-based differences in several aspects:

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anatomical, physiological, biological, functional, social, and response to treatments [9]. Indeed, the need to better investigate the possible factors contributing to the sexual dimorphism in RA susceptibility, pattern on presentation, disease activity, and outcome is urgent for its potential to offer new insights into interventions that may limit the morbidity of this debilitating chronic disease. Moreover, the common strategies for the management of RA may be affected by concomitant pregnancy or childbearing desire, with particular regard to the choice of synthetic and biologic disease-modifying therapies (DMARDs) according to their potential teratogenic effects or their impact on fertility [10]. Therefore, gender medicine applied to RA may be one of the most crucial points for managing the disease according to the tailored approach recommended by more recent international guidelines [11, 12].

Moving from the role of sex in influencing RA pathogenesis, epidemiology, and disease characteristics, this review explores the evidence on how sex can affect the strategies for managing patients with RA.

The Link Between Sex and RA: from Epidemiologic Evidences to Pathogenic Background

RA affects about 1% of the Western population with a peak of onset around the fourth and fifth decade of life. The majority of patients with RA are middle-aged women, generally greater than 70% in any RA cohort, although RA can occur at any age in either gender. Epidemiologic data showed RA and sex to be strongly associated, with an age-dependent demonstrated three-fold increased disease frequency in women versus men [13]. For women, the incidence increases steadily with age, whereas for men the incidence is stable over the third through fifth decades and rises thereafter [14]. In particular, RA is three times more frequent in females from the late teen to the forties, dropping to 2:1 ratio in the age range from 55 to 65, and finally shifting to a male predominance in people over 65 [15].

Possible reasons for this sexual disparity in RA may be explained at multiple levels, from genetic factors to hormonal changes. Specific genes on the Y and X chromosomes are responsible for gonadal differentiations and hormonal products of the gonads, establishing the "phenotypic sex" of an individual, which contribute along with societal and behavioral factors to the process known as sexual differentiation and provide a framework for considering how an individual's sex may be involved in a disease process such as RA [8]. As a consequence, gonad-specific hormone production may influence the incidence or course of RA. Disease activity tends to spontaneously improve in 75% of women in pregnancy, whereas delivery is followed by disease flares in up to 90% [16]. Oral contraceptives may be protective against RA [17], whereas the role of HRT is more controversial but seems to be modestly beneficial on RA disease activity according to the results of various randomized controlled trials [18–20]. Estrogens show a dichotomous impact on immune system functions by both up-regulating immunoglobulin production and down-regulating inflammatory immune responses [21]. On the other hand, reduced levels of androgens such as testosterone, dihydrotestosterone (DHT) and dehydroepiandrosterone (DHEA) have been observed in both men and women with RA [22]. Beyond the direct pathogenic effect of sex hormones on immune system, gender may indirectly contribute to increase RA susceptibility by influencing environmental/behavioral factors, such as smoking, known to be implicated in seropositive RA pathogenesis and to be more frequent in men than women [23].

Sex and RA Phenotype

Although there is agreement about the impact of sex in modifying susceptibility and prevalence of RA, the consensus on how sexual dimorphism may influence the pattern and burden of disease in males and females is incomplete.

The Impact of Sex on RA Presentation and Progression

At the end of the 1990s, Weyand et al. [24] reported an apparently more aggressive disease among men rather than women in a cohort of RA patients with a disease duration of at least 10 years. In particular, men were slightly (but not significantly) more likely to be RF positive, to have arthritis in large joints, to develop early radiographic damage, and to have a different pattern of extra-articular manifestations (more nodules and lung and pericardial disease, but less keratoconjunctivitis sicca). This scenario was not confirmed by subsequent studies. In a retrospective analysis conducted on a French cohort of 133 males compared with 133 females matched for RA duration, no difference in clinical, biological, or radiological indicators was observed between the two populations, even if female patients underwent significantly more distal joint arthrodesis (6.7 versus 1.5%; $p = 0.03$) [25]. Similarly, data from a cohort of 292 DMARD-naïve early RA patients collected in the Western Consortium of Practicing Rheumatologists showed that men ($n = 67$) and women ($n = 225$) had similar disease activity and radiographic damage at baseline, even if men had significantly worse erosion, while women had worse joint space narrowing [26].

On the other hand, several authors reported an overall milder disease in men than women. In a prospectively followed Dutch cohort including 209 females and 123 males with early RA, baseline disease activity (DAS score), radiographic damage (Sharp score), and physical disability (HAQ-DI) were all higher in females than males and in postmenopausal than in pre-menopausal women, as well as 3-year radiographic progression [27]. Similarly, in the early RA cohort of the Swedish

BARFOT Study group [28], both DAS28 and HAQ-DI were significantly higher in women compared with men, in spite of a similar radiographic progression at 2 and 5 years of follow-up. However, women below 50 years of age at study entry had milder disease than older women and close to that of men. More recently, data from a cross-sectional analysis of a large ($n = 4823$) Japanese observational cohort of RA patients revealed that women had overall higher disease activity and a 3-fold more rapid disease progression to disability than males [29]. The same topic has been addressed by the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) program considering clinical and questionnaire data from over 6000 RA patients in 25 countries [30]. Disease activity and disability scores resulted higher in women versus men (Disease Activity score 28 [DAS28] 4.3 versus 3.8, Health Assessment Questionnaire Disability Index [HAQ-DI] 1.1 versus 0.8; $p < 0.001$ for both). Men had rheumatoid nodules and were smokers more often than women, whereas no differences were found in RF prevalence among female and male [30]. On the other hand, in a large group of 1004 patients recruited from the North American Rheumatoid Arthritis Consortium (NARAC), male patients showed a significantly later onset of RA, were more likely to be seropositive for RF, and had significantly higher titers of anti-cyclic citrullinated peptide antibodies (ACPA) compared with female patients, even after adjustment for covariates in multivariate analyses [31]. Furthermore, baseline DAS28 was significantly higher (5.32 versus 4.93; $p < 0.001$) in females than males receiving a first-line TNFi in the NOR-DMARD registry [32] and female patients have higher HAQ scores than male patients at any timepoints in the large ($n = 3666$) inception cohort of Norfolk Arthritis Register [33]. Finally, a retrospective analysis conducted on 10,299 RA patients from the Consortium of Rheumatology Researchers of North America (CORRONA) network found both baseline Clinical Disease Activity Index (CDAI) scores (early RA 18.7 ± 13.5 versus 17.4 ± 13.2, $p = 0.02$; established RA 16.6 ± 12.3 versus 15.8 ± 12.0, $p = 0.02$) and HAQ-DI scores (early RA 0.41 ± 0.45 versus 0.36 ± 0.45, $p = 0.02$; established RA 0.42 ± 0.47 versus 0.35 ± 0.43, $p < 0.0001$) to be significantly higher in women than men [34].

Summarizing, RA phenotype seems to be overall more severe in women than men, especially in study where age and in particular female hormonal status (pre- and postmenopausal) have been considered in the analysis along with sex as predictors of disease severity. However, in the interpretation of these findings, it should be considered that women are known to generally report more symptoms and poorer scores on most questionnaires [35], including scores for pain [36], depression, and other health-related items [37, 38], potentially affecting disease activity measure and amplifying sex disparity in RA phenotype. Thus, comparison of health status in patients across sexes should ideally adjust for this underlying difference in reporting subjective health [39]. Despite an overall higher disease activity, the majority of published studies did not report difference in radiographic progression of RA according to sex. These findings are consistent with no impact of gender in predicting damage progression observed in a Norwegian inception RA cohort ($n = 149$) [40] and in an extensive US database ($n = 256$) [41], both evaluating radiographic outcomes over a long follow-up period of one and two decades, respectively.

The Impact of Sex on RA Comorbidities

According to a more recent and comprehensive definition, RA should be considered as a syndrome including extra-articular manifestations and comorbidities which contribute to increase the burden of disease and must be taken into account when a personalized treatment strategy is decided. The prevalence and the pattern of comorbidities may differ according to sex.

Fibromyalgia is much more common in women than in men, with a female:male ratio ranging between 3.0 and 6.8 [42], and may complicate RA in approximately 20% of patients, compared to 2.5% in the general population [43]. Similarly, the prevalence of major depression is at least 1.7-fold higher in females than in males [44, 45] and is reported as a frequent RA comorbidity with a prevalence of 13–42% depending on the sociodemographic and disease characteristics of the population studied [46], at least double to four-times that in the general population. Both these conditions have been associated with substantially higher self-reported disease activity [47, 48] and worse functional status [49, 50] in RA patients, potentially affecting the choice of therapy and the global evaluation of treatment response between females and males.

Osteoporosis has indicated to be twice as common in patients with RA as in controls, with an overall prevalence nearly 30% [51]. Female gender and postmenopausal status have been reported as risk factors associated with RA osteoporosis [51, 52]. This sexual disparity in the distribution of osteoporosis may be a driver for the choice of common treatment for RA, such as glucocorticoids, known to be involved in increasing the risk of lower bone mineral density and fractures [53]. Moreover, the prescription of HRT may be an option for the treatment of RA women affected by concomitant postmenopausal osteoporosis [54].

Cardiovascular (CV) risk in RA is increased, and the "excess" risk of CVD in this condition is not explained by "traditional" risk factors but by the effects of inflammation [55]. In the general population, CV risk is known to be higher in men compared to women [56, 57], and treatment strategies for the management of risk factors take into account this gender disparity. Conversely, RA females and males showed a similar higher risk ($p = 0.57$) to develop stroke, coronary artery disease, and cardiovascular, as reported by a recent meta-analysis of the literature [58].

Sex as Predictor of Clinical Response in RA

The ability to favorably respond to RA treatment and achieve remission widely varies among patients and may be related to different factors, including gender (Table 1). A number of studies have been focused on comparative analysis of remission rates between men and women mainly treated with csDMARDs. A study conducted in the BARFOT early RA cohort ($n = 698$) reported a significantly lower proportion of female than male achieving DAS28 remission at both 2 (32.1 versus 48%; $p = 0.001$) and 5 years (30.8 versus 52.4%; $p = 0.001$), with a multiple logistic regression analyses founding sex to be a main predictor for remission [59]. Similarly, in a previously mentioned Dutch prospective cohort, DAS28 values were higher at all timepoints over a 3-year follow-up period in women (especially postmenopausal ones) than men [27]. Moreover, in a multivariate stepwise logistic regression analysis from the CORRONA registry, maleness was associated with sustained remission in early RA (OR 1.38, 95% CI 1.07, 1.78, $p = 0.01$), but not in established RA; whereas for point remission, an inverse association was observed with maleness in established (OR 0.65, 95% CI 0.48, 0.87, $p = 0.005$) but not in early RA [34]. Finally, data from the early RA study (ERAS) cohort ($n = 704$) indicated male sex as a predictor of DAS sustained remission (OR 2.6; 95% CI 1.6–4.2) [60] and in the QUEST-RA program, women achieved remission less frequently than men, irrespectively of the definition used [61].

Similarly, several studies analyzed the impact of sex as predictor of clinical response and/or retention rate in large registries of RA patients receiving biologic drugs. Data from the British Society for Rheumatology Biologics Register (BRSBR) showed females to be significantly less likely to achieve remission compared with males in both etanercept- (OR 0.61; 95% CI 0.38–0.94) and infliximab (OR 0.60; 95% CI 0.40–0.89)-treated patients [62]. In the Danish DANBIO registry, sex influenced response to TNFis in early RA, with a significantly higher ($p = 0.003$) rate of EULAR good/moderate response in men compared to women over a 48-month follow-up period, irrespective of methotrexate and/or prednisolone combination therapy [64]. An analysis from the Swedish Biologics Register (ARTIS), including 9139 RA patients initiating a TNFi as a first biological therapy, showed a greater discontinuation rate in female versus male for all drugs (adjusted HR 1.12; 95% CI 1.04 to 1.21; $p = 0.004$) [79]. In the Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilization Study (RADIUS) registry, female sex was associated with significantly higher infliximab overall discontinuation (HR 1.24, 95% CI 1.01–1.51; $p = 0.040$) and etanercept withdrawal because of adverse events (HR 2.27, 95% CI 1.03–4.98; $p = 0.041$) [67]. In the Hellenic registry including 1208 RA patients treated with infliximab, adalimumab, and etanercept, male gender was associated with increased risk for both DAS28 low disease activity and EULAR good response (HR 1.33 and 1.45, respectively) [65]. Finally, logistic regression analysis for predictors of remission in the Italian registry GISEA identified male sex as a predictor of 6-month remission in TNFi-treated patients [63], while in the Italian longitudinal prospective observational GOAREL study, 2-year golimumab risk of discontinuation was strongly associated with female sex (HR 1.9; 95% CI 1.18–3.23) [68]. Moreover, a meta-analysis evaluating TNFi discontinuation rate confirmed female sex as a predictor of drug withdrawal (HR 1.18; 95% CI 1.03–1.36) [71].

Otherwise, no association between gender and TNFi retention rate was found in the Italian Lombardy Rheumatology Network (LOHREN) registry [66], in the Dutch DREAM registry [69], and in the South Swedish Arthritis Treatment Group (SSATG) register [70]. Similarly, to date no study reported a predictive role of gender in clinical response/retention rate to biologic drugs with a mechanism of action other than TNF blockade such as abatacept [72–75], rituximab [76, 77], or tocilizumab [78].

Sex and Treatment Strategy in RA

The best strategies for the management of RA are well described in available recommendations provided by international society of rheumatology. A treat-to-target approach aiming to achieve clinical remission in both male and female RA patients by the use of synthetic or biologic DMARDs is the core of the most recent strategy proposed by the European League Against Rheumatisms (EULAR) and by the American College of Rheumatology (ACR) [11, 12]. Nevertheless, at the beginning of this millennium, there was a diffuse concern that RA women might be less likely aggressively treated compared with men. This concept was further reinforced by the result of several studies conducted in cardiologic diseases, showing that men are generally treated more intensively than women [80, 81]. Consistently, two studies from The Netherlands [82] and Norway [83] highlighted a longer delay of female referral to an early arthritis clinic compared with men, potentially affecting the clinical response in women. Of note, these findings are in contrast with the well-known assumption that men are much less likely to seek medical care than women [84]. However, more recent analyses from previously mentioned large observational cohorts did not show any significant difference in the treatment approach between male and female RA population [25, 30]. In particular, in the QUEST-RA study, similar proportions of women and men received prednisone (60.6 versus 61.5%), methotrexate (68.4 versus 72.0%), and biologic drugs (29.1 versus 30.8%). Moreover, the delay between the first RA symptoms and introduction of the first DMARD was 10 months in the entire group, with no statistically significant gender differences [30]. Similarly, in the CORRONA study, men and

Table 1 Clinical response to synthetic and biologic DMARDs according to sex

Study	Study design	No. of patients (F)	Mean disease duration	Response outcome measures and gender influence	Ref.
BARFOT	Multicenter observational prospective study	689 (446)	6.2 months	DAS28 remission at 18 and 24 months—more frequent in male (OR 1.557 [CI 1.062–2.283] and 1.713 [CI 1.208–2.431], respectively)	[59]
CORRONA (early RA)	Multicenter observational prospective study	3017 (2263)	0.9 years	CDAI remission at 6 months—more frequent in male (OR 1.38 [CI 1.07–1.78])	[34]
ERAS	Multicenter observational cohort study	704 (462)	< 6 months	DAS28 remission at 3, 4, and 5 years—more frequent in male (OR 2.6 [CI 1.6–4.56])	[60]
CORRONA (established RA)	Multicenter observational prospective study	7282 (5630)	13 years	CDAI remission at 6 months—no sex differences (OR 0.93 [CI 0.75–1.22])	[34]
QUEST-RA	Multicenter cross-sectional cohort study	6004 (4755)	11.2 years	DAS28 remission—more frequent in male versus female (30 versus 16.9%, respectively)	[61]
BRSBR	Multicenter observational prospective study	2711 (2114)	15 years	DAS28 remission at 6 months—less frequent in female (ETN, OR 0.61 [CI 0.38–0.94]; IFX, OR 0.60 [CI 0.40–0.89])	[62]
GISEA	Multicenter observational cohort study	591 (404)	11.6 years	DAS28 remission at 6 months—more frequent in male (OR 0.659 [CI 0.450–0.965], $p = 0.032$)	[63]
DANBIO (early RA)	Multicenter observational prospective cohort study	476 (328)	1.22 years	EULAR good/moderate response at 48 months—more frequent in male (OR 0.93 [CI 0.31–1.55], $p = 0.003$)	[64]
Hellenic registry	Multicenter observational prospective cohort study	2216 (1297)	Established RA	DAS28 low disease activity and EULAR good response at 12 months—more frequent in male (HR 1.33 [CI 1.02–1.73] and 1.45 [CI 1.10–1.90], respectively)	[65]
Prospective Dutch RA cohort	Multicenter observational prospective cohort study	296 (173)	n.a.	DAS28 values over 3 years—higher in female than in male patients, $p < 0.001$	[27]
LORHEN	Multicenter observational cohort study	1064 (885)	9.44 years	TNFi retention rate at 12, 24, and 36 months—no sex differences (p = n.s.)	[66]
RADIUS	Multicenter observational cohort study	2418 (1881)	Established RA	TNFi discontinuation—higher in female for IFX (HR 1.24 [CI 1.01–1.51], $p = 0.040$), ETN (HR 1.3 [CI 0.95–1.78], p = n.s.) and ADA (HR 1.08 [CI 0.70–1.64], p = n.s.)	[67]
GOAREL	Longitudinal prospective observational study	88 (71)	8.1 years	Golimumab 2-year discontinuation risk—higher in female (HR 1.9 [CI 1.182–3.236]; $p = 0.009$)	[68]
DREAM	Multicenter observational cohort study	1560 (1085)	Established RA	TNFi retention rate at 5 years—no sex differences (p = n.s.)	[69]
SSATG	Multicenter observational cohort study	1565 (1212)	Established RA	TNFi retention rate at 6 months—no sex differences (p = n.s.)	[70]
Meta-analysis	Up to February 2014	> 200,000	n.a.	TNFi retention rate at 4 years—no sex differences (HR 1.18 [CI 1.03–1.36], p = n.s.)	[71]
DANBIO	Multicenter observational cohort study	150 (116)	8.5 years	ABT retention rate at 48 weeks—no sex differences (p = n.s.)	[72]
ORA	Multicenter observational cohort study	773 (608)	14 years	ABT retention rate at 6 months—no sex differences (p = n.s.)	[73]
ROC	Multicenter pragmatic open-label randomized clinical study	300 (243)	10 years	ABT retention rate at 52 weeks—no sex differences (HR1.01 [CI 0.85–1.20], p = n.s. including ACPA status; or HR 0.98 [CI 0.84–1.14], p = n.s. including RF status)	[74]
ACTION	Non-interventional international multicenter cohort study	865 (719)	n.a.	ABT retention rate at 2 years—no sex differences (p = n.s.)	[75]
BSRBR	National prospective cohort study	646 (497)	14.3 years	RTX retention rate at 6 months—no sex differences (p = n.s.)	[76]
AIR	Multicenter prospective cohort study	1709 (1321)	16 years	RTX retention rate at 18 months—no sex differences (p = n.s.)	[77]
Pers et al.	Retrospective cohort study	222 (183)	14 years	TCZ retention rate at 6 months—no sex differences (p = n.s.)	[78]

(F), female; *DAS*, Disease Activity score; *OR*, odd ratio; *RA*, rheumatoid arthritis; *CDAI*, Clinical Disease Activity Index; *ETN*, etanercept; *IFX*, infliximab; *EULAR*, European League Against Rheumatism; *HR*, hazard ratio; *n.a.*, not applicable; *TNFi*, tumor necrosis factor inhibitors; *n.s.*, not significant; *ABT*, abatacept; *TCZ*, tocilizumab

women did not differ in their use of either csDMARDs or prednisone [34] and the NOR-DMARD study showed a similar access to TNFis in a cohort of 1754 RA patients (39% of the females and 38.9% of the males) [32].

Beyond the therapy of overall RA population, gender may be determinant for the treatment choice in case of childbearing desire, pregnancy, or lactation [10]. In fact, concerns about teratogenicity and the absorption by the baby of potentially harmful drugs from breast milk may influence the treatment women with RA receive during this period (Table 2).

Limitation to the Use of RA Therapies During Pregnancy

Consistently with international recommendations [11, 12], methotrexate should be the anchor drug for the management of RA as first line of treatment in all newly diagnosed RA patient and as concomitant drug in combination strategies with other synthetic or biologic DMARDs [86]. However, the teratogenic effects of this drug are clearly established, with described and dose-related malformation patterns, dependent on the timing of pregnancy in which the drug is administered [87]. Thus, RA women receiving methotrexate should be counseled to use contraceptive methods and to discontinue the drug at least 1–3 months before conception, as suggested by the EULAR "points to consider" for the use of anti-rheumatic drugs before and during pregnancy [85]. Given that leflunomide must be discontinued 2 years before pregnancy or a washout procedure with cholestyramine should be adopted before conception [85], sulfasalazine and antimalarials, as not embryo/fetotoxic, should be considered as the only alternative csDMARDs to be administered before and during pregnancy [88], even if the effectiveness of this approach is often inadequate for the treatment of moderate to severe RA. Non-

Table 2 Drug compatibility with pregnancy or lactation [85]

Drug	Compatibility with pregnancy	Compatibility with lactation
Non-selective COX inhibitors	No increased risk of congenital malformations. They can be continued during the first and second trimesters	Compatible with lactation
Selective COX II inhibitors	Insufficient data. To be avoided in pregnancy	Only celecoxib is compatible with lactation
Non-fluorinated corticosteroids	No increased risk of congenital malformations. Prednisolone/prednisone can be continued at the lowest effective dose throughout pregnancy	Compatible with lactation
Fluorinated corticosteroids	To be used only to treat fetal problems	Compatible with lactation
Antimalarials	No increased risk of congenital malformations. It can be continued throughout pregnancy	Compatible with lactation
Methotrexate	Increased risk of congenital malformations. To be withdrawn 1–3 months before pregnancy	Avoid in lactation
Sulfasalazine	No increased risk of congenital malformations. It can be continued at doses up to 2 g/day with concomitant folate supplementation throughout pregnancy	Compatible with lactation in healthy, full-term newborn
Leflunomide	To be avoided in pregnancy. A washout procedure should be completed before pregnancy	Avoid in lactation
Azathioprine	No increased risk of congenital malformations. It can be continued at doses up to 2 mg/kg/day throughout pregnancy	Compatible with lactation
Ciclosporin	No increased risk of congenital malformations. It can be continued throughout pregnancy	Compatible with lactation
Infliximab	No increased rate of congenital malformations. It can be continued up to gestational week 20. If indicated, it can be used throughout pregnancy	Compatible with lactation
Adalimumab	No increased rate of congenital malformations. It can be continued up to gestational week 20. If indicated, it can be used throughout pregnancy	Compatible with lactation
Golimumab	No increased rate of congenital malformations. Alternative medications should be considered	Compatible with lactation
Etanercept	No increased rate of congenital malformations. It can be continued up to gestational week 30–32. If indicated, it can be used throughout pregnancy	Compatible with lactation
Certolizumab pegol	No increased risk of congenital malformations. It can be continued throughout pregnancy	Compatible with lactation
Rituximab	No increased risk of congenital malformations. In exceptional cases, it can be used early in gestation. To be aware of the risk of B cell depletion and other cytopenias in the neonate if used at later stages of pregnancy	Avoid in lactation
Anakinra	No increased risk of congenital malformations. To use before and during pregnancy only in case of contraindications to other available options	Avoid in lactation
Tocilizumab	Insufficient data. To be avoided in pregnancy	Avoid in lactation
Abatacept	Insufficient data. To be avoided in pregnancy	Avoid in lactation

COX, cyclooxygenase

fluorinated glucocorticoids can be continued throughout pregnancy at the lowest effective dose [85] because of the minimized molecular transfer due to partial inactivation at placental level [89]. Biologic drugs should be considered as the next step in csDMARD failures. Being either complete or in part IgG1 molecules, biologics start to be transferred across the placenta by the fetal Fc receptor expressed in the trophoblast since the beginning of the 2nd trimester, with a progressive increase until term when fetal and maternal serum levels are equal or higher in cord serum [90]. Thus, the transplacental passage of biological agents is most extensive for monoclonal antibodies, less for receptor fusion proteins (such as etanercept and abatacept) and minimum for certolizumab pegol, which is not actively transported through the placenta because of the lack of Fc fragment [91], with consequent significantly lower cord serum levels at delivery compared with other TNF blockers [92, 93]. So far, TNFis are the best studied biologics in regard to human pregnancy. In studies comparing exposed pregnancies (especially in the 1st trimester) to disease-matched controls, no increased risk of spontaneous abortion, low birth weight, prematurity or congenital malformations has been observed, whereas some concerns (in particular increase in infections in infants at age 12 months) have been reported after TNFi continuation till late pregnancy [94]. EULAR recommends to withdraw anti-TNF monoclonal antibodies (infliximab, adalimumab, and golimumab) around gestational week 20 and etanercept around week 30 [85]. Certolizumab has the potential to be the preferred option because of the minimal transplacental passage, but its safety profile during pregnancy should be confirmed through extended prospective studies [85]. Conversely, data on bDMARDs with a mechanism of action other than TNF blockade (such as rituximab, tocilizumab, abatacept, and anakinra) are still inconclusive since they are derived only from case reports/series and registries [95–98], suggesting to limit their use in pregnancy only when no other therapeutic option is available to treat severe maternal disease [85]. Since half of pregnancies are unplanned, a challenging question is how to manage pregnancies that occur in patients receiving treatment with teratogenic drugs. Some patients decide for immediate termination whereas others consider continuation of the pregnancy. In these cases, determination of exact exposure dates and detailed ultrasound examination of the fetus are mandatory for individual risk assessment, whereas chorionic villous biopsy or amniocentesis is usually not indicated after maternal drug exposure [85].

Beyond the abovementioned limitations, the results of some decades of retrospective observational reports reinforced in the last century the assumption that almost all RA women experience a spontaneous remission of disease during pregnancy [99]. However, two more recent larger prospective studies clarify that, despite a confirmed decrease of disease activity scores, the proportion of patients achieving a clinical remission during the third trimester is lower than previously expected, ranging from 16% in a UK cohort of 140 patients [100] to 25% of 84 women enrolled in the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study [16]. Anyway, considering that medication use was remarkably reduced during pregnancy compared with before conception, these findings confirmed a spontaneous improvement of RA during pregnancy. Interestingly, amelioration seen during pregnancy can have long-lasting effects, as demonstrated by a study from the Norfolk Arthritis Register, which recorded lower HAQ scores in RA women who had experienced one or more pregnancies after the onset of arthritis, suggesting that even a limited period of disease improvement could lead to overall reduced severity in subsequent years [101].

Apart from the favorable effect of pregnancy on the disease activity, there is nowadays more attention for a potentially negative impact of active RA on pregnancy outcome. Modestly increased risk of pre-eclampsia [102, 103], preterm delivery [102, 103], and small-for-gestational-age infants [102–104] have been observed in RA patients compared with unaffected women, especially in patients showing higher disease activity [105]. Furthermore, pregnancy outcome in RA may be influenced by the presence of anti-phospholipids antibodies, associated with an increased risk of spontaneous miscarriage, and anti-Ro/SS-A and anti-La/SS-B autoantibodies, predictive of congenital heart block and neonatal lupus [106, 107]. All these data recommend the importance of a preconceptional counseling in RA patients and the significance of a tight disease control to obtain the better chances of pregnancy success [108]. Particular attention must be focused on therapy, balancing the risk of discontinuation and the potential benefit of any therapeutic changes [105].

Limitation to the Use of RA Therapies During Lactation

Delivery is usually followed by a re-establishment of the non-pregnant status, translating in RA flares depending on a Th1-dominated immune response with reduction of steroid hormones and an increase of pro-inflammatory cytokines [109]. Furthermore, the risk of postpartum disease flare in RA women could be related to the release of prolactin during breastfeeding [110]. Because of these reasons, a proportion ranging from 40 to 60% of women experience at least a moderate flare postpartum [16, 100]; thus, the management of RA after delivery is particularly challenging, as several antirheumatic drugs are contraindicated during lactation. Corticosteroids, NSAIDs, antimalarials, sulfasalazine, azathioprine, and cyclosporine may be considered compatible with breastfeeding, but methotrexate should be avoided during lactation, even if only small amounts of the drug appear in breast milk [85]. Data on biologic drugs are very reassuring. Excretion of maternal IgG antibodies into human breast milk is very limited, and maternal IgG levels in milk comprise only

about 2% [111]. Moreover, even when maternal IgG is assumed during breast feeding, the major part will be degraded by digestive enzymes in the infant's gastrointestinal tract [111]. Thus, all available TNFis are compatible with breastfeeding, but the concentration in breast milk and the estimation of the average daily infant dose of maternal drug was recently evaluated only for certolizumab pegol [112]. No data exist on concentration in breast milk of biologics with a mechanism of action other than TNF blockade, with the exception of rituximab, whose minimal excretion of RTX into breast milk has been recently demonstrated in a patient affected by ANCA-associated vasculitis [113]. Nowadays, according to EULAR indications, all non-TNF-targeted biologics should be avoided during breastfeeding [85].

Limitation to the Use of RA Therapies Related to Fertility and Sterility

Although the occurrence of RA in women of childbearing age is relatively low [14], conceiving a child is an important aspect to be considered in the management on the disease. In fact, the proportion of female RA patients diagnosed before the completion of childbearing who experience a significant increase of the time between the start of actively trying to conceive and actually becoming pregnant (time to pregnancy [TTP]) ranges between 30 and 40% [114, 115]. Consequently, women with RA have in general lower family sizes and have lower birth rates than the general population [116, 117]. Beyond personal choices due to RA-related concerns (such as child health and personal welfare) [115], the reasons for impaired fertility lie in disease activity and treatments [118]. In patients with high DAS28 (> 5.1), TTP exceeded 12 months in 67% of women versus only 30% in women in remission (DAS28 < 2.6) [115], highlighting the importance of preconception treatment strategies aiming at maximum suppression of RA activity. NSAID therapy during the peri-conceptional period could be associated with prolonged TTP and miscarriage, due to the inhibition of prostaglandins involved in ovulation and blastocyst implantation [119]. Furthermore, glucocorticoids in a dose exceeding 7.5 mg daily could impair TTP by directly acting on endometrium and ovarian function [115, 120] and by producing a transient suppression of the hypothalamic-pituitary-ovarian axis [121]. On the other hand, prior MTX treatment does not affect TTP [115] and seems to have no impact on the ovarian reserve in patients with RA [120]. So far, no data on the role of other synthetic and biologic DMARDs on fertility have been published yet.

Data on RA male sterility are lacking. Sulfasalazine may alter sperm morphology reducing sperm motility and causing oligospermia, with a complete resolution after drug withdrawal [122]. Conversely, there is a lack of evidence regarding effects of methotrexate on male fertility. The recommendation to stop the drug 3 months prior to conception is safe, but is not supported by a clear knowledge of the impact of methotrexate on spermatogenesis or paternal-mediated teratogenicity [123]. Also, tumor necrosis factor inhibitors seem not to impair male fertility [124], whereas no data on biologic agents with a mechanism of action other than TNF blockade are still available.

Conclusions

In summary, sex contributes to several pathogenic and epidemiologic aspects of RA, generating important differences between affected males and females. Consequently, rheumatologists should expect different patterns of disease onset and presentation, disease activity, response to treatments, disability, radiographic progression, and extra-articular manifestations/comorbidities according to gender. Overall, RA seems to be more severe in women, who show higher baseline DAS28 and HAQ-DI scores and lower rates of remission and drug survival when treated with both synthetic and biologic DMARDs. More frequent comorbidities in females, such as fibromyalgia, depression, and osteoporosis, may impact on treatment choice and outcomes of RA. Moreover, the use of common drugs for treating RA may be conditioned during childbearing age, pregnancy, and lactation by the potential teratogenicity and by the effects on female fertility and male sterility. All these aspects suggest that sex should be carefully considered in the personalization of RA treatments over the whole course of the disease.

Compliance with Ethical Standards

Ethical Statement The paper is a review of the literature; thus, no original clinical data are reported. Therefore, no ethical approval and informed consent are needed for the publication.

References

1. Lleo A, Battezzati PM, Selmi C, Gershwin ME, Podda M (2008) Is autoimmunity a matter of sex? Autoimmun Rev 7(8):626–630. https://doi.org/10.1016/j.autrev.2008.06.009
2. Pennell LM, Galligan CL, Fish EN (2012) Sex affects immunity. J Autoimmun 38(2-3):J282–J291. https://doi.org/10.1016/j.jaut.2011.11.013
3. Smolen JS, Aletaha D, Mcinnes IB (2016) Rheumatoid arthritis. Lancet 388(10055):2023–2038. https://doi.org/10.1016/S0140-6736(16)30173-8
4. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE (2010) Is the incidence of rheumatoid arthritis rising?: Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheumatol 62(6):1576–1582. https://doi.org/10.1002/art.27425
5. Ghosh S, Klein RS (2017) Sex drives dimorphic immune responses to viral infections. J Immunol 198(5):1782–1790. https://doi.org/10.4049/jimmunol.1601166
6. Furman D (2015) Sexual dimorphism in immunity: improving our understanding of vaccine immune responses in men. Expert Rev

Vaccines 14(3):461–471. https://doi.org/10.1586/14760584.2015.966694
7. Ngo ST, Steyn FJ, McCombe PA (2014) Gender differences in autoimmune disease. Front Neuroendocrinol 35(3):347–369. https://doi.org/10.1016/j.yfrne.2014.04.004
8. Kovacs WJ, Olsen NJ (2011) Sexual dimorphism of RA manifestations: genes, hormones and behavior. Nat Rev Rheumatol 7(5):307–310. https://doi.org/10.1038/nrrheum.2010.231
9. Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V (2013) Gender medicine: a task for the third millennium. Clin Chem Lab Med 51(4):713–727. https://doi.org/10.1515/cclm-2012-0849
10. Østensen M, Andreoli L, Brucato A, Cetin I, Chambers C, Clowse MEB, Costedoat-Chalumeau N, Cutolo M, Dolhain R, Fenstad MH, Förger F, Wahren-Herlenius M, Ruiz-Irastorza G, Koksvik H, Nelson-Piercy C, Shoenfeld Y, Tincani A, Villiger PM, Wallenius M, von Wolff M (2015) State of the art: reproduction and pregnancy in rheumatic diseases. Autoimmun Rev 14(5):376–386. https://doi.org/10.1016/j.autrev.2014.12.011
11. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D, Aringer M, Boers M, Buckley CD, Buttgereit F, Bykerk V, Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg JE, Hazes JMW, Huizinga T, Jani M, Karateev D, Kouloumas M, Kvien T, Li Z, Mariette X, McInnes I, Mysler E, Nash P, Pavelka K, Poór G, Richez C, van Riel P, Rubbert-Roth A, Saag K, da Silva J, Stamm T, Takeuchi T, Westhovens R, de Wit M, van der Heijde D (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76(6):960–977. https://doi.org/10.1136/annrheumdis-2016-210715
12. Singh JA, Saag KG, Bridges SL et al (2016) 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 68(1):1–26. https://doi.org/10.1002/art.39480
13. Gerosa M, De Angelis V, Riboldi P, Meroni PL (2008) Rheumatoid arthritis: a female challenge. Women's Health 4(2):195–201. https://doi.org/10.2217/17455057.4.2.195
14. Symmons DPM, Barrett EM, Bankhead CR et al (1994) The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. Br J Rheumatol 33(8):735–739. https://doi.org/10.1093/rheumatology/33.8.735
15. Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F, Shoenfeld Y (2016) Sex-based differences in autoimmune diseases. Ann Ist Super Sanita 52(2):205–212. https://doi.org/10.4415/ANN_16_02_12
16. de Man YA, Dolhain RJEM, van de Geijn FE, Willemsen SP, Hazes JMW (2008) Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum 59(9):1241–1248. https://doi.org/10.1002/art.24003
17. Brennan P, Bankhead C, Silman AJ, Symmons DPM (1997) Oral contraceptives and rheumatoid arthritis: results from a primary care-based incident case-control study. Semin Arthritis Rheum 26(6):817–823. https://doi.org/10.1016/S0049-0172(97)80025-X
18. D'Elia HF, Larsen A, Mattsson L-A, Waltbrand E, Kvist G, Mellström D, Saxne T, Ohlsson C, Nordborg E, Carlsten H (2003) Influence of hormone replacement therapy on disease progression and bone mineral density in rheumatoid arthritis. J Rheumatol 30(7):1456–1463
19. Hall GM, Daniels M, Huskisson EC, Spector TD (1994) A randomised controlled trial of the effect of hormone replacement therapy on disease activity in postmenopausal rheumatoid arthritis. Ann Rheum Dis 53(2):112–116. https://doi.org/10.1136/ard.53.2.112
20. MacDonald AG, Murphy EA, Capell HA, Bankowska UZ, Ralston SH (1994) Effects of hormone replacement therapy in rheumatoid arthritis: a double blind placebo-controlled study. Ann Rheum Dis 53(1):54–57. https://doi.org/10.1136/ard.53.1.54
21. Carlsten H (2005) Immune responses and bone loss: the estrogen connection. Immunol Rev 208(1):194–206. https://doi.org/10.1111/j.0105-2896.2005.00326.x
22. Cutolo M (2009) Androgens in rheumatoid arthritis: when are they effectors? Arthritis Res Ther 11(5):126. https://doi.org/10.1186/ar2804
23. Krishnan E, Sokka T, Hannonen P (2003) Smoking-gender interaction and risk for rheumatoid arthritis. Arthritis Res Ther 5(3):R158–R162. https://doi.org/10.1186/ar750
24. Weyand CM, Schmidt D, Wagner U, Goronzy JJ (1998) The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum 41(5):817–822. https://doi.org/10.1002/1529-0131(199805)41:5<817::AID-ART7>3.0.CO;2-S
25. Gossec L, Baro-Riba J, Bozonnat M-C, Daurès JP, Sany J, Eliaou JF, Combe B (2005) Influence of sex on disease severity in patients with rheumatoid arthritis. J Rheumatol 32(8):1448–1451
26. Jawaheer D, Maranian P, Park G et al (2010) Disease progression and treatment responses in a prospective DMARD-naive seropositive early rheumatoid arthritis cohort: does gender matter? J Rheumatol 37(12):2475–2485. https://doi.org/10.3899/jrheum.091432
27. Kuiper S, van Gestel AM, Swinkels HL, de Boo TM, da Silva JA, van Riel PL (2001) Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis. J Rheumatol 28(8):1809–1816
28. Tengstrand B, Ahlmén M, Hafström I (2004) The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. J Rheumatol 31(2):214–222
29. Iikuni N, Sato E, Hoshi M et al (2009) The influence of sex on patients with rheumatoid arthritis in a large observational cohort. J Rheumatol 36(3):508–511. https://doi.org/10.3899/jrheum.080724
30. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, Skakic V, Badsha H, Peets T, Baranauskaite A, Géher P, Ujfalussy I, Skopouli FN, Mavrommati M, Alten R, Pohl C, Sibilia J, Stancati A, Salaffi F, Romanowski W, Zarowny-Wierzbinska D, Henrohn D, Bresnihan B, Minnock P, Knudsen LS, Jacobs JW, Calvo-Alen J, Lazovskis J, Pinheiro Gda R, Karateev D, Andersone D, Rexhepi S, Yazici Y, Pincus T, QUEST-RA Group (2009) Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 11(1):R7. https://doi.org/10.1186/ar2591
31. Jawaheer D, Lum RF, Gregersen PK, Criswell LA (2006) Influence of male sex on disease phenotype in familial rheumatoid arthritis. Arthritis Rheum 54(10):3087–3094. https://doi.org/10.1002/art.22120
32. Kvien TK, Heiberg, Lie E, Kaufmann C, Mikkelsen K, Nordvåg BY, Rødevand E (2005) A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 23(5 Suppl 39):S188–S194
33. Camacho EM, Verstappen SMM, Lunt M, Bunn DK, Symmons DPM (2011) Influence of age and sex on functional outcome over time in a cohort of patients with recent-onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. Arthritis Care Res 63(12):1745–1752. https://doi.org/10.1002/acr.20609
34. Jawaheer D, Messing S, Reed G, Ranganath VK, Kremer JM, Louie JS, Khanna D, Greenberg JD, Furst DE (2012) Significance of sex in achieving sustained remission in the consortium of rheumatology researchers of North America cohort of

rheumatoid arthritis patients. Arthritis Care Res 64(12):1811–1818. https://doi.org/10.1002/acr.21762
35. Barsky AJ, Peekna HM, Borus JF (2001) Somatic symptom reporting in women and men. J Gen Intern Med 16(4):266–275. https://doi.org/10.1046/j.1525-1497.2001.00229.x
36. Keogh E, Herdenfeldt M (2002) Gender, coping and the perception of pain. Pain 97(3):195–201. https://doi.org/10.1016/S0304-3959(01)00427-4
37. Loge JH, Kaasa S (1998) Short Form 36 (SF-36) Health Survey: normative data from the general Norwegian population. Scand J Soc Med 26(4):250–258. https://doi.org/10.1177/14034948980260040401
38. Bowling A, Bond M, Jenkinson C, Lamping D (1999) Short Form 36 (SF-36) Health Survey questionnaire: which normative data should be used? Comparisons between the norms provided by the Omnibus Survey in Britain, the Health Survey for England and the Oxford Healthy Life Survey. J Public Health 21(3):255–270. https://doi.org/10.1093/pubmed/21.3.255
39. Kvien TK, Uhlig T, Ødegård S, Heiberg MS (2006) Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci 1069(1):212–222. https://doi.org/10.1196/annals.1351.019
40. Ødegård S, Landewé R, van der Heijde DM et al (2005) Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year, longitudinal observational study in 238 patients. Arthritis Rheum 54(1):68–75. https://doi.org/10.1002/art.21548
41. Wolfe F, Sharp JT (1998) Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. Arthritis Rheum 41(9):1571–1582. https://doi.org/10.1002/1529-0131(199809)41:9<1571::AID-ART7>3.0.CO;2-R
42. Yunus MB (2001) The role of gender in fibromyalgia syndrome. Curr Rheumatol Rep 3(2):128–134. https://doi.org/10.1007/s11926-001-0008-3
43. Wolfe F, Michaud K (2004) Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize ra patients with fibromyalgia. J Rheumatol 31(4):695–700
44. Albert PR (2015) Why is depression more prevalent in women? J Psychiatry Neurosci 40(4):219–221. https://doi.org/10.1503/jpn.150205
45. Kuehner C (2017) Why is depression more common among women than among men? Lancet Psychiatry 4(2):146–158. https://doi.org/10.1016/S2215-0366(16)30263-2
46. Margaretten M, Julian L, Katz P, Yelin E (2011) Depression in patients with rheumatoid arthritis: description, causes and mechanisms. Int J Clin Rheumatol 6(2):617–623. https://doi.org/10.2217/IJR.11.6
47. Ranzolin A, Brenol JCT, Bredemeier M, Guarienti J, Rizzatti M, Feldman D, Xavier RM (2009) Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and Short Form 36 scores in patients with rheumatoid arthritis. Arthritis Rheum 61(6):794–800. https://doi.org/10.1002/art.24430
48. Imran MY, Saira Khan EA, Ahmad NM et al (2015) Depression in rheumatoid arthritis and its relation to disease activity. Pak J Med Sci 31(2):393–397. https://doi.org/10.12669/pjms.312.6589
49. Naranjo A, Ojeda S, Francisco F, Erausquin C, Rúa-Figueroa I, Rodríguez-Lozano C (2002) Fibromyalgia in patients with rheumatoid arthritis is associated with higher scores of disability. Ann Rheum Dis 61(7):660–661. https://doi.org/10.1136/ard.61.7.660
50. Margaretten M, Yelin E, Imboden J, Graf J, Barton J, Katz P, Julian L (2009) Predictors of depression in a multiethnic cohort of patients with rheumatoid arthritis. Arthritis Rheum 61(11):1586–1591. https://doi.org/10.1002/art.24822
51. Hauser B, Riches PL, Wilson JF, Horne AE, Ralston SH (2014) Prevalence and clinical prediction of osteoporosis in a contemporary cohort of patients with rheumatoid arthritis. Rheumatology (Oxford) 53(10):1759–1766. https://doi.org/10.1093/rheumatology/keu162
52. Oelzner P, Schwabe A, Lehmann G, Eidner T, Franke S, Wolf G, Hein G (2008) Significance of risk factors for osteoporosis is dependent on gender and menopause in rheumatoid arthritis. Rheumatol Int 28(11):1143–1150. https://doi.org/10.1007/s00296-008-0576-x
53. Maricic M (2011) Update on glucocorticoid-induced osteoporosis. Rheum Dis Clin N Am 37(3):415–431– **vi**. https://doi.org/10.1016/j.rdc.2011.07.003
54. Talsania M, Scofield RH (2017) Menopause and rheumatic disease. Rheum Dis Clin N Am 43(2):287–302. https://doi.org/10.1016/j.rdc.2016.12.011
55. Nurmohamed MT, Heslinga M, Kitas GD (2015) Cardiovascular comorbidity in rheumatic diseases. Nat Rev Rheumatol 11(12):693–704. https://doi.org/10.1038/nrrheum.2015.112
56. Martin LA, Critelli JW, Doster JA, Powers C, Purdum M, Doster MR, Lambert PL (2013) Cardiovascular risk: gender differences in lifestyle behaviors and coping strategies. Int J Behav Med 20(1):97–105. https://doi.org/10.1007/s12529-011-9204-3
57. Wenger NK (2011) Gender differences in cardiovascular risk: a varying variable. Gend Med 8(4):221–223. https://doi.org/10.1016/j.genm.2011.05.004
58. Fransen J, Kazemi-Bajestani SMR, Bredie SJH, Popa CD (2016) Rheumatoid arthritis disadvantages younger patients for cardiovascular diseases: a meta-analysis. PLoS One 11(6):e0157360. https://doi.org/10.1371/journal.pone.0157360
59. Forslind K, Hafström I, Ahlmén M et al (2006) Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis 66(1):46–52. https://doi.org/10.1136/ard.2006.056937
60. Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, Prouse P, Young A, on behalf of the Early Rheumatoid Arthritis Study (ERAS) (2012) Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. Rheumatology (Oxford) 51(1):169–175. https://doi.org/10.1093/rheumatology/ker250
61. Sokka T, Hetland ML, Mäkinen H, Kautiainen H, Hørslev-Petersen K, Luukkainen RK, Combe B, Badsha H, Drosos AA, Devlin J, Ferraccioli G, Morelli A, Hoekstra M, Majdan M, Sadkiewicz S, Belmonte M, Holmqvist AC, Choy E, Burmester GR, Tunc R, Dimić A, Nedović J, Stanković A, Bergman M, Toloza S, Pincus T, Questionnaires in Standard Monitoring of Patients With Rheumatoid Arthritis Group (2008) Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. Arthritis Rheum 58(9):2642–2651. https://doi.org/10.1002/art.23794
62. Hyrich KL, Watson KD, Silman AJ, Symmons DPM, The BSR Biologics Register (2006) Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 45(12):1558–1565. https://doi.org/10.1093/rheumatology/kel149
63. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, Massara A, Nacci F, Secchi ME, Manganelli S, Salaffi F, Bambara ML, Bombardieri S, Cutolo M, Ferri C, Galeazzi M, Gerli R, Giacomelli R, Grassi W, Lapadula G, Cerinic MM, Montecucco C, Trotta F, Triolo G, Valentini G, Valesini G, Ferraccioli GF, GISEA group (2007) Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol 34(8):1670–1673

64. Jawaheer D, Olsen J, Hetland ML (2012) Sex differences in response to anti-tumor necrosis factor therapy in early and established rheumatoid arthritis—results from the DANBIO registry. J Rheumatol 39(1):46–53. https://doi.org/10.3899/jrheum.110548
65. Flouri I, Markatseli TE, Voulgari PV, Boki KA, Papadopoulos I, Settas L, Zisopoulos D, Skopouli FN, Iliopoulos A, Bertsias GK, Geborek P, Drosos AA, Boumpas DT, Sidiropoulos P (2013) Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: low rates of remission and 5-year drug survival. Semin Arthritis Rheum 43(4):447–457. https://doi.org/10.1016/j.semarthrit.2013.07.011
66. Marchesoni A, Zaccara E, Gorla R, Bazzani C, Sarzi-Puttini P, Atzeni F, Caporali R, Bobbio-Pallavicini F, Favalli EG (2009) TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci 1173(1):837–846. https://doi.org/10.1111/j.1749-6632.2009.04621.x
67. Markenson JA, Gibofsky A, Palmer WR et al (2011) Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. J Rheumatol 38(7):1273–1281. https://doi.org/10.3899/jrheum.101142
68. Iannone F, Santo L, Anelli MG, Bucci R, Semeraro A, Quarta L, D'Onofrio F, Marsico A, Carlino G, Casilli O, Cacciapaglia F, Zuccaro C, Falappone PC, Cantatore FP, Muratore M, Lapadula G (2017) Golimumab in real-life settings: 2 years drug survival and predictors of clinical outcomes in rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. Semin Arthritis Rheum 47(1):108–114. https://doi.org/10.1016/j.semarthrit.2017.01.008
69. Kievit W, Fransen J, Adang EMM, den Broeder AA, Bernelot Moens HJ, Visser H, van de Laar MAF, van Riel PLCM (2011) Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. Rheumatology (Oxford) 50(1):196–203. https://doi.org/10.1093/rheumatology/keq325
70. Kristensen LE, Kapetanovic MC, Gulfe A, Soderlin M, Saxne T, Geborek P (2008) Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford) 47(4):495–499. https://doi.org/10.1093/rheumatology/ken002
71. Souto A, Maneiro JR, Gomez-Reino JJ (2016) Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford) 55:523–534. https://doi.org/10.1093/rheumatology/kev374
72. Leffers HC, Østergaard M, Glintborg B et al (2011) Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 70(7):1216–1222. https://doi.org/10.1136/ard.2010.140129
73. Gottenberg JE, Ravaud P, Cantagrel A, Combe B, Flipo RM, Schaeverbeke T, Houvenagel E, Gaudin P, Loeuille D, Rist S, Dougados M, Sibilia J, le Loët X, Marcelli C, Bardin T, Pane I, Baron G, Mariette X (2012) Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the "Orencia and Rheumatoid Arthritis" registry. Ann Rheum Dis 71(11):1815–1819. https://doi.org/10.1136/annrheumdis-2011-201109
74. Gottenberg JE, Courvoisier DS, Hernández MV et al (2016) Association of rheumatoid factor and anti-citrullinated protein antibody positivity with better effectiveness of abatacept: results from the Pan-European Registry Analysis. Arthritis Rheumatol 68(6):1346–1352. https://doi.org/10.1002/art.39595
75. Nüßlein HG, Alten R, Galeazzi M, Lorenz HM, Nurmohamed MT, Bensen WG, Burmester GR, Peter HH, Pavelka K, Chartier M, Poncet C, Rauch C, le Bars M (2015) Prognostic factors for abatacept retention in patients who received at least one prior biologic agent: an interim analysis from the observational, prospective ACTION study. BMC Musculoskelet Disord 16(1):176. https://doi.org/10.1186/s12891-015-0636-9
76. Soliman MM, Hyrich KL, Lunt M et al (2012) Effectiveness of rituximab in patients with rheumatoid arthritis: observational study from the British Society for Rheumatology Biologics Register. J Rheumatol 39(2):240–246. https://doi.org/10.3899/jrheum.110610
77. Couderc M, Gottenberg J-E, Mariette X, Pereira B, Bardin T, Cantagrel A, Combe B, Dougados M, Flipo RM, le Loet X, Shaeverbeke T, Ravaud P, Soubrier M, on behalf of Club Rhumatismes et Inflammations (2014) Influence of gender on response to rituximab in patients with rheumatoid arthritis: results from the Autoimmunity and Rituximab registry. Rheumatology (Oxford) 53(10):1788–1793. https://doi.org/10.1093/rheumatology/keu176
78. Pers Y-M, Schaub R, Constant E, Lambert J, Godfrin-Valnet M, Fortunet C, Bourichi W, Prades BP, Wendling D, Gaudin P, Jorgensen C, Maillefert JF, Marotte H (2015) Efficacy and safety of tocilizumab in elderly patients with rheumatoid arthritis. Joint Bone Spine 82(1):25–30. https://doi.org/10.1016/j.jbspin.2014.07.010
79. Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, Askling J, ARTIS Study Group (2015) Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 74(2):354–360. https://doi.org/10.1136/annrheumdis-2013-204128
80. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, French WJ, Rubison M (1998) Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med 158(9):981–988. https://doi.org/10.1001/archinte.158.9.981
81. Heer T, Schiele R, Schneider S, Gitt AK, Wienbergen H, Gottwik M, Gieseler U, Voigtländer T, Hauptmann KE, Wagner S, Senges J (2002) Gender differences in acute myocardial infarction in the era of reperfusion (the MITRA registry). AJC 89(5):511–517. https://doi.org/10.1016/S0002-9149(01)02289-5
82. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JMW (2001) Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 111(6):446–451. https://doi.org/10.1016/S0002-9343(01)00872-5
83. Palm O, Purinszky E (2005) Women with early rheumatoid arthritis are referred later than men. Ann Rheum Dis 64(8):1227–1228. https://doi.org/10.1136/ard.2004.031716
84. Mansfield A, Addis M, Mahalik J (2003) "Why won't he go to the doctor?": The psychology of men's help seeking. Int J Men's Health 2(2):93–109. https://doi.org/10.3149/jmh.0202.93
85. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, da Silva J, Nelson-Piercy C, Cetin I, Costedoat-Chalumeau N, Dolhain R, Förger F, Khamashta M, Ruiz-Irastorza G, Zink A, Vencovsky J, Cutolo M, Caeyers N, Zumbühl C, Østensen M (2016) The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 75(5):795–810. https://doi.org/10.1136/annrheumdis-2015-208840
86. Favalli EG, Biggioggero M, Meroni PL (2014) Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an "anchor" drug? Autoimmun Rev 13(11):1102–1108. https://doi.org/10.1016/j.autrev.2014.08.026

87. Förger F, Villiger PM (2016) Treatment of rheumatoid arthritis during pregnancy: present and future. Expert Rev Clin Immunol 12(9):937–944. https://doi.org/10.1080/1744666X.2016.1184973
88. Gerosa M, Schioppo T, Meroni PL (2016) Challenges and treatment options for rheumatoid arthritis during pregnancy. Expert Opin Pharmacother 17(11):1539–1547. https://doi.org/10.1080/14656566.2016.1197204
89. Benediktsson R, Calder AA, Edwards CR, Seckl JR (1997) Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. Clin Endocrinol 46(2):161–166. https://doi.org/10.1046/j.1365-2265.1997.1230939.x
90. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H (1996) Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol 36(5):248–255. https://doi.org/10.1111/j.1600-0897.1996.tb00172.x
91. Porter C, Armstrong-Fisher S, Kopotsha T, Smith B, Baker T, Kevorkian L, Nesbitt A (2016) Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer. J Reprod Immunol 116:7–12. https://doi.org/10.1016/j.jri.2016.04.284
92. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, Ullman T, Glover S, Valentine JF, Rubin DT, Miller J, Abreu MT (2013) Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 11(3):286–292. https://doi.org/10.1016/j.cgh.2012.11.011
93. Mariette X, Flynn A, Förger F et al (2017) Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, multicenter, pharmacokinetic study [abstract]. Ann Rheum Dis 76:57
94. Østensen M (2017) The use of biologics in pregnant patients with rheumatic disease. Expert Rev Clin Pharmacol 10(6):661–669. https://doi.org/10.1080/17512433.2017.1305268
95. Sangle SR, Lutalo PMK, Davies RJ, Khamashta MA, D'Cruz DP (2013) B-cell depletion therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. J Autoimmun 43:55–59. https://doi.org/10.1016/j.jaut.2013.03.001
96. Hoeltzenbein M, Beck E, Rajwanshi R, Gøtestam Skorpen C, Berber E, Schaefer C, Østensen M (2016) Tocilizumab use in pregnancy: analysis of a global safety database including data from clinical trials and post-marketing data. Semin Arthritis Rheum 46(2):238–245. https://doi.org/10.1016/j.semarthrit.2016.05.004
97. Kumar M, Ray L, Vemuri S, Simon TA (2015) Pregnancy outcomes following exposure to abatacept during pregnancy. Semin Arthritis Rheum 45(3):351–356. https://doi.org/10.1016/j.semarthrit.2015.06.016
98. Chang Z, Spong CY, Jesus AA, Davis MA, Plass N, Stone DL, Chapelle D, Hoffmann P, Kastner DL, Barron K, Goldbach-Mansky RT, Stratton P (2014) Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). Arthritis Rheumatol 66(11):3227–3232. https://doi.org/10.1002/art.38811
99. Nelson JL, Østensen M (1997) Pregnancy and rheumatoid arthritis. Rheum Dis Clin N Am 23(1):195–212. https://doi.org/10.1016/S0889-857X(05)70323-9
100. Barrett JH, Brennan P, Fiddler M, Silman AJ (1999) Does rheumatoid arthritis remit during pregnancy and relapse postpartum? Results from a nationwide study in the United Kingdom performed prospectively from late pregnancy. Arthritis Rheum 42(6):1219–1227. https://doi.org/10.1002/1529-0131(199906)42:6<1219::AID-ANR19>3.0.CO;2-G
101. Camacho EM, Farragher TM, Lunt M, Verstappen SMM, Bunn D, Symmons DPM (2010) The relationship between post-onset pregnancy and functional outcome in women with recent onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. Ann Rheum Dis 69(10):1834–1837. https://doi.org/10.1136/ard.2010.128769
102. Nørgaard M, Larsson H, Pedersen L, Granath F, Askling J, Kieler H, Ekbom A, Sørensen HT, Stephansson O (2010) Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. J Intern Med 268(4):329–337. https://doi.org/10.1111/j.1365-2796.2010.02239.x
103. Wolfberg AJ, Lee-Parritz A, Peller AJ, Lieberman ES (2004) Association of rheumatologic disease with preeclampsia. Obstet Gynecol 103(6):1190–1193. https://doi.org/10.1097/01.AOG.0000126279.87151.e1
104. Skomsvoll JF, Østensen M, Irgens LM, Baste V (1999) Perinatal outcome in pregnancies of women with connective tissue disease and inflammatory rheumatic disease in Norway. Scand J Rehabil Med 28(6):352–356. https://doi.org/10.1080/03009749950155337
105. Bharti B, Lee SJ, Lindsay SP, Wingard DL, Jones KL, Lemus H, Chambers CD (2015) Disease severity and pregnancy outcomes in women with rheumatoid arthritis: results from the Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project. J Rheumatol 42(8):1376–1382. https://doi.org/10.3899/jrheum.140583
106. Chighizola CB, Raimondo MG, Meroni PL (2017) Does APS impact women's fertility? Curr Rheumatol Rep 19(6):33. https://doi.org/10.1007/s11926-017-0663-7
107. Martínez-Sánchez N, Pérez-Pinto S, Robles-Marhuenda Á, Arnalich-Fernández F, Martín Cameán M, Hueso Zalvide E, Bartha JL (2017) Obstetric and perinatal outcome in anti-Ro/SSA-positive pregnant women: a prospective cohort study. Immunol Res 65(2):487–494. https://doi.org/10.1007/s12026-016-8888-5
108. Østensen M (2017) Preconception counseling. Rheum Dis Clin N Am 43(2):189–199. https://doi.org/10.1016/j.rdc.2016.12.003
109. Østensen M, Villiger PM (2007) The remission of rheumatoid arthritis during pregnancy. Semin Immunopathol 29(2):185–191. https://doi.org/10.1007/s00281-007-0072-5
110. Tang MW, Garcia S, Gerlag DM, Tak PP, Reedquist KA (2017) Insight into the endocrine system and the immune system: a review of the inflammatory role of prolactin in rheumatoid arthritis and psoriatic arthritis. Front Immunol 8. https://doi.org/10.3389/fimmu.2017.00720
111. Hurley WL, Theil PK (2011) Perspectives on immunoglobulins in colostrum and milk. Nutrients 3(12):442–474. https://doi.org/10.3390/nu3040442
112. Clowse MEB, Förger F, Hwang CC et al (2017) Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicenter, pharmacokinetic study [abstract]. Ann Rheum Dis 76:548
113. Bragnes Y, Boshuizen R, de Vries A, Lexberg Å, Østensen M (2017) Low level of rituximab in human breast milk in a patient treated during lactation. Rheumatology (Oxford) 56(6):1047–1048. https://doi.org/10.1093/rheumatology/kex039
114. Clowse MEB, Chakravarty E, Costenbader KH, Chambers C, Michaud K (2012) Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res 64(5):668–674. https://doi.org/10.1002/acr.21593
115. Brouwer J, Hazes JMW, Laven JSE, Dolhain RJEM (2015) Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis 74(10):1836–1841. https://doi.org/10.1136/annrheumdis-2014-205383
116. Ince-Askan H, Dolhain RJEM (2015) Pregnancy and rheumatoid arthritis. Best Pract Res Clin Rheumatol 29(4-5):580–596. https://doi.org/10.1016/j.berh.2015.07.001
117. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KA, Nordvag BY, Koldingsnes W, Mikkelsen K, Kaufmann C, Kvien TK (2011) Fertility in women with chronic inflammatory arthritides.

Rheumatology (Oxford) 50(6):1162–1167. https://doi.org/10.1093/rheumatology/keq458

118. de Jong PHP, Dolhain RJEM (2017) Fertility, pregnancy, and lactation in rheumatoid arthritis. Rheum Dis Clin N Am 43(2):227–237. https://doi.org/10.1016/j.rdc.2016.12.004
119. Provost M, Eaton JL, Clowse MEB (2014) Fertility and infertility in rheumatoid arthritis. Curr Opin Rheumatol 26(3):308–314. https://doi.org/10.1097/BOR.0000000000000058
120. Brouwer J, Laven JSE, Hazes JMW, Schipper I, Dolhain RJEM (2013) Levels of serum anti-Müllerian hormone, a marker for ovarian reserve, in women with rheumatoid arthritis. Arthritis Care Res 65(9):1534–1538. https://doi.org/10.1002/acr.22013
121. Whirledge S, Cidlowski JA (2013) A role for glucocorticoids in stress-impaired reproduction: beyond the hypothalamus and pituitary. Endocrinology 154(12):4450–4468. https://doi.org/10.1210/en.2013-1652
122. O'Morain C, Smethurst P, Doré CJ, Levi AJ (1984) Reversible male infertility due to sulphasalazine: studies in man and rat. Gut 25(10):1078–1084. https://doi.org/10.1136/gut.25.10.1078
123. Gutierrez JC, Hwang K (2017) The toxicity of methotrexate in male fertility and paternal teratogenicity. Expert Opin Drug Metab Toxicol 13(1):51–58. https://doi.org/10.1080/17425255.2017.1230198
124. Puchner R, Danninger K, Puchner A, Pieringer H (2012) Impact of TNF-blocking agents on male sperm characteristics and pregnancy outcomes in fathers exposed to TNF-blocking agents at time of conception. Clin Exp Rheumatol 30(5):765–767