

The Factors Associated with the Condition of
Rheumatoid Arthritis among Mid-Aged Women

by

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Master of Public Health, California Baptist University, 2019

Thesis Submitted in Partial Fulfillment of the Requirements
for the degree of Master of Public Health

California Baptist University

August, 2019

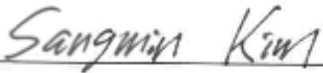
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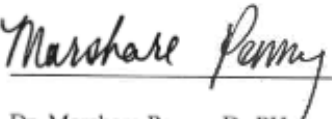
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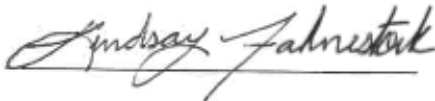
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Abstract

Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory condition that negatively impacts the quality of life of individuals diagnosed with it. This cross-sectional study measured the correlation between female hormones, such as pregnancy hormones, use of oral contraceptive pills, menopause, and the severity of RA. A total of 136 females aged more than 45 years from all ethnic groups were recruited from India at a local clinic in 2017-2018. After obtaining permission from the original researchers, secondary data was obtained for this research. A 3-page Stanford Health Assessment Questionnaire Disability instrument was administered to patients to participate in the study, and a set of de-identified data was obtained from local rheumatologists. The result showed that there was a significant relationship found between parity, menopause, and the severity of rheumatoid arthritis. However, the study suggests that oral contraceptive pills may not influence the condition of rheumatoid arthritis.

Key Words: Rheumatoid Arthritis, Pregnancy, Menopause and Oral contraceptive pills.

Acknowledgements

Firstly, I would like to thank my thesis chair, Dr. Sangmin Kim, for his continuous support, patience, motivation during my research study. Secondly, I would like to extend my gratitude to my other committee members, Dr. Marshare Penny and Dr. Lindsay Fahnestock, for their encouragement and valuable comments on my thesis paper. Additionally, I would also like to thank Dr. Nibha Jain, a rheumatologist from India who was involved with the data collection process. Without her permission, I would not have been able to use dataset for this research study. Lastly, I must express my sincerest gratitude to my parents, my husband, and my sister for their support and consistent encouragement during the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you!

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Literature Review

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disorder that causes pain, swelling, inflammation, and loss of function of the joints in individuals diagnosed with it (Duarte-Garcia, 2019). Rheumatoid arthritis is an incurable disease that negatively impacts the quality of the affected individuals. About 1.3 million people are affected by RA in the U.S. (Duarte-Garcia, 2019). In general, arthritis affects 15% of the population in India which equates to over 180 million people within the country (Wagh, 2014). A pre-RA phase that lasts months to years can be characterized by circulating antibodies such as anti-immunoglobulin G (IgG) or rheumatoid factors and increased concentration of inflammatory cytokines (Firestein & McInnes, 2017). In the pre-RA phase, there is generation of autoantibodies such as anti-citrullinated protein antibodies (ACPAs), which cause metabolic disturbance prior to clinical development of the disease (Firestein & McInnes, 2017). RA is the most common form of autoimmune arthritis. RA is an abnormal autoimmune response which leads to the synovial inflammation and articular destruction (Crawford & Harris, 2015). The role of the autoimmune process is poorly understood, but it may be initiated by the activation of CD4⁺ T helper cells and local release of inflammatory mediators and cytokines that cause the destruction of the joints (Crawford & Harris, 2015). The prevalence of RA varies between 0.3% to 1% worldwide (World Health Organization [WHO], 2016).

There are four different stages of rheumatoid arthritis. The first stage is early stage RA, which is comprised of initial inflammation of the joint capsule and synovial tissue (Freeman, 2018). In the second, or moderate, stage of RA, inflammation of the synovial tissues becomes so

severe that it causes cartilage damage; people experience loss of movement and decreased range of motion (Freeman, 2018). The third stage of RA involves bone structures along with joint capsules and cartilages. The symptoms of this stage include increased pain and swelling of the joints, decreased muscle strength, and the development of physical deformities of the affected joints (Freeman, 2018). The final stage of RA consists of a complete loss of joint function, pain, swelling, stiffness, loss of mobility, etc. (Freeman, 2018).

The most common signs and symptoms of RA include fever, weight loss, fatigue, pain, stiffness, tenderness, and swelling in more than one joint. The same symptoms can occur on both sides of the body (Centers for Disease Control and Prevention [CDC], 2019). It can affect more than one joint at once, but most the commonly affected joints are wrist and fingers (National Institute of Health [NIH], 2019). In the early phase of RA, smaller joints such as fingers and toes, are affected, but as the disease progresses, symptoms can spread to the wrists, knees, elbows, shoulder, and hip joints (CDC, 2019). About 40% of the RA patients, however, experience symptoms that affect parts of the body other than joint structures, such as skin, eyes, lungs, heart, kidneys, salivary glands, nervous tissues, bone marrow, blood vessels, etc. (NIH, 2019). The condition of increased disease activity is called flares, and decreased disease activity is called remission (Siebert, Lyall, Mackay, Porter, McInnes, Sattar, & Pell, 2016). The complications of RA include rheumatoid nodules, osteoporosis, infections, Sjogren's syndrome, lymphoma, carpal tunnel syndrome, lung disorders, cardiovascular manifestations, etc. (Kahlenberg & Fox, 2011).

People with RA are at higher risk of developing chronic disorders such as heart disease and diabetes. The other complications include disability and work loss, which affects people the most in their daily routine (CDC, 2019). RA patients are less likely to get work compared to the

general population. As the disease progresses, people with RA cannot do much work or move around due to physical limitations, and this then may affect their mental health. The leading cause of death among RA patients is cardiovascular diseases with a more than 50% risk in RA patients than general population (Siebert et al., 2016).

Types of Rheumatoid Arthritis

There are mainly two types of rheumatoid arthritis: seropositive and seronegative (Duckworth, 2018). The patients with RA seropositive disease have the presence of anti-citrullinated protein antibodies (ACPAs) in their blood, and these ACPAs can be detected as early as five to 10 years before the clinical onset of the disease (Duckworth, 2018). Seronegative RA patients, on the other hand, do not have ACPAs in their system, so these patients do not test positive for the antibodies (Duckworth, 2018). Seronegative patients can be diagnosed for rheumatoid arthritis by clinical symptoms and X-ray results showing articular inflammation or destruction (Duckworth, 2018). There is also Juvenile RA, which affects patients under the age of 17 years, and their symptoms can last for the rest of their lives (Duckworth, 2018). Further research, however, is being conducted to define the signs and the progression of each type to provide more specified treatment options (Duckworth, 2018). Generally, the seropositive type is the most common type of RA, affecting 60-80% of the RA patients. But, no matter the type of RA, the symptoms remain the same. Seropositive patients, however, feel more pain and inflammation of the joints compared to seronegative patients (Martin, 2017).

Risk Factors

RA can occur at any age, but there are several factors that increase an individual's risk of developing RA: being a middle-aged adult, a family history of RA, smoking cigarettes (which may also worsen the symptoms and lastly, and obesity (CDC 2019). Further, according to the

CDC (2019), RA predominantly affects women as women are two to three times more likely than men to develop it. It is suggested that hormonal factors can influence pathogenesis and the disease progression (Pikwer, Nilsson, Bergstrom, Jacobsson, & Turesson, 2012). Women who suffer from RA also experience more severe functional decline and increased disability compared to men who have RA (Mollard et al., 2018).

Diagnosis

Rheumatoid arthritis can be diagnosed by clinical symptoms, a physical examination, lab tests, and X-rays. The diagnosis of RA should be done early – within six months of onset of symptoms to prevent or stop the progression of the disease (CDC, 2019). Early diagnosis and treatment can slow down the disease progression in up to 90% of patients (Aletaha & Smolen, 2018). For diagnosis, rheumatologists ask patients about their personal and family history as well as past or current symptoms; later, the physicians complete a physical examination to check joint inflammation or pain and stiffness of the joints. The physical examination may also reveal the presence of any rheumatoid nodules. Blood tests are performed to measure inflammation levels and identify any antibodies specific to RA such as ACPAs (Kahlenberg & Fox, 2011).

In the initial stage of RA, nearly 70% radiographs appear normal, but MRI and ultrasound with power Doppler are done to detect smaller erosions or damages to the joints (Kahlenberg & Fox, 2011). After the confirmation of present antibodies in the blood, imaging tests are performed to check the joint damage or erosions and narrowing of the joint spaces in the body to justify the decreased range of motion. However, the main criteria for diagnosing RA are when an individual has been experiencing symptoms for more than six weeks and specifically, if he or she has the symmetrical appearance and multiple joints being affected at once (NIH, 2019).

It is difficult to prevent the onset of rheumatoid arthritis due to its unknown cause, but it can be effectively treated with medications and self-management strategies. The main goal of the treatment is to reduce pain and swelling of the joints and improve ability to perform daily activities. The main treatment of RA is Disease Modifying Anti-Rheumatic Drugs (DMARDs), usually Methotrexate along with glucocorticoids (Kahlenberg & Fox, 2011). The combination treatment therapy has proven more effective than monotherapy in RA patients (Kahlenberg & Fox, 2011). Biologic DMARDs also play a vital role in the blockage of the immune system that causes inflammation of the joints (Kahlenberg & Fox, 2011). Weight loss, physical activity, and a balanced diet can also help reduce the symptoms.

Genetic and Environmental Factors

The exact cause of RA is unknown, but previous studies have suggested that genes, environmental factors, and hormones play an important role in its pathophysiology (Yarwood, Huizinga, & Worthington, 2014). Genetic markers associated with this disease, along with environmental risk factors, influence the transition from one RA stage to another (Yarwood et al., 2014). The major histocompatibility (MHC) class two, human leucocyte antigen (HLA) gene, HLA DRB1 confer a genetic risk of RA (Okada, Eyre, Suzuki, Kochi, & Yamamoto, 2018). The contribution of HLA genes to the genetic variance is 40% for seropositive RA patients, and only 2% for seronegative RA type (Kurkó et al., 2013). Another gene, HLA DR3 is associated with the seronegative RA, which results in less severe disease symptoms (Kurkó et al., 2013).

Several studies suggested that non-HLA genes, such as phosphatase protein tyrosine phosphatase non-receptor type 22 (PTPN22) and IL23R, also play an important role in the pathogenesis of RA (Kurkó et al., 2013). The gene PTPN22 has the second strongest association with RA disease after HLA DRB1, and PTPN22 is helpful for the early diagnosis of rheumatoid

arthritis (Kurkó et al., 2013). In addition, the peptidyl arginine deiminase 4 (PADI4) enzyme, most commonly found within the Asian race, is associated with the protein citrullination process that determines the pathogenesis of RA (Kurkó et al., 2013).

Several environmental risk factors associated with the development of rheumatoid arthritis, such as smoking, diabetes mellitus, and obesity have potential increased risk for developing RA, whereas alcohol, breastfeeding, and higher social class were implicated with the decreased risk of RA (Yarwood et al., 2014). The identification of environmental risk factors affecting RA would be very beneficial as it could help avoid the exposure to risk factors, but it is difficult to establish due to patients' recall bias. Smoking is the most acknowledged risk factor for rheumatoid arthritis. Several studies found a strong interaction between tobacco smoking and an increased risk of developing seropositive RA (Yarwood et al., 2014). Smoking is not associated with seronegative RA, because smoking causes RA specific immune reactions to citrullinated proteins which result in proliferation, differentiation, cytokine production, and generation of T cell memory against citrullinated proteins (Yarwood et al., 2014).

Another study asserted that an increased dose of cigarettes (pack-years smoking) is associated with the increased risk of RA (Liao, Alfredsson, & Karlson, 2009). People with 40 pack-years of heavy smoking history have two-fold increased risk of developing RA than people who never smoked in their lives (Liao et al., 2009). Smoking is also associated with the extrarticular manifestations, such as nodules, and cardiovascular complications of RA (Kurkó et al., 2013). However, moderate alcohol consumption and fasting followed by a vegetarian diet are associated with decreased RA symptoms (Liao et al., 2009).

Menopause

Hormonal factors such as menopause, parity, and use of oral contraceptive drugs also affect RA disease activity, but the exact mechanism is unknown (Yarwood et al., 2014).

Menopause is defined as an absence of menses for 12 consecutive months, and it usually occurs at about 50 years of age in females (Sammaritano, 2012). Females are now expected to spend about one-third of their lives in post-menopausal period due to increased life expectancy.

Menopause is divided into various stages such as early perimenopause, which is described as a change in the length of menstruation cycle; late perimenopause, which is the period after one or more skipped menstrual cycles; early menopause which happens five years after amenorrhea; and late menopause, which occurs due to complete life-long amenorrhea (Sammaritano, 2012).

The risk factors for early onset menopause include smoking, null parity, low body mass index, and a high fiber diet, whereas high parity is associated with late onset of menopause (Sammaritano, 2012).

A decrease in hormonal levels of estradiol and estrone are seen after menopause, and this may lead to significant changes in cardiovascular system, skeletal system, central nervous system etc. (Sammaritano, 2012). An early onset of menopause may be associated with rheumatoid arthritis, and an increased incidence of rheumatoid arthritis can be seen during the peri- and postmenopausal period in women (Pikwer et al., 2012). While a pronounced effect of menopause is not clearly stated, there is an age of peak of RA disease activity among woman largely associated with an average age of menopause (Sammaritano, 2012). Physiologically low doses of estrogen are suggested to enhance cellular immunity, which may implicate the possible involvement of menopause in the pathological process of the disease (Sapir-Koren & Livshits, 2016). Additionally, low levels of estrogen hormones affect the production of different cytokines

that can play a crucial role in activating chronic inflammatory reaction following RA (Sapir-Koren & Livshits, 2016). Future studies are needed to confirm the role of estrogen hormones and menopausal age in the pathogenesis of rheumatoid arthritis.

Pregnancy

Though the results derived from the research studies are controversial, pregnancy is known to have beneficial effects on rheumatoid arthritis (Mittal et al., 2015). A decrease in RA incidence cases is found during the pregnancy (Pikwer et al., 2012). About two-thirds of RA patients go into partial or complete remission during pregnancy, and new onset of the disease is less likely to occur during pregnancy (Mittal et al., 2015). During the postpartum period, flare is the most common symptom, and clinical onset of RA disease is more likely to occur in this period (Sammaritano, 2012). After delivery, an excessive reduction in the hormonal levels may be a potential threat to increased RA risk (Orellana et al., 2014).

Parity is defined as the number of times a woman gets pregnant and carries the pregnancy to a gestational viable age (Ren et al., 2017). There is no association found between RA and parous women who are in their post-menopausal age (Orellana et al., 2014). Some studies have shown an inverse relationship between parity and RA disease, whereas other studies found weak associations between them (Ren et al., 2017). Women who have had at least one live birth have more likely adopted healthier lifestyles compared to those with no live births, which ultimately results in reduction in RA disease activity (Ren et al., 2017). Concurrently, women with multiparity may get exposed to increased anxiety, stress, and workload due to many children, which may lead to increased risk of getting RA. Additional research is required to demonstrate the exact relationship between parity and rheumatoid arthritis because of the conflicted results.

Oral Contraceptive Pills

The effect of oral contraceptives on disease progression is poorly understood, but it may be associated with the milder type of the disease and less disability (Pikwer et al., 2012). Oral contraceptive pills contain ethinylestradiol, which suppresses the secretion of estradiol follicle via negative feedback mechanism (Jeong, Hong, Choi, Kim, Song, & Jung, 2018). It is hypothesized that estrogen may be able to reduce cell-mediated immune response and inhibit the secretion of pro-inflammatory cytokines (Chen, Zin, Xiang, Cai, Shi, & He, 2014). Rheumatoid arthritis leads to synovial inflammation and estrogen receptors are usually embedded in RA synovial tissues which interact with estradiol (Jeong et al., 2018). Therefore, when inflammation occurs, these estrogen receptors stimulate pro-inflammatory cytokines in the synovial tissues which result in amelioration of disease activity due to the presence of estrogen (Jeong et al., 2018). Some studies have suggested that the use of oral contraceptive drugs has been found to be protective against RA development (Sammaritano, 2012). However, the difference in the incidence of RA due to the use of oral contraceptives is yet not clear, and extensive research is required to understand the pathogenesis of the disease.

Summary

Rheumatoid arthritis is an autoimmune disorder which causes inflammatory reactions of the smaller joints and ultimately leads to the destruction of both smaller and larger joints in the body (Kurkó et al., 2013). Seropositive RA has more severe clinical symptoms than seronegative RA due to its cell-mediated immune reactions (Duckworth, 2018). The common symptoms of RA include pain, swelling, stiffness, and destruction of the joints such as fingers, toes, wrists, knees, shoulder, and hip joints (Freeman, 2018). The higher prevalence of RA in women than in men may be originated from differences in reproductive hormones following parity, menopause,

and oral contraceptive drug use (Jeong et al., 2018). The interaction between genes and environmental factors, such as smoking, high body mass index, and stress, may contribute to the onset or worsening of the clinical disease (Kurkó et al., 2013). The exact cause of RA is yet to be found, but this research study will help people understand the influence of hormonal factors on RA disease activity.

Purpose of the Study

Currently, a gap exists concerning the correlation between hormones and the onset or worsening of RA; therefore, this research explored the relationship between different hormonal factors such as parity, menopause, oral contraceptive use, and the severity of rheumatoid arthritis. The purpose of this study was to investigate the relationship between hormonal factors such as pregnancy hormones, use of oral contraceptive drugs, menopausal period, and the severity of rheumatoid arthritis. The epidemiology of RA is necessary to understand for better disease management. Further, the population of India does not distinctly understand the differences between different types of arthritic conditions, so this research study will increase the knowledge of the RA disease burden in India.

Research Questions

1. Is there any relationship between the parity and the severity of rheumatoid arthritis?
2. Is there any correlation between the use of oral contraceptive drugs and rheumatoid arthritis?
3. Is there any relationship between menopause and the severity of rheumatoid arthritis?

Research Hypothesis

Hypothesis #1: There is a relationship between parity and severity of rheumatoid arthritis.

Hypothesis #2: There is a correlation between the use of oral contraceptive pills and rheumatoid arthritis.

Hypothesis #3: There is a relationship between menopause and the severity of rheumatoid arthritis.

Methods

Research Design

This study used a cross-sectional design to measure the correlation between the hormonal factors and the severity of rheumatoid arthritis among 136 female adults in India.

Participants

A total of 136 women aged 45 years and older of all ethnic groups from India were recruited for this study. All female participants with a previous diagnosis of rheumatoid arthritis by the rheumatologist were included for this study, but women who had hysterectomies in the past were excluded. A sample size was calculated by using G*power, based on statistical power of 0.80, an alpha coefficient of 0.05, and an effect size of 0.21. A total of 136 female participants were required for this study.

Procedure

This study utilized data from a secondary source. The data was collected in 2017-2018 by a local rheumatologist in India with the consent from the participants. The de-identified data were obtained from the local rheumatologist upon being given permission to use it for this study. The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) (Bruce & Fries, 2003) was provided to the participants during their hospital visit by local rheumatologists, and it took about 12 minutes to complete. The HAQ-DI assesses patients' functional ability regarding RA. There were 20 questions divided into 8 categories to assess fine movements of upper and lower extremities along with involved activities such as walking, rising up, grip, dressing, bathing, etc. (Bruce & Fries, 2003). The responses were made by patients on a scale from 0 to 3; "0 = without any difficulty," "1 = with some difficulty," "2 = with much difficulty," and "3 = unable to do the activity." This questionnaire also assessed participants' pain level caused by RA

based on 1 to 10 scale. Other questions regarding patients' demographics, number of children, menopausal period, and use of oral contraceptive pills were asked and recorded by the rheumatologist during the hospital visit.

Independent and Dependent Variables

The dependent variable for this study was the severity of RA as measured by a self-administered HAQ-DI questionnaire. The independent variables for this study were pregnancy, menopause, and use of oral contraceptive pills. The independent variables were measured based on the participants' self-identified demographics during their hospital visit.

Data Analysis Plan

The severity of participants' RA will be correlated with factors such as demographics and pregnancy, menopause, and use of oral contraceptive pills. Pearson correlation coefficient tests were executed to measure the relationships between these variables.

Results

Demographics

Among the 136 patients the average age was 60.97 ($SD = 9.17$) with a range of 45 to 83 years of age. The number of women who did not have any children was 2; out of the remaining 134 participants, 15 women had one child, 61 women had 2 children, and 58 women had more than 3 children. The mean average for women who were using oral contraceptive pills was 59.09 ($n = 23$; $SD = 39.14$), and the average for women who were not using oral contraceptive pills was 70.42 ($n = 113$; $SD = 39.35$). The average for women who were in menopause was 70.66 ($n = 110$; $SD = 39.17$), and the mean for women who were not in menopause was 59.35 ($n = 26$; $SD = 39.82$). Overall, 110 women were in menopausal stage whereas 26 women were not in the menopause. Out of the 136 participants, arthritis affected 7.35% ($n = 10$) women very poorly, 36.03% participants ($n = 49$) were affected poorly, 32.35% women ($n = 44$) were affected moderately, and 24.27% participants ($n = 33$) were affected mildly.

Major Findings

For the first research question exploring the relationship between parity and severity of rheumatoid arthritis, a Pearson correlation test was performed to measure the correlation between the variables, and there was a statistically significant relationship found ($r = 0.59$, $p = 0.01$).

Parity has a strong positive relationship with the severity of RA.

For the second research question exploring the correlation between the use of oral contraceptive pills and rheumatoid arthritis, a Pearson correlation test was performed to measure the correlation between the variables, and there was no significant relationship found ($r = -0.35$, $p = 0.07$). The use of oral contraceptive pills was not correlated with the milder form of the condition of RA.

For the third research question exploring the relationship between menopause and the severity of RA, a Pearson correlation test was performed to measure the correlation between the variables, and there was a statistically significant relationship found ($r = 0.26$, $p = 0.03$).

Menopause is positively correlated with the severity of RA.

Discussion

Summary

The current findings are consistent with the previous studies which found that women with children and women who are in menopause have significant effects on the condition of rheumatoid arthritis. Women who are in a menopausal stage and who do not have any children experience a more severe form of RA. A recent study suggested that the use of oral contraceptive pills reduced the effects of rheumatoid arthritis (Pikwer et al., 2012). In this study, however, there was no significant difference found among oral contraceptive users and nonusers. A negative moderate relationship was found between use of oral contraceptive pills and severity of rheumatoid arthritis.

Public Health Implications

The current study findings have some potential implications for clinical practice. They suggest that female hormones may influence the progression of RA. Healthcare providers should consider the effects of menopause and pregnancy hormones on severe clinical outcomes and prescribe an earlier treatment to prevent the disease's progression. Health care providers should also measure the use of oral contraceptive pills and smoking habits of the patients in order to improve the patients' clinical outcomes. Based on this research, health care providers should encourage pregnancy in women with an increased risk of developing RA during their fertile periods to delay the disease's progression.

The results of this study begin to support an understanding of the pathogenesis of the RA which may lead to better disease management for patients. However, rheumatologists should weigh the benefits of parity and use of oral contraceptive pills for a particular patient before making treatment recommendations.

This research study also suggests that the decreased levels of female hormones can lead to a severe, progressive form of rheumatoid arthritis. Therefore, during menopause, females can be self-aware about the disease progression and let their rheumatologists know about their condition, so they can be diagnosed in earlier stage which will result in an earlier treatment of the symptoms.

Study Limitations

The major limitations for this research study are recall bias and self-report bias. In this study, participants were asked questions regarding the events in the past years. For example, use of oral contraceptive pills during their reproductive years, their age at menopause, severity of symptoms of rheumatoid arthritis in the past week, etc. Participants may not have remembered the past events or may have responded in a way that they thought they should respond. Therefore, the results should be interpreted with caution.

Other limitations for this study may include selection bias due to a non-random sample of a population and interactive effects of different environmental factors; maybe two or more independent factors may worsen the condition of rheumatoid arthritis or only one independent variable has greater impact on the disease.

The strength of this study was its data collection instrument, the Health Assessment Questionnaire Disability Index (HAQ-DI), which has high validity and sensitivity. In many observational studies and clinical trials, HAQ-DI has been validated for face and content validity via comparison with other data collection instruments (Bruce & Fries, 2003).

Conclusion

The current study found that menopause and pregnancy have significant effects on the severity of RA. Female hormones may influence the disease's pathogenesis, leading to more

severe, progressive form of the disease. However, more research studies are needed to find out the relation between use of oral contraceptive pills and the severity of rheumatoid arthritis.

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Appendix A: Tables

Table 1
Age of Participants

N=	Valid	136
N =	Missing	0
Mean		60.97
Median		60.00
Mode		57
Range		38
Maximum		83
Minimum		45

Table 2
Characteristics of female participants with rheumatoid arthritis

	Number of Participants, N =	Mean	Standard Deviation
Menopause			
Yes	110	70.66	39.17
No	26	59.35	39.82
Parity			
Nulliparous	2	20.00	19.80
Multiparous	119	64.85	37.81
Use of OC pills			
Yes	23	59.09	39.14
No	113	70.42	39.35