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**Safety of biologic therapies during pregnancy in women with rheumatic disease**

Mena-Vazquez N *et al*.Biologic therapies in pregnant rheumatic patients

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**Abstract**

Inflammatory rheumatic diseases frequently affect women of childbearing age. Biologic therapy during pregnancy is an important topic that is yet unresolved. The majority of documented experiences are in case series, case reports, or registries. Tumor necrosis factor (TNF) inhibitors are now better known. Some evidence suggests that it is possible that differences between drugs regarding safety are associated with the structure and capacity to cross the placenta, but we are not aware of any study that supports unequivocally this statement. Most of the monoclonal antibodies are actively transferred to fetal circulation using the neonatal Fc receptor. Although this transfer does not appear to be associated with the risk of miscarriage, stillbirth, or congenital abnormality, the rate of premature births and lower birth weight may be increased. During fetal development, the neonatal period, and childhood, the immune system is constantly maturing. The ability to produce cytokines in response to infectious stimulus remains low for years, but is similar to that of an adult around the age of 3 years owing to the adaptive nature of the newborn’s immune system as a result of exposure to microbes. Therefore, exposure to TNF inhibitors may have serious consequences on the newborn, such as severe infections or allergic reactions. Regarding the former, an anecdotal case report described a fatal case of disseminated bacillus Calmette-Guérin (BCG) infection in an infant born to a mother taking infliximab for Crohn’s disease. Although the baby was born and progressed well initially, he died at 4.5 mo after he was vaccinated with BCG. Fortunately, serious infections do not appear to be frequent in newborns exposed to in utero biologic therapy. However, very limited short-term experiences are available regarding complications in an exposed fetus, and no data are available about long-term implications on the child’s developing immune system. Therefore, we must be aware of potential complications in later years. Although the clinical data to date are promising, no firm conclusions can be drawn about the safety of biologic drugs during pregnancy, and, without further evidence, guidelines that suggest these drugs should be avoided at the time of conception cannot yet be changed.

**Key words:** Biologic therapy; Safety; Pregnancy; Rheumatic diseases; Monoclonal antibodies

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**Core tip:** Biologic therapy during pregnancy is an important topic that remains unresolved. Most of the monoclonal antibodies are actively transferred to fetal circulation using the neonatal Fc receptor. Some evidence suggests that differences may exist between drugs relating to safety associated with structure and the capacity to cross the placenta, but we are not aware of any study that supports this statement. Although the clinical data to date are promising, no firm conclusions can be drawn about the safety of biologic drugs during pregnancy, and, without further evidence, guidelines that suggest these drugs should be avoided at the time of conception cannot yet be changed.

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**INTRODUCTION**

Inflammatory rheumatic diseases affect women of childbearing age. Therapy for these diseases during pregnancy is an important topic that remains unresolved. Although there is considerable evidence for interaction of pregnancy and rheumatic diseases, little information is available about the safety of biologic drugs in pregnancy in humans. Most of the information is based on experimental studies with animals, but animal pregnancies differ considerably from human pregnancies in many aspects; as a result, the manufacturers of biological drugs advise that these agents be discontinued prior to a planned pregnancy for varying periods of time (Table 1). Despite this advice, numerous new pregnancies that occur during therapy with biological agents have been reported.

The reasons for exposure to biological agents during pregnancy are diverse. Many cases involve unintended pregnancies. However, in other cases, the pregnancy was planned, but the treatment is continued until the pregnancy is verified to avoid a flare-up of the condition. This behavior is reinforced owing to the unknown time to conception, and both patients and physicians fear that the disease may become active. Although the biological therapy is discontinued in the majority of cases when the pregnancy is confirmed, other cases are treated throughout pregnancy to avoid a flare-up of the disease and ensure a successful pregnancy outcome. Because this occurs in women with more severe disease during pregnancy in particular, most of the information regarding exposure to biologic drugs throughout pregnancy is based on patients with severe inflammatory bowel disease[1]. Because these reports have generally been positive, there is growing interest among rheumatologists about the possibility of prolonging the biological treatment until the second trimester or later. Unfortunately, too many uncertainties remain about the potential long-term effects of treatment during pregnancy, as has happened with other drugs in the past[2].

Because of an increasing use of biological agents, the aim of this paper was to examine some of the safety issues of biologic therapies during pregnancy, specifically in women with rheumatic diseases.

**BIOLOGICAL AGENTS TARGETING CYTOKINES**

***Tumor necrosis factor inhibitors***

Currently, there are 5 licensed tumor necrosis factor inhibitors (TNF) inhibitors. Three of these - infliximab (IFX), adalimumab (ADA), and golimumab - are structurally complete IgG1 monoclonal antibodies, *i.e.,* they contain a fragment crystallizable (Fc) region that interacts with Fc receptors, including neonatal Fc receptor (RnFc). These receptors transfer IgG from mother to fetus through the placenta and from mother to infant in milk in addition to protecting IgG from degradation[3].

In contrast, both etanercept (ETN) and certolizumab pegol (CZP) have structural peculiarities that may influence their fetal toxicity. The former is a fusion protein directed against the TNF receptor with a low affinity for RnFc[4], while the latter is an incomplete antibody that contains only a pegylated Fab fragment against TNF. Because CZP does not have an Fc part, it cannot interact with RnFc.

The United States Food and Drug Administration (FDA) classifies all 5 biologic agents as pregnancy category B drugs, *i.e.,* animal reproduction studies have not shown any risk to the fetus, but adequate and well-controlled studies in pregnant women are lacking.

**Potential risks to pregnant women:** The risks of biologic therapy in pregnant rheumatic women should be at least equivalent to non-pregnant rheumatic patients. Therefore, the main risks with biologic therapy use should include infections, allergic reactions, infusion reactions, or local reactions. Although pregnancy implies a relative immunosuppression, studies do not exist that suggest the risk of infections associated with biologic drugs increase during pregnancy. However, there are also no studies that address this topic specifically. Only Casanova *et al*[5] retrospectively studied 66 pregnant women with inflammatory bowel disease who were exposed to anti-TNF drugs and compared their outcomes with patients exposed to thiopurines (*n* = 187) and non-exposed controls (*n* = 318). The infection rates were similar in all of the participants (3%, 1.5%, and 2.5% in those exposed to anti-TNF, those exposed to thiopurines, and the non-exposed, respectively).

Nevertheless, because these results are very limited, physicians should be aware of the infection risks in these patients. In this sense, it is worth remembering that anti-TNF increases the risk of infections such as *Listeria* or *Salmonella*[6]. These infections may occur in pregnant women and their unborn fetuses, in whom life-threatening infections and fetal miscarriage can occur. Therefore, pregnant women who are in treatment or have been recently treated with biologic drugs should particularly follow the preventive measures to avoid food consumption of unpasteurized milk, raw eggs, or raw meat[7].

On the other hand, both patients and rheumatologists should weight up the risks and benefits of continuing biologic therapy with planned pregnancies. One of the most important considerations is the diagnosis and level of control. The risks of flare-up may differ based on the disorder; for example, upto 60% of patients with rheumatoid arthritis improve during pregnancy, while the symptoms of ankylosing spondylitis do not improve[8]. However, studies regarding the impact of biologic drug discontinuation are limited in patients with rheumatic disease owing to the incidental nature of the main exposure, and three-quarters of the cases with confirmed pregnancy in the first trimester discontinue biologic drugs[4,9-43]. Only a minority of cases continue biologic therapy throughout their pregnancy, in agreement with their doctors. It is possible that these patients were treated to avoid the high risk of flare-ups.

**Potential risks to pregnancy outcomes:** In normal fetus, responsiveness to infection is low and associated with spontaneous abortion[44]. Therefore, an increased risk of miscarriage might be expected with infection related to TNF inhibitor exposure. However, intrauterine production of pro-inflammatory cytokines during the pregnancy is associated with intrauterine growth restriction and spontaneous abortion[45]. Therefore, the use of TNF inhibitors during pregnancy may have be theoretically advantageous.

Only a few clinical studies have provided data regarding pregnancy outcomes in patients with inflammatory rheumatic disease undergoing anti-TNF therapy. The majority of this evidence is based on women with inflammatory bowel disease. A recent systematic review identified 472 cases with exposure to anti-TNF drugs during pregnancy[46]. The rates of miscarriage, stillbirth, and congenital abnormalities were similar to previously reported rates in the general population; however, the rates of preterm/premature births (19.9% in anti-TNF-exposed *vs* 12.3% in the general population) and low birth weight/small for gestational age (6.1% in anti-TNF-exposed *vs* 8.2% in the general population) were not as expected for the general United States population. However, the authors indicated that sufficient evidence, particularly from controlled trials, was not available to guarantee absolute safety with the use of these drugs during pregnancy.

Clinical data from registries of rheumatic patients are consistent with some but not all of these results (Table 2). As a result, the Organization of Teratology Information Specialists autoimmune disease in pregnancy project did not find a specific pattern of defects in infants prenatally exposed to etanercept[17] or ADA[47]. Spontaneous abortions were higher in women exposed to ADA when compared to the controls who were never exposed, but had the disease, and non-diseased controls; however, the proportion was within the expected range of 10%–15% in clinically recognized pregnancies in the general population. The other pregnancy outcomes were similar to the comparison group and within the expected range for the general population.

The British Society for Rheumatology Biologics Register published a review of 130 pregnancies in patients who received anti-TNF before or during pregnancy[11]. The spontaneous abortion rate was highest among patients exposed to anti-TNF at the time of conception. Comparatively, the rate of spontaneous abortions was 17% in those with prior exposure to anti-TNF and 10% in the control group. Although 20 of these patients became pregnant while receiving methotrexate or leflunomide, the authors did not believe that this was not related to the outcomes. The authors suggested that data are available to suggest that women with severe RA may have unfavorable pregnancy outcomes and those patients unable to discontinue anti-TNF therapies may be those with the most severe disease[48,49].

The Spanish registry BIOBADASER identified 13 women (14 pregnancies) among a total of 3550 women treated with anti-TNF (4 with infliximab, 8 with etanercept, and 2 with adalimumab)[50]. Although the number of observations was small, all pregnancy outcomes were within the expected range.

The German biologics register (RABBIT) identified, among 5244 patients, 37 pregnancies in 29 women treated with anti-TNF (*n* = 27) and anakinra (*n* = 2)[10]. Two patients were exposed to biologics and methotrexate or leflunomide until confirmation of pregnancy, and 3 restarted treatment after week 20 and continued until delivery. The remaining patients discontinued the biologic treatment prior to conception. The authors did not find an increased risk for congenital malformations, miscarriages, or low birth weight.

**Potential risks to newborns:** During fetal development, the neonatal period, and childhood, the immune system is constantly maturing. The ability to produce cytokines in response to infectious stimulus remains low for years, but is similar to that of an adult around the age of 3 years owing to the adaptive nature of the newborn’s immune system as a result of exposure to microbes. Therefore, the exposure to TNF inhibitors may have serious consequences on a newborn. An unfortunate example of this was presented by Cheent *et al[*51]. They described a fatal case of disseminated Bacillus de Calmette y Guérin infection in an infant born to a mother taking infliximab for Crohn’s disease. Although the baby born and initially progressed well, he died at 4.5 mo, after he was vaccinated with Bacillus de Calmette y Guérin.

The majority of monoclonal antibodies actively cross the placenta, resulting in higher concentrations of these drugs in neonates than that in their mothers. Because of possible immunosuppression, live vaccines are contraindicated in newborns of mothers who have been treated with biologic therapy (Table 1).

Because the immune system is not yet completely developed in the newborn, the majority of antibodies are actively transferred from the mother to the offspring to confer short-term passive immunity. As mentioned earlier, the specific transport of IgG is conducted by the RnFc[3]. IgG transfer from mother to fetus begins as early as 13 wk of gestation, and transport happens in a linear fashion as the pregnancy progresses. The fetus acquires the majority of IgG during the last 4 wk of pregnancy, and the concentrations usually exceed those of the mother by 20%–30% at full term[52]. Therefore, the primary risk occurs after week 30.

Most monoclonal antibodies are of the IgG1 class and use the RnFc to actively cross the placenta. Because of this, newborns have a higher concentration than the mothers, and vaccinations containing live attenuated microorganisms are contraindicated. However, certolizumab pegol has the lowest capacity to cross the placenta owing to the absence of the Fc fraction. Mohadevan *et al*[53] studied 31 pregnant women with intestinal bowel disease receiving IFX, ADA, or CZP. Although IFX and ADA were detected in infants up to 6 mo after birth (up to 160% that of the mother), CZP had the lowest level of placental transfer (3.9%-22% that of the mother) of the drugs tested, based on the levels measured in the cord and infants at birth. Nevertheless, CZP was present to an extent; therefore, some passive placental transport may occur. It is possible that the small size and polyethylene glycol polymer chains attached to the Fab fragment may result in different qualities to cross the placenta.

On the other hand, ETN is also different to IFX and ADA because it has low affinity to the neonatal IgG transporter; this could also account for the limited placental transfer of this fusion protein[54]. The concentration of ETN in cord blood can be 4%–7% of the concentration present in maternal blood[55].

Although only limited short-term experiences are available with regards to complications in an exposed fetus, there no known data available regarding long-term effects on the child’s developing immune system. Therefore, we must be aware in the years beyond the available data.

***Others biological agents targeting cytokines***

Published information about the pregnancy experience with anakinra (ANK) and tocilizumab (TCZ) is limited to case reports, but the preventive principles should be the same as that with TNF inhibitors. Table 3 summarizes the studies of other biological agents, including non-TNF inhibitors, during the conception period and pregnancy.

**Anakinra:** ANK is an IL (interleukin)-1 receptor antagonist, but it is currently possible to block IL-1 with monoclonal antibodies that are directly targeted at IL-1, such as canakinumab or rinolacept. ANK has been used throughout pregnancy in 3 pregnant patients with adult-onset Still’s disease, and the children were born at term with no complications[56,57]. However, measurements of ANK in the maternal or cord serum were not performed.

**Tocilizumab:** TCZ is a humanized anti-human IL-6 receptor monoclonal antibody that inhibits IL-6. Experience with TCZ is limited to case series from the clinical trials reporter at the ACR Annual Meeting in 2010[58]. Thirty-three pregnancies were reported in 32 patients, despite a requirement for contraceptive use, among 4009 patients enrolled in several clinical trials. The small number of cases and high rate of therapeutic abortions, as well as concomitant medication use, limit the conclusions that can be drawn regarding the safety of TCZ during pregnancy. The authors reported that a pregnancy registry was being established to assess pregnancy outcomes in women exposed to TCZ during pregnancy.

**BIOLOGICAL AGENTS TARGETING CELLS**

Currently, there are 2 different licensed biological agents targeting B cells in rheumatology (rituximab and belimumab) and 1 targeting T cells (abatacept). All of these drugs can cross the placenta; therefore, women should be advised to discontinue these drugs prior to a planned pregnancy (Table 1).

***Rituximab***

Rituximab (RTX) is a chimeric monoclonal antibody against the antigen CD20 on the surface of B-cells. Because its B-cell depletion capacity has been shown useful for the treatment of lymphomas, leukemias, transplant rejections, and autoimmune disorders. In rheumatology, it is licensed to treat RA and ANCA-positive vasculitis and is also widely used off-label for systemic lupus erythematosus (SLE).

Like other monoclonal antibodies, RTX contains IgG1, which can cross the placenta using RnFc. RTX is classified as a pregnancy category C drug by the FDA (*i.e.,* animal reproduction studies have shown some risk to the fetus, but there adequate and well-controlled studies in pregnant women are lacking).

The majority of experiences with RTX in pregnant women are documented from the BiogenIdec/Genentech/Roche rituximab global drug safety database[59]. This registry collects information about RTX from patients with diverse diseases, including mothers with lymphoma, autoimmune cytopenias, and other autoimmune diseases (Table 3). The majority of the mothers had RA (*n* = 29), non-Hodgkin lymphoma (*n* = 24), SLE (*n* = 11), or idiopathic thrombocytopenia (*n* = 11). This database identified 231 pregnancies (153 with known outcomes) associated with maternal RTX exposure (Table 3). Most cases were confounded by concomitant use of potentially teratogenic drugs and severe underlying diseases. Ninety resulted in live births, of which 22 were born prematurely. One neonatal death occurred at 6 wk. Eleven neonates had hematologic abnormalities: *n* = 1, low white blood cell count; *n* = 4, depleted B-cells; *n* = 3, thrombocytopenia; *n* = 2 neutropenia; and *n* = 1, lymphopenia. However, none of these neonates had infections. Four additional neonates had neonatal infections: fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis. Two congenital malformations were identified: clubfoot in one twin and cardiac malformation in a singleton birth. One maternal death from pre-existing autoimmune thrombocytopenia occurred. In all but 2 cases, RTX was administered during the second or third trimester of pregnancy.

***Belimumab***

Although belimumab and tofacitinib were also included in our search strategy, no report was found in humans. However, data from 83 unintended pregnancies with known outcomes in phase II and III studies indicated elective termination in 24%, spontaneous abortion in 27%, and live births in 42%[60]. No increase in birth defects was observed.

***Abatacept***

ABT is a fusion recombinant molecule containing cytotoxic T lymphocyte-associated antigen 4 and the Fc fragment of IgG1 (CTLA4Ig) that blocks the CD80/CD86:CD28 co-stimulatory signal for T-cell activation.

The experience of ABT in humans is limited to one case report[22]. The patient was a 33-year-old woman with RA treated with ABT plus MTX until gestation week 2.5. Delivery occurred at 40 wk of gestation. The newborn washealthy and was well after a 3.5-year follow-up.

**CONCLUSIONS**

Almost all of the experiences with the safety of biologic drugs during pregnancy in women with rheumatic diseases are documented in case series, case reports, or registries. TNF inhibitors are now better known. Some evidence suggests that differences in safety between drugs are associated with structure and the capacity to cross the placenta, but we are not aware of any study that supports this statement.

Although the clinical data to date are promising, no firm conclusions can be drawn regarding the safety of biologic drugs during pregnancy, and, without further evidence, guidelines that suggest these drugs should be avoided at the time of conception cannot yet be changed.

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**P- Reviewer:** Chui YL **S- Editor:** Gong XM

**L- Editor:** **E- Editor:**

**Table 1 Current European Medicines Agency recommendations about licensed biologic therapies and pregnancy (from http://www.ema.europa.eu/ema/)**

|  |  |  |
| --- | --- | --- |
| **Biologic drug** | **Recommendations for women of childbearing potential** | **Recommendations for the infant exposed in utero** |
| Infliximab1 | Adequate contraception for at least 6 mo after the last infusion | Neither live vaccines administration nor breast-feeding is recommended while treated and for 6 mo following the mother’s last infliximab infusion during pregnancy |
| Etanercept | To use appropriate contraception during therapy and for 3 wk after discontinuation of therapy | Neither live vaccines administration nor breast-feeding is recommended while treated and for 16 wk after the mother’s last dose of Enbrel is generally not recommended |
| Adalimumab2 | Adequate contraception for at least 5 mo after the last injection | Neither live vaccines administration nor breast-feeding is recommended while treated and for 5 mo following the mother’s last injection during pregnancy |
| Golimumab | Adequate contraception for at least 6 mo after the last injection | Neither live vaccines administration nor breast-feeding is recommended while treated and for 6 mo following the mother’s last injection during pregnancy |
| Certolizumab | Adequate contraception for at least 5 mo after the last injection | Neither live vaccines administration nor breast-feeding is recommended while treated and for 5 mo following the mother’s last injection during pregnancy |
| Anakinra | Not recommended during pregnancy and in women of childbearing potential not using contraception | No data |
| Tocilizumab | Adequate contraception for at least 3 mo after the last infusion | A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman  Advice about live vaccine use in newborns is not given |
| Rituximab | Adequate contraception for at least 12 mo after the last infusion | No breast-feeding is recommended while treated and for 12 mo following the mother’s last infusion during pregnancy  Advice about live vaccine use in newborns is not given |
| Abatacept | Adequate contraception for at least 14 wk after the last dose | No breast-feeding is recommended while treated and for 14 wk following the mother’s last infusion during pregnancy  Advice about live vaccine use in newborns is not given |

1Remicade®, Inflectra® and Remsima®; 2Humira® and Trudexa®.

**Table 2 Tumor necrosis factor inhibitors use during pregnancy and the conception period**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref./registry** | **No. of pregnancies** | **Disease** | **Biologic drugs** | **Pregnancy stage** | **Pregnancy outcome** |
| Lichtenstein *et al*[61]  TREAT registry | 36 | CD | IFX | Any exposure | 11.1% miscarriage (NS), 8.3% neonatal complications (NS) |
| Katz *et al*[62]  Infliximab safety database | 96 | CD, UC, RA | IFX | 7 prior to conception, 53 conception, 30 T1, 6 unknown | 67% live births, 15% miscarriages, and 19% elective termination. Results similar to those expected for the general United States population or pregnant women with CD not exposed to infliximab |
| Garcia *et al*[50]  BIOBADASER | 14 | RA, AS, PsA | IFX, ETN, ADA | First trimester | 7 live births, 1 miscarriage, 3 therapeutic termination, 3 therapeutic termination, 2 on-going pregnancies, 0 malformations |
| Strangfeld *et al*[10]  RABBIT | 37 |  | IFX, ETN, ADA, ANK | 22 first-trimester (2 restarted biologic after week 20)  15 prior to conception | Similar miscarriage (4.5% *vs* 6.6%); 0 marformations |
| Johnson *et al*[17]  OTIS | 175 | RA, PsA, AS, CPs | ETN | 139 first trimester  67 disease matched | Similar live births (93.5% *vs* 88.1%); more miscarriage (14% *vs* 5% *vs* 1.1%); malformations (9.4% *vs* 4.5%) |
| Verstappen *et al*[11]  BSRBR | 140 | RA, PsA, JIA, AS, SLE, AOSD | IFX, ETN, ADA | 59 prior conception  71 at conception  10 controls never exposed | In post-conception exposures *vs* never exposed: less live births (59% *vs* 100%; *P* = 0.012), more miscarriages (27% *vs* 10%; *P* = 0.437), elective terminations (11% *vs* 10%; *P* = 0.587) |
| Chambers *et al*[14]  OTIS | 239 | RA, CD | ADA | 94 first trimester  58 disease-matched controls  87 non-disease controls | Similar live births (85% *vs* 91.4% *vs* 89.7%), miscarriages (4.3% *vs* 9%); similar preterm deliveries (15% *vs* 17% *vs* 4%); malformations (9.6% *vs* 5.4% *vs* 5%) |

Experience from national registries. CD: Crohn’s disease; UC: Ulcerative colitis; RA: Rheumatoid arthritis; PsA: Psoriatic arthritis; JIA: Juvenile idiopathic arthritis; AS: Ankylosing spondylitis; SLE: Systemic lupus erythematosus; AOSD: Adult onset Still disease; CPs: Cutaneous psoriasis; BSRBR: British Society for Rheumatology Biologics Register; NS: Non-significant; T1: First-trimester.

**Table 3 Others biological agents use during pregnancy and the conception period**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref./study** | **No. of pregnancies** | **Disease** | **Biologic drugs** | **Pregnancy stage** | **Pregnancy outcome** |
| Berger *et al*[56]  Fischer-Betz *et al*[57]  Case report | 3 | AOSD | ANK | Through pregnancy | 3 healthy live birth, full-term deliveries |
| Rubbert-Roth *et al*[58]  Case series from clinical trials | 33 | RA | TCZ | Non-data | 26/32 treated wit TCZ + MTX, 6/32 TCZ monotherapy or concomitant with DMARD other than MTX  10/33 healthy live birth at term; 1/33 (1 infant died of ARDS 3 d after emergency cesarean section for intrapartum fetomaternal hemorrhage due to placenta previa; 13/33 elective terminations, 7/33 miscarriages |
| Chakravarty *et al*[59]  Biogen Idec/Genentech/Roche rituximab global drug safety database | 153 | NHL, RA, SLE, Others1 | RTX | 132 prior to the conception  21 after the concption | 90 live births: 68 full-term deliveries; 22 preterm; 1 neonatal death at 6 wk; 2 malformations (clubfoot in one twin, and cardiac malformation in a singleton birth)  11 newborns had hematologic abnormalities (none with infections); 4 neonatal infections (fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis) |
| Ojeda-Uribe *et al*[22] | 1 | RA | ABT | First trimester | No complications. One healthy live birth |

1Idiopathic purpura thrombocytopenic, autoimmune haemolytic anaemia, multiple sclerosis, thrombotic thrombocytopenia.

Purpura, Castleman disease, mixed connective tissue disease, and renal transplantation. AOSD: Adult onset Still disease; RA: Rheumatoid arthritis; NHL: No Hodgkin lymphoma; SLE: Systemic lupus erythematosus; ANK: Anakinra; TCZ: Tocilizumab; RTX: Rituximab; ABT: Abatacept; ARDS: Acute respiratory distress syndrome.