

Adverse effects of maternal rheumatoid arthritis during pregnancy on children

Rong Li¹, Dan Ma², Ya-Zhen Su^{1,2}, Gai-Lian Zhang², Ke Xu², Li-Yun Zhang²

¹Department of Rheumatology, Bethune Hospital Affiliated to Shanxi Medical University, Taiyuan, Shanxi 030032, China;

²Department of Rheumatology, Shanxi Bethune Hospital, Taiyuan, Shanxi 030032, China.

To the Editor: Rheumatoid arthritis (RA) is an autoimmune disease characterized by invasive arthritis, affecting approximately 1% of the global population. Young and middle-aged women are prone to RA and can experience one or more pregnancies during the course of the disease. The developmental origins of health and disease describes how health hazards occurring at a young age could affect one's health in later life.^[1] RA exposure during pregnancy can consequently influence the health of the offspring. This paper discusses the pregnancy status of women with RA and the possible influence of RA on the health of the offspring.

Women with RA have long pregnancy periods and reduced pregnancy rates, which could be associated with individual medical conditions and their use of non-steroidal anti-inflammatory drugs, glucocorticoids, and other drugs during treatment. The relationship between RA and abortion remains controversial as some people believe that the abortion rate among women with RA is relatively high, and improper medication during pregnancy can lead to abortion. Assisted reproductive technology (ART) includes follicular stimulation, improved estrogen level, artificial insemination, and *in vitro* fertilization-embryo transfer, thus giving hope to infertile women with RA given their low embryo implantation rate and high potential abortion risk. A study found that the frequency of ART in women with RA was significantly higher than that of the general population (23.0% *vs.* 5.1%, $P < 0.001$), and the average maternal age of women with RA was relatively higher than that of the general population (34.7 *vs.* 31.8 years). However, despite successful conception via ART, the live birth rate of transplanted embryos in women with RA was lower than that of women who were not diagnosed with RA. Therefore, rheumatologists and obstetricians and gynecologists should jointly guide patients with RA, standardize the use of drugs to maintain the stability of the condition, and administer ART in patients with RA

before the age of 35 years, to effectively improve fertility rates.

Pregnancy has the potential to greatly influence the condition of RA patients. The condition of women with RA can be partially improved during pregnancy, but there is a risk of postpartum deterioration. The balance of proinflammatory and anti-inflammatory mechanisms tends to shift during pregnancy in women with RA, and a combined improved disease activity rate between 48% and 65% has been observed. Fetal antigens and high levels of estrogen, progesterone, and human chorionic gonadotropin are important factors that induce this beneficial type of immune regulation. During pregnancy in women with RA, disease activity was more likely to improve if rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) were negative than positive.^[2] Furthermore, pregnant RA women with low levels of disease activity score in 28 joints (DAS28)-C-reactive protein (CRP) and hormone use in the first trimester of pregnancy were likely to experience the remission of RA disease activity. In contrast to the partial improvement of disease observed in women with RA during pregnancy, the risk of elevated disease activity in women with RA throughout the 6-month postpartum period increased between 62% and 90%, and the risk peaked around 12 weeks postpartum. Changes in immune cells, cytokine patterns, and hormones mediate elevated postpartum disease activity in women with RA. Studies have shown that prolonged breastfeeding (>17 months) is associated with an increased risk of RA disease activity. Hypertension and pre-eclampsia are more common in pregnant women with RA than in the general population. According to data from the Norwegian Birth Registry, the risk of pre-eclampsia in RA patients was 5.0%, compared with 3.4% in women overall. Knowledge necessary for ensuring the safety of women with RA during pregnancy and preventing post-pregnancy enhancement of disease activity is urgently needed.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000001374

Rong Li and Dan Ma were contributed equally to this work.

Correspondence to: Li-Yun Zhang, Department of Rheumatology, Shanxi Bethune Hospital, Taiyuan 030032, Shanxi, China
E-Mail: 1315710223@qq.com

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(9)

Received: 13-11-2020 Edited by: Ning-Ning Wang

The risk of intrauterine growth restriction, preterm birth, and low birth weight is increased in mothers with elevated RA activity during pregnancy. Tsuda *et al*^[3] surveyed pregnant women in a Japanese hospital and showed that women with RA had higher rates of preterm birth than the general population (27.5% *vs.* 5.6%, $P < 0.001$), reduced offspring birth weight (51.6% *vs.* 9.5%, $P < 0.001$), and increased fetal growth restriction (28.6% *vs.* 4.1%, $P < 0.001$). The concentration of circulating cytokines in the blood of pregnant women with RA can affect fetal growth. In the first trimester, even after adjusting for disease activity, high interleukin-6 levels were associated with decreased birth weight. Furthermore, as disease activity (DAS28 score) in women with RA increased during pregnancy, the birth weight of infants tended to decrease. Low infant weight leads to a period in which offspring growth tends to compensate for the prior deficiency. Cardiovascular and metabolic conditions, however, are more likely to deteriorate in adulthood. Disease activity in women with RA increases the risk of cesarean section. In a parallel cohort, the cesarean section rate in pregnant women with RA experiencing high disease activity (DAS28-CRP >3.2) was 22%, while that of the group with low disease activity (DAS28-CRP <3.2) was 10%.

Drug use during pregnancy can also lead to premature birth, low birth weight, and an increased risk of infection. Studies have shown that pregnant women with RA who received daily doses of prednisone >7.5 mg had higher preterm birth rates and lower fetal weight rates than those taking lower doses or no prednisone, which was determined to be related to the effect of hormones on conditions of pregnancy. Placental transfer of biologic disease-modifying anti-rheumatic drugs (bDMARDs) may result in intrauterine drug exposure that extends as long as 12 months, with a median clearance time of 6 months and a longer clearance time of ublituximab or adalimumab than for infliximab. The timing of maternal biologics also plays a role in assessing potential continuing risk to the infant, while the late trimester of pregnancy increases risk. Berkhout *et al*^[4] reviewed literature to investigate the impact of perinatal exposure to bDMARDs in women with RA on the infant immune response, the safety of live vaccines, and the vaccine efficacy in the first year of life. It is currently recommended that healthy infants exposed to bDMARDs during perinatal periods receive a rotavirus vaccine under the recommended schedule. It has been reported that an infant who was exposed to bDMARDs during the perinatal period died of disseminated tuberculosis after being vaccinated with bacille Calmette-Guérin (BCG) at 4.5 months. Although additional evidence is lacking, we must be aware of the possibility that the spread of BCG may cause infection. For infants receiving intrauterine tumor necrosis factor inhibitor (TNFi) treatment, the postponement of all live vaccines until 6 months after birth is recommended, and BCG vaccination in the first 12 months after birth is not recommended. Currently, methotrexate, leflunomide, mycophenolate mofetil, and cyclophosphamide have been confirmed to have teratogenicity, and treatment with the drugs should be halted before conception. Cyclophosphamide also accumulates to a degree in breast milk, so its use is forbidden while breastfeeding. Sulfasalazine (up to 2000 mg/day), hydrox-

ychloroquine (200–400 mg/day), azathioprine (up to 2 mg·kg⁻¹·d⁻¹), and cyclosporine are safe during pregnancy.^[5]

Mothers with RA increase the risk of chronic diseases in their children. Cytokine-mediated inflammation in the circulatory system of mothers with RA has the potential to affect the development of the fetus, especially in sensitive organs such as the lungs, brain, and intestines. Based on the Danish Health Register, Rom *et al*^[6] conducted a nationwide epidemiological study to evaluate the impact of parents with RA on RA incidence in children. They found that for children whose mothers experienced RA, eight out of 11 diagnostic groups had a statistically significant increase in disease incidence. Among these, type 1 diabetes incidence increased by 30%, and the incidence of juvenile idiopathic arthritis increased threefold. They also found that the risk of developing autism spectrum disorder (ASD) increased by approximately 30%. However, Tsai *et al*^[7] conducted a paired analysis of 1,893,244 newborns born in Taiwan (China) over 12 years and found that the risk of ASD in newborns born to RA mothers ($n = 673$) was 0.04%, which was not significantly higher than that of infants born to mothers without RA. Jølvig *et al*^[8] found that, compared with children born to mothers without RA, infants of mothers with RA have a risk of epilepsy that is elevated 61%, and a three-fold increase in RA. In 2019, Knudsen *et al*^[9] conducted a retrospective study that included Danish boys born alive throughout the past 27 years. The work reported that 40 (3.9%) of 1026 boys born to mothers with RA had cryptorchidism. The incidence of cryptorchidism in boys born to mothers with RA was higher than that of the general population in which 19,497 (2.82%) out of the total 690,240 boys were affected.

To explore changes in the epigenetics of children born to mothers with RA, Ince-Askan *et al*^[10] collected blood samples from 80 children born to mothers with RA (average age = 6.8 years) and 354 children (average age = 6.0 years) from the general population. The illuminated 450K gene chip method was used to detect cytosine-phosphate-guanine (CpG) sites, which indicate genome-wide DNA methylation.^[8] A linear mixed model was used to study DNA methylation differences between groups. We found that there were 147 CpG sites in which differential DNA methylation patterns between the blood samples of the children born to mothers with RA and the control group were observed. The five CpG sites most significantly related to methylation differences were cg06642177, cg08867893, cg06778273, cg07786668, and cg20116574. Some CpG sites with significant differences in methylation were found to be related to type 2 diabetes, cardiovascular disease, and obesity, or were located near key disease genotypes. After expression quantitative trait DNA methylation (eQTM) analysis, it was determined that cg11220663 was associated with decreased expression of the *ADD2* gene (β -adductor protein). *ADD2* changes have been associated with the pathogenesis of many diseases such as hypertension, cancer, and systemic lupus erythematosus. An analysis of 37,482 patients with RA based on data from the National Health Insurance Database in Taiwan (China) revealed that individuals with a family history of RA had an increased risk of RA and other autoimmune diseases, and

that about two-thirds of the phenotypic variation observed in RA patients was explained by familial factors. These findings are also consistent with the increased risk of certain diseases observed in children with mothers who have RA, as mentioned above. To fully elucidate, epigenetic features of children with mothers diagnosed with RA and their correlations with disease additional research with a larger sample size is needed.

Women with RA suffer from impaired fertility, prolonged conception time, and reduced conception rate, which are conditions affected by disease activity and commonly prescribed drugs. Although women with RA may experience partial remission during pregnancy, the risk of enhanced disease activity after pregnancy remains. The disease activity of mothers with RA and the use of drugs during pregnancy increased the risk of infant intrauterine growth restriction, premature delivery, and low birth weight. At the same time, DNA methylation differences in 147 CpG sites were found in children born to RA mothers relative to the general population. These may have adverse effects on children born to RA mothers. Mothers with RA should use drugs reasonably during pregnancy to control disease activity, and it is recommended that children born to mothers with RA pay special attention to indicators of cardiovascular and metabolic diseases.

Funding

This work was supported by grants from the National Natural Science Foundation (No. 81771768) and the Applied Basic Research Program of Shanxi Province (No. 201801D221380).

Conflicts of interest

None.

References

1. Lacagnina S. The developmental origins of health and disease (DOHaD). *Am J Lifestyle Med* 2020;14:47–50. doi: 10.1177/1559827619879694.

2. Li C, Zhang Y, Song H, Gao J, Zhao DB, Zhu Q, *et al.* Anti-cyclic citrullinated peptide antibody predicts the development of rheumatoid arthritis in patients with undifferentiated arthritis. *Chin Med J (Engl)* 2019;132:2899–2904. doi: 10.1097/CM9.0000000000000570.
3. Tsuda S, Sameshima A, Sekine M, Kawaguchi H, Fujita D, Makino S, *et al.* Pre-conception status, obstetric outcome and use of medications during pregnancy of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) in Japan: multi-center retrospective descriptive study. *Mod Rheumatol* 2020;30: 852–861. doi: 10.1080/14397595.2019.1661592.
4. Berkhout A, Clark JE, Wen SC. In utero exposure to biologic disease-modifying anti-rheumatic drugs and effects to the infant: infectious complications, vaccine response, and safety of live vaccine administration. *Expert Rev Vaccines* 2019;18:495–504. doi: 10.1080/14760584.2019.1599286.
5. Lau CS, Chia F, Dans L, Harrison A, Hsieh TY, Jain R, *et al.* 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. *Int J Rheum Dis* 2019;22:357–375. doi: 10.1111/1756-185X.13513.
6. Rom AL, Wu CS, Olsen J, Jawaheer D, Hetland ML, Ottesen B, *et al.* Parental rheumatoid arthritis and long-term child morbidity: a nationwide cohort study. *Ann Rheum Dis* 2016;75:1831–1837. doi: 10.1136/annrheumdis-2015-208072.
7. Tsai PH, Yu KH, Chou IJ, Luo SF, Tseng WY, Huang LH, *et al.* Risk of autism spectrum disorder in children born to mothers with systemic lupus erythematosus and rheumatoid arthritis in Taiwan. *Joint Bone Spine* 2018;85:599–603. doi: 10.1016/j.jbspin.2017.11.005.
8. Jølving LR, Nielsen J, Kesmodel US, Nielsen RG, Beck-Nielsen SS, Nørgård BM. Children born by women with rheumatoid arthritis and increased susceptibility for chronic diseases: a nationwide cohort study. *Arthritis Care Res* 2018;8:1192–1197. doi: 10.1002/acr.23461.
9. Knudsen SS, Bech BH, Deleuran BW, Ramlau-Hansen CH, Arendt LH. Maternal rheumatoid arthritis and systemic lupus erythematosus and risk of cryptorchidism and hypospadias in boys: a Danish nationwide study. *Rheumatology* 2020;59:1871–1877. doi: 10.1093/rheumatology/kez538.
10. Ince-Askan H, Mandaviya PR, Felix JF, Duijts L, van Meurs JB, Hazes JMW, *et al.* Altered DNA methylation in children born to mothers with rheumatoid arthritis during pregnancy. *Ann Rheum Dis* 2019;78:1198–1204. doi: 10.1136/annrheumdis-2018-214930.

How to cite this article: Li R, Ma D, Su YZ, Zhang GL, Xu K, Zhang LY. Adverse effects of maternal rheumatoid arthritis during pregnancy on children. *Chin Med J* 2021;134:1113–1115. doi: 10.1097/CM9.0000000000001374