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REVIEW

Rheumatoid arthritis-associated complications during pregnancy and its effect on offspring: comprehensive review

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Abstract

This study comprehensively explores the complexities of rheumatoid arthritis during pregnancy and its impact on offspring. Through an extensive review of existing literature, we investigate maternal and fetal risks, including adverse pregnancy outcomes and developmental issues in offspring. Utilizing reputable databases such as PubMed, Google Scholar, and Science Direct, we meticulously examined studies exploring the connection between rheumatoid arthritis and pregnancy complications, with a focus on outcomes for offspring. We excluded studies lacking sufficient data or peer review. Synthesizing findings from selected studies, we identified common themes and patterns, presenting results in a clear, organized manner. Our examination reveals a heightened likelihood of preterm birth and preeclampsia among pregnant individuals with rheumatoid arthritis, often correlated with disease activity. Furthermore, we highlight the impact on fetal and neonatal outcomes, such as low birth weight, underscoring the importance of meticulous disease management throughout pregnancy. Balancing the necessity of disease-modifying agents with potential risks, and consideration of medication safety is paramount. A multidisciplinary approach involving rheumatologists and obstetricians is crucial for optimizing outcomes. In conclusion, this synthesis underscores the nuanced challenges of rheumatoid arthritis in pregnancy. A comprehensive understanding and personalized, multidisciplinary approach to an organization is essential for informed decision-making in clinical practice. Our review contributes to ongoing discourse, providing insights for enhanced patient care and guiding future research endeavors.

Keywords Rheumatoid arthritis · Pregnancy complications · Offspring outcomes · DMARDs · Autoimmune condition

Introduction

Rheumatoid arthritis is a chronic inflammatory joint disease characterized by pain, swelling, and synovial joint degradation, which reduces joint functionality. Characterized by an uncertain origin, this condition impacts multiple joints and leads to the deterioration of cartilage. While rheumatoid arthritis primarily targets joints, it can also have repercussions on the skin and lungs, as well as other organ systems (Sharma et al. 2021). The approach to managing rheumatoid arthritis has undergone substantial transformations over the last two decades. Conventional therapies initially focused on treating acute inflammation with glucocorticoids and nonsteroidal anti-inflammatory drugs, while long-term maintenance therapy included disease-modifying anti-rheumatic drugs such as methotrexate, hydroxychloroquine, and sulfasalazine. Disease-modifying anti-rheumatic drugs, particularly methotrexate, have proven effective in addressing extra-articular symptoms, reducing radiographic advancement, and relieving joint discomfort. Consequently, they remain the primary choice for initial therapeutic intervention (Siebert et al. 2015). One of the most prevalent chronic illnesses affecting women in their reproductive years is rheumatoid arthritis. It is more difficult for women with rheumatoid arthritis to become parents. This has to do with both the illness itself and taking medicine. It is a persistent inflammatory condition primarily impacting the synovial joints, often triggered by a combination of genetic and environmental factors, including the use of tobacco (Smeele and Dolhain 2019). It usually begins in tiny peripheral joints, is symmetrical, and if treatment is not received, proceeds to

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affect proximal joints. Prolonged inflammation of the joints causes cartilage loss and bone erosion, ultimately resulting in joint degeneration (Nelson and Østensen 1997). It is estimated that people globally are diagnosed with rheumatoid arthritis. It is a progressive illness that increases mortality and morbidity if left untreated (Silman and Hochberg 1993). According to reports, the adult population in India has a 0.75% prevalence of rheumatoid arthritis. It affects approximately 25 men and 54 women out of 100,000 people, and it is the cause of over 1 million cases annually, 9 million doctor visits, and 250,000 hospital admissions in the US.[1] Women are impacted approximately three times more than men. It is untrue despite what is occasionally stated that women experience the highest incidence of rheumatoid arthritis throughout their middle years. Many epidemiologic studies have shown that the incidence of rheumatoid arthritis in females rises with age, at least until the patient reaches their seventies or eighties (Nelson and Østensen 1997). When there is a greater chance of difficulties during pregnancy, birth, or the postpartum period for the mother, the growing fetus, or both, the pregnancy is considered high risk. Preterm delivery (less than 37 week's gestation), multiple gestations, congenital abnormalities, inadequate fetal growth, placental abruption, and stillbirth are among the dangers for the fetus. Pregnancy-induced hypertension, or elevated blood pressure after 20 weeks of pregnancy, preeclampsia or elevated blood pressure with proteinuria greater than 0.3 g per 24-h period, eclampsia, or preeclampsia with seizures, gestational diabetes mellitus, (GDM), sepsis, a worsening or flare-up of their underlying illness, and thrombotic events are among the conditions that mothers may experience (Soh and Nelson-Piercy 2015). Particular histocompatibility genes (human leukocyte antigens) HLA-DR4 are associated with rheumatoid arthritis. Certain rheumatoid arthritis populations also exhibit enrichment in specific subtypes of DR1 and DR14. Men and women both have higher frequencies of the HLA genes linked to rheumatoid arthritis. Nevertheless, variations in HLA linkages based on gender have been reported (Nelson and Østensen 1997).

Rheumatoid arthritis involves a complex interaction of factors contributing to its pathogenesis

Rheumatoid arthritis is believed to primarily stem from genetic factors, arising through the interplay between an individual's genetic makeup and various environmental conditions (Kłodziński and Wisłowska 2018). The presence of certain HLA-DRB1 alleles, specifically HLA-DRB1*04, HLA-DRB1*01, and HLA-DRB1*10, has been associated with a heightened likelihood of developing rheumatoid arthritis. These specific HLA-DRB1 alleles contain a segment that consists of a consistent sequence of 5 amino acids referred to as the "shared epitope" (SE), located within the third highly variable region of their DRB1 chain. The shared epitope has been linked to an elevated risk of rheumatoid arthritis development (Weyand et al. 1992). Variations in additional genes, such as PAD14, PTPN22, CTLA4, IL-2RA, STAT4, TRAF1, CCR6, and are to be connected or linked to rheumatoid arthritis.

These genetic differences or polymorphisms have been identified as having associations with the occurrence or development of rheumatoid arthritis (Dedmon 2020). Additional environmental factors linked to rheumatoid arthritis encompass various infectious agents such as the Epstein–Barr virus, cytomegalovirus, Proteus species, and Escherichia coli, along with substances they produce like heat-shock proteins (McInnes and Schett 2011). An autoimmune inflammatory reaction occurring in the joints might be prompted by exposure to different antigens found in areas of the body distant from those joints, including the lungs, oropharynx, and gastrointestinal tract (Klareskog et al. 2020).

2.1 Triggering stage

This phase initiates either in the bone marrow or secondary lymphoid tissues. Epitope spreading refers to the progression of immune responses toward self-antigens, often occurring beyond the joints and preceding the manifestation of joint symptoms for several years. Before the onset of joint symptoms, there is a gradual increase in (anti-citrullinated protein antibodies) ACPA levels, persisting for an extended period during this phase. Early anti-citrullinated protein antibody levels appear to be important in determining when a disease will manifest. The generation of anti-citrullinated protein antibodies signals a breakdown in immune tolerance, causing T cells to become activated and causing B cells to release additional anti-citrullinated protein antibodies. Anti-citrullinated protein antibody exacerbates inflammation, discomfort, and bone loss in rheumatoid arthritis. Certain autoantigens, such as filamin A and N-acetylglucosamine-6-sulfatas, establish a connection between microbial immunity and joint autoimmune responses. The gradual onset of rheumatoid arthritis might be elucidated by the engagement of citrullination in activating osteoclasts, alongside various biochemical, vascular, neurological, biomechanical, and microtrauma-related factors (Guo et al. 2018). Figure 1 represents the pathophysiology of rheumatoid arthritis (Sharma et al. 2021).

Maturation stage

The expansion of epitopes signifies the maturation of the immune system reacting to self-antigens released by the body, often occurring years before the manifestation of a

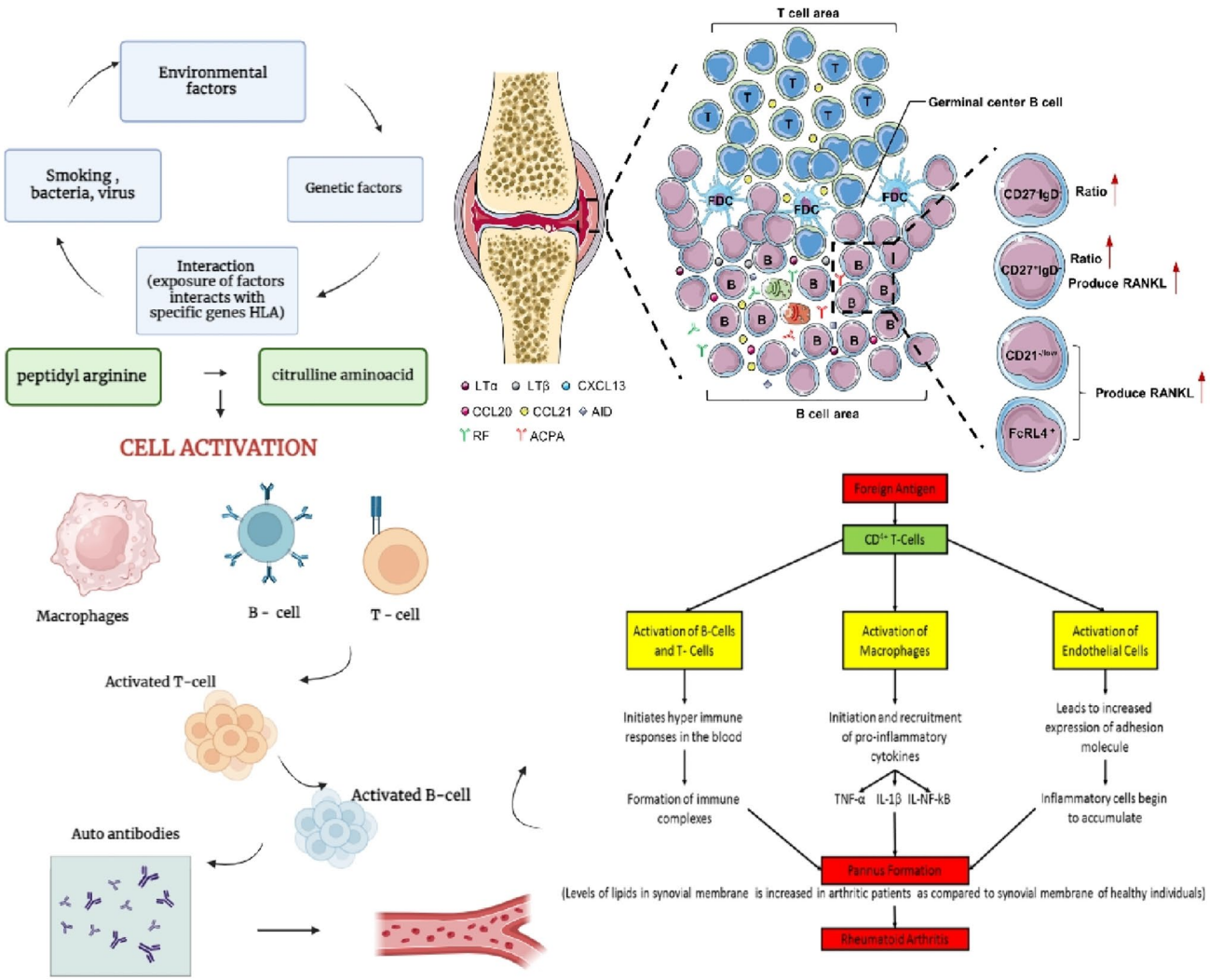

Fig. 1 The pathophysiology of rheumatoid arthritis

disease and commonly situated distant from the joints. In the period preceding the onset of joint symptoms, epitope spreading and a gradual elevation in ACPA levels may persist for several years (Nishimura et al. 2007; Bizzaro et al. 2013). Predicting how long until a disease manifest appears to depend critically on the early levels of anti-citrullinated protein antibodies. The body's immunological tolerance is compromised by the formation of anti-citrullinated protein antibodies. Numerous citrullinated neoantigens can activate T cells reliant on MHC class II, facilitating the enhanced production of anti-citrullinated protein antibodies by B cells. The occurrence of anti-citrullinated protein antibodies in rheumatoid arthritis is associated with reduced bone density, pain, and inflammation (Krishnamurthy et al. 2016; Wigerblad et al. 2016). The interplay of genetic elements and environmental influences, marked by the initiation of self-protein citrullination and the subsequent formation of autoantibodies targeting citrullinated peptides, could potentially lead to the onset of rheumatoid arthritis at likely trigger sites (lung, mouth, gut, etc.). Exposure of the lungs to harmful chemicals, infectious agents (including Aggregatibacter actinomycetemcomitans, Epstein–Barr virus, and Porphyromonas gingivalis), gut microbiota, and dietary factors can trigger the maturation and self-protein citrullination of Anti-citrullinated protein antibodies. The post-translational modification, citrullination, is facilitated by the calcium-dependent enzyme PAD, leading to the conversion of positively charged arginine to the polar but neutral citrulline. In rheumatoid arthritis, granulocytes and macrophages possess the capability to release PAD. An abnormal antibody response may then develop against various citrullinated proteins, such as fibrin and vimentin. Given that citrullination has a distinct impact on both osteoclast differentiation and ACPA-induced osteoclast activation, it could potentially

elucidate certain crucial facets of the gradual progression of rheumatoid arthritis, including the specific targeting of joints. Other potential factors contributing to this process include the biological characteristics of the targeted autoantigen, along with local microvascular, neurologic, and biomechanical elements. Furthermore, mechanisms associated with microtrauma might also play a role (McInnes and Schett 2011).

Targeting stage

Symmetrical inflammation, referred to as synovitis, occurs in small joints due to rheumatoid arthritis. Joint swelling is a manifestation of the immune system-induced inflammation in the synovial membrane. An inflammatory process is started by immune cells such as leukocytes and pro-inflammatory mediators. Fibroblast-like synoviocytes engage with both innate immune cells (such as monocytes and macrophages) and adaptive immune cells (including T and B lymphocytes), contributing to the progression of ACPA-positive rheumatoid arthritis and persistent synovitis. Notably, during this condition, synovial membranes experience substantial infiltration by monocytes and macrophages (Burmester et al. 1983). A recent study found that osteoclastogenesis in rheumatoid arthritis patients particularly in those with ACPA-positive rheumatoid arthritis is influenced by an imbalance in M1/M2 monocytes (Fukui et al. 2018). Furthermore, research indicates that mast cells serve as the predominant site for the localization of the pro-inflammatory cytokine interleukin (IL)-17A in samples from joints affected by rheumatoid arthritis (Hueber et al. 2010). Additionally, mast cells can be triggered by anti-citrullinated protein antibodies and Toll-like receptors (TLRs) ligands (Suurmond et al. 2015). The progression of rheumatoid arthritis encompasses the participation of numerous cells and their cytokines. Initiated by leukocyte infiltration and the existence of pro-inflammatory mediators within the synovial compartment, an inflammatory cascade unfolds. This cascade involves interactions among cells from the innate immune system (including monocytes, macrophages, mast cells, and dendritic cells) and the adaptive immune system (T cells and B cells) with fibroblast-like synoviocytes. Additionally, endothelial cells play a role in promoting widespread angiogenesis. The severe stage is characterized by bone erosion, cartilage destruction, hyperplastic synovium, and systemic effects. Because of certain anatomical features, the area where the periosteum and synovial membrane meet is commonly referred to as the “bare area” when bone resorption results in erosions. Articular cartilage degeneration may ultimately result from subchondral bone disintegration because of elevated osteoclast, decreased osteoblast, and enhanced synoviocyte activity (Guo et al. 2018).

Fulminant stage

In addition to breaking down waste materials, synovial cells play a crucial role in joint health by secreting hyaluronic acid and lubricin for lubrication. This helps to sustain the joint’s stability. The hyperplastic synovium observed in rheumatoid arthritis is a result of dysfunctional fibroblast-like synoviocytes. The breakdown in contact inhibition leads to abnormal FLS proliferation, a significant contributor to rheumatoid arthritis. This lack of inhibition triggers the release of inflammatory cytokines and proteinases, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), contributing to joint degradation. This microenvironment fosters neutrophil accumulation and supports the survival of T cells and B cells (Filer et al. 2006). Cartilage, a vital component of synovial joints primarily comprised of chondrocytes and a well-organized extracellular matrix (ECM) rich in type II collagen and glycosaminoglycans (GAGs), plays a crucial role. In rheumatoid arthritis, the hyperplastic synovium promotes adhesion and invasion, resulting in severe damage to the cartilage. Conversely, inflammatory signals, including those emanating from the ECM, can enhance fibroblast-like synoviocyte activity. Mediators of cartilage degradation in this context involve MMPs (matrix metalloproteases), specifically a disintegrin-like metalloprotease with thrombospondin type 1 motifs 4 and 5, and cathepsins. FLS-produced MMPs contribute to the disintegration of the type II collagen network, potentially leading to biomechanical dysfunction. Membrane-type I MMP is believed to be the primary proteinase responsible for breaking down the collagenous cartilage matrix (Sabeh et al. 2010). As a pathogenic aspect of rheumatoid arthritis, bone loss can manifest globally, periarticularly, or locally. This involves the suppression of osteoblasts and the induction of osteoclasts, resulting in bone loss. The term "periarticular" bone loss likely refers to changes in subchondral bone marrow cells, particularly osteoclast differentiation and the emergence of inflammatory infiltrates. The primary cause of bone loss remains a subject of debate, whether it is inflammation or autoimmunity. Existing data supports the conventional inflammatory theory, indicating that sufficient signals, such as those from the receptor activator of nuclear factor Kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF), may enable inflammatory cytokines like TNF-α, IL-6, IL-1β, IL-17, and others implicated in rheumatoid arthritis to exert pro-osteoclastogenic effects. Under the right conditions, these signals can suppress bone formation (Okamoto et al. 2017). There are two potential pathways for bone loss in rheumatoid arthritis. The first involves autoimmune processes that cause structural bone destruction. The first pathway deals with immune complex formation and osteoclast differentiation mediated by Fc receptors. Antibodies targeting citrullinated

vimentin are generated in response to the highly citrullinated protein, specifically the second most citrullinated protein. Consequently, anti-citrullinated protein antibodies find ideal antigenic targets in osteoclasts. Research indicates that the binding of ACPA to osteoclast precursors is linked to osteoclastogenesis, bone resorption, and subsequent bone loss (Harre et al. 2012). Bone resorption creates a void, often noticeable where the synovial membrane interfaces with the periosteum, termed as "naked" due to specific anatomical features. The equilibrium of weight-bearing joints relies on the integrity of the subchondral bone, and its progressive degeneration can result in the deterioration of articular cartilage. In the initial phases of rheumatoid arthritis, human bone marrow edema is commonly detected in the region of the subchondral bone (Borrero et al. 2011).

Maternal complications

Disease activity during pregnancy

Women are three times more likely than males to acquire rheumatoid arthritis, and throughout the past 20 years, the number of patients becoming pregnant has increased dramatically, divisively focusing increased attention on reproductive health issues (Østensen et al. 2015). It is widely recognized that experiencing an active disease while pregnant raises the likelihood of low birth weight and premature delivery resulting from placental insufficiency. However, there is an ongoing debate regarding the association between active rheumatoid arthritis and preeclampsia (PE) as well as gestational hypertension (de Man et al. 2009; Bharti et al. 2015). Women may choose not to become pregnant out of concern that having a child could result in the baby inheriting the illness or that taking rheumatoid arthritis medication could have a detrimental effect on the pregnancy (Chakravarty 2011). Recent research indicates that babies who are tiny for gestational age and or born prematurely are more likely to experience both short and long-term difficulties. These can include adult morbidities and increased rates of admissions to neonatal intensive care units (NICUs) (Al Rayes et al. 2021). It involved a prospective case–control study conducted across multiple centers. According to research, there is a direct link between Rheumatoid arthritis and several adverse pregnancy-related problems. Individuals with active rheumatoid arthritis had a higher likelihood of experiencing adverse pregnancy outcomes, including an increased risk of preterm labor leading to admission to the neonatal intensive care unit and abortion. However, it is crucial to emphasize the importance of rigorous disease management. It is strongly recommended to achieve remission of the illness before conception. Empowering and educating pregnant women with rheumatoid arthritis is essential, and they should be encouraged to collaborate with their healthcare providers in planning pregnancies, similar to patients with other chronic conditions (Al Rayes et al. 2021). Elevated serum levels of cytokines are a hallmark of active rheumatoid arthritis, although they are not usually visible in healthy pregnancies. Cytokines play a crucial role in driving the disease activity of rheumatoid arthritis, a persistent and systemic autoimmune disorder. Excessive levels of maternal cytokines can start and speed up the cascade of inflammatory cytokine production in a healthy pregnancy, which can lead to placental maldevelopment and spontaneous abortion, intrauterine growth restriction (IUGR), or premature birth. Several perinatal problems, including preeclampsia, preterm delivery, threatening miscarriages, and altered maternal cytokine levels, have been linked to these abnormalities (de Steenwinkel et al. 2013). Multiple factors contribute to the complexity of managing diseases during pregnancy, including an elevated burden of pregnancy morbidity and unfavorable pregnancy outcomes linked to heightened disease activity (Chakravarty et al. 2006; de Man et al. 2009) reported that 39% of individuals in the PARA cohort encountered a moderate flare-up postpartum. This suggests that pregnancy had a more significant positive influence on disease activity during the third trimester, particularly for those with moderate to high disease activity at the study's commencement. Subsequent investigations within the PARA cohort focused on diverse aspects of rheumatoid arthritis during pregnancy, such as exploring the impact of ACPA positivity through serial assessments of disease activity (de Man et al. 2008, 2010). Even while many studies included data on antibody status, their format made it difficult to understand how antibody status affects disease activity during or after pregnancy. Anticyclic citrullinated peptide antibody levels were shown to be higher in patients with high disease activity during pregnancy than in those with low disease activity, according to research by Forger et al. (2012). Despite the findings of de Man et al. (2008) in sub-analyses, it was revealed that the course of disease activity during pregnancy or the postpartum period remained unaffected by the presence of rheumatoid factor or anti-CCP. Additionally, the limited information on drug use in some publications made it challenging to conclude its impact on disease activity (Förger et al. 2012). A thorough assessment of future-oriented studies employing objective indicators for disease activity and related scoring systems indicates that 60% of individuals with rheumatoid arthritis observe improvement during pregnancy, whereas 47% encounter a relapse in the postpartum period. These data are of notable importance when counseling

individuals diagnosed with rheumatoid arthritis before childbirth (Jethwa et al. 2019).

Medication management (risks of anti-rheumatic medications during pregnancy and offspring)

Managing pregnancy in women with rheumatic diseases involves adapting the treatment plan to include medications that effectively control the underlying maternal condition while being safe for embryonic and fetal development. Ceasing all pre-conception medications, leading to a resurgence of the disease, can have equally detrimental effects on pregnancy outcomes as persisting with agents that may pose risks to the developing child (Østensen et al. 2006). Pregnancy risks for a mother with rheumatic disease are determined by the degree of organ involvement, the existence of specific autoantibodies, and the disease's activity both before and during conception. Maternal therapy, autoantibodies, and disease activity all carry risks for the developing fetus. A recent prospective study looked into 57 pregnancies when the first trimester was exposed to mycophenolate**.** Abortions occurred spontaneously in 45% of the pregnancies. Four of the 29 live-born infants displayed a clinical phenotype that was compatible with mycophenolate embryopathy, and six of the 29 children had congenital malformations Following mycophenolate exposure, the deformity rate for all pregnancies was 26 per cent (Anderka et al. 2009; Hoeltzenbein et al. 2012).

Disease-modifying anti-rheumatic drugs

Rheumatoid arthritis and other rheumatic illnesses can be effectively treated with methotrexate, a dihydrofolate reductase inhibitor that inhibits DNA synthesis and cell proliferation.

(a) Non-biologics

- Methotrexate use during pregnancy carries a high risk because of its well-documented teratogenic effects (Smolen et al. 2010). Numerous case reports and case series have demonstrated that exposure to methotrexate between six weeks and eight of gestation is linked to a particular embryopathy marked by craniosynostosis, pulmonary atresia, and limb deficits (Gerosa et al. 2016). There have been accounts of babies with congenital defects born to pregnant mothers who were exposed to methotrexate after this sensitive time. These include a variety of birth deformities such microtia, congenital diaphragmatic hernia, cleft palate, and numerous congenital heart defects like Fallot tetralogy, atrial or ventricular septal defects, pulmonary valve stenosis, and total anomalous pulmonary venous return (Dawson et al. 2014; Poggi and Ghidini 2011; Nurmohamed et al. 2011; Piggott et al. 2011). Moreover, unintentional methotrexate exposure in the first few weeks of pregnancy has been linked to a higher incidence of miscarriages; however, the evidence for this link varies throughout research. The data emphasizes how crucial it is to avoid methotrexate exposure during pregnancy because of its known teratogenic effects, which increase the chance of miscarriages and serious fetal abnormalities. Women and men of reproductive age who use methotrexate for rheumatic disorders must use proper contraception and talk to their doctors about family planning to lower the possibility of unintentional exposure during pregnancy (Gerosa et al. 2016).
- Azathioprine is used to treat a range of rheumatologic disorders, including rheumatoid arthritis and SLE. It works by inhibiting purine synthesis, which is essential for the generation of white blood cells. Under the previous FDA categorization scheme, azathioprine is classified as pregnancy category D; however, subsequent studies have shown that it can be taken appropriately during pregnancy where the benefit justifies the potential dangers. Studies have indicated that when used during pregnancy, such as encephalocele, stromatopelvic malformation higher chance of congenital defects and premature, congenital cataracts, and problems in the atrial and ventricular septa. While a few current investigations have identified no negative pregnancy risks, others have continued to find lower birth weight and higher rates of premature. Generally speaking, with careful consideration and collaborative decision-making, the use of azathioprine may be suitable when it is required to control rheumatic disease effectively and to prevent damage to the mother's end organs (Cleary and Källén 2009; Nørgård et al. 2003).
- Colchicine stops β-tubulin from polymerizing into microtubules, which stops neutrophils from activating, degranulating, and migrating to inflammatory areas. It is employed to address Behcet's illness, familial Mediterranean fever (FMF), and crystal arthropathies. One category C agent that can pass through the placenta is colchicine. Its usage is advised only in cases when the probable benefit outweighs the risk to the developing fetus (Michael et al. 2003). Due to early high-dosage animal studies that found teratogenic effects, miscarriages, and significant congenital abnormalities, use during pregnancy is highly contentious. The use of colchicine has been linked to lower median birth weight and higher risks of premature delivery; however, these unfavorable outcomes may also have been caused by baseline rheumatic illness (Diav-Citrin et al. 2010; Rabinovitch et al. 1992).
- Hydroxychloroquine in triple therapy for rheumatoid arthritis, hydroxychloroquine is commonly used with

methotrexate and sulfasalazine (Singh et al. 2012). Although hydroxychloroquine is usually seen as safe to use during pregnancy, there are some possible dangers involved which are, however, usually regarded as minimal. Among these dangers are possibility of harm to the fetus, research has not revealed any appreciable negative effects on the fetus, even though hydroxychloroquine crosses the placental barrier and reaches comparable amounts in mother and cord blood. Nevertheless, it is impossible to rule out the chance of unidentified threats due to the paucity of data on long-term results. Long-term hydroxychloroquine use can cause retinopathy, or damage to the retina of the eye, which can cause alterations in vision or perhaps permanent blindness. For patients using hydroxychloroquine, especially pregnant women, routine ophthalmologic monitoring is advised to identify early signs of retinal toxicity and prevent permanent damage. Exacerbation of specific conditions, although hydroxychloroquine helps treat rheumatoid arthritis and SLE, stopping the treatment during pregnancy may increase the chance of flare-ups. Disease flare-ups can be harmful to the health of the mother and fetus (Costedoat-Chalumeau et al. 2002). The results of a recent prospective study included 114 pregnant women exposed to hydroxychloroquine for a variety of therapeutic reasons indicating some links with unfavorable pregnancy outcomes. In particular, women who took hydroxychloroquine during pregnancy tended to give birth to babies that were smaller at birth, had babies born at an earlier gestational age, and had a higher risk of preterm delivery than women who did not take the medicine. Notwithstanding these results, there were not any obvious variations between the two groups in the frequency of congenital abnormalities (Diav-Citrin et al. 2013).

- Leflunomide: Leflunomide is frequently used in cases of methotrexate intolerance and is FDA-approved for the treatment of rheumatoid arthritis (Singh et al. 2012). Even at doses similar to those used in humans, leflunomide, a drug frequently prescribed for rheumatoid arthritis and other inflammatory diseases, has been demonstrated to cause notable abnormalities in animal models. Numerous adverse effects have been reported in research investigations on mice, including skeletal abnormalities, neural tube malformations, ventricular septal defects, chronic truncus arteriosus, and fetal death (Fukushima et al. 2007). These results indicate that leflunomide carries a high risk of harm to the fetus and is categorized as a category X pregnancy drug. In a different study, 45 conceptions totaling 16 throughout pregnancy and 29 before conception were evaluated for leflunomide exposure (Cassina et al. 2012).

(b) Biologics

1. B Lymphocyte depletion:

- **Rituximab:** Rituximab is often selected for patients whose condition all of the pregnant women who were exposed, along with most of the women (93.1%) who were exposed before becoming pregnant, gave birth to healthy children. Nevertheless, spina bifida occulta, patent ductus arteriosus, chondrodysplasia punctata, congenital heart block, and congenital abnormalities such as aplasia cutis congenita plagued two of the exposed kids during pregnancy. Among infants exposed before conception, no congenital problems have been found. Remarkably, most patients followed the cholestyramine wash-out strategy, highlighting its significance in minimizing leflunomide exposure to the fetus, which cannot be effectively treated with DMARDs and TNFα inhibitors together (Singh et al. 2012). Rituximab, targeting CD20 to deplete B cells, lacks comprehensive animal teratogenicity studies but has shown B cell reduction in offspring. Although thorough animal teratogenicity studies are lacking for rituximab, which targets CD20 to decrease B cells, B cell reduction in offspring has been demonstrated. The rituximab global medication safety database's analysis of 231 pregnancies yields results for 153 pregnancies. 58.8% of newborns were live, while spontaneous abortions accounted for 21.6% and therapeutic abortions for 18.3% of all abortions. Twenty-two incidents of premature deliveries were recorded, one of which resulted in baby death. Furthermore, two babies had congenital defects, one had a clubfoot, and the other had heart issues. These results point to potential risks related to rituximab use during pregnancy; therefore, those who need to take this medicine during their pregnancy should exercise caution and close observation (Chakravarty et al. 2011). Four of the six people in a sequence of cases by (Sangle et al. 2013) who received rituximab treatment five had SLE and one had GPA went on to have normal pregnancies. But there were two instances where difficulties occurred: one included a woman with lupus nephritis who gave birth prematurely and developed esophagal atresia, and another involved the same woman. There was a range of 8–22 months from the time of rituximab treatment and pregnancy. This study highlights the need for individualized screening and thorough monitoring throughout pregnancy by highlighting the variation in pregnancy outcomes among rituximab recipients. These discoveries advance our knowledge of the effects of rituximab on the health of the mother and the fetus and guide the selection of treatments for autoimmune disease-affected pregnant patients. One patient who was receiving rituximab treatment for ANCA-associated vasculitis miscarried at 15 weeks, which revealed results that were in

line with Beckwith-Wiedemann syndrome. The seven remaining pregnancies, however, ended in live births. Notably, fetal cord blood tests in three newborns showed B cells in every instance, indicating possible fetal transmission of rituximab's effects. This highlights the need for strict monitoring and additional research into the consequences of rituximab over time exposure during pregnancy and raises concerns regarding hematologic adverse effects in babies (Pendergraft et al. 2013).

2. T-cell-modulating agent

- **Abatacept:** By preventing antigen-presenting cells from interacting with T cells, abatacept inhibits T-cell activation. By attaching itself to CD80 and CD86 molecules found on antigen-presenting cells, it does this. Abatacept efficiently reduces T-cell activation by obstructing these connections, which modulates the immunological response. Because of its mode of action, abatacept is a useful treatment option for diseases like rheumatoid arthritis that are marked by dysregulated immune activity. Notable results were noted in the biggest group of mothers exposed to abatacept, which included 151 pregnancies with 86 live babies. Abatacept reduces T-cell activation by inhibiting antigen-presenting cells from engaging with T cells. It accomplishes this by binding to CD80 and CD86 molecules present in antigen-presenting cells. By blocking these linkages, abatacept effectively lowers T-cell activation and regulates the immune response. Abatacept is a helpful treatment choice for conditions like rheumatoid arthritis that are characterized by dysregulated immune activity because of its manner of action. The largest group of moms who received abatacept showed notable outcomes: 151 pregnancies resulted in 86 live births (Skorpen et al. 2016; Flint et al. 2016).

3. **Tumor necrosis factor inhibitors**: Discoveries regarding congenital defects associated with exposure to tumor necrosis factor inhibitors during pregnancy. The initial studies referenced the VACTERL connection and suggested an elevated incidence of congenital defects. VACTERL is an acronym representing limb defects, cardiac defects, tracheoesophageal abnormalities, anal atresia, and renal, and radial anomalies. Pregnant women who were exposed to this during their pregnancy showed this combination of abnormalities, which prompted inquiries about potential risks—connected to these drugs (Carter et al. 2009). In addition, a Danish and Swedish register-based study examining 683 cases of TNF inhibitors exposure during early pregnancy among women with chronic inflammatory disorders suggested a slightly higher rate of birth abnormalities in compared to other groups, neonates treated with TNF inhibitors (Bröms et al. 2016). The British Society for Rheumatology's Biologics Register observed an increased occurrence of spontaneous abortions in pregnancies with exposure to TNF inhibitors (Verstappen et al. 2011).

4. IL-1 antagonist

- **Anakira:** Anakira is a recombinant interleukin-1 receptor antagonist. In animal studies, tocilizumab has not been proven to be teratogenic. However, high dosages were associated with an increased chance of abortion. An abstract on thirty-two individuals revealed that there had been seven spontaneous abortions and thirteen elective abortions; the majority of these patients were also on methotrexate and tocilizumab. Regretfully, one baby died from placenta previa-induced hemorrhaging three days after birth due to acute respiratory distress syndrome (ARDS). Tocilizumab has been categorized by the FDA as category C, which indicates that there is less information regarding its safety during pregnancy. This classification highlights the need for thoughtful consideration and individualized risk assessment when prescribing tocilizumab to pregnant individuals. What it means throughout pregnancy is largely unknown. There are fewer than twenty examples reported in the literature. In the largest series, nine births to women exposed to Anakira and with cryopyrin-associated periodic syndromes were evaluated. In the context of renal agenesis in a twin pregnancy, one fetus with an NLRP3 mutation passed away. There were no longer any documented early deliveries or birth defects (Chang et al. 2014).

Steroids and non-steroidal anti-inflammatory drugs

Steroids Glucocorticoids taken during pregnancy can cause birth defects or abnormalities in the fetus due to their teratogenic effects (Krause and Makol 2016). Findings from animal studies suggest that glucocorticoids can induce teratogenic effects, specifically contributing to the development of cleft palate and potentially influencing aggressive behavior in the offspring (Reinisch et al. 1980; Pinsky and DiGeorge 1965). The outcomes of human investigations regarding the teratogenic effects of glucocorticoids have been mixed. While some research has shown that babies born to mothers who used glucocorticoids during pregnancy are more likely to have orofacial clefts, other studies have not found a direct link between glucocorticoid usage and this specific birth abnormality (Carmichael and Shaw 1999; Carmichael et al. 2007). After conducting a thorough meta-analysis, Park-Wyllie et al. confirmed that fetuses exposed to glucocorticoids had a higher incidence of cleft palate formation (Park-Wyllie et al. 2000). Danish Registry-Based Study: Using data from over 50,000 pregnancies exposed to glucocorticoids in the first trimester, this study could not identify a direct link between the usage of glucocorticoids and the overall incidence of orofacial clefts. A sub-analysis, however, revealed a statistically significant association

between topical glucocorticoids and cleft lip, with or without cleft palate (Hviid and Mølgaard-Nielsen 2011). The use of systemic glucocorticoids in the initial trimester aims to reduce the risk of cleft palate malformations during pregnancy. Furthermore, caution is advised in employing them later in pregnancy as it may be associated with increased risks, including gestational diabetes, gestational hypertension, osteoporosis, and early membrane rupture leading to preterm delivery, and intrauterine growth restriction (Guller et al. 1995; Østensen et al. 2006).

Effect of non-steroidal anti-inflammatory drugs on the fetus and newborn Some physicians recommend aspirin to expectant patients who are displaying arthritic symptoms. Nearly 10,000 of the 14,864 women who took aspirin in moderation during their pregnancies did not exhibit a higher incidence of congenital abnormalities, according to a study of their data. But because aspirin increases the risk of bleeding during delivery, especially cerebral hemorrhage, and constricts the ductus arteriosus, it is best to stop taking aspirin during the third trimester (Rumack et al. 1981). Non-steroidal anti-inflammatory drug use during pregnancy may disrupt the fetus's ability to synthesize prostaglandins. Reduced fetal renal output and a drop in amniotic fluid volume may result from this interaction. These side effects have been linked to specific non-steroidal anti-inflammatory medicines, such as ibuprofen, ketoprofen, and indomethacin. Within 72 h of birth, typical doses of these non-steroidal anti-inflammatory medications have been linked to impaired renal function in preterm newborns. Nonetheless, data indicate that fetal renal function usually returns rapidly following the cessation of these medications (Hickok et al. 1989).

Miscarriage

NSAID use during pregnancy has been associated with a higher incidence of miscarriage; studies have suggested a dose–response association. According to recent studies, taking NSAIDs during pregnancy can increase the chance of miscarrying by up to 80%, especially if the usage of the medication happens around conception or lasts longer than a week. It is believed that this correlation results from NSAIDs inhibiting prostaglandin synthesis in reproductive organs, which may cause aberrant implantation of the embryo. This notion is supported by animal studies that show the role that prostaglandins play in the process of implantation. Pregnancy may also be adversely affected by NSAIDs. NSAIDs may occasionally be given to pregnant patients with antiphospholipid antibody syndrome, a condition that increases the risk of miscarriage. Pregnancy outcomes in such circumstances have been reported to be improved by therapy with NSAIDs in conjunction with heparin, prednisone, and low-dose aspirin. Placental perfusion and circulation, which increases the risk of fetal death (Li et al. 2003; Dawood 1993; Van der Weiden and Wouters 1997).

Cardiac effects Studies conducted in the last ten years have connected NSAID use by pregnant mothers to congenital heart abnormalities. According to studies on animals, NSAID use may cause ventricular septal defects (VSD), especially when COX-1 is inhibited. NSAID use by mothers, particularly in the early stages of pregnancy, has been linked to an increased occurrence of VSD in human studies. However, contradicting information is available, perhaps as a result of different NSAID prescriptions, and mother fever may additionally influence the development of the septum (Antonucci et al. 2012).

Persistent pulmonary hypertension of the newborn (PPHN) The possibility of fetal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) causing ductus arteriosus closure in utero has been suggested as a possible cause of persistent pulmonary hypertension in newborns. Elevated pulmonary resistance, which leads to poor pulmonary circulation adaptation to extrauterine life, is a characteristic of PPHN. The creation of prostaglandin and thromboxane, which are essential for preserving ductal patency and controlling pulmonary vasculature, is blocked by NSAIDs' inhibition of COX enzymes. Since 1976, research on animals has demonstrated that NSAIDs, such as indomethacin, can cause ductal constriction, which can result in primary pulmonary hypertension in developing fetuses. Prenatal indomethacin therapy has been associated with pulmonary arterial hypertension, right ventricular injury, and ductal constriction in fetuses. This process may enhance the smooth muscle tone of the pulmonary arteries and cause vasoconstriction in infants, hence contributing to PPHN (Manchester et al. 1976). Maternal intake of NSAIDs and aspirin during pregnancy, or the circumstances leading to the use of these drugs, was demonstrated to be associated with an elevated risk of PPHN in a case–control interview study conducted by Van Marter et al. (1996). Long-term indomethacin medication has been shown to have a severe negative impact on the ductus arteriosus and the pulmonary vasculature; this can occur even hours before delivery and result in pulmonary hypertension in the preterm newborn.

Cystic periventricular leukomalacia (cPVL) Premature newborns that suffer from cystic periventricular leukomalacia have a significant ischemic brain injury that results in white matter necrosis and frequently causes spastic motor impairments such as cerebral palsy or epilepsy. According to recent data, cPVL might happen in utero. Several studies have found a connection between antenatal NSAID exposure

and an increased incidence of cPLV. Previous studies discovered that newborns exposed to any tocolytic medication, especially indomethacin, and born before 30 weeks' gestation had a greater incidence of periventricular leukomalacia. This correlation has been validated by more recent research in cohorts of premature infants, which demonstrates that prenatal exposure to indomethacin raises the incidence of cPVL by two to three times. These results suggest that prenatal therapies, together with maternal and fetal variables, are frequently linked to cPVL (Murata et al. 2005; Baerts et al. 1990).

"Navigating rheumatoid arthritis complications associated during pregnancy: a comprehensive case study analysis"

Rheumatoid arthritis impacts 0.7–9% of the overall population, with a higher prevalence among women of childbearing age, particularly affecting females. During pregnancy, various hormonal and immunological changes can take place, potentially modifying the immune response and, as a result, influencing the clinical presentation of the disease. We felt it was intriguing and pertinent to discuss these 2 clinical instances of rheumatoid arthritis during gestation because the development of the disease during pregnancy is a very rare occurrence that has not been documented in the literature (Silman and Pearson 2002). Even though rheumatoid arthritis peaks in incidence around menopause age (Symmons et al. 1994). It is estimated that between 800 and 2,100 deliveries among patients with rheumatoid arthritis occur in the United States each year. Many women develop rheumatoid arthritis during the reproductive years (Gabriel 2001). Due to this, ensuring the safety of pregnancy becomes a critical clinical consideration for both the mother and the fetus. There was a time when it was thought that the activity of illnesses would diminish during pregnancy (Golding et al. 2007). Recent literature indicates that the response of diseases to pregnancy might be more diverse than previously believed, revealing that some women do not witness significant improvement in symptoms during gestation as traditionally thought (Barrett et al. 1999). Moreover, as researchers focus more on comprehending the impact of rheumatoid arthritis on pregnancy outcomes, several studies have identified elevated instances of adverse results, including low birth weight and premature births. It is hypothesized that these occurrences may be linked to the effects of systemic inflammation throughout the pregnancy (de Man et al. 2009; Nørgaard et al. 2010; Reed et al. 2006). They conducted a comprehensive examination of each pregnancy complicated by rheumatoid arthritis that took place at our facility from June 2001 to June 2009, following approval from the institutional review board. The study focused on diverse aspects, including disease activity throughout pregnancy and associated outcomes such as preterm delivery and neonatal complications. Statistical analysis was utilized to investigate these relationships. The research identified heightened rates of adverse pregnancy outcomes, encompassing issues such as low birth weight, preterm delivery before 37 weeks gestation, preterm premature rupture of membranes, preeclampsia, intrauterine fetal demise (IUFD), and neonatal complications resulting in admission to the neonatal intensive care unit (NICU) (Langen et al. 2013). The study by Wallenius et al. highlights the underexplored area of infertility among women with chronic inflammatory arthritis, particularly rheumatoid arthritis. Unlike women without rheumatoid arthritis, those with the condition experience a reduced birth rate during their reproductive years due to various factors. Owing to worries regarding the possible impacts of potential effects of these including not just the potential for infertility but also decreased libido as a result of long-term joint problems and choosing not to have children mother sickness on the child. To fully understand and meet the reproductive health needs of women with rheumatoid arthritis, a more comprehensive study is needed to address these complex factors (Katz 2006; Kraaimaat et al. 1996). The examination of 732 women who developed rheumatoid arthritis after the age of 15 unveiled diverse patterns in the onset and progression of the disease linked to pregnancy. While a portion found relief during pregnancy, a majority encountered a resurgence of symptoms after childbirth. Among 93 patients, 70 reported symptom relief during pregnancy, but 82 out of 101 patients observed a recurrence, typically within four months after giving birth. Joint symptom aggravation was noted in 58.4% of 101 patients and 58.3% of 132 deliveries or sections. The post-miscarriage progression of the disease exhibited variability among cases (Oka 1953).

Pregnancy challenges

Women with rheumatoid arthritis experienced elevated rates of pregnancy complications compared to the reference population. Severe problems, such as serious fetal abnormalities or perinatal death, were not, however, more common in babies born to rheumatoid arthritis-positive mothers.

Chronic hypertension

Compared to the reference population, rheumatoid arthritis patients had a higher diagnosis rate of chronic hypertension before their first pregnancy.

Preeclampsia risk

This study found that preeclampsia was more common among rheumatoid arthritis patients who were pregnant

for the first time, despite inconsistent results from other research. In contrast to the reference group, this difference was not statistically significant.

Vaginal hemorrhage

During their first and subsequent pregnancies, women with rheumatoid arthritis saw higher rates of vaginal hemorrhage. This may be related to the widespread use of NSAIDs up until week 32 of pregnancy (Wallenius et al. 2014). Higher Incidence of Antepartum Hemorrhage (APH) and Cesarean Section (CS): More mothers with rheumatoid arthritis experienced APH and underwent CS compared to those without rheumatoid arthritis. Higher Likelihood of Disseminated Intravascular Coagulation (DIC): Although the incidence of DIC was threefold greater in the rheumatoid arthritis cohort, the absolute number of cases remained low, and there were no fatalities attributed to DIC. Stillbirths and fetal abnormalities: Contrary to some expectations, the study did not find a higher risk for stillbirths or fetal abnormalities among pregnancies in women with rheumatoid arthritis (Tsai et al. 2022).

Fetal abnormalities

Before accounting for predefined covariates, infants born to mothers with rheumatoid arthritis exhibited an elevated likelihood of fetal abnormalities (7.05% in pregnancies with rheumatoid arthritis compared to 5.65% in pregnancies without rheumatoid arthritis). This incidence is notably higher than the estimated 2%–3% incidence of malformations in the general population (Moorthie et al. 2018). The study's use of the term "fetal abnormalities" in its definition may have resulted in an overestimation, as some conditions identified by ICD-9 code 655 may not necessarily qualify as fetal malformations or congenital defects (Ngeh and Bhide 2006).

Antepartum hemorrhage

The study found that pregnant women diagnosed with rheumatoid arthritis had a 24% higher risk of experiencing APH compared to women without rheumatoid arthritis. This suggests that rheumatoid arthritis might be associated with a higher incidence of APH during pregnancy. Elevated risk of APH in rheumatoid arthritis pregnant mothers. Identified as bleeding from the vagina during the last stages of pregnancy (Ngeh and Bhide 2006). Correlations were noted between antepartum hemorrhage (APH) and specific unfavorable pregnancy occurrences such as preterm delivery and cesarean section (CS) within the rheumatoid arthritis group. Nonetheless, these incidents did not result in severe adverse consequences such as maternal mortality, significant bleeding necessitating transfusion, hysterectomy, or stillbirths (Erez et al. 2015).

Disseminated intravascular coagulation

There were three cases of DIC identified among patients in the rheumatoid arthritis group, resulting in a threefold higher odd of DIC in this group compared to the reference group.[81] While systemic inflammatory disorders like rheumatoid arthritis are known risk factors for hypercoagulable states, DIC has not been commonly associated with rheumatoid arthritis. The observed rates of DIC in both groups were within reported ranges during pregnancy, and the study did not observe adverse outcomes associated with DIC (Erez et al. 2015; Rattray et al. 2012).

Cesarean sections

About 43% of expectant mothers diagnosed with rheumatoid arthritis opted for cesarean sections. This corresponds to results from various studies that consistently demonstrate elevated CS rates among pregnant women with rheumatoid arthritis. Limitations in the data did not allow for distinguishing between elective and emergent CS cases or determining the reasons for choosing cesarean delivery in these cases, warranting further research for a deeper understanding of the risk of CS in pregnant women with rheumatoid arthritis (Tsai et al. 2022). The rate of emergency cesarean sections was greater (11%) among women with inflammatory arthritis, including rheumatoid arthritis. Fetal discomfort and inadequate progress during birth accounted for an equal share of the causes. Comparable data from control women were not available; hence, this unexpected finding was made. While preeclampsia was not observed in this study, nor was there any indication of a difference in gestational age, a Norwegian study found higher rates of surgical delivery in women with inflammatory arthritis, along with slightly higher rates of prematurity and preeclampsia (Bowden et al. 2001). Research has confirmed that women who belong to a lower socioeconomic status and are of advanced age are more prone to experiencing rheumatoid arthritis. There seems to be a connection between the autoimmune origin of rheumatoid arthritis and an elevated susceptibility to acute infectious infections in pregnant women affected by rheumatoid arthritis. It is crucial to highlight that pregnant women with rheumatoid arthritis face an augmented risk of vascular disorders, encompassing migraine, chronic/essential hypertension, phlebitis, and hemorrhoids. This heightened risk is attributed to the occurrence of extra-articular symptoms, such as blood vessel diseases, in individuals with rheumatoid arthritis. The increased likelihood of cardiovascular complications and esophageal atresia/stenosis may be associated with chronic hypertension (Banhidy et al. 2011).

Miscarriage

A recent study found that the 17 per cent miscarriage risk in women with rheumatoid arthritis is equivalent to the 11–22% miscarriage rate in the general population. They do point out that there's a chance the miscarriage rate among rheumatoid arthritis patients is underestimated. They clarify that, among various factors, their cohort comprised a higher proportion of patients with advanced education and fewer individuals who smoked compared to the general population. Additionally, the patients in their cohorts had deliberately planned pregnancies and abstained from using any medications, including MTX, associated with an elevated risk of miscarriages (Brouwer et al. 2015).

Preeclampsia

In a comprehensive prevalence study spanning from 1994 to 2006 in Denmark and Sweden, Wolfberg et al. found that among 1199 women with rheumatic diseases, including conditions like rheumatoid arthritis and SLE, there was a notable increase in the occurrence of preeclampsia (8.8% vs. 2.3%) compared to women without such conditions. The investigation focused on women with rheumatoid arthritis and their first-time singleton births, utilizing data from population-based healthcare databases (Wolfberg et al. 2004). According to Norgaard et al. study, women diagnosed with rheumatoid arthritis exhibited a slightly elevated risk of experiencing preeclampsia (5.0% compared to 3.4% in women without rheumatoid arthritis) (Nørgaard et al. 2010).

Mode of delivery

Reed and colleagues noted a heightened probability of primary cesarean section among 243 women documented in Washington State birth records who had rheumatoid arthritis compared to the control group (34% vs. 19.5%). Within the rheumatoid arthritis population, the primary reasons for cesarean sections included fetal distress (18%), dysfunctional labor (31%), and cephalopelvic disproportion (32%). Interestingly, these statistics showed no significant deviations from those observed in women without rheumatoid arthritis (Reed et al. 2006).

Risk of neonatal complications

The research indicates that newborns delivered by mothers with rheumatoid arthritis exhibited a higher probability of being small for gestational age, having low birth weights (LBW), and facing an elevated risk of preterm delivery. Association between rheumatoid arthritis in women and diverse neonatal and maternal outcomes during the peripartum period. Here is a summary of the study's discoveries: Offspring born to mothers with rheumatoid arthritis exhibited elevated risks for several adverse outcomes are double increase in low birth weight (LBW) and prematurity: These infants were twice as likely to have low birth weight and be born prematurely. 1.7 times more prone to being small for gestational age (SGA): These babies had a 1.7 times higher likelihood of being smaller than expected for their gestational age. Heightened risk of low Apgar scores: There was a 50% higher probability of having Apgar scores < 7 at 1 min post-birth (Nørgaard et al. 2010; Bowden et al. 2001). 35% greater likelihood of fetal distress: Offspring born to mothers with rheumatoid arthritis were more predisposed to experiencing fetal distress.

Birth weight

Babies born to women with arthritis, including rheumatoid arthritis and undifferentiated IP, showed a slightly lower birth weight compared to control subjects, even after adjusting for the potential confounding factors and any reduced length of gestation (Musiej-Nowakowska and Ploski 1999). The birth weight of infants was lower in women with active disease during the final trimester of pregnancy when compared to those whose disease had achieved complete remission. However, the group in complete remission did not exhibit any significant difference in birth weight compared to controls (Barrett et al. 1999).

Mode of delivery

The study observed a high rate (11%) of emergency cesarean sections among women with arthritis in pregnancy. The reasons for these surgical deliveries were evenly split between fetal distress and failure to progress in delivery (Skomsvoll et al. 1998).

Associations with other factors

The study found no instances of preeclampsia among the subjects and no evidence of a difference in gestational age. However, it raised questions about whether active inflammatory arthritis increased the likelihood of intrapartum fetal distress and if it was associated with growth retardation.

Gender distribution and disease activity

Although variations in the percentage of female infants were not deemed statistically significant, the active disease group exhibited a greater prevalence of female infants. This observation led to speculation about potential male fetal loss in earlier trimesters due to the stress of active disease, favoring female fetuses. Lower birth weight, even within the normal

range, has been associated with an increased risk of cardiovascular and metabolic diseases in adulthood (Ong and Dunger 2002; Leunissen et al. 2009). When infants exhibit rapid weight gain during their initial year of life, this impact becomes even more pronounced (Steenwinkel et al. 2014a). Examined the growth patterns of 167 children born to mothers with rheumatoid arthritis. Among these children, 28 per cent displayed accelerated weight catch-up growth, correlating with maternal illness. A subset of 108 of these children underwent reassessment around the age of 7. In comparison to the offspring of healthy mothers, these children did not manifest a high-risk profile in anthropometric parameters, including elevated blood pressure or altered body composition. The study also observed that maternal prednisone use during pregnancy was associated with slightly increased cortisol levels throughout the day in children under seven. Despite the absence of clinical indications for elevated cortisol levels related to this finding, the clinical implications remain uncertain. Limited research has explored the long-term challenges faced by children born to rheumatoid arthritis patients. Research has indicated a potential correlation with autoimmune diseases, hematologic malignancies (blood cancer), and neurodevelopmental abnormalities. To find out more about whether rheumatoid arthritis exposure can result in long-term issues for exposed children, more research is required (Steenwinkel et al. 2014b).

Conclusion

In conclusion, the examination of "rheumatoid arthritis-associated complications in pregnancy and offspring" highlights the multifaceted challenges inherent in managing this autoimmune condition during gestation. The increased risk of maternal complications, coupled with potential adverse fetal and neonatal outcomes, underscores the need for a nuanced and personalized approach to care. Ensuring a crucial balance between managing disease control and maintaining medication safety is essential, all while recognizing the significant influence of disease activity on pregnancy. The collaborative, multidisciplinary model of care emerges as a cornerstone for optimizing outcomes, emphasizing the synergy between rheumatologists and obstetricians. As we deepen our understanding, this review serves as a guide for clinicians, offering insights into the complexities of rheumatoid arthritis and pregnancy, and as a catalyst for future research endeavors aimed at refining clinical strategies and ultimately improving the well-being of both mothers and their offspring.

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