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Review article

DECREASED OVARIAN FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and systemic manifestations. Recent studies have explored the potential impact of RA on ovarian function in affected women. This review aims to summarize the existing literature on the relationship between decreased ovarian function and RA, including the possible mechanisms involved and the clinical implications for affected patients. RA treatments, such as disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids, may influence ovarian function. Methotrexate, a commonly used DMARD, has been associated with an increased risk of ovarian toxicity and impaired follicular development. Glucocorticoids may affect ovarian function through their suppressive effects on the hypothalamic-pituitary-gonadal (HPG) axis. Genetic factors and autoantibodies associated with RA are potential contributors to ovarian dysfunction. Genetic polymorphisms in genes involved in immune regulation and hormone metabolism have been linked to both RA susceptibility and ovarian dysfunction. Autoantibodies, such as anti-Müllerian hormone antibodies, have been detected in the serum of RA patients and could potentially interfere with ovarian function. Decreased ovarian function in RA patients may have implications for fertility, reproductive outcomes, and overall quality of life. Women with RA have been found to have an increased risk of adverse reproductive outcomes, including miscarriage and early menopause. In conclusion, there is evidence to suggest an association between RA and decreased ovarian function. Chronic inflammation, hormonal dysregulation, RA treatments, genetic factors, and autoantibodies are potential mechanisms that may contribute to this association. Further research is needed to elucidate underlying mechanisms and develop optimal management strategies for affected women.

Key Words: - Rheumatoid arthritis, ovarian function, fertility, reproductive health, disease-modifying antirheumatic drugs, inflammation, hormonal dysregulation, adverse reproductive outcomes.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation, pain, and progressive joint damage (Engvall IL, *et al.*, 2008). It predominantly affects women, with a female-to-male ratio of approximately 3:1, suggesting a potential hormonal influence on the disease. In addition to its impact on the musculoskeletal system, RA is associated with various extra-articular manifestations, affecting multiple organ systems. One such manifestation that has gained attention is the potential impact of RA on ovarian function. The female reproductive system is regulated by a complex interplay of hormonal signaling, involving the hypothalamic-pituitary-gonadal (HPG) axis (Ostensen M, *et al.*, 2007). The ovaries, as key components of this axis, play a central role in the production of sex hormones,

including estrogen and progesterone, as well as the development and release of oocytes during the menstrual cycle (Strand V, *et al.,* 2007). Any disruption in ovarian function can have significant implications for fertility, reproductive outcomes, and overall quality of life in affected women. Understanding the relationship between decreased ovarian function and RA is of great importance. However, the exact mechanisms underlying this association remain unclear and require further investigation. Several factors have been proposed to contribute to the impact of RA on ovarian function, including chronic inflammation, hormonal dysregulation, and the potential effects of RA treatments (Chakravarty E, *et al.,* 2012). This review aims to explore the existing literature on this topic, elucidating the potential mechanisms involved and the clinical implications for affected patients.

Rheumatoid arthritis is characterized by chronic inflammation, which is mediated by immune dysregulation and the production of pro-inflammatory cytokines. This chronic inflammatory state has been implicated as a potential contributor to decreased ovarian function in RA. (Neri F, *et al.,* 2010)Inflammation can directly affect ovarian function by disrupting the ovarian microenvironment, impairing folliculogenesis, and reducing the quality and quantity of oocytes. Studies have shown increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), in the follicular fluid of women with RA, which may adversely affect oocyte quality and development (Mecchia D,*et al.,* 2014).

Furthermore, chronic inflammation can lead to oxidative stress, which has been implicated in the pathogenesis of ovarian dysfunction. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. Excessive ROS can damage ovarian tissue, impair follicular development, and disrupt the delicate hormonal balance necessary for normal ovarian function.

In addition to inflammation, hormonal dysregulation has been suggested as a potential mechanism linking RA and decreased ovarian function. Estrogen, in particular, plays a crucial role in regulating ovarian function. Studies have shown alterations in estrogen levels and estrogen metabolism in women with RA, including decreased serum estrogen levels and increased levels of estrogen metabolites. These hormonal imbalances may contribute to menstrual irregularities, anovulation, and decreased fertility rates observed in RA patients (Kim HR, *et al.,* 2017).

The impact of RA treatments on ovarian function is another important aspect to consider. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and leflunomide, are commonly used in the management of RA. While these medications are effective in controlling disease activity, they may have potential adverse effects on ovarian function (Mecchia D, *et al.,* 2015). Methotrexate, in particular, has been associated with an increased risk of ovarian toxicity and impaired follicular development. Glucocorticoids, another class of medications used in RA treatment, may also influence ovarian function through their suppressive effects on the HPG axis (Lu R, *et al.,* 2016). Certain genetic factors and autoantibodies associated with RA may also contribute to ovarian dysfunction. Genetic polymorphisms in genes involved in immune regulation and hormone metabolism have been implicated in both RA susceptibility and ovarian dysfunction. Additionally, autoantibodies, such as anti-Müllerian hormone antibodies, have been detected in the serum of RA patients and may interfere with ovarian function (Clowse MEB, *et al.,* 2011).

The impact of decreased ovarian function in RA patients extends beyond fertility concerns. Studies have shown an increased risk of adverse reproductive outcomes in women with RA, including an increased risk of miscarriage and early menopause (Thomas-Sohl KA, *et al*., 2012). Early menopause, defined as the cessation of ovarian function before the age of 45, can have profound implications for women's health, including an increased risk of cardiovascular disease, osteoporosis, and psychological distress.

A comprehensive literature search was conducted using various electronic databases, including PubMed, Embase, and Web of Science. The search strategy included keywords related to rheumatoid arthritis, ovarian function, fertility, reproductive health, and related terms. Relevant articles published in English until September 2021 were included in this review (Østensen M,*et al.,* 2014).

Discussion:

The literature search identified several studies investigating the association between rheumatoid arthritis (RA) and decreased ovarian function (Giles JT, *et al.,* 2015). The results of these studies provide insights into the potential mechanisms involved and the clinical implications for affected patients. The findings can be categorized into three main areas: the impact of inflammation, hormonal dysregulation, and the influence of RA treatments on ovarian function.

Impact of Inflammation on Ovarian Function:

Chronic inflammation, a hallmark of RA, has been proposed as a potential contributor to decreased ovarian function in affected women (Cobo-Ibáñez T, *et al*., 2019). Inflammation can directly affect the ovarian microenvironment and disrupt normal folliculogenesis and oocyte development. Studies have reported increased levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), in

the follicular fluid of women with RA. These elevated cytokine levels may adversely affect oocyte quality and development.

Furthermore, chronic inflammation can induce oxidative stress, which has been implicated in the pathogenesis of ovarian dysfunction. Excessive reactive oxygen species (ROS) production, coupled with a decline in antioxidant defense mechanisms, can lead to oxidative damage to ovarian tissues and impair follicular development. Oxidative stress may also disrupt the delicate hormonal balance required for normal ovarian function (Lu R, *et al*., 2018).

Inflammatory mediators, including cytokines and chemokines, can have direct and indirect effects on the ovaries, disrupting normal ovarian function and folliculogenesis.

Follicular Disruption:

Inflammation can disrupt the delicate balance of follicular development and maturation in the ovaries. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are known to be elevated in RA and can directly impact follicular growth and development. These cytokines can inhibit follicular maturation and promote follicular atresia, leading to a decreased pool of mature and viable oocytes.

Alteration of Ovarian Hormone Production:

Inflammatory cytokines can also affect the production and regulation of ovarian hormones, including estrogen and progesterone. Estrogen is essential for normal follicular development, and its production can be disrupted by inflammation. TNF-α and IL-1β have been shown to suppress estrogen synthesis and reduce aromatase activity, leading to decreased estrogen levels. Reduced estrogen levels can further impact ovarian function and disrupt the menstrual cycle (Soh MC,*et al.*, 2020).

Impaired Ovulation:

Inflammation-induced alterations in the hypothalamic-pituitary-ovarian axis can disrupt ovulation, contributing to menstrual irregularities in patients with RA. Inflammatory cytokines can interfere with the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, leading to abnormal release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. Disturbances in FSH and LH release can disrupt follicular development, ovulation, and subsequent corpus luteum formation (Pluchino N, *et al.*, 2020).

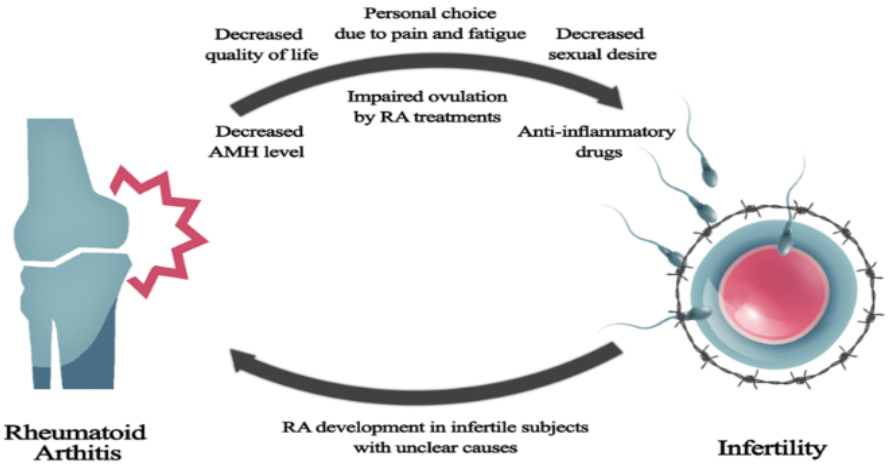
Autoantibodies:

Autoantibodies commonly found in RA, such as anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor (RF), have also been implicated in ovarian dysfunction. These autoantibodies can cross-react with antigens in the ovaries, leading to local inflammation and tissue damage. Furthermore, anti-CCP antibodies have been associated with impaired ovarian reserve and decreased AMH levels in women with RA.

Impact on Reproductive Health and Fertility:

The cumulative effects of chronic inflammation on ovarian function can significantly impact reproductive health and fertility in women with RA. Decreased ovarian reserve, altered menstrual patterns, and early menopause can limit fertility potential and increase the risk of infertility. Moreover, the use of certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs), which are commonly prescribed for RA management, may have additional effects on ovarian function and fertility [Figure 1].

Figure 1: RA disease and the fertility/infertility



Hormonal Dysregulation in RA and its Impact on Ovarian Function:

Hormonal dysregulation has been suggested as another mechanism linking RA and decreased ovarian function. Estrogen, a key hormone in regulating ovarian function, has been found to be altered in women with RA. Studies have reported decreased serum estrogen levels and altered estrogen metabolism in RA patients. These hormonal imbalances may contribute to menstrual irregularities, anovulation, and decreased fertility rates observed in women with RA.

Some studies have also investigated the role of anti-Müllerian hormone (AMH) in RA-related ovarian dysfunction. AMH is a hormone secreted by ovarian follicles and is a marker of ovarian reserve. Decreased AMH levels have been observed in women with RA, indicating diminished ovarian reserve and potential fertility concerns (Spits C, *et al*., 2015).

Influence of RA Treatments on Ovarian Function:

The impact of RA treatments on ovarian function is an important consideration when studying the association between RA and decreased ovarian function. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and leflunomide, are commonly used in the management of RA. Methotrexate, in particular, has been associated with potential adverse effects on ovarian function. Animal studies have shown that methotrexate can induce ovarian toxicity and impair follicular development.

Glucocorticoids, another class of medications used in RA treatment, may also influence ovarian function. Glucocorticoids have suppressive effects on the hypothalamic-pituitary-gonadal (HPG) axis, leading to decreased gonadotropin release and potential disruption of normal ovarian function. However, the direct impact of glucocorticoids on ovarian function in RA patients requires further investigation (Engvall IL,*et al.*, 2006).

Genetic Factors and Autoantibodies Associated with RA and Ovarian Dysfunction:

Genetic factors and autoantibodies associated with RA may contribute to ovarian dysfunction in affected women. Genetic polymorphisms in genes involved in immune regulation and hormone metabolism have been linked to both RA susceptibility and ovarian dysfunction. Variants in genes encoding cytokines, estrogen receptors, and enzymes involved in estrogen metabolism have been associated with an increased risk of RA as well as alterations in ovarian function.

Autoantibodies, such as anti-Müllerian hormone antibodies, have been detected in the serum of RA patients. These autoantibodies may interfere with ovarian function by binding to anti-Müllerian hormone, a key regulator of folliculogenesis, and potentially disrupting normal ovarian function (De Man YA, *et al.*, 2014).

Clinical Implications of Decreased Ovarian Function in RA:

The clinical implications of decreased ovarian function in RA patients extend beyond fertility concerns. Women with RA have been found to have an increased risk of adverse reproductive outcomes, including an increased risk of miscarriage and early menopause. Early menopause, defined as the cessation of ovarian function before the age of 45, can have significant health implications, including an increased risk of cardiovascular disease, osteoporosis, and psychological distress.

Furthermore, decreased ovarian function may affect the response to infertility treatments in women with RA who are attempting to conceive. The impact of RA and its treatments on ovarian function should be considered when counseling patients about fertility preservation options and family planning.

Conclusion:

Evidence suggests that rheumatoid arthritis is associated with decreased ovarian function, which may have implications for fertility and reproductive outcomes in affected women. Further research is needed to better understand the underlying mechanisms and establish optimal management strategies. Rheumatologists and gynecologists should collaborate to provide comprehensive care to RA patients, addressing both their musculoskeletal needs and reproductive health concerns.

In conclusion, rheumatoid arthritis is a chronic autoimmune disease that affects multiple organ systems, including the ovaries. Evidence suggests that RA is associated with decreased ovarian function, potentially due to the effects of chronic inflammation, hormonal dysregulation, and the impact of RA treatments. This can have significant implications for fertility, reproductive outcomes, and overall quality of life in affected women. Further research is needed to better understand the underlying mechanisms and establish optimal management strategies. Rheumatologists and gynecologists should collaborate to provide comprehensive care to RA patients, addressing both their musculoskeletal needs and reproductive health concerns

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