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SECOND-TO-FOURTH DIGIT RATIO (2D:4D) IN RHEUMATOID ARTHRITIS: A CASE-CONTROL STUDY

Mustafa Gür[1], Mesude Seda Aydoğdu[2], Rabia Pişkin Sağır[2], İbrahim Gündüz[2], Aylin Dolu Karaca[2], Tuba Kaya Karataş[3], Ramazan Fazıl Akkoç[4], Nevzat Gözel[5], Ahmet Karataş[2]

[1]University of Health Sciences Turkey, Elazığ Fethi Sekin City Hospital, Clinic of Rheumatology, Elazığ, Turkey
[2]Fırat University Faculty of Medicine, Department of Rheumatology, Elazığ, Turkey
[3]Fırat University Faculty of Medicine, Department of Biochemistry, Elazığ, Turkey
[4]Fırat University Faculty of Medicine, Department of Anatomy, Elazığ, Turkey
[5]Fırat University Faculty of Medicine, Department of Internal Medicine, Elazığ, Turkey

Abstract

Aim: The second-to fourth-digit ratio (2D:4D), the ratio of the second finger length to the fourth finger length, is associated with exposure to prenatal sex steroids. Rheumatoid arthritis (RA) is more common in women, suggesting the effect of hormonal factors. The aim of the present study was to determine whether 2D:4D, which is associated with sex hormone levels, is affected in patients with RA.

Material and Methods: Digital images of the right and left hands of 205 RA patients (mean age 47.8±11.3 years; 84% female) and 205 age and gender matched healthy controls (mean age 47.3±11.6 years; 84% female) were obtained. 2D:4D was calculated by dividing the 2nd digit length by the 4th digit length. The 2D:4D difference between the right and left hand (ΔR-L 2D:4D) was obtained by subtracting the left hand 2D:4D ratio from the right hand 2D:4D ratio.

Results: No difference was found between patients with RA and the control group in terms of the 2D:4D ratio in the right and left hand. In female patients with RA, ΔR-L 2D:4D was higher compared with the control group. For both hands, the 2D:4D increase rate in women compared to men was higher in patients with RA compared to the control groups.

Conclusion: The detected 2D:4D ratio differences suggest that prenatal estrogen/androgen balance may be altered in female patients with RA. To the best of our knowledge, this is the first study to evaluate 2D:4D change in patients with RA.

Keywords: 2D:4D, digit ratio, rheumatoid arthritis, sex hormones

INTRODUCTION

Rheumatoid arthritis (RA) is the most common systemic, autoimmune, and inflammatory rheumatic disease and affects 0.5-1% of the adult population. RA is approximately 4 times more common in women (1,2), and the disease activation and progression tend to be more serious in women than in men (3). Although the pathogenesis of RA is not fully understood, the current consensus is that it occurs as a result of activation of the immune system due to environmental factors in individuals with genetic predisposition. The high prevalence of RA in women suggests that hormonal factors play a role in the development of the disease, and there are many arguments

Address for Correspondence: Mustafa Gür, University of Health Sciences Turkey, Elazığ Fethi Sekin City Hospital, Clinic of Rheumatology, Elazığ, Turkey
Phone: +90 505 262 56 65 **E-mail:** mustafagur917@gmail.com **ORCID ID:** orcid.org/0000-0002-3841-5282
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about this issue. Both factors related to low and high estrogen exposure have been associated with increased RA risk. In general, estrogens have pro-inflammatory effects and androgens have anti-inflammatory effects (4). However, estrogens may have different effects on different immune cells due to various factors such as serum concentration and reproductive stage (5,6). In animal experiments, estradiol suppresses T-cell autoimmunity, stimulating the production of autoantibodies from B cells (7). The 2D:4D ratio obtained by dividing the 2nd digit length by the 4th digit length is sexually dimorphic and lower in men than in women. Manning et al. (8) suggested that the 2D:4D ratio was associated with exposure to prenatal sex steroids. A low 2D:4D ratio is associated with low prenatal estrogen and high androgen levels, while a high 2D:4D ratio is associated with low prenatal androgen and high estrogen levels (9). The relationship between the 2D:4D ratio and prenatal sex steroids was found to be stronger in the right hand. The difference between the right and left hand 2D:4D ratio (ΔR-L 2D:4D) is also associated with high prenatal estrogen and low androgen levels (10). This relationship between exposure and prenatal sex steroids and the 2D:4D ratio have also been reported in animal experiments. These studies showed that gender differences in the 2D:4D ratio were due to the balance between prenatal testosterone and estrogen during fetal digit development (11,12). Studies investigating early-life risk factors in autoimmune diseases that develop in adult life, such as RA are few. These studies have investigated many factors such as birth weight, breastfeeding status, and infections in early life (13). Similarly, there are very few studies on the relationship between hormonal environment and RA in the prenatal period, and the sample size is very small in these studies (14-16). Since it is difficult to evaluate hormones in the prenatal period for ethical and technical reasons, the 2D:4D ratio can indirectly provide information about the prenatal hormonal environment. Therefore, the aim of this study was to compare the 2D:4D ratio between patients with RA and healthy controls.

MATERIAL AND METHODS

Participants

This case-control included 205 consecutive patients who applied to the rheumatology clinic at Fırat University Hospital between 2019 and 2020 and were diagnosed with RA according to the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria. The control group consisted of 205 patients who applied to the rheumatology clinic with the complaint of joint pain in the same period and were compatible with the RA group in terms of age and gender. The patients in the control group did not have inflammatory rheumatic disease or systemic disease in the evaluations and follow-ups, and the autoantibody profile was negative for RA. Participants with a disorder in the fingers that would affect digit measurement, such as arthritis, deformity, and scars, and participants with a previous history of surgery on the upper extremity were excluded from the study. Basic demographic data of the participants were recorded.

Ethical approval was obtained from the Ethics Committee of Fırat University (decision no: 06, date: 05.01.2018). Informed consent was obtained from all patients before the study.

Measurements

The palmar side of the hands of all participants was scanned by a researcher blinded to the study groups (S.H.) with the same digital scanner in accordance with previous literature recommendations and the image of both hands was obtained. Participants were informed about the procedure before the scan and were asked to place their hands firmly on the scanner without applying too much pressure and with all fingers straight, and not to move their hands during the scan (17,18). All images were examined to determine if the folds on the base of the finger were clearly visible. If not, the hands were rescanned. Measurements of the second and fourth digit lengths were made from digital images by two independent researchers (M.G. and A.K.) who were blinded to the study groups. The distance from the midline of the 2nd and 4th digit basal fold to the fingertips was measured. Each finger was measured three times and the measurements were averaged. Then, the 2nd and 4th digit lengths were determined by averaging the results of the two researchers. 2D:4D was calculated by dividing the 2nd digit length by the 4th digit length. ΔR-L 2D:4D was obtained by subtracting the left hand 2D:4D ratio from the right hand 2D:4D ratio. The height and body weight of all participants were measured and the Body Mass Index (BMI) [body weight (kg)/height^2(m^2)] was calculated.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Science (SPSS) 26 program. Intraclass correlation coefficients (ICCs) were calculated for the second and fourth digit lengths in men and women to assess the reliability of digit length measurements. Descriptive statistics were presented as number, percentage, mean ± standard deviation. Kolmogorov-Smirnov test was used to test whether the data were normally distributed or not. Pearson correlation test was used to evaluate the correlation between height, weight, BMI, and 2D:4D ratio. Student's t-test was used to compare the 2P:4P ratio in men and women between the RA and control groups. The receive

operating characteristic (ROC) mode was used to detect the prediction performance of 2D:4D ratio and ΔR-L 2D:4D for RA. P<0.05 was considered statistically significant in all analyses.

RESULTS

The demographic characteristics, height, body weight, and BMI values of the RA and control groups are summarized in Table 1. No statistical difference was found between the RA and control groups in terms of age and gender characteristics (p>0.05). While body weight and BMI were higher in the control group, height was significantly higher in the RA group (p=0.002, p<0.001 and p<0.001, respectively). In both the RA and control groups, the 2nd and 4th digit lengths measured for the right and left hand were normally distributed. ICC were computed to determine inter-rater reliability. ICC for right - hand 2nd digit lengths was calculated as 0.920 and 0.932, respectively, and ICC for left - hand 4th digit lengths was calculated as 0.927 and 0.926, respectively. These results indicated that the measurements were highly similar and reliable. No statistically significant correlation was found between the 2D:4D ratio and height, weight, and BMI for both hands (p>0.05). Measurements in male and female patients in the RA and control groups are summarized in Table 2. When all patients were evaluated, 2D:4D ratios for the right and left hand were higher in women (right hand: 0.956±0.304; left hand: 0.958±0.323) compared to men (right hand: 0.946±0.324; left hand: 0.946±0.334) (p=0.015 and p=0.07, respectively). No significant difference was found between the 2D:4D ratios for the right and left hand between the two groups (p>0.05). ΔR-L 2D:4D values were significantly higher in the RA group compared to the control group (p=0.004). In men and women, no significant difference was found between the 2D:4D ratios for the right and left hand between the two groups (p>0.05). ΔR-L 2D:4D values in women were significantly higher in the RA group compared to the control group (p=0.011). In addition, the 2D:4D ratio of women in the RA group was 1.35% higher in the right hand and 1.67% higher in the left hand compared to the men, while it was 0.73% higher in the right hand and 0.83% higher in the left hand in the control group. ROC analysis showed that of ΔR-L 2D:4D was predictive for the diagnosis of RA [area under the curve (AUC): 0.574, 95% confidence interval (CI): 0.517-0.630, p=0.011]. For -0.002 cut-off value of ΔR-L 2D:4D, sensitivity and specificity was 53% (Figure 1). The AUC for the right hand 2D:4D ratio in patients with female RA was 0.543 (95% CI: 0.481-0.604, p=0.174) but not meaningful. The optimal cutoff point of the right hand 2D:4D ratio in female patients for RA was 0.953 with sensitivity of 54% and specificity of 53% (Figure 2).

Table 1. Demographic characteristics of the study groups

Parameter	RA	Control	p value
Number	205	205	
Age (mean ± SD)	47.8±11.3	47.3±11.6	0.648
Gender			
Males (%)	34 (16)	34 (16)	
Females (%)	171 (84)	171 (84)	
Weight (kg)	71.8±12.6	75.8±14.0	0.002
Height (cm)	164.2±7.8	160.2±7.8	<0.001
BMI	26.7±4.9	29.6±5.7	<0.001

RA: Rheumatoid arthritis, SD: Standard deviation, kg: kilogram, cm: centimeter, BMI: Body Mass Index

DISCUSSION

According to the results obtained in this study, no significant difference was found between the RA group and the control group in terms of the left and right hand 2D:4D ratio of male and female patients. In women, ΔR-L 2D:4D values were higher in the

Table 2. Comparison of digit ratios of patients with RA and the control group

Parameter (mean ± SD)	RA	Control	p value
Both gender right-hand 2D:4D	0.956±0.297	0.953±0.341	0.271
Female right-hand 2D:4D	0.958±0.288	0.954±0.317	0.163
Male right-hand 2D:4D	0.945±0.321	0.947±0.331	0.758
Both gender left-hand 2D:4D	0.954±0.342	0.958±0.313	0.210
Female left-hand 2D:4D	0.957±0.331	0.959±0.317	0.423
Male left-hand 2D:4D	0.941±0.371	0.951±0.289	0.202
Both gender ΔR-L 2P:4P	0.002±0.026	-0.005±0.023	**0.004**
Female ΔR-L 2P:4P	0.002±0.257	-0.004±0.024	**0.011**
Male ΔR-L 2P:4P	0.004±0.026	-0.004±0.021	0.178

RA: Rheumatoid arthritis, SD: Standard deviation, 2D:4D: Ratio of the second-to-fourth digit length, ΔR-L 2P:4P: Right hand 2D:4D-left hand 2D:4D

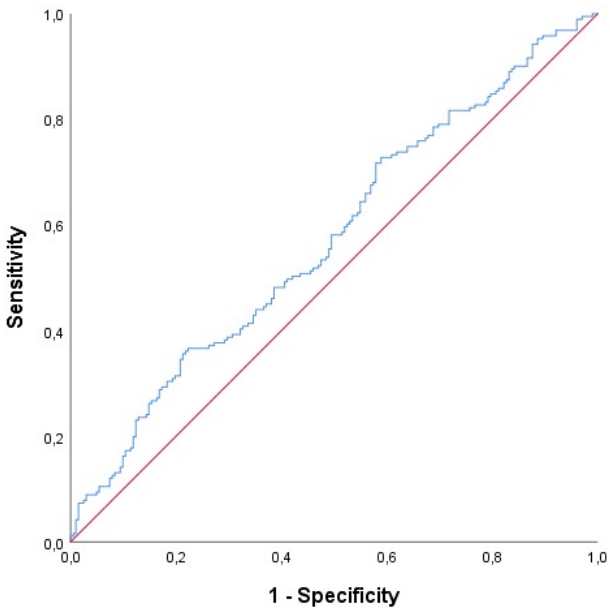

Figure 1. Receiver operating characteristic curve for predictive value of ΔR-L 2D:4D in rheumatoid arthritis patients

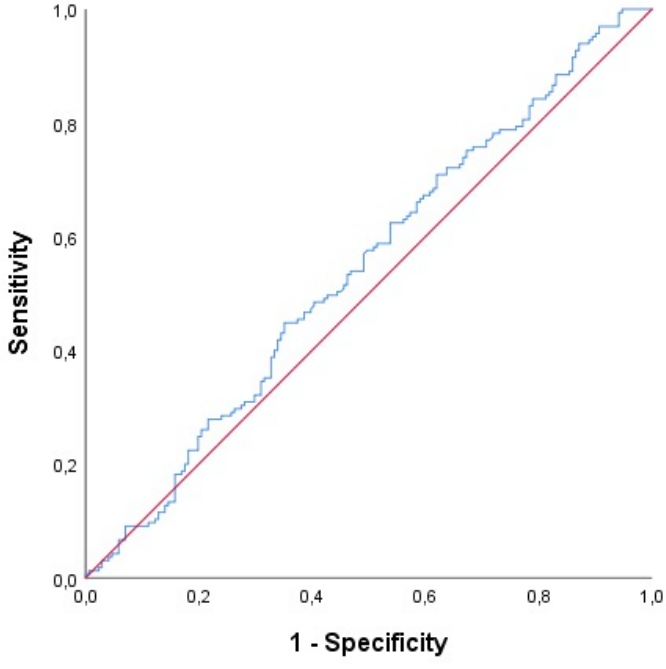

Figure 2. Receiver operating characteristic curve for predictive value of the right hand 2D:4D ratio in female rheumatoid arthritis patients

RA group than in the control group. In the RA group, the rate of increase in the 2D:4D ratio between men and women was higher compared with the control group. To the best of our knowledge, this is the first study in the literature comparing 2D:4D ratios of patients with RA with a healthy control group. In general, studies show that factors related to the reduction of estrogens are risk factors for RA, whereas factors related to high exposure to estrogens are protective against RA (19). The postmenopausal period and anti-estrogen drug use reduce estrogen levels. The increased risk of seronegative RA development during the postmenopausal period has been shown in various studies (20,21). The use of selective estrogen receptor modulators and aromatase inhibitors, which are anti-estrogen drugs, has been associated with the development of RA depending on the dose and duration (22).

Oral contraceptive (OCC) use and hormone replacement therapy (HRT) are among the situations that increase estrogen exposure. The relationship between OCC use and RA is controversial (19). Meta-analyses investigating the relationship between RA development and OCC found no significant relationship (23-25). Previous studies reported that OCC was predominantly protective against RA, which was associated with higher estrogen doses at the time of these studies (25). In general, the available evidence supports the protective effect of OCCs against RA, especially when used for a long time or at high doses. In a case–control study on HRT, a protective relationship was reported between the use of combined HRT and anti-citrullinated peptide antibody positive RA. However, this relationship could not be demonstrated in HRT containing only estrogen (26). In situations such as pregnancy and breastfeeding, multiple hormone changes are seen. Pregnancy is a condition characterized by high estrogen exposure, but these effects are modified with other hormones such as high levels of progesterone. Cohort studies reported that pregnancy is protective against RA development (27,28). Breastfeeding was shown to be associated with a decrease in RA risk (29,30). A systematic review reported that breastfeeding for more than 12 months is protective against RA (31). In contrast, the postpartum period in which estrogen levels decreased was associated with an increased RA risk (28,32).

Androgens suppress peripheral mononuclear cell activity and inhibit the differentiation of Th1 and Th17 (23). Androgen levels were found to be lower in men with RA compared with healthy controls (33,34). Men and women diagnosed with RA had a lower androgen/estrogen ratio (35). It was reported that men with hypogonadism had higher RA risk compared with those without hypogonadism (36). Although there are limited studies on androgen levels in patients with RA during the preclinical period, it was shown that androstenedione levels were lower in women in the period before RA diagnosis compared to the control group (37). Systemic estrogen/androgen ratio is increased in patients with RA. In patients with RA, the estrogen/androgen

ratio in synovium is also increased and is higher than in the systemic circulation (38). There are no clinical trials investigating estrogen/androgen ratio in the prenatal period in patients with RA. The 2D:4D ratio, which is an indirect indicator of estrogen/androgen ratio during this period, may provide information about the hormonal environment in the prenatal period in patients with RA. According to the results of this study, no significant difference was found in the 2D:4D ratio in both hands between patients with RA and the control group. However, the change in the 2D:4D ratio between men and women was greater in the RA group. The relationship between sex steroids and digit length was stronger in the right hand. Therefore, high ΔR-L 2D:4D is associated with an increased estrogen/androgen ratio (8). In this study, ΔR-L 2D:4D values in women were higher in the RA group than in the control group. These results suggest that the estrogen load in the prenatal period may be higher in patients with RA. It can also be an indirect evidence of increased estrogen/androgen ratio in patients with female RA during the prenatal period.

Study Limitations

This study has certain limitations. First, it should be remembered that the 2D:4D ratio is not a direct but rather an indirect indicator of the prenatal hormonal environment. Second, measuring digit lengths indirectly using digital images reduces digit length ratios and reduces the strength of the study (39). The high number of patients included in the study and the measurements made by two independent researchers who were blinded to the study groups are the strengths of the present study.

CONCLUSION

Many factors play a role in RA pathogenesis. The effect of hormonal factors on RA pathogenesis is complex, but, in eneral, systethe systemicogen/androgen ratio is increased in patients with RA. In RA patients, the ΔR-L 2D:4D value in women and the rate of increase in the 2D:4D ratio in women compared to men was higher compared to the control group. These results suggest that the sex steroid balance may be more predominantly altered in female patients diagnosed with RA, especially during the prenatal period.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Fırat University (decision no: 06, date: 05.01.2018).

Informed Consent: Informed consent was obtained from all patients before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., A.D.K., R.F.A., A.K., Concept: M.G., R.P.S., R.F.A., A.K., Design: M.G., A.D.K., R.F.A., N.G., A.K., Data Collection or Processing: M.G., M.S.A., R.P.S., İ.G., R.F.A., A.K., Analysis or Interpretation: M.G., T.K.K., N.G., A.K., Literature Search: M.G., İ.G., T.K.K., R.F.A., A.K., Writing: M.G., A.K.

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REFERENCES

1. de Hair MJ, Lehmann KA, van de Sande MG, Maijer KI, Gerlag DM, Tak PP. The clinical picture of rheumatoid arthritis according to the 2010 American College of Rheumatology/European League Against Rheumatism criteria: is this still the same disease? Arthritis Rheum 2012;64:389-93.
2. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci 2006;1069:212-22.
3. Sokka T, Toloza S, Cutolo M, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 2009;11:R7.
4. Cutolo M, Sulli A, Capellino S, et al. Anti-TNF and sex hormones. Ann N Y Acad Sci 2006;1069:391-400.
5. Straub RH. The complex role of estrogens in inflammation. Endocr Rev 2007;28:521-74.
6. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97:1159-68.
7. Carlsten H, Nilsson N, Jonsson R, Bäckman K, Holmdahl R, Tarkowski A. Estrogen accelerates immune complex glomerulonephritis but ameliorates T cell-mediated vasculitis and sialadenitis in autoimmune MRL lpr/lpr mice. Cell Immunol 1992;144:190-202.
8. Manning JT, Scutt D, Wilson J, Lewis-Jones DI. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod 1998;13:3000-4.
9. Manning JT. Resolving the role of prenatal sex steroids in the development of digit ratio. Proc Natl Acad Sci U S A 2011;108:16143-4.
10. Breedlove SM. Minireview: Organizational hypothesis: instances of the fingerpost. Endocrinology. 2010;151:4116-22.
11. Zheng Z, Cohn MJ. Developmental basis of sexually dimorphic digit ratios. Proc Natl Acad Sci U S A 2011;108:16289-94.
12. Auger J, Le Denmat D, Berges R, et al. Environmental levels of oestrogenic and antiandrogenic compounds feminize digit ratios in male rats and their unexposed male progeny. Proc Biol Sci 2013;280:20131532.
13. Parks CG, D'Aloisio AA, DeRoo LA, et al. Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood. Ann Rheum Dis 2013;72:350-6.
14. Noller KL, Blair PB, O'Brien PC, et al. Increased occurrence of autoimmune disease among women exposed in utero to diethylstilbestrol. Fertil Steril 1988;49:1080-2.

15. Baird DD, Wilcox AJ, Herbst AL. Self-reported allergy, infection, and autoimmune diseases among men and women exposed in utero to diethylstilbestrol. J Clin Epidemiol 1996;49:263-6.

16. Vingerhoets AJ, Assies J, Goodkin K, Van Heck GL, Bekker MH. Prenatal diethylstilbestrol exposure and self-reported immune-related diseases. Eur J Obstet Gynecol Reprod Biol 1998;77:205-9.

17. Jeevanandam S, Muthu PK. 2D:4D Ratio and its Implications in Medicine. J Clin Diagn Res 2016;10:CM01-CM03.

18. Neyse L, Brañas-Garza P. Digit Ratio Measurement Guide. Kiel Working Papers Kiel Institute for the World Economy (IfW). 2014;1914: 1-11. Available from: URL: https://www.ifw-kiel.de/fileadmin/Dateiverwaltung/IfW-Publications/Levent_Neyse/digit-ratio-measurement-guide-2/Working_Paper_Levent_Neyse_MPRA_paper_54134.pdf

19. Alpízar-Rodríguez D, Finckh A. Environmental factors and hormones in the development of rheumatoid arthritis. Semin Immunopathol 2017;39:461-8.

20. Beydoun HA, el-Amin R, McNeal M, Perry C, Archer DF. Reproductive history and postmenopausal rheumatoid arthritis among women 60 years or older: Third National Health and Nutrition Examination Survey. Menopause 2013;20:930-5.

21. Pikwer M, Bergström U, Nilsson JÅ, Jacobsson L, Turesson C. Early menopause is an independent predictor of rheumatoid arthritis. Ann Rheum Dis 2012;71:378-81.

22. Chen JY, Ballou SP. The effect of antiestrogen agents on risk of autoimmune disorders in patients with breast cancer. J Rheumatol 2015;42:55-9.

23. Alpízar-Rodríguez D, Pluchino N, Canny G, Gabay C, Finckh A. The role of female hormonal factors in the development of rheumatoid arthritis. Rheumatology (Oxford) 2017;56:1254-63.

24. Chen Q, Jin Z, Xiang C, Cai Q, Shi W, He J. Absence of protective effect of oral contraceptive use on the development of rheumatoid arthritis: a meta-analysis of observational studies. Int J Rheum Dis 2014;17:725-37.

25. Pladevall-Vila M, Delclos GL, Varas C, Guyer H, Brugués-Tarradellas J, Anglada-Arisa A. Controversy of oral contraceptives and risk of rheumatoid arthritis: meta-analysis of conflicting studies and review of conflicting meta-analyses with special emphasis on analysis of heterogeneity. Am J Epidemiol 1996;144:1-14.

26. Orellana C, Saevarsdottir S, Klareskog L, Karlson EW, Alfredsson L, Bengtsson C. Postmenopausal hormone therapy and the risk of rheumatoid arthritis: results from the Swedish EIRA population-based case-control study. Eur J Epidemiol 2015;30:449-57.

27. Peschken CA, Robinson DB, Hitchon CA, et al. Pregnancy and the risk of rheumatoid arthritis in a highly predisposed North American Native population. J Rheumatol 2012;39:2253-60.

28. Silman A, Kay A, Brennan P. Timing of pregnancy in relation to the onset of rheumatoid arthritis. Arthritis Rheum 1992;35:152-5.

29. Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. Arthritis Rheum 2004;50:3458-67.

30. Adab P, Jiang CQ, Rankin E, et al. Breastfeeding practice, oral contraceptive use and risk of rheumatoid arthritis among Chinese women: the Guangzhou Biobank Cohort Study. Rheumatology (Oxford) 2014;53:860-6.

31. Chen H, Wang J, Zhou W, Yin H, Wang M. Breastfeeding and Risk of Rheumatoid Arthritis: A Systematic Review and Metaanalysis J Rheumatol 2015;42:1563-9.

32. Wallenius M, Skomsvoll JF, Irgens LM, et al. Postpartum onset of rheumatoid arthritis and other chronic arthritides: results from a patient register linked to a medical birth registry. Ann Rheum Dis 2010;69:332-6.

33. Tengstrand B, Carlström K, Hafström I. Gonadal hormones in men with rheumatoid arthritis--from onset through 2 years. J Rheumatol 2009;36:887-92.

34. Pikwer M, Giwercman A, Bergström U, Nilsson JÅ, Jacobsson LT, Turesson C. Association between testosterone levels and risk of future rheumatoid arthritis in men: a population-based case-control study. Ann Rheum Dis 2014;73:573-9.

35. Cutolo M, Seriolo B, Villaggio B, Pizzorni C, Craviotto C, Sulli A. Androgens and estrogens modulate the immune and inflammatory responses in rheumatoid arthritis. Ann N Y Acad Sci 2002;966:131-42.

36. Baillargeon J, Al Snih S, Raji MA, et al. Hypogonadism and the risk of rheumatic autoimmune disease. Clin Rheumatol 2016;35:2983-7.

37. Masi AT, Elmore KB, Rehman AA, Chatterton RT, Goertzen NJ, Aldag JC. Lower Serum Androstenedione Levels in Pre-Rheumatoid Arthritis versus Normal Control Women: Correlations with Lower Serum Cortisol Levels. Autoimmune Dis 2013;2013:593493.

38. Capellino S, Straub RH, Cutolo M. Aromatase and regulation of the estrogen-to-androgen ratio in synovial tissue inflammation: common pathway in both sexes. Ann N Y Acad Sci 2014;1317:24-31.

39. Ribeiro E, Neave N, Morais RN, Manning JT. Direct versus indirect measurement of digit ratio (2D:4D): A critical review of the literature and new data. Evolutionary Psychology 2016;14:1-8.