Reproductive health in women with ankylosing spondylitis: contraception and fertility. A narrative review

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SUMMARY

Objective. The knowledge of ankylosing spondylitis is rising, and more and more attention is being paid to the diagnosis of this pathology in females. The purpose of this narrative review is to emphasize the role of reproductive health in women with ankylosing spondylitis, with particular attention to contraception and fertility.

Methods. A comprehensive review of the literature was performed to evaluate the reproductive health of women with ankylosing spondylitis.

Results. Oral contraception has been shown to be safe in women with ankylosing spondylitis, with no contraceptive benefits that should be evaluated during counseling. In the literature, there is no strong data regarding fertility in women with ankylosing spondylitis. It seems that these women may have impaired fertility due to reduced ovarian reserve, pharmacological treatments, and reduced sexual activity due to the concern that offspring may contract the disease. A multidisciplinary approach is needed in these women to ensure an adequate evaluation of sexual activity as an important aspect of quality of life and to counsel regarding family planning to address patients' concerns on contraception, fertility desire, and fertility preservation.

Conclusions. Lifestyle factors should be investigated to improve fertility and disease activity without medications. Further trials are needed to investigate the reproductive health of women with ankylosing spondylitis.

***Key words**: Ankylosing spondylitis, contraception, fertility, fertility preservation, reproductive health.*

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INTRODUCTION

Ankylosing spondylitis (AS) is a rheumatologic disorder characterized by chronic inflammation, affecting primarily the sacroiliac joints and the spine, and occasionally peripheral joints with extra-articular manifestations (1). Although AS has been considered a predominantly male disease, with a sex ratio of up to 10:1, trials in the literature show that the incidence in females is as high as 1:2 in favor of men (2). The reason for the perception of the disease as predominantly male is due to the fact that the clinical presentation of AS is different depending on gender, and this can lead to incorrect recognition of the disease in women with a significant diagnostic delay compared to men. In fact, it seems that women have less structural damage to the spine but greater limitations in physical function (3). AS is often associated with other autoimmune disorders (4, 5), and it is typically diagnosed during the second and third decades of life (6); therefore, most women are diagnosed with the disease during their reproductive age.

The average age of first-time mothers has progressively moved forward for social and cultural reasons (7), and many women might desire contraception when they are diagnosed with AS. Among women who desire to conceive at a young age, most have not conceived yet or have not completed the reproductive plan when they are diagnosed with AS.

Other autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome have been correlated with hormonal contraceptive is-

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sues (8-10), fertility problems (9), and pregnancy complications (3, 11, 12). Few data are available in the literature regarding contraception and fertility in women with AS, and therefore it becomes difficult to carry out correct counseling for the patient, provide adequate family planning, ensure adequate contraception, and discuss the possible impact of the disease on fertility when women wish to become pregnant and evaluate the possibility of preserving fertility at a young age.

This study aims to summarize the available data from the literature regarding contraception and fertility in women with AS.

CONTRACEPTION IN WOMEN WITH ANKYLOSING SPONDYLITIS

Effective contraception in women with rheumatic diseases can be extremely important to avoid the risks of an unplanned pregnancy that could worsen disease activity and lead to organ damage or adverse pregnancy outcomes (pregnancy loss, severe prematurity, and intrauterine growth restriction) (12). It has been shown that before seeking pregnancy, it is necessary for the disease to have been in remission for at least 6 months to avoid flare-ups and adverse outcomes (13). The effect of estrogens on inflammation and rheumatic disease activity is complex, as their immunomodulatory role can be paradoxical. In fact, estrogen is associated with the suppression of inflammation, while estrogen metabolites can have the opposite effect. In systemic lupus erythematosus and rheumatoid arthritis, increased levels of estrogen metabolites have been found in synovial tissue, suggesting a correlation between estrogens and disease activity. In women with AS, oral contraceptive pills have been shown to be safe, and it has been demonstrated that there is no association with a measurable effect on the initiation or severity of AS (14). When combined estrogen-progestin pills are administered, not only contraception but also no contraceptive benefits should be evaluated. Estrogens are associated with the suppression of bone resorption. This aspect should be considered particularly in women with AS, as the prevalence of osteoporosis and fractures in AS reaches 34.4% and 24.6%, respectively (15). The beneficial effect of hormonal contraceptives on bone density has long been known (16). As a routine, before prescribing estrogen-progestin therapy, knowing the patients's personal and family history and clinical evaluation is critical for their appropriate prescription. In particular, attention should be paid to requests for information on hormone-sensitive oncological pathologies, thrombophilia or previous venous thromboembolism, heart disease, vasculopathy, smoking, obesity, hypertension, migraine, diabetes, hyperlipidemia, and hepatobiliary disease (17). In women with AS, possible complications of the disease should be ruled out since they have a higher risk of cardiovascular issues such as aortic insufficiency, cardiomegaly, aorta dilatation, cardiac conduction anomalies (18), pulmonary fibrosis (19), inflammatory bowel disease (20). If any of these complications are present, the pros and cons of systemic estrogen-progestin hormone ther-

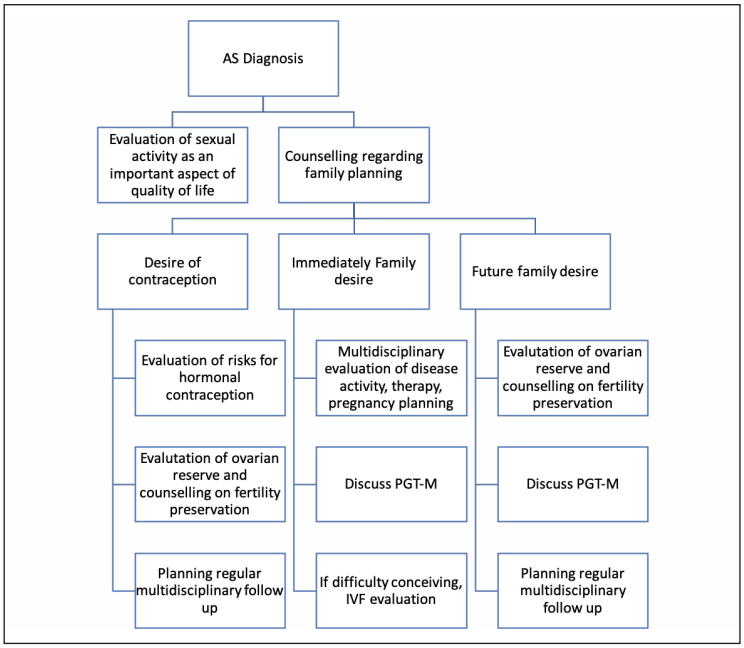

Figure 1 - Flowchart of reproductive health management in women with ankylosing spondylitis. AS, ankylosing spondylitis; PGT-M, preimplantation genetic testing for monogenic defect; IVF, *in vitro* fertilization.

apy should be evaluated, and if necessary, other contraceptive measures, such as intrauterine devices, should be considered (Figure 1).

FERTILITY IN WOMEN WITH ANKYLOSING SPONDYLITIS

There is a lack of literature data regarding the correlation between fertility and AS; the available data are scanty and of poor quality, deriving from studies with limitations (21-26).

While nulliparity is significantly higher in women with autoimmune diseases than in controls, few trials have focused specifically on AS. In 1998, Ostensen *et al.* investigated fertility in women affected by AS through a questionnaire applied in 13 different countries and found no evidence of impaired fertility, but a healthy control group was lacking in this study (21). Moreover, since 1998, the diagnostic capacity and therapeutic proposals for AS have changed considerably.

In several studies (21-27), data regarding disease activity and characteristics that can affect fertility, such as smoking, body mass index, accompanying diseases, ovarian reserve, and characteristics of the partner, have not always been investigated. A higher proportion of women with AS were childless compared to birth-year-matched references, but the enrolled women were not asked if they were looking for a baby (28). Assuming these data are correct, there could be many hypotheses about why a woman with AS is, on average, more frequently childless than a healthy woman. In fact, an active and aggressive disease could reduce sexual activity and, consequently, the chance of getting pregnant.

While several studies investigated the association between rheumatic diseases and ovarian reserve (22, 23, 29), data investigating this association in AS women is lacking. In 2008, Aslanidis *et al*. described a case report of a woman with AS who underwent premature ovarian insufficiency (POI), a condition that is often associated with reduced ovarian reserve (24). AS therapy can interfere with the possibility of getting pregnant (30). Women with significant disease activity use non-steroidal anti-inflammatory drugs (NSAIDs) for long periods, which can have a negative impact on ovulation and implantation (30, 31). The use of COX-2 inhibitors, a type of NSAID, has been associated with luteinized unruptured follicle syndrome, resulting in infertility (25). This has been demonstrated in women exposed to continuous high-dose administration of NSAIDs, particularly in patients with inactive disease. A possible explanation is that in these cases there is an inflammation suppression that prevents the release of follicular prostaglandins, resulting in the failure of follicle rupture (25).

Moreover, the risk of miscarriage with the use of NSAIDs has been well documented in the literature. As a consequence, women with AS should wait to be in remission before trying to conceive (30, 31). Another factor that can limit the desire to conceive is the concern that offspring may contract the disease. After genetic counseling, the possibility of performing assisted reproductive techniques and preimplantation genetic testing for monogenic disorders, such as HLA-B27, should be discussed to ensure the possibility of transferring the embryo without genetic predisposition (32, 33). Also, when AS is diagnosed after the first birth, there is a delay in conceiving again, with an increased interval between the previous and the next pregnancy (28). It is advisable to periodically discuss family planning, considering the severity of the pathology, the type of treatment, the time necessary for the stabilization of the pathology, and the time from diagnosis to pregnancy. Moreover, sexual activity should be investigated, and the ovarian reserve should be periodically assessed in relation to age and other possible concomitant causes of infertility (Figure 1).

In these patients, particular attention should be paid to changing the modifiable factors that may contribute to a worse outcome of the disease or fertility, such as smoking (34, 35). Several studies have demonstrated a dose-dependent adverse effect of smoking on fertility, with an association with shorter menstrual cycles that could result in re-

duced fecundity and accelerated follicular depletion. In addition, an earlier age of menopause, occurring 1-4 years earlier in smoking women than in nonsmokers, has been demonstrated (34, 35). While smoking has a clear role in other autoimmune diseases like rheumatoid arthritis, the effect of smoking on women with AS is far from simple (36).
It seems that smoking is associated with higher disease activity, probably due to increased inflammation (3, 37). Women with AS should be educated on the benefits of a healthy lifestyle that is complementary to their drug and can improve the course of the disease and fertility (3, 37).

FERTILITY PRESERVATION IN WOMEN WITH ANKYLOSING SPONDYLITIS

Because the ovarian reserve might be compromised in women with AS (23, 24), it is important to counsel them at diagnosis regarding the possibility of issues with conception (Figure 1). Moreover, pregnancy should be planned in women with AS to try to conceive during remission of the disease (3, 11, 31). If a woman has a low ovarian reserve, the duration of treatment to obtain disease remission could worsen the ovarian reserve even further (38-40).
Oocyte and embryo cryopreservation are established techniques for fertility preservation in post-pubertal women (41). The choice of preservation techniques may be restricted by law in certain countries. The choice to cryopreserve oocytes or embryos is related to personal as well as social and cultural preferences (41). As most women with AS are diagnosed within the third decade of life, the most appropriate technique might be the cryopreservation of oocytes, as these women might not have a stable relationship (7).
Once fertility preservation has been achieved, women can also undergo rheumatological therapies, which may be contraindicated during pregnancy, until the disease is remitted (42). The patient can subsequently try to become pregnant naturally, and only in the event of failure to conceive can they utilize previously cryopreserved oocytes.
Another fertility preservation technique for medical reasons is cryopreservation and transplantation of ovarian tissue (43, 44), no longer considered experimental by the American Society of Reproductive Medicine since December 2019 (45). As POI can occur in systemic rheumatic diseases and is probably multifactorial (23, 24, 46), the transplantation of ovarian tissue could restore both fertility and endocrine function in these women (44). As discussed in the literature, the success of this approach depends on advances in cryopreservation, thawing, and transplantation techniques (44, 47). It is known that typically both the freezing-thawing process and the temporary ischemia after reimplantation result in the loss of about 2/3 of the follicles (44, 47).
An unresolved question is whether total or partial removal of an ovary reduces reproductive lifespan by a time equal to the duration of endocrine function acquired after autotransplantation (48). Unless there is a "zero" or positive balance, it is necessary to evaluate whether ovarian cryopreservation is truly the best fertility preservation technique for these patients (48).
Women with AS who undergo fertility preservation should do so in centers with appropriate expertise and a multidisciplinary approach. Gynecologists with experience in reproductive medicine should consult rheumatologists to find the best approach for fertility preservation and to minimize the risk to the patient.

CONCLUSIONS

Women diagnosed with AS face limitations in terms of reproductive health. Therefore a multidisciplinary approach is necessary to evaluate the possibility of contraception, if desired, and to evaluate the ovarian reserve and the reproductive plan. Further trials are needed to investigate the reproductive health of women with AS.

Contributions
LM, AA, conception and design; LM, draft of the manuscript; AA, manuscript revision.

Conflict of interest
The authors declare no potential conflicts of interest.

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