Review paper

The exposure to biologic and targeted synthetic disease-modifying antirheumatic drugs in pregnancy and lactation

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Abstract

Chronic inflammatory diseases often affect women of childbearing age. Since biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) are more available, their use during conception, pregnancy and lactation has become a matter of concern. Current studies prove the safety of innovative therapy in pregnant women and may contribute to its wider use than before in pregnancy and lactation. It mainly concerns tumour necrosis factor α (TNF-α) inhibitors. We searched PubMed using Medical Subject Headings (MeSH) terms and identified relevant studies and guidelines. We present up-to-date knowledge of bDMARDs and tsDMARDs safety in pregnant and breastfeeding women.

Key words: bDMARDs, tsDMARDs, inflammatory disease, pregnancy, lactation.

Introduction

Chronic inflammatory diseases often affect women of reproductive age. The common use of biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) has allowed to manage disease activity, prevent joint damage and organ complications. However, there is a lack of evidence from randomized clinical trials determining the safety profile of these drugs during pregnancy and lactation and their impact on the child's development. Therefore, it is very important for women treated with innovative therapies to receive prenatal care concerning pregnancy planning and modifying treatment during pregnancy. It should also be noted that discontinuing effective treatment may lead to exacerbation of the underlying disease and to complications in both the mother and the child.

There are more and more research confirming the safety of bDMARDs and tsDMARDs during pregnancy and lactation. In our study we focused on the most widely used and approved agents in rheumatic conditions. However, regarding the limited data of their use during pregnancy we included also studies conducted in women with a range of other chronic inflammatory conditions like psoriasis. Many data come from research in tumour necrosis factor α inhibitors (TNF-αi) treatment of pregnant women with inflammatory bowel diseases. Tsao *et al.* have analysed patterns of taking and discontinuing biologics before and during pregnancy in patients with autoimmune diseases. They found that patients with rheumatoid arthritis (RA) are three times more likely to stop treatment during pregnancy than patients with inflammatory bowel diseases [1].

In our study we address clinicians who provide long-term care of patients with chronic inflammatory diseases and the most common questions about the pregnancy practitioners might have in their everyday practice. We believe that dissemination of the current data based on up-to-date best evidence to the clinicians and patients, as well as their implementation into everyday clinical practice may help to improve the management of pregnant and lactating patients with autoimmune diseases, which cannot be controlled otherwise than with bDMARDs or tsDMARDs.

We searched PubMed using Medical Subject Headings (MeSH) terms ("rheumatology" or "psoriasis arthri-

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tis" or "rheumatoid arthritis") and ("biologic drugs") and ("pregnancy" or "neonatal"). We identified meta-analysis, systemic reviews, observational studies, guidelines and selected relevant English-language publications based on their abstracts. Reference lists of the applicable studies were hand-searched to select additional papers.

Autoimmune disease and pregnancy

Active inflammation, organ complications and treatment of the primary disease may affect pregnancy [2, 3]. RA in pregnant women is linked to more frequent complications in the mother and the newborn, such as eclampsia/pre-eclampsia, gestational diabetes mellitus, placental abruption, placenta praevia, preterm birth, low birth weight and foetal congenital disorders [3, 4]. This relation is visible especially with high disease activity [5]. Similarly, highly active systemic lupus erythematosus (SLE) increases the risk of pre-eclampsia, preterm birth and low birth weight [6].

The effect of pregnancy on autoimmune diseases varies. In patients suffering from RA, symptoms usually improve during pregnancy, but worsen in the first months after labour [7, 8]. There is evidence that SLE becomes more severe during pregnancy and in the postpartum period [9]. Similarly, symptoms of psoriatic arthritis (PsA) worsen as well [10, 11]. It has been established that discontinuing effective biologic treatment before a planned pregnancy leads to exacerbation of PsA during pregnancy and puerperium. Therefore Berman *et al.* recommend considering continuing biologics during pregnancy [11].

International recommendations

2016 European League Against Rheumatism (EULAR) recommendations provide rules concerning the use of antirheumatic drugs during conception, pregnancy and lactation. Treatment should be adjusted before conception and focused on preventing exacerbation or decreasing disease activity in the mother along with ensuring the foetuses safety [12] (Tables 1, 2).

Similarly, recently updated Asia-Pacific League of Associations for Rheumatology (APLAR) recommendations suggest continuing certolizumab and etanercept throughout pregnancy if the disease (RA) cannot be managed otherwise [13].

The safety of bDMARDs and tsDMARDs during pregnancy and lactation – TNF-α inhibitors

Currently the most thoroughly studied biologics used during pregnancy and lactation are TNF-αi. They are also the only innovative therapy allowed to continue in these indications.

The effect on pregnancy and incidence of congenital disorders

Prospective follow-up studies did not show a teratogenic effect of TNF-αi [14]. A higher number of congenital disorders in comparison with the general population has not been observed and reported cases among pregnancies exposed to TNF-αi did not show a consistent pattern of anomalies as in the other teratogenic drugs [15]. While working on their recommendations the EULAR team analysed almost 2.5 thousand pregnancies during which TNF-αi were used, they did not notice higher incidence rates of miscarriages or congenital disorders compared to the control group [12].

A meta-analysis comparing pregnancy complications in women with autoimmune diseases did not describe a higher risk of preterm birth, miscarriage or low birth

Table 1. Selected EULAR recommendations concerning the use of bDMARDs and tsDMARDs during pregnancy

Drug	Recommendations
Infliximab Adalimumab	Therapy can be continued up to week 20 of pregnancy If indicated, it can be used throughout pregnancy
Etanercept	Therapy can be continued up to week 30–32 of pregnancy If indicated, it can be used throughout pregnancy
Certolizumab	Therapy can be continued throughout pregnancy
Golimumab	Insufficient evidence to support the use of the medication
Rituximab	It can be used in early stages of pregnancy in exceptional cases The use of the medication in later stages of pregnancy may result in decreased b cell levels and other types of cytopenia in the newborn
Tocilizumab Abatacept Anakinra Ustekinumab Belimumab	Insufficient evidence regarding the drug's safety during pregnancy Treatment should be altered before the pregnancy May be used only if no other, safer options allow for adequate management of disease activity in the mother
Tofacitinib	Should be discontinued before conception Insufficient data concerning safety during pregnancy

Table 2. Selected EULAR recommendations concerning the use of bDMARDs and tsDMARDs during lactation

TNF-α inhibitors	Approved for use
Rituximab Tocilizumab Abatacept Anakinra Belimumab Ustekinumab	Due to no sufficient data, should be avoided if other therapy is available Due to pharmacological properties of these medications, breast feeding may be allowed if other treatment options are not available
Tofacitinib	Insufficient data concerning the use of the medication

weight in the group of patients treated with anti-TNF compared to patients not treated with biologics [16].

Eight thousand, six hundered and seven pregnancies in 6218 women with autoimmune diseases (rheumatoid arthritis – 49%, inflammatory bowel diseases – 46%, psoriasis and psoriatic arthritis, juvenile idiopathic arthritis, autoimmune rheumatic diseases including systemic lupus erythematosus and other connective tissue diseases) have been analysed in a cohort population study including large population database. A hundred and nine women were qualified for the final analysis (120 pregnancies). They were treated with biologics for 3 months before the pregnancy or during the pregnancy (94% with TNF-αi; most commonly infliximab (39%), etanercept (30%), and adalimumab (25%)). Each woman was matched by 5 other women with autoimmune diseases who did not receive biologics during pregnancy (585 women and 600 pregnancies). It has been established that biologic therapy in pregnant women with autoimmune diseases does not increase the risk of preterm labour nor giving birth to a baby who is small for gestational age (SGA) compared to the control group [17].

Is has also been discovered that miscarriages occurred more often in patients who stopped anti-TNF treatment in the first trimester of pregnancy compared to women who were exposed to TNF-αi during all three trimesters [18]. In women with high disease activity more spontaneous miscarriages are observed due to the uncontrolled inflammatory process. Therefore, controlling disease activity, including anti-TNF therapy, is an effective way to carry pregnancy to term [19].

Transplacental drug transfer, the effect on the immune system development and susceptibility to infections in newborns exposed to anti-TNF *in utero*

The active transport of biologics containing the Fc fragment of the IgG1 immunoglobulin into the foetal circulation occurs due to the presence of the foetal Fc receptor which is expressed in the placenta. Transplacental transfer is considered to be very low during organogenesis but increases steadily after week 13 of pregnancy. Treating the mother with antibodies of high affinity to the foetal Fc receptor after week 30 of pregnancy may lead to an increased concentration of the drug in foetal blood, at a level equal to or higher than the mother's level [20].

TNF-αi vary by their biological half-life and structure, which causes differences in placental transport and safety during pregnancy. Infliximab, adalimumab and golimumab are monoclonal TNF-α specific IgG1 antibodies. Etanercept is a fusion protein containing the extracellular human TNF-α receptor domain and human Fc domain of IgG1. Certolizumab is a Fab' fragment of the anti-TNF-α monoclonal antibody without the Fc domain. The affinity to the foetal Fc receptor on trophoblast cells is the highest in complete monoclonal antibodies, like infliximab and adalimumab, low for etanercept and practically non-existent in certolizumab. Adalimumab administered in the third trimester can be detected in the infant's serum up to 4 months after birth and infliximab up to 12 months [21]. Therefore, in infants exposed to TNF-αi *in utero* it is not recommended to administer live vaccines for a minimum 5 months after the last dose of medication during pregnancy [22, 23]. According to some guidelines, this period should be extended up to 7 months of age in the case of treatment with infliximab, adalimumab or etanercept [15]. *In utero* exposure to anti-TNF (especially those transported through the placenta in the second and third trimester) can potentially affect the development of the newborn's immune system and susceptibility to infections. More immature B and Th cells were observed in newborns of mothers treated with infliximab or adalimumab throughout the entire pregnancy. This normalized within 12 months. It has also been hypothesized that a reduced number of regulatory T cells may lead to hypersensitivity and atopy, while interleukin 12/interferon γ pathway may contribute to a higher incidence of intracellular infections caused by e.g. *Mycobacterium tuberculosis* [24]. However, studies have not shown a higher incidence rate of serious infections in children of mothers treated with anti-TNF during pregnancy compared to the untreated group. The mean observation time was 47 months in the group exposed to TNF-αi [25]. Moreover, it has been established that biologics do not disrupt the response of these infants to vaccination [26].

The prospective multicentre pharmacokinetic study evaluated placental transfer of certolizumab used in the third trimester. In 13 newborns the concentration of certolizumab at birth was below the limit of quantification and in one case an amount of 0.09% of maternal plasma level was detected. At week 4 and 8 all infants had no quantifiable certolizumab levels [27]. An extremely low level of certolizumab placental transport suggests no foetal exposure to the drug in the third trimester of pregnancy in contrast to other TNF-αi. It is reflected in international recommendations allowing the use of certolizumab throughout the entire pregnancy [12, 15]. The Summary of Product Characteristics has been updated according to the above-mentioned studies. However, there are no long-term follow-up studies on children exposed to certolizumab during foetal life.

Anti-TNF treatment during lactation

Despite the limited data concerning anti-TNF treatment during pregnancy, it is believed that the transfer of these biologics from the serum to the mother's milk is minimal and their concentration in the milk amounts to 0.1–1% of the concentration in the serum. Moreover, orally administered immunoglobulins undergo intestinal proteolysis and have low bioavailability [23, 28]. Studies show no adverse effects in breast-fed newborns.

Innovative therapy with a different mechanism of action

Targeted synthetic disease-modifying antirheumatic drugs

Janus kinases (JAK) inhibitors

The above mentioned group includes tofacitinib and baricitinib. These drugs inhibit JAK kinases, weakening intracellular interleukin and interferon signalling pathways, affecting DNA transcription and modulation of immune responses.

According to safety database, more frequent complications were not observed in the course of pregnancy exposed to tofacitinib compared to the general population, irrespective of the type of treated disease [29, 30]. In the case of baricitinib, the only available data come from preclinical animal trials. They showed a teratogenic effect, especially negative impact on the development of the skeletal system *in utero*. This relation was seen while using much higher doses of baricitinib than in humans. Decreased fertility in females was observed as well [31].

Apremilast

Apremilast, a phosphodiesterase 4 (PDE4) inhibitor, affects intracellular transmitter pathways and decreases the concentration of pro-inflammatory cytokines by lowering PDE4 levels.

In animal trials the use of apremilast during gestation led to more frequent miscarriages, death during the peri- and post-natal stage, decreased birth weight and delayed ossification. This relation was dependent on the drug's dose. The above-mentioned adverse effects of apremilast have not been observed with doses used in humans [32].

Since 2014 a prospective population study has been conducted comparing the course and complications of pregnancy in the following groups of women: patients treated with apremilast during pregnancy, non-treated patients and healthy women. The results are unknown so far [33].

Biologic disease-modifying antirheumatic drugs

Secukinumab, ixekizumab, brodalumab

Secukinumab and ixekizumab are human monoclonal antibodies that bind and neutralise the pro-inflammatory cytokine – interleukin 17A (Il-17A). The brodalumab antibody blocks the biological activity of Il-17A due to its affinity to Il 17A receptor.

Available study results do not confirm the negative effect of secukinumab on pregnancy when used in its early stage [34]. In 2018 data from the secukinumab safety registry were published, comprising 292 pregnancies exposed to the drug, including 153 with known outcome. The incidence of congenital disorders and miscarriages was comparable to that reported in the general population. In most patients the treatment was discontinued in the first trimester, while 18 women continued their therapy also after the first trimester [35]. Animal trials conducted on monkeys did not show a teratogenic effect of secukinumab when used during the entire pregnancy [34].

According to animal trials, ixekizumab and brodalumab did not affect fertility and administration during pregnancy did not cause side effects in the developing foetus [36, 37]. No disorders were observed in the development of the immune system after birth [38].

Ustekinumab

Ustekinumab, a monoclonal antibody, due to binding to interleukins IL-12 and IL-23, disrupts the pathways of Th1 and Th17 cytokines, which are central to the pathophysiology of psoriasis, PsA and Crohn's disease. According to data from registries and case series, no increased risk of congenital disorders nor miscarriages was observed due to the drug continuation during pregnancy [12, 39]. However, there are few reports in the literature describing miscarriages during the first trimester [40, 41]. Moreover, in case of using ustekinumab up till week 33 of pregnancy, the cord blood ustekinumab levels were nearly 2-fold higher than contemporaneous maternal serum levels. The clinical significance of this discovery has not been established [42].

Interleukin 6 (IL-6) inhibitors

This group includes: tocilizumab and sarilumab – IL-6 receptor antibodies; olokizumab and sirukumab – antibodies which bind directly to IL-6.

A retrospective analysis based on safety databases did not show an increased incidence of miscarriages and congenital disorders in newborns of patients treated with tocilizumab before the pregnancy and during its first trimester [43, 44]. The authors of case studies highlight that controlling RA activity with tocilizumab may be an alternative for patients who do not respond to anti-TNF therapy but desire to have children. In described cases, tocilizumab treatment was discontinued after the pregnancy was confirmed [45]. There are also few cases of tocilizumab treatment during lactation, where the drug's concentration in the mother's milk was established at 0.1% of the concentration in the mother's serum and there were no adverse effects in the infants [46].

Animal trials showed no adverse effects in females and foetuses during sarilumab therapy and no fertility disorders [47].

Rituximab

It is a chimeric mouse/human monoclonal antibody which binds to the CD 20 antigen in pre-B cells and mature B cells, causing lysis of these cells.

Although prospective data concern small groups of patients, they do not confirm the negative effect of rituximab on the course of pregnancy and the incidence of congenital disorders in patients using rituximab before conception [48]. The largest retrospective registry, including 153 pregnancies in patients treated with rituximab before and during pregnancy, concerned mainly patients suffering from serious haematological diseases, using additional medication with teratogenic potential. This makes the data difficult to interpret. There were reported: 90 live births, 22 preterm births, 2 cases of congenital disorders, 4 infectious complications and 11 cases of haematological disorders in newborns [49].

It is believed that rituximab exposure during the first trimester is not dangerous, since there is no transplacental transfer until week 16 of pregnancy. Treatment during the second and third trimester may lead to decreased B cell levels in the newborn.

Belimumab

It is a human monoclonal antibody against the B-lymphocyte stimulator (BLyS). Blocking the binding of BLyS with its receptors on lymphocytes prevents the survival of B cells.

The effect of belimumab treatment on the increased incidence of congenital malformations and pregnancy loss have not been confirmed before pregnancy and in early pregnancy [50, 51].

Danve *et al.* have described the case of a patient with systemic lupus erythematosus whose treatment had to be modified since she was planning to get pregnant despite high disease activity. Azathioprine, hydroxychloroquine, prednisone and rituximab therapy did not sufficiently control the symptoms and resulted in adverse effects. Belimumab was used in the pre-conceptive stage, leading to good disease activity control. The treatment was continued during the entire pregnancy, which allowed the patient to bring the pregnancy to term and keep SLE in the state of remission. The newborn was diagnosed with a benign form of Ebstein syndrome [52].

Abatacept

Abatacept is a fusion protein composed of the extracellular domain of CTLA-4 antigen (cytotoxic T lymphocyte associated antigen 4) and the modified Fc fragment of immunoglobulin IgG1. It inhibits the co-stimulation of T cells by binding to CD 80 and CD 86 molecules on the surface of antigen presenting cells.

A hundred and ninety-six pregnancies with known outcome have been reported in the registry of patients exposed to abatacept during pregnancy. Most cases were limited to the exposure in the first trimester. No increased risk of miscarriage, preterm labour or low birth weight was established. Congenital disorders have been described in 10 cases but the affected patients had other risk factors [53].

Conclusions

The results of available studies suggest the safety of bDMARDs and tsDMARDs in pregnant women with autoimmune diseases and could contribute to more frequent use of these drugs during pregnancy and lactation [17]. It refers mainly to TNF-αi.

Moreover, based on the analysed literature, the authors prove that there are no solid data confirming the negative effect of TNF-αi, rituximab and abatacept on fertility and an increased number of complications due to paternal exposure [54].

There are also cases concerning effective anti-TNF treatment in patients with recurring miscarriages and unsuccessful *in-vitro* fertilization procedures [55, 56]. These patients had higher levels of TNF-α. The possibility to include etanercept in the treatment of infertility in women suffering from endometriosis is currently being researched [57].

Unfortunately, a lot of data regarding the newest drugs used during pregnancy and lactation come from retrospective studies conducted on small groups of patients or case reports.

Therefore, there is a need to carry out prospective registries comprising:

– large populations of women
– adequately matched control groups of patients not treated with targeted agents and healthy women
– analysis of confounders, such as disease activity, organ complications, comorbidities, other medication
– long follow-up period of children exposed *in utero*, taking into account potential immune system disorders, neoplasms and mental development.

Conflict of interest

The authors declare no conflict of interest.

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