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REVIEW

The positive effect of pregnancy in rheumatoid arthritis and the use of medications for the management of rheumatoid arthritis during pregnancy

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Abstract

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disorder that is mostly characterised by progressive symmetrical joint destruction, particularly in the wrist and fingers, while it may also affect additional joints and several organs, such as the skin, heart, blood vessels, and lungs. It is identified by raised anti-rheumatoid factor and anti-cyclic citrullinated peptide antibodies. The chemical mediators involved in the activity of RA are IL-1β, TNF-α, and IL-6. Pregnancy exerts a positive effect on RA that helps to modulate the disease condition. Different hypotheses are recommended to explain the ameliorating effect of pregnancy in RA. RA cannot be completely cured. The treatment goal is the attrition of pain and inflammation and the further progression of the disease. Long-term management of RA is carried out using disease-modifying antirheumatic drugs (DMARDs). Therapy of acute flares can be done with Non-steroidal anti-inflammatory drugs (NSAIDs) accompanied by ad interim usage of glucocorticoids. Biologic response modifiers are also available; they act by abolishing the activity of T- cells. However, it is necessary to select the correct treatment regimen when it comes to the management of RA in pregnancy.

Keywords Rheumatoid arthritis · Pregnancy · DMARDs · Biologics · NSAIDs · Corticosteroids

Introduction

Rheumatoid arthritis (RA) is an unknown etiologic inflammatory autoimmune condition that affects several joints and induces erosion of the cartilage. RA mainly impacts the joints, but other organ systems such as the skin and lungs may also be affected. RA prevalence ranges from 0.3% to 1% globally, and is more widespread in developing countries (Snekhalatha et al. 2013). The prevalence of RA in the adult population has been reported to be 0.75% in India. It afflicts about 25 men and 54 women per 100,000 and is accountable for 250,000 hospitalisations and 9 million physician visits in the US each year, and more than 1 million cases per year in India (Firestein 2003). RA can impact reproduction, the course of pregnancy, and the growth of the foetus. In terms of improvement or aggravation of the rheumatic symptoms, RA itself can be changed in its behaviour (Marker-Hermann and Fischer-Betz 2010). In this review, the association between RA and pregnancy will be conferred with possible mechanisms for the amelioration of RA in pregnancy and the use of RA medications during pregnancy.

Pathophysiology of RA

A healthy joint has two bones with articular cartilage covering the ends. Articular cartilage is a type of connective tissue that acts as a cushion to allow bones to move smoothly against one another. One such joint is termed a synovial joint, like a knee joint. A synovial joint attaches 2 bones by a fibrous capsule that is continuous with either bone's periosteum or exterior layer. A synovial membrane containing cells that generate synovial fluid and take away debris is lined with the fibrous capsule. RA is an autoimmune mechanism usually caused by an association between

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the environment and a genetic factor. For instance, after exposure to something in the atmosphere, such as a particular pathogen like bacteria that survive in the oesophagus or cigarette smoke, an individual with a certain gene for an immune protein, like the human leukocyte antigen (HLA), or HLA-DR4 and HLADR1, may develop RA. These environmental variables can modify our antigens, such as IgG antibodies or additional proteins like vimentin or collagen type II, via a process termed citrullination. That is when the arginine present in this protein is transformed into a separate citrulline amino acid. In the meantime, immune cells are not aware enough because of the susceptibility genes HLA-DR1 and HLA DR4, so they get confused by this alteration and no longer identify these proteins as our self-antigens. To activate CD4 T-helper cells, the antigens are taken up by antigen-presenting cells and taken into the lymph nodes. The neighbouring B-cells are stimulated by T-helper cells to proliferate and differentiate into plasma cells that generate unique auto-antibodies against these self-antigens. T-helper cells and antibodies go into the circulation and cross the joints. T-cells produce cytokines like interleukin-17 and interferon γ once in the joints to volunteer further inflammatory cells into the joint space, such as macrophages. Macrophages can also generate inflammatory cytokines like IL-1, IL-6 and TNF-α that cause synovial cells to proliferate along with the cytokines of the T-cell. Pannus is a dense, inflamed synovial membrane with granulation or scar tissue of myofibroblasts, fibroblasts and inflammatory cells, and is formed by a rise in synovial cells and immune cells. The pannus can degrade cartilage and other soft tissues over time and also weaken bone. Triggered synovial cells correspondingly produce proteases that breakdown the articular cartilage proteins. The fundamental bones are contacted without the protective cartilage and may rub against each other directly. Also, inflammatory cytokines raise the protein on the surface of T cells known as RANKL (receptor activator of nuclear factor kappa-B ligand). RANKL helps the T-cells to attach to RANK, which is a protein present on the surface of the osteoclast, so that they can start destructing the bone. Meanwhile, antibodies also penetrate the space of the joint. One such antibody is called the rheumatoid factor, which is an IgM antibody that attacks transformed IgG antibodies in the constant Fc domain. The anti-cyclic citrullinated peptide antibody, which attacks citrullinated proteins, is another antibody. They make immune complexes that gather in the synovial fluid when these antibodies attach to their targets. There they can stimulate the complement system, a family of 9 small proteins that work to promote joint inflammation and injury in an enzymatic cascade. Ultimately, chronic inflammation results in angiogenesis or the development of newer blood vessels across the joints, enabling the arrival of even more inflammatory cells. Multiple joints on either side of the body are inflamed and progressively destructed as the disease progresses. These inflammatory cytokines, however, do not only stay within the rigid space of the joint but, instead, outside the joint room, they outflow via the bloodstream and go into multiple organ systems that cause extra-articular problems. For instance, IL-1 or IL-6 migrates to the brain, where they serve as a fever-tempting pyrogen. They facilitate protein breakdown in the skeletal muscle, and they contribute to the development of rheumatic nodules in the skin along with several visceral organs. Rheumatic nodules are round, formed of assortments of macrophages and lymphocytes with a central region of necrosis or tissue death. It is also possible for blood vessels to be affected. Their walls become inflamed, followed by numerous types of vasculitis, making them vulnerable to atheromatous or fibrofatty plaques. The liver also begins to generate large concentrations of hepcidin, a protein that reduces serum-iron levels by hindering its absorption by the gut and trapping it into macrophages or liver cells, in reaction to inflammatory cytokines. In the meantime, fibroblasts are activated and proliferate inside the lung interstitium, creating fibrotic or scar tissue that makes it more difficult to exchange alveolar gas. The pleural cavities around the lungs can often turn out to be inflamed, stodgy with fluid, acknowledged as pleural effusion, and this can also hinder the spread of the lungs. RA usually involves several joints, generally five or more, evenly, meaning on both sides of the body, for example, the same joint groups, like both hands. The small joints such as the proximal interphalangeal and metacarpophalangeal joints of the hands and the metatarsophalangeal of the feet are usually affected. It may start to affect larger joints such as the elbow, shoulder, knee and ankle as the disease worsens. The affected joints become enormously swollen, warm and red, and throbbing during flares or rapid waning of the disease. They turn stiff over time, particularly in the morning or after being dormant for a longer time (Guo et al. 2018; Taylor 2014; Harris 1990; Rheumatoid arthritis 2020) (Fig. 1).

Pregnancy and RA

In the nineteenth century, studies (Trousseau 1871, Charcot 1881, Bannatyne and Wohlmann 1896) found that pregnancy is complementary for RA. This was set out in the rheumatologist Philip S Hench's Nobel Prize lecture, 11 December 1950. This fascinating finding enthused clinical and fundamental research into endocrine immune interactions and rheumatics disease studies, especially in RA and systemic lupus erythematosus (SLE) (Straub et al. 2005; Hench 1938). There have been numerous retrospective and prospective series indicating that most RA patients (between 54 and 94%) undergo an impulsive change in the behaviour of their disease, and even remission is seen. RA behaviour reduction typically begins in the 1st trimester

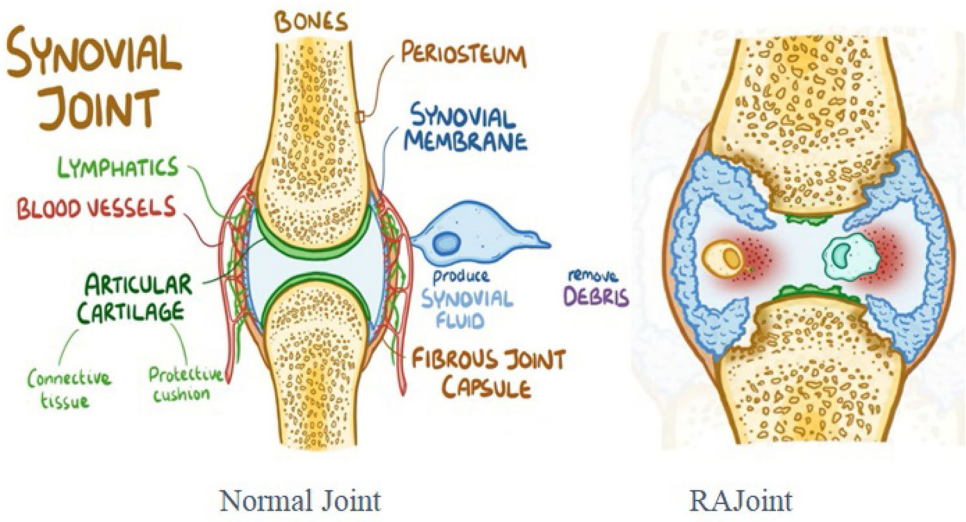

Fig. 1 Normal and RA joints

and could endure for the next 2 trimesters. In contrast, a recurrent decline of RA activity is found after delivery. The specific processes underlying the disease-modifying effect of pregnancy and the post-partum period are, however, not yet understood (Marker-Hermann and Fischer-Betz 2010; Gromnica-Ihle and Ostensen 2006; Marker-Hermann et al. 2008). A prospective study to assess the activity of RA disease during pregnancy found that patients would experience a diminution in pregnancy and post-partum deterioration. The study involved 84 patients, a disease activity score in 28 joints and drug usage was collected at every trimester of pregnancy and at 6, 12 and 26 weeks post-partum. The activity of the disease decreased during pregnancy with a statistical significance of $P = 0.035$ and was raised post-partum (De Man et al. 2008; Nelson and Ostensen 1997; Barrett et al. 1999).

Possible mechanisms underlying the ameliorating effect of RA in pregnancy

Effect of sex hormones

Gonadotropins and sex steroids interact in a complex manner with the immune system. Changes in neuroendocrine functions are involved in the production of auto-immunity (Østensen 1999; Wilder 1995). Increases in the levels of estrogen and progesterone can play an indirect role in the immune response. The cumulative effect of elevated levels of cortisol, estrogen and vitamin D during pregnancy is associated with a decrease in inflammatory cytokines, IL-12 and TNF-α (Hazes et al. 2011; Whitacre 2001; Masi et al.1995). Estrogen and progesterone levels are raised during pregnancy. As a result, the initial predominant cellular immune response (type Th1) is reduced, while the humoral response (type Th2) is increased. Many of the Th2 anti-inflammatory cytokines IL-4 and IL-10 are synthesized due to this change. Treg lymphocyte levels are elevated during the last months of pregnancy, leading to overexpression of IL-10 and IL-4. Because of these pathways, the disease activity of rheumatoid arthritis (RA) has been decreased (Florea and Job-Deslandre 2008; Kåss et al. 2010, 2015). Loss of matrix components (collagen and glycosaminoglycan) in the cartilage and synovium is the main consequence of joint dysfunction in RA. A research was conducted to understand the impact of physiological estrogen, testosterone and progesterone levels in oxidative stress-induced alterations in matrix composition in rat synovium in arthritis. The analysis concluded that extracellular matrix loss is attenuated by oestrogen and testosterone in collagen-induced arthritis rats (Ganesan et al. 2008a, b).

Effect on the inflammatory cytokine levels

During pregnancy, inflammatory cytokine levels are found to increase. These increases in cytokine levels can be associated with corresponding changes in the luteinizing hormone and follicle-stimulating hormone concentrations in pregnancy, post-partum, and menopause, for instance. Kass et al.[22] explored the case of minor variations in these hormones which may be correlated with related variations in cytokines and activity of the disease in RA (Oestensen et al. 2005).

Effect of regulatory T-cells

In a prospective study, it was found that numerical and functional deviations in high regulatory T cells (Treg) of CD4+CD25 were related to deviations in disease action detected in patients with RA during pregnancy and

post-partum. In 12 individuals with RA and 14 healthy women during later pregnancy, the frequency of CD4+CD25 high-T cells was determined by flow cytometry (Förger et al. 2008; Baecher-Allan et al. 2005; Hara et al. 2001). To arrange CD4+CD25 high T-cells, fluorescence-activated cell sorting was utilised and CD4+CD252 T-cells were stimulated to investigate proliferation and cytokine secretion with anti-CD3 and anti-CD28 monoclonal antibodies alone or in co-culture. The improvement in disease activity in the 3rd trimester was found to correspond to the raised number of Tregs that brought a marked anti-inflammatory cytokine environment (Somerset et al. 2000; Saito et al. 1992).

Gene expression profiles

The aspects that cause a diminution of RA during pregnancy and the reversion arising later in parturition continues to be a mystery. In research, the gene-expression contours of peripheral blood mononuclear cells (PBMC) in individuals with RA and healthy women in late pregnancy and post-partum were examined. The contours of samples from both groups were identical in late pregnancy with raised monocyte and reduced lymphocyte signs. Post-partum, in RA PBMC, the raised degree of monocyte transcripts continued. The additional upsurge was detected in the migration, adhesion and signalling processes associated with monocytes, but likewise in lymphocytes, despite analogous clinical behaviour owing to increased opioid treatment (Häupl et al. 2008). A comparative study of RA patients' PBMC expression profiles before and after pregnancy with RA Disease Activity Index (RADAI) and C-reactive protein (CRP) showed a connection of these parameters of disease activity primarily with accounts of monocytes. The genes associated with cellular programs of migration, adhesion and infection retort have been up-regulated. The comparison of clinically active and non-active post-partum RA patients exposed a collection of 19 genes that could also recognize lively pregnancy diseases. The information recommends that a rise in RADAI and CRP are a result of monocyte molecular activation. Also, they designate that T-lymphocyte molecular activation may persist as clinically un-recognised post-partum. It is plausible that a group of 19 genes may succeed as a marker of action for molecular diseases (Crocker et al. 2000; Edwards et al. 2004).

Immunoglobulin G (IgG) N-glycans galactosylation

Upgrading of RA in pregnancy has been causatively correlated with raised immunoglobulin G (IgG) N-glycans galactosylation during pregnancy. A study was conducted to determine this activity. Serum was obtained from 148 RA cases and 32 safe controls at several stages. Referring to the European League Against Rheumatism (EULAR) response criteria, progress in pregnancy and post-partum flare were detected. IgG galactosylation and sialylation and the occurrence of bisecting N-acetylglucosamine (GlcNAc) were analysed by matrix-assisted laser desorption/ionization (flight time) mass spectrometry (Marker-Hermann and Fischer-Betz 2010). Cases and controls of IgG1 and IgG2 galactosylation were raised in pregnancy to a median in the 3rd trimester. Galactosylation reduced immediately after childbirth. The control IgG galactosylation was higher than the case level ($P < 0.001$) and an analogous trend was detected for sialylation. In addition, a sturdy association was detected with galactosylation and sialylation. For cases with improvement, the rise in galactosylation was substantially more marked than for cases without improvement during pregnancy (Van de Geijn et al. 2009), while for deteriorators and post-partum non-deteriorators, the opposite was true. The occurrence of bisecting GlcNAc in cases and controls were not substantially affected by pregnancy or post-partum. Thus, this vast cohort study shows the correlation of galactosylation alteration mutually with pregnancy-induced enhancement and post-partum flare in RA patients, indicating a part for glycosylation variations in RA improvement induced by pregnancy (Förger and Østensen 2010).

HLA—disparate foetal microchimerism

There is a huge difference between the mother and the foetus in HLA class II antigens. The processes accountable for the effect on the action of RA diseases have not been explained, but they have been suggested as follows: occurrence of HLA antibodies acting as antibody blockers, stimulation of regulatory mechanisms and enhanced responses to TH2. Foetal HLA antigens could influence the TCR repertoire of the mother. Molecules of HLA class II also contain peptides from HLA self-antigens. In RA mothers, peptides derived from foetal class II HLA antigens can contend with self-antigens and redirect the immune response of the mother away from an auto-immune response. In a population-based prospective study in Washington, USA, the allotment of parity in cases referring to the HLA genotype compared women with newly diagnosed RA ($n = 310$) to control women ($n = 1418$) (Østensen and Villiger 2002; Nelson et al. 1993). According to previous epidemiological studies, a substantial reduction in the risk of RA related to parity was marked in this research (Marker-Hermann and Fischer-Betz 2010; Østensen and Villiger 2002). The disparity of HLA class II on the output of pregnancy in RA patients has been studied further by Zrour et al. (2010).

Adoption of RA therapies during pregnancy

The illness state as well as the treatment regime accounts for the care of RA patients who intend to become pregnant. Pregnancy can be prepared in a state of a steady idle disease, and treatment can be modified with medications consistent with pregnancy. Methotrexate, leflunomide, rituximab, tocilizumab, tofacitinib and abatacept are drugs to be stopped before pregnancy. Anti-malarial drugs and sulfasalazine are pregnancy-compatible disease-altering drugs. In the initial trimester of pregnancy, TNF-α inhibitors may continue, but TNF- α inhibitors with a lower transplacental passage rate should be consumed as recommended during week 27 of pregnancy. At the lower effective dose, glucocorticoids can be considered. Up to pregnancy week, non-selective COX inhibitors may be continued. Together, with reasonable security, personalised treatment all through pregnancy is feasible. For both foetal and maternal health, managing disease progression in pregnancy is salient (Förger and Villiger 2016).

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are used in RA to relieve pain and swelling. These agents fall into the US Food and Drug Administration (FDA) category B (Table 1) (Krause et al. 2014). While NSAIDs are reasonably indulged for use in the first 6 months of pregnancy, they are not recommended during the conception period, to not hinder implantation. These drugs should be ceased following week 30 of gestation, as they might induce premature closure of the ductus arteriosus (Bermas 2014). Nielsen et al. (2001), Li et al. (2003), Nakhai-Pour et al. (2011), Edwards et al. (2012), Momma and Takeuchi (1983), Momma et al. (1984), Koren et al. (2006), Takahashi et al. (2000), Hickok et al. (1989) and Makol et al. (2011) conducted studies to determine the safety of NSAIDs in pregnancy. In RA, cyclooxygenase (COX), that is COX-1 and 2, is adapted for the treatment of osteo-arthritis associated with acute flares or post-arthritis by inhibiting luteinised follicle rupture based on COX-1 and COX-2. The current literature reveals no elevated degree of congenital deformities for non-selective COX inhibitors, which can continue gestation until week 32, especially those with a short half-life. Via occasional usage of NSAIDs in the lower effective dose, the likelihood of adverse foetal effects can be minimised. As regards the COX-2 selective inhibitors, existing shreds of evidence are inadequate. Therefore, COX-2 selective inhibitors need to be avoided in pregnancy (Förger and Villiger 2016; Østensen and Förger 2009; Skorpen et al. 2016).

Glucocorticoids

Glucocorticoids are usually used in pregnant women with RA for management, and are deemed by the FDA to be category B (Krause et al. 2014). Cortisone or hydrocortisone and prednisone show rapidity in symptom relief and minimum transplacental transfer, and are thus considered as the best option for handling RA flare in pregnancy. Betamethasone and dexamethasone should be avoided as they pass the placenta with equal foetal and maternal levels (Beitins et al. 1972). Glucocorticoids can cross the placenta, with the degree of transfer related to the molecular structure. The non-fluorinated glucocorticoids, such as prednisone, are primarily metabolized by the placenta, so less than 10% of the medication reaches the foetus. Non-fluorinated glucocorticoids are, in general, not considered teratogenic. On the other hand, intrauterine growth restriction, shorter gestational age and premature rupture of the membranes are correlated with the use of glucocorticoids, so both the glucocorticoids dosage and the duration should be reduced. The placenta is not involved in the metabolism of fluorinated glucocorticoids and should therefore be limited to foetal indications (Förger and Villiger 2016; Bermas 2014; Blanford and

Table 1 FDA Pregnancy Categories

FDA pregnancy categories	
Category	Indication
Category-A	In the 1st trimester of pregnancy, suitable and well-controlled trials have not shown a hazard to the foetus (and there is no indication of hazard in later trimesters)
Category-B	Animal tests have not indicated a danger to the foetus and no appropriate and well-controlled studies have been performed in pregnant women
Category-C	Studies in animal reproduction have revealed an adverse event on the foetus, and there are no appropriate and well-controlled studies in humans; however, considering possible risks and aids may justify the use of the drug in pregnant women
Category-D	Optimistic proof of human foetal risk is available based on adverse events results from testing or publicizing practice or trials in humans; however, considering possible risks and aids may justify drug use in pregnant women
Category-X	Animal or human reports have shown foetal anomalies and/or positive proof of human foetal risk is accessible, based on adverse event results from testing or marketing experience, and the risks associated with drug use in pregnant women outweigh the likely assistance

Murphy 1977; Østensen et al. 2006). Studies are showing the compatibility of glucocorticoids with breast-feeding. Not more than 10% of the prednisone or prednisolone dosage, on average, is secreted into breast milk (Sammaritano and Bermas 2014; Öst et al. 1985). Reports indicate that glucocorticoids use in pregnancy can raise the menace of cleft lip abnormalities, but not additional significant inborn abnormalities (Park-Wyllie et al. 2000; Bjørn et al. 2014; Hviid and Mølgaard-Nielsen 2011). Glucocorticoids tend to be a safe choice for RA treatment during pregnancy and, if required, the aim is to maintain the patient at the lowermost conceivable dosage to monitor the commotion of the disease. It is fair to warn the mother about the lower risk of 1st-trimester exposure to foetal oral clefts. In addition to the above, therapy can be good practice concerning a close reflection of blood pressure and blood glucose values (Krause et al. 2014).

Disease-modifying antirheumatic drugs (DMARDs)

Anti-malarials

Among the earliest DMARDs used in RA were anti-malarials (Bermas 2014), used as a part of triple therapy under sulfasalazine, hydroxychloroquine (HCQ) and methotrexate in RA. They are marked Category-C by the FDA. Most of the pregnancy safety data for HCQ stems from its use for connective tissue disease and malaria, mainly SLE. Transplacental transition with identical concentrations between cord and maternal blood during delivery has been noted for HCQ. Without an elevated liability of congenital deformity or ocular toxicity, antimalarials can be safely used in pregnancy. Recommended anti-malarial medication in pregnancy should be HCQ, but it should not be considered to treat disease flares, because the initiation of action is slow, andd so should be started before a scheduled conception as a pregnancy-compatible drug (Krause et al. 2014; Singh et al. 2012; Costedoat-Chalumeau et al. 2003; Diav-Citrin et al. 2013). The combination treatment with sulfasalazine and HCQ was shown to be superior to MTX monotherapy in a randomised control trial over 2 years. HCQ is therefore used in alliance along with sulfasalazine as a DMARD treatment consistent with pregnancy which is initiated before a scheduled conception (Förger and Villiger 2016; O'Dell et al. 1996). Anti-malarial medications are weak bases with restricted distribution in breast milk (Sammaritano and Bermas 2014). HCQ is a justifiable RA therapy choice for women of child-bearing age, predominantly in the context of minor illnesses, based on the harmony of indication accessible to time, and can be continuous without harm during pregnancy if clinically designated (Krause et al. 2014).

Methotrexate

Methotrexate (M.X.) is a folate antagonist and is used for RA control as the foundation drug. However, when beginning care for RA in women of child-bearing age, this poses a problem (Singh et al. 2012). The functionally essential M.X. poly-glutamate derivates are produced after entering cells. M.X. poly-glutamate derivatives have prolonged cell retention times and even more potent inhibitory features when compared to that of the parent compound, whereas the serum concentration of M.X. drops below the detecting limit in 52 h (Förger and Villiger 2016; Chabner et al. 1985; Dalrymple et al. 2008). M.X. poly-glutamates attach to and inhibit many enzymes within the cell, such as dihydrofolate-reductase, leading to reduced methylation of DNA and thus interfering with the synthesis of RNA and DNA. The medium half-life varies from 1 to 4 weeks for M.X. poly-glutamates. M.X. is used in low doses for RA, in high doses for ectopic pregnancy therapy, or at high doses for some forms of cancer. M.X. was both embryo-lethal and teratogenic in pre-clinical studies given at higher doses. The placental transport of maternal substances to the foetus is identified by the 5th week of embryonic life. It was shown that, by determining poly-glutamate derivatives of M.X. in the neonate's cord blood and erythrocytes, M.X. crosses the human placenta (Hyoun et al. 2012; Schleuning and Clemm 1987). This drug is both embryo-toxic and teratogenic in animals, contributing to foetal for feature and skeletal abnormalities (Bermas 2014; Skalko and Gold 1974). Methotrexate is also embryo-toxic and teratogenic in humans and is deemed by the FDA to be category X for protection during pregnancy. M.X. is used to facilitate surgical miscarriage for the treatment of ectopic pregnancies because of its abortogenic properties. Exposure to in-utero M.X. may result in methotrexate syndrome: cranial–facial defects in affected children, limb foreshortening, and mental retardation. The ultimate danger of exposure tends to be at dosages greater than 10 mg per week during the 6th–8th weeks of gestation, although another analysis of 42 pregnancies outlining in-utero M.X. exposure determined that no benign duration exists (Hoppe et al. 1994; Bawle et al. 1998; Feldkamp and Carey 1993; Lloyd et al. 1999). Given the alarm about spontaneous abortion, Donnenfeld et al. (1994) recommend that 12 weeks before conception, this drug should be stopped, although this may be too restrictive. While there are no conclusive data about whether there is an elevated risk of teratogenicity in the offspring of men taking M.X., some rheumatologists suggest that men should terminate this drug for 1–3 months before attempting to impregnate their partner. The threat of aminopterin syndrome, categorized by the foetal central nervous system, skeletal and cardiac defects, is increased in pregnant women exposed to MTX. A baby with aminopterin syndrome was born by a woman with juvenile

idiopathic arthritis who took a total of 100 mg of MTX during the 1st 8 weeks of pregnancy. There have been records of toxicity, including skull anomalies, even for the lowest doses (5 mg weekly for 8 weeks) (Buckley et al. 1997; Powell and Ekert 1971). In lesser concentrations, nonetheless, through indicated accretion in neo-natal tissue MTX is excreted into breast milk. MTX was detectable 2 h after administration into a 25-year-old woman given a dosage of 22.5 mg/day for choriocarcinoma in breast milk and serum: the peak amount of milk was achieved between 4 and 10 h later at a plasma level of 8%. However, 6 milk samples obtained over 24 h after an intramuscular 65-mg dosage for ectopic pregnancy did not reveal any signs of drug use. While low once-weekly dosages of RA do not pose a high danger to infants (particularly if milk has been discontinued for the first 24 h after the dosage), it is suggested that breast-feeding should be circumvented due to an absence of evidence and concerns about neonatal accretion (Johns et al. 1972; Saarikoski and Seppälä 1973). MTX is completely contra-indicated in pregnancy, and strict contraception should be recommended using two different methods when used in women of childbearing age. MTX is also advised to be terminated at least 3 months preceding to attempted pregnancy. MTX should be stopped immediately in the instance of an accidental pregnancy while on MTX, and the patient recommended to the genetic counsellor for consideration of acceptable possibilities for reflection against action (Krause et al. 2014).

Azathioprine (AZA)

Azathioprine (AZA) is sometimes used in RA management. It is not metabolised by the placenta into its active form; thus, none, if any, of this drug enters the developing foetus. Cases of pancytopenia and chromosomal anomalies in new-borns after in-utero contact to AZA have been reported; yet larger transplant registries have not corroborated nor demonstrated an elevated menace of inborn disorder for these findings. Reassuringly, there was no rise in congenital abnormalities or pregnancy complications in a recent review of thiopurines in inflammatory bowel disease (IBD) pregnancies (DeWitte et al. 1984; Haugen et al. 1994; Chaparro et al. 2013). While the FDA considers these medicines to be category D for protection during pregnancy, there is significant indication demonstrating that these medicines are not teratogenic. In the literature, there are contradictory studies as to whether these drugs raise the danger for infants of gestational age. There was no variance in gestational age-attuned birth weight in new-borns exposed to thiopurines during gestation in one study by Goldstein; however, others observed a small increase for infants in gestational age (Goldstein et al. 2007; Cleary and Källén 2009). Almost all of the evidence on the impact of AZA on foetal growth came from experiments to avoid the rejection of transplants. There have been reported records of around 90 babies born to women treated with AZA for rheumatic diseases. In all of these studies, no enhanced risk of structural defects was reported, even though test sizes were too limited to rule out any of the most drastic risks. According to a personal correspondence from its author, M. Berkovich, a recently finished broad prospective controlled study of the use of AZA did not show a raised teratogenic risk (Chambers et al. 2007). AZA level assessment is not valuable for evaluating the levels in breast milk: AZA is inactive, but its active metabolite 6-mercaptopurine (6-MP) in-vivo is hepatically metabolized. 6-methyl mercaptopurine and 6-thioguanine are further metabolized into AZA and 6-MP. Mothers have long been prevented from breastfeeding on AZA therapy; however, many case studies indicate that the drug may pose a lower hazard to the nursing baby. 8 breastfeeding women with AZA for IBD were examined with 6-MP milk and plasma concentrations calculated 30 and 60 min after drug supervision and 5 hourlies afterwards, respectively (Christensen et al. 2008). No studies have reported the identification of 6-MP or AZA metabolites in new-born serum and no immunological or developmental defects have been revealed in lasting proceedings of babies breast-fed by mothers on AZA. Statistics indicate little to no drug transfer to new-borns, despite theoretical questions about immune suppression in breastfeeding mothers on AZA. This implies a low risk of breast-feeding while on AZA in term babies, which may not, nevertheless, be relevant to pre-term new-borns with thiopurine methyltransferase (TPMT) mutations. It may be prudent to check the status of the baby before breast-feeding if maternities are considered to have a lower or intermediate TPMT level (Coulam et al. 1982; Moretti et al. 2006; Sau et al. 2007; Gardiner et al. 2006).

Cyclosporine

Cyclosporine is seldom used for RA control. Whether cyclosporine A passes the human placenta in essential concentrations is unknown (Bermas 2014). Cyclosporine A (CsA) transfer to the human placenta has been studied in vitro using the isolated placental lobule dual perfusion technique. Antipyrine has been used as a comparative reference marker. A marginal shift of CsA from the maternal circulation to the foetal circulation was seen in our tests, representing less than 5% of the maternal drug load (Nandakumaran and Eldeen 1990). While animal information suggests an increased risk of inborn defects, it was concluded in a broad meta-analysis that cyclosporine does not seem to be a significant human teratogen. Therapy with CsA also has to be persistent in pregnancy in such cases as organ transplantation and autoimmune disease to preserve maternal fitness. To examine whether CsA exposure during pregnancy is associated with an increased risk of congenital malformations, preterm

delivery or lower birth weight, a meta-analysis was performed (Oz et al. 2001). This indicated that CsA may be pregnancy-compatible. Cyclosporine will flow into breast milk, and a sequence of 7 cyclosporine levels in both the blood of mothers and babies and breast milk was documented by infant couples after transplantation (Nyberg et al. 1998).

Sulfasalazine

Sulfasalazine is an ancient DMARD that is rarely used for the treatment of RA as monotherapy, but is one of the drugs in the renowned triple DMARD combination treatment along with methotrexate and HCQ (Förger and Villiger 2016). Sulfasalazine is known to be FDA Category B, and much of the pregnancy safety information for it came from patients with IBD (Krause et al. 2014). For the time between 2008 and 2015, in the systematic literature review, results from 525 analysed pregnancies after gestational exposure to sulfasalazine showed no elevated levels of miscarriage or congenital abnormalities (Rahimi et al. 2008). It is recommended that reversible congenital neutropenia br correlated with 3 g of sulfasalazine, thus the daily dose does not surpass 2 g during pregnancy (Levi et al. 1988). Since sulfasalazine should be elevated progressively, measurable therapeutic effects typically take several weeks. Therefore, sulfasalazine is not appropriate to aid flares in pregnancy; rather, it needs to be introduced to substitute pregnancy-incompatible DMARD treatment, such as MTX or leflunomide before expected conception. 5-aminosalicylic acid and sulfapyridine are metabolized in vivo by sulfasalazine. In breast milk, sulfapyridine is present in substantial amounts, the levels of maternal serum being 30–60%. In a study of new-borns exposed to sulfasalazine by lactation, there is only a single recorded case of bloodstained diarrhoea. As a result, close observation of the occurrence of diarrhoea in infants is recommended when using sulfasalazine in stable full-term infants. In premature or ill new-borns with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficit, since sulfapyridine can replace bilirubin, this drug should be avoided (Sammaritano and Bermas 2014; Berlin and Yaffe 1980; Branski et al. 1986).

Leflunomide

Leflunomide (Lef) is an immune-modulatory agent that is utilized as a DMARD. Lef's active metabolites attach to the dihydro-orotate dehydrogenase enzyme and thus inhibit the de-novo biosynthesis of pyrimidine. Leflunomide inhibits their clonal expansion, resulting in immune suppression, as stimulated lymphocytes are especially susceptible to this outcome (Fox et al. 1999). At a pharmacokinetic dosage close to those used in human beings, Lef has been shown to cause serious anomalies in animal models. A large range of defects, extending from foetal death to ventricular septal blemish, chronic truncus arteriosus and skeletal abnormalities, have been reported in mice. Defects of the neural tube are also indicated. Given these accounts, this is known to be a Class X pregnancy drug (Fukushima et al. 2007). Lef, a pyrimidine synthesis inhibitor, has a longer half-life (14 days). No data on lef levels in breast milk or infant serum have been published. Assumed the absence of evidence and the very long half-life, on theoretical grounds, this medication is best dodged in breast-feeding (Sammaritano and Bermas 2014).

Etanercept

Etanercept is a soluble fusion protein that is administered by subcutaneous injection and consists of a part of the human TNF-receptor and the Fc portion of human IgG1. There is a case study of a VATER-associated baby (tracheal atresia, oesophageal atresia, tracheoesophageal fistula, vertebral irregularity, imperforate anus and patent foramen ovale) born late in pregnancy, during which etanercept 50 mg was used by the mother for treatment of psoriasis and psoriatic arthritis, taken subcutaneously twice weekly (Youssef and Kennedy 2009). However, there are some supportive case reports of good pregnancy results in the therapy of conditions like SLE and RA in women taking etanercept (Sills et al. 2001). At low concentrations, etanercept was found in breast milk with little passage to the baby during breast-feeding (Ostensen and Eigenmann 2004).

Infliximab

Infliximab is a chimeric IgG monoclonal human TNF-α antibody and is used to treat both RA and serious Crohn's disease. By attaching to both the soluble and the membrane-bound protein, infliximab neutralizes the biological function of TNF-α. The fact that thalidomide, a chief teratogen, is a powerful inhibitor of TNF-α production, raises a hypothetical apprehension concerning the probable teratogenicity of infliximab. Although the exact reason for the teratogenicity of thalidomide is uncertain, it reduced the production of TNF-α by hastening the deprivation of the protein-coding messenger RNA, while infliximab acts both as a cytokine carrier and as a TNF antagonist, resulting in biologically inactive TNF. Katz et al. (2004) reported the first larger studies of pregnancy results in women exposed to infliximab in 2004, which involved pregnancies established in the infliximab safety database in women treated for both Crohn's disease and RA. A retrospective study of 10 women given infliximab for the induction or conservation of diminution

during pregnancy of Crohn's disease recorded that all 10 pregnancies led to live births without congenital deformities and no limitation of intra-uterine development, although 3 premature births were observed (Mahadevan et al. 2005). Despite significant cord blood levels of infliximab when given during pregnancy, case studies indicate a limited allocation of infliximab to breast milk when the drug is given during lactation.

Adalimumab

Adalimumab (Humira) is a human monoclonal recombinant which is the TNF antibody (IgG1) that has been accepted for RA treatment and psoriatic arthritis treatment. Also, it is used for the treatment of further auto-immune diseases, such as Crohn's. Adalimumab has a longer half-life (about 2 weeks with a period of 10–20 days), so when contemplating drug cessation for pregnancy, women need to take this into account. The European Summary of Product Characteristics recommends, for at least 5 months after the last treatment, contraception should be continued. There is very little information available about its use and protection in pregnancy, as with other biological agents (Youssef and Kennedy 2009). There have been reports of one 26-year-old Crohn's disease patient given adalimumab in lactation. Adalimumab was excreted at lower concentrations, at less than 1/100 the parental serum level in breast milk (Ben-Horin et al. 2010).

Anakinra

Anakinra is a recombinant antagonist of the IL-1 receptor. In 2001, it became an FDA-permitted treatment for RA. While anakinra is listed as a Category B pregnancy drug, very little information is available on its impact on pregnancy. By competitively inhibiting IL-11, anakinra inhibits the biological activity of IL-1 by binding to the type I receptor (IL-1RI) for interleukin-1, which is stated to be in an extensive range of organs and tissues. No well-controlled pregnancy trials have been performed, but rat and rabbit studies have not demonstrated diminished fertility or signs of teratogenicity in dosages up to ten times the normal human doses (Simon 2004). Anakinra persisted during pregnancy in a single female with adult onset of Still's disease. She experienced placenta retention that involved manual abruption, but there were no other anomalies (Berger et al. 2009). This medication should only be considered after all further treatment choices have been tried, given the lack of human pregnancy data.

Golimumab

Another IgG1 monoclonal antibody is golimumab. Sufficient data are not available for the use of golimumab during pregnancy. No human breast-feeding records are currently available for golimumab. No adverse effects were found in infants with golimumab-treated breast-feeding macaques in a single animal study (Sammaritano and Bermas 2014; Martin et al. 2000).

Abatacept

Abatacept (Orencia) is an Fc receptor-bound recombinant CTLA4 analogue that modifies T-lymphocyte incentive and is given i.v. to treat moderate to extreme RA. By preventing contacts between T cells and antigen-presenting cells through attaching to CD80/CD86 on antigen-presenting cells, abatacept inhibits T-cell activation (Kremer et al. 2000). In terms of the risk in pregnancy, abatacept is FDA class C (Krause et al. 2014). Abatacept crosses the placenta, and, in comparison to full IgG1monoclonal antibodies such as rituximab or adalimumab, attachment to the neonatal-Fc receptor is less severe (Suzuki et al. 2010; Pham et al. 2009). Animal studies show no elevated risk when given with the maximum prescribed human dosage, although improvements in immune function were reported at extremely high doses. In humans, an enhanced level of miscarriages and congenital abnormalities were recorded in 152 pregnancies with abatacept exposure (8%), but regular associated MTX acquaintance may have skewed this verdict (Kumar et al. 2015). Insufficient information is available to complete a statement on the protection of abatacept in pregnancy. It was therefore recommended that abatacept be avoided during pregnancy and that this biologics agent be stopped at least 10 weeks earlier than the expected pregnancy. Abatacept has been observed in lactating animal milk, but there are no data on human milk involvement (Østensen and Förger 2013).

Rituximab

Rituximab, a monoclonal chimeric antibody against the CD20 antigen on the B-lymphocytes, has been used mostly to treat non-lymphoma Hodgkin's and, more recently, RA and SLE (Eisenberg and Albert 2006). Rituximab is classified as pregnancy category-C, and it is advised to wait 12 months before attempting conception after exposure to rituximab. There is no evidence available concerning exposure to rituximab in males. Information is accessible for 11 out of 22 pregnancies, of which 2 resulted in impulsive abortions, 7 in live births and the remaining 2 pregnancies are ongoing at the time of reporting (Chakravarty et al. 2011). In the 2nd and 3ird trimesters, rituximab is a full IgG1 monoclonal antibody and triggers transplacental passage, whereas exposure to rituximab in the 1st

trimester does not increase adverse events. Contacts in the 2nd and 3rd trimesters can lead to depletion of B-cells, thrombocytopenia and neutropenia.[115] Rituximab should be withdrawn under the official label, 12 months ahead of conception. Nevertheless, pharmacological and developmental considerations and recent in-depth consultations with scientific experts have contributed to the suggestion that the indication should focus on disease sternness. Rituximab can also be administered early during gestation in rare cases (Förger and Villiger 2016).

Tocilizumab

Tocilizumab is a monoclonal antibody which blocks downstream signalling directed against interleukin-6 receptors. In 2010, it was accepted for RA either alone or in conjunction with MTX or other DMARDs. In a systematic literature review by EULAR, the introduction of tocilizumab in pregnancy was reported in 218 cases. There was no enhanced level of abnormality, but an enhanced level of miscarriages was seen in those exposed pregnancy cases that often used MTX as an accompanying drug. The IL-6 pathway leads to the development of trophoblasts and placenta, which may explain the increased rate of miscarriage. Limited information on tocilizumab is available and it is categorised C by the FDA (Förger and Villiger 2016; Krause et al. 2014; Nishino et al. 1990).

Tofacitinib

Tofacitinib is an inhibitor of oral Jannus kinase for RA therapy. Extremely little information on the safety of tofacitinib in pregnancy is available. In preclinical animal research, foetotoxic and teratogenic effects have been seen. One case study of 27 births, sometimes paired with MTX, explains exposures to tofacitinib. There was an augmented miscarriage rate, but there was no sign of an increased congenital malformation rate (Förger and Villiger 2016; Skorpen et al. 2016). It is under category C by the FDA. Tofacitinib should be discontinued before conception due to insufficient evidence. Although the half-life of this medicine is only 3 h, 2 months of withdrawal before conception is suggested. This is demonstrated by the adverse effect of natural killer cells on tofacitinib, which can last for up to 6 weeks. It is delivered by the oral route and has a lower 504.5 Da MW. Since small molecules are easily diffused into breast milk and there is no issued evidence, it is suggested that breastfeeding should be avoided (Sammaritano and Bermas 2014).

Conclusion

Several hypotheses are put forward to analyse the positive effects on RA in pregnancy. There are data suggesting that RA improves during pregnancy, although many RA patients will still have active disease. A treatment strategy that will decrease the activity of the disease in patients who wish to conceive is therefore important. The more acceptable therapy should be chosen because most of the anti-rheumatic drugs are contra-indicated in pregnancy. Women with minor RA may contemplate discontinuing their medicines before conception, as many RA patients improve during conception. In pregnancy, women who are on HCQ and sulfasalazine may remain on these drugs as they are not teratogenic. In advance of conception, it is essential that women on MTX and leflunomide to cease these medicines since they are teratogenic. NSAIDs can be taken later after implantation until gestational week 30 for flares, although use in the 1st trimester should be minimised because of the credible risk of spontaneous abortion. With the caveat concerning use in the 1st trimester, glucocorticoids can be used throughout pregnancy, but there may be a slight upsurge in cleft palate formation, and use during pregnancy ionvolves the risk of hypertension and gestational diabetes.

Declarations

Conflicts of interests There are no conflicts of interest.

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