Fertility, Pregnancy, and Lactation in Rheumatoid Arthritis

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KEYWORDS

• Rheumatoid arthritis • Pregnancy • Fertility • Disease activity • Lactation

KEY POINTS

- Fertility is impaired in women with rheumatoid arthritis (RA), which is related to disease activity and the use of certain medications (nonsteroidal anti-inflammatory drugs and prednisone >7.5 mg daily).
- Although disease activity often improves in pregnancy, a substantial number of patients with RA still have active disease during pregnancy.
- Pregnancy outcomes in patients with RA are slightly less favorable compared with the general population, especially in patients with active disease.
- A treat-to-target strategy, aiming for low disease activity, is recommended for patients with RA who wish to conceive.
- Increasing evidence exists to suggest safety of tumor necrosis factor inhibitors in patients with RA who are pregnant or have a desire for pregnancy.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of multiple joints. Approximately 1% of people in western countries suffer from RA. RA often affects women and men in the prime of their lives, which is the period wherein decisions about parenthood are made. In women with RA, however, it seems to be more difficult to conceive, as a result of the disease and/or treatment.[1–3]

During pregnancy, disease activity often improves, although less than previously thought. A substantial number of patients with RA still have active disease during pregnancy and so use of antirheumatic drugs may be unavoidable, especially given

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that active disease is negatively associated with pregnancy outcome. However, some drugs, including methotrexate, are known to be teratogenic during pregnancy; additionally, safety data on other medications during pregnancy are lacking. Nevertheless, more medications are compatible with pregnancy than previously appreciated. Therefore, this review considers fertility, pregnancy, and lactation issues in relation to RA (activity) and/or use of antirheumatic drugs.

FERTILITY

Female Perspective

Several studies indicate that family size is diminished in women with RA as a result of impaired fertility, which already may be present before the diagnosis of RA is made.[1–3] Women with RA experience more difficulties in conceiving, as indicated by a longer time to pregnancy (TTP). Previous studies showed that 25% to 42% of patients with RA did not conceive within 1 year.[4] For comparison, in the general population, the median prevalence of subfertility, defined as TTP of greater than 12 months, is 9%, with a range of 3.5% to 24.2% depending on the geographic area.[5]

Different factors might be associated with the impaired fertility. Earlier menopause has been reported in women with RA, and it has been postulated that these patients may have a smaller ovarian reserve.[6] This could explain both impaired fertility as well as earlier menopause. In early RA, the levels of serum anti-Müllerian hormone (AMH), a reliable biomarker for ovarian reserve, did not differ from healthy controls.[7] On the other hand, Henes and colleagues[8] showed that AMH levels are decreased in established RA, suggesting that ovarian reserve declines secondary to the RA disease process.

Personal choices, due to RA-related concerns, have been shown to be at least partially responsible for the smaller family size, but cannot account for the observed impaired fertility.[9] Disease activity, on the other hand, appears to contribute to impaired fertility. Brouwer and colleagues[4] showed that 67% of women with active disease (Disease Activity Score-28 [DAS28] >5.1) had a TTP of more than 1 year compared with 30% in women in remission (DAS28 <2.6).

Antirheumatic drugs also have been associated with increased TTP,[4,10] including nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone (in a dose >7.5 mg daily).[4] NSAIDs inhibit the production of prostaglandins, which play a role in ovulation and blastocyst implantation.[6] The effect of glucocorticoids on fertility is possibly due to (1) a transient suppression of the hypothalamic-pituitary-ovarian axis or (2) a direct effect on the ovarian function and/or endometrium.[11,12] It has been postulated that previous use of methotrexate (MTX) might impair fertility. The association between MTX and impaired fertility is mainly based on studies in oncology and animal models.[6] Recent studies, however, demonstrated that prior and short-term MTX treatment, respectively, did not affect the TTP and ovarian reserve.[4,7]

Another reason for the impaired fertility in patients with RA might be a result of a lower intercourse frequency.[6] These studies, however, were mainly conducted in postmenopausal patients with RA, and it is unclear whether this also applies to younger patients with RA with a desire to conceive.[6]

Male Perspective

Less is known about fertility problems and pregnancy outcomes in male patients with RA, because no good studies have been performed. Lower testosterone levels have been described in men with RA, but whether this results in lower fertility is not known.[13]

Additionally, literature about the effect of antirheumatic drugs on fertility are scarce. Sulfasalazine (SSZ) may cause oligospermia, reduce sperm motility, and increase