Effect of reproductive factors on rheumatoid arthritis

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Rheumatoid arthritis is a progressive autoimmune disease that has long been observed to preferentially affect women. Many studies have tried to elucidate the relationship between disease activity and fertility, pregnancy, breastfeeding, oral contraceptives and hormone replacement therapy. Data from large prospective cohorts, as well as an enhanced understanding of its pathophysiology, have helped to more completely characterize this complicated relationship.

Rheumatoid arthritis (RA) is a chronic, multisystemic disease whose pathogenesis remains imprecisely defined. Advances in molecular biology have led to the current description of a chronic inflammatory disorder mediated by both B and T lymphocytes [1,2] that primarily affects synovial tissue and leads to increased morbidity and mortality through widespread joint and vascular injury [3–8]. It is generally accepted that RA affects approximately 1% of North American and Northern European adults and overall strikes approximately two- to three-times as many women as men [9–11]. The ratio of women to men affected ranges from approximately 4:1 before 30 years of age to 1:1 after 59 years of age [12,13]. These patients may also experience poor outcomes due to an increasing burden of comorbidities with age. The clinical course of RA is fluctuating and unpredictable, with approximately 10–20% of patients having minimal disability 10 years after diagnosis and approximately 50% having significant physical impairment [14]. The presentation of RA in persons over 60 years of age tends to differ from that of younger-onset RA, with less peripheral joint involvement, more constitutional inflammatory symptoms and a lower prevalence of serum rheumatoid factor [15,16]. The presence of rheumatoid factor and decreased functional capacity at diagnosis are poor prognostic factors, as are the early emergence of radiographic erosions [17]. Overall, the lives of RA patients are shortened by 5–10 years [18,19].

Given the general predilection of RA to preferentially affect women and the recognition that pregnancy often results in variation of disease severity [20,21], we will review the factors that may partially account for true sex differences. These include exposure to contraceptive and noncontraceptive hormones, fecundity and fertility, breastfeeding and lactation, persistent microscopic expression of nonself molecules (microchimerism) and perturbations in sex hormones with the resulting dysregulation of neuroendocrine–immune regulation.

Neuroendocrine dysregulation

In the study of RA as a neuroendocrine disorder, the varied effects of sex hormones must be considered. It is understood that, in autoimmune diseases, physiologic concentrations of estrogens act to enhance the immune response while progestins, androgens and pharmacologic levels of estrogens serve to mute it [22–24]. This change in the immune-response profile is postulated to occur through the switching of the immune response from a T helper (Th)1 to a Th2 effect through alterations in the levels of Th1 and Th2 cytokines [22,25,26]. Evidence also exists demonstrating that this hormonal milieu can directly influence both the cellular [27] and humoral [28] immune response. In addition, strong evidence exists for the impaired secretion of adrenal androgens in both men and women with RA [29,30]. Further experimental data have demonstrated that plasma levels of the androgen precursor dihydroepiandrosterone sulfate (DHEA-S) were significantly lower in premenopausal women with RA than in healthy controls, both before and after the onset of disease [31], while the cytokine tumor necrosis factor-α has been shown to impair the conversion of precursor DHEA-S to the active form DHEA in the synovium of RA patients [32]. Taken together, these data are consistent with empiric observations of female predominance, along with pregnancy and exogenous hormonal protective roles that have been suggested in the development of RA.

Pregnancy & microchimerism

The ameliorative effect of pregnancy on RA was first recognized by Hench, who, in 1938, described the relief of symptoms in 22 pregnant

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women [33]. A total of 20 of these 22 women experienced significant relief during multiple pregnancies (37 pregnancies in total). Further case series have confirmed the substance of these observations, with a case–control study demonstrating RA remitting in approximately 75% of 345 pregnancies [34]. An attempt to more precisely define this effect prospectively, using validated disease measures and consistent case definitions, encountered difficulty in accruing enough patients to reach definitive conclusions [35]. A nationwide prospective survey of 140 women from the UK demonstrated significant variation in outcomes of arthritis during pregnancy but with general confirmation of earlier results that show pregnancy is an ameliorating factor [36]. Furthermore, recently available studies demonstrate that prospectively followed pregnant women with RA develop a statistically significant (although clinically small) disease amelioration, as measured by a common disease activity score (the DAS28-CRP3); a change from 3.8 in the first trimester to 3.4 in the third trimester ($p = 0.003$) [37]. Overall, the model of disease remission in pregnancy is supported by the majority of evidence, with the risk for disease relapse being highest in the first 6 months after delivery [38] and after the first pregnancy [39].

As noted previously, a postulated mechanism for the disease modulation of RA in pregnancy and post-partum is the Th1 to Th2 shift. Evidence that maternal–fetal human leukocyte antigen (HLA) class II incompatibility contributed to this modulation was initially reported by Nelson and colleagues in 1993 [40]. In this study, patients experienced the most significant degree of disease remission when the maternal–fetal *HLA-DQA* alleles were discordant (i.e., not matched as *DQA1* or *DQA2*), [41]. This concept was supported in a 1998 study by van der Horst-Bruinsma, who demonstrated a likelihood of disease remission, given a maternal–fetal mismatch at major histocompatibility complex-II. The odds ratio (OR; 95% confidence interval [CI]) of remission for pairs mismatched at *DQA1* was 8.02 (0.97–66.06) and 8.79 (1.07–72.46) for those mismatched at *DQB1* [42]. As reported by Nelson and colleagues, the estimated OR for disease remission was 9.7 (2.2–43.9) for combined disparities at the *HLA-DRB1*, *-DQA* and *-DQB* alleles [40]. A prospective study that included women with any inflammatory arthritis attempted to replicate these findings but was unable to confirm a statistically significant relationship [43]. Microchimerism leads to the presence and persistence of nonself, potentially immunogenic particles in the circulation, which have been acquired frequently through pregnancy [44,45]. Early studies reported the presence of maternal–fetal disparities in HLA-II antigens, while later work compared microscopic levels of foreign DNA. This direct relationship between maternal serum levels of nonself DNA and the remission and relapse of inflammatory arthritis during pregnancy and post-partum is beginning to be studied and characterized [46]. Recent studies have found the existence of male microchimerism in women without male children, suggesting methods of acquiring nonself molecules other than through pregnancy, and possibly a higher prevalence in women [47]. Although mechanisms are unclear at this point, an enhanced understanding of this phenomenon holds promise [48,49].

Lactation & breastfeeding

An early published description of RA flares with lactation was made by Osler, who described atrophic (rheumatoid) arthritis that had remained quiescent during pregnancy and then clinically worsened after breastfeeding began [50]. Retrospective analysis of 176 women found increasing disease severity with longer duration of breastfeeding, as well as with a history of more breast-fed children [51]. This prospective study of 137 women showed that having three or more breast-fed children was associated with having more severe disease [52]. This study also showed a general worsening course post-partum, corresponding with lactation, although statistical significance was not reached [52]. These data demonstrate that a worsening disease course corresponds directly with prolonged lactation. However, some investigators have found an inverse relationship between disease progression and prolonged lactation. Two retrospective Scandinavian studies presented nonsignificant trends toward a decreased risk of RA in women with increased duration of lactation and breastfeeding [53,54]. Similar data have been enumerated from the Nurses' Health Study of 121,700 women [55]. Briefly, the Nurses' Health Study followed 121,700 female registered nurses (30–55 years of age) who returned mailed health questionnaires. This cohort is well-described elsewhere and has been used to study epidemiologic trends in cancer and cardiovascular disease [56,57].

These epidemiologic observations showing potential links of disease activity with lactation are made more plausible by the elucidation of a potential biologic mechanism. Reports have

Box 1. Disease-modifying factors and their effects.

Pregnancy

- A large minority of patients – approximately one-third – achieve significant amelioration

Post-partum

- A significant rate of relapse, most within 6 months post-partum

Exogenous hormonal effects

- Neither oral contraceptives nor hormone-replacement therapy have been consistently shown to have a beneficial or deleterious effect on rheumatoid arthritis

Fertility and fecundity

- Women with decreased fecundity have a higher incidence of rheumatoid arthritis

suggested a linkage disequilibrium between *HLA-DR4* and prolactin gene (*prl*) polymorphisms on chromosome 6p22 [58]. Earlier studies have shown a potential role for prolactin in autoimmunity [59] and in the development of RA [60]. There is also evidence suggesting that prolactin influences immunity by predisposing toward a Th1 versus Th2 response [61]. This Th1/Th2 paradigm is believed to be relevant to pregnancy and autoimmune disease through the promotion of cellular immune response cytokines by Th1, while the Th2 phenotype tends toward a humoral or antibody-mediated immune response [62,63]. Our current knowledge of RA as a Th1-mediated process suggests that a neuroendocrine environment that promotes such a response would lead to disease progression or flare, while an environment that promotes a Th2 response would lead to amelioration of the disease [64,65].

Fertility & childbearing

To examine the effect of childbearing on disease activity, various authors have examined the effects of fecundity (the potential for childbearing), fertility (the number of children born) and adverse pregnancy outcomes (defined by those cited as spontaneous abortion ≤25 weeks) on RA. These studies used clear clinical end points, such as the development or progression of disease and long-term outcome. The conclusions in these studies are not completely cohesive, but show that longer time before childbearing increases the risk of developing RA. A case–control study of 1517 women showed decreased fecundity (defined here as ≥1 year before conception) in RA patients versus age-matched, disease-free controls [66]. This is consistent with a proposed 'pregnancy protective' role in RA, while two other studies (one involving 102 women and the other 15,441 women) showed no significant association between fecundity or fertility and RA [67,68]. In an examination of adverse pregnancy outcomes, studies carried out in The Netherlands demonstrated that there was a trend for women with a history of miscarriage to have greater disease progression [69], while another noted that women with multiple pregnancies tended toward less radiographic joint damage [70].

Exogenous hormonal influences

The role of exogenous sex hormones has been debated extensively for many years. Studies of oral contraceptives and other female sex hormone are inconclusive and conflicting with respect to the risk of developing RA or existing disease. Observational studies of this type have many inherent self-selection and ascertainment biases that may compromise the validity of conclusions drawn about cause–effect relationships [71–73]. The Royal College of General Practitioners study in 1978 found that the development of RA was reduced by half in women who used oral contraceptive pills (OCPs) [74]. Other additional studies replicated these findings [75], and further suggested that the protective effect extended to the use of any noncontraceptive hormone [76]. However, two case–control studies performed in Olmstead County (MN, USA) showed no association with the use of either contraceptive or noncontraceptive hormones [77,78]. Later studies have provided conflicting results, including a report that found OCPs reduced the risk of RA in a time-dependent fashion, with the greatest protection in those who had taken OCPs between the ages of 31 and 40 years (relative risk [RR]: = 0.15; 95% CI: 0.05–0.44) [79]. In a subset analysis of this same study, it was observed that only those who had 'ever used' OCPs had a statistically significant reduction in risk, while those with 'current use' demonstrated a nonsignificant trend toward risk reduction. Contradicting these results, another retrospective study found that only current OCP use was protective [80].

A meta-analysis conducted in 1989 examined the conflicting studies of OCPs in RA to that point. As of 1989, a total of 3977 patients had been examined in case–control studies and 184,732 had been studied in three cohort studies. Analysis of the case–control studies showed an OR of 0.79 (95% CI: 0.58–1.08) for disease

development in patients who had 'ever used' OCPs, an OR of 0.98 (0.34–2.77) for current use and an OR of 0.73 (0.49–1.08) for past use. The overall evaluation of risk-to-benefit showed an OR of 0.65 (0.39–1.08) [81]. The cohort studies included 184,732 patients and, of the nine subgroups evaluated (past use, current use or ever use for each), only one showed an unambiguous risk reduction – an OR of 0.49 (0.29–0.83) – in the current use of OCPs. These were reviewed but not included in the meta-analyses, as the authors believed methodological differences would be too great to include them with the case–control studies. The conclusion of these analyses was that the data were sufficiently ambiguous and therefore no clear relationship could be discerned [81].

A second meta-analysis of the same studies was performed using the 'odd-man-out' technique, removing the most visually discordant value of each set of prospective and retrospective studies, as they were plotted [82,83]. This report showed an adjusted OR of 0.60 (0.48–0.75) for case–control studies and 0.88 (0.70–1.12) for cohorts. The combined adjusted OR was 0.73 (0.61–0.85), supporting a protective effect of OCPs on the development of RA. Notably, there has been some work that has examined this topic since these meta-analyses were published. A cohort studied in the Iowa Women's Health Study (IWHS) concluded that there was no evidence of a relationship between the use of contraceptive hormones and the development of RA in older women [84]. The IWHS cohort has been described elsewhere [85,86] but, briefly, it is a population-based, prospective study that began in 1986, using results from returned postal questionnaires. It enrolled 41,836 women, aged 55–69 years, with a response rate of 43%. Divergent from the IWHS result, however, a significant risk reduction was found in the 'ever used OCPs' group of women in a case–control study of Rochester County (MN, USA) [87].

The use of noncontraceptive hormones has also been studied. A case–control study of perimenopausal and post-menopausal women in 1986 demonstrated a fourfold reduction in risk as an effect of HRT [76]. This result could not be replicated, however, as a cohort study sponsored by the Arthritis and Rheumatism Council (UK) found a trend toward increased risk (OR: 1.62) but with such a wide-ranging 95% CI (0.56–4.74) that a clear trend could not be elucidated [88]. Concurrent and later studies have confirmed that, in essence, the effects of HRT are widely divergent [89–91]. Such divergent results are observed in the IWHS, which showed an age adjusted RR of 1.02 (0.61–1.72) for current users of HRT, whereas former users showed an increased RR of 1.47 (1.04–2.06) [84].

Executive summary

Introduction & fundamental concepts

- Rheumatoid arthritis (RA) is a chronic, multisystemic disease that affects approximately 1% of the North American and European population and leads to significantly increased morbidity and mortality.
- RA preferentially affects women throughout the reproductive years; however, after the menopause, the male to female ratio becomes approximately 1:1.

Exposure to exogenous hormones (contraceptive & noncontraceptive)

- Extensive studies have been performed on the role of exogenous hormones (such as oral contraceptives and hormone-replacement therapy) in RA.
- The role that these medications play in the pathogenesis of RA is unclear at this time.

Fertility & fecundity

- The preponderance of evidence suggests:
  – In general, women with decreased fecundity have a higher incidence of RA than age-matched controls
  – The rate of relapse of RA is worst in the 6 months post-partum.

Expression of nonself molecules – microchimerism

- Evidence supports a role for persistence of discordant, human leukocyte antigen (HLA) unmatched fetal antigens in maternal circulation. This may serve as an immunomodulator and act to suppress disease activity, especially depending on the degree of HLA disparity.

Neuroendocrine-immune axis dysregulation & alterations in circulating sex hormones

- The neuroendocrine environment in RA – characterized by a relative androgen to estrogen deficiency – is altered to one that promotes a primarily cellular (T helper type 1–T-lymphocyte meditated) versus a primarily humoral (T helper type 2–B-lymphocyte/plasma cell and antibody-mediated immune response).

In short, there appears to be a trend toward protection with exogenous hormone therapy; however, given the wide confidence intervals, the effect is likely to be relatively small.

Summary & conclusion

In summary, RA is a complex inflammatory disorder with an as yet undefined etiology. There is a clear predilection for women in the reproductive age that dissipates as menopause is reached. Remission with pregnancy is frequently observed, although the effect is variable and often fades after parturition, often concomitant with breastfeeding. Several studies have suggested a link between exogenous contraceptive and non-contraceptive hormones but the evidence is not sufficient to discern an unambiguous relationship. Future research in topics, such as microchimerism and androgen to estrogen ratios, will probably play a large role in continuing to elucidate this complicated relationship between RA outcome and reproductive factors.

Disclosures

The authors declare that they have no financial conflict of interest relevant to this manuscript.

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