

THE NEW BIOLOGICS IN PREGNANCY

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ABSTRACT

Growing numbers of women of reproductive age are prescribed new biological agents. This is resulting in more pregnancies exposed to these drugs. What are the new biologics (also referred to as biologicals) and what are their indications? How are they currently used in pregnant women? What are the concerns when treating pregnant women with biologics? What do we know about the reproductive safety of these agents? Current and future research is discussed.

Key Words: *Pregnancy, biologics, chronic diseases, abatacept, anakinra, tolicizumab, rituximab, tumour necrosis factor-alpha inhibitors, registries*

INTRODUCTION

The new biologics have come a long way to help us treat autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, Crohn's Disease, ulcerative colitis, and also malignancy. Examples include abatacept (T-cell costimulation inhibitor), tocilizumab (interleukin 6 inhibitor), anakinra (interleukin 1 inhibitor), rituximab (B-cell depletor), and a number of tumour necrosis factor-alpha inhibitors: adalimumab, certolizumab, golimumab, infliximab, and etanercept.

Many of the conditions mentioned above are prevalent among women of reproductive age. In the past, these women have been too sick to consider pregnancy. Now, with the new treatments, they feel healthy, lead fuller lives, and want to be able to entertain the possibility of pregnancy. As with every drug given to a woman who wants to become pregnant, effects on fertility and on the fetus, such as the possibility of miscarriage, intrauterine growth retardation, congenital malformations, effect on immunological development and on long-term development, should be considered.

In order for any drug to have an effect on the fetus, it has to cross the placenta. Do the new biologics cross the placenta?

Newborn immunity is acquired through transfer of antibodies from mother to fetus via the placenta. Maternal immunoglobulins (IgGs) are actively transported across the placenta by binding to the neonatal Fc receptor (FcRn).¹ Kane and Acquah reported that IgG was found in fetal serum as early as 13 weeks' gestation, with a continuous rise in the transfer of IgG to the fetus as the pregnancy advances. Furthermore, IgG1 levels are higher than IgG4, which is higher than IgG3, and IgG2 has the lowest detectable levels.¹ At the time of birth, the IgG levels in cord blood for full term neonates are much higher than in the maternal circulation.

Now that we know biologic drugs can transfer to the fetus, why not just stop the treatment?

Because of the nature of these drugs and the diseases they treat, discontinuing therapy can be problematic. Often the treatment of a relapse is more aggressive than maintenance management. And both the relapse and its treatment might have an adverse effect on the pregnancy and on the fetus. Furthermore, some women will develop allergic reactions to the molecule when

reintroduced following discontinuation of treatment.²

How much really transfers to the fetus?

Mahadevan and colleagues studied 31 pregnant women with inflammatory bowel disease who were on one of infliximab, adalimumab, or certolizumab.³ Their findings are summarized in

Table 1. Certolizumab had much lower levels in cord blood than the other two tumour necrosis factor antagonists. This is to be expected, as certolizumab does not contain the Fc portion needed to bind to the receptor, therefore its transfer across the placenta is not active transport via the neonatal Fc receptor (FcRn).

TABLE 1 Disposition of Infliximab, Adalimumab, and Certolizumab in Mother and Neonate³

Drug	Infliximab	Adalimumab	Certolizumab
Number of women	11	10	10
Number of infants	11	10	12
Median ratio of cord to maternal blood level at parturition	160%	153	3.9 (Note: 3 infants had levels below the limit for quantification)
Median time of last drug dose (Range)	35 days (2-91)	5.5 days (7-56)	19 days (5-42)
Median length of gestation (Range)	40 weeks (38-41)	39 weeks (38-41)	37.8 weeks (36-40)

How long are these agents measurable in children’s serum?

Elimination half-lives, in adults, of specific tumour necrosis factor-alpha inhibitors are listed below:

- Adalimumab - 10 to 20 days
- infliximab - 7.7 to 10 days in rheumatoid and psoriatic arthritides, Crohn’s Disease -12.3 to 14.7 days in ulcerative colitis
- Certolizumab - 14 days
- Golimumab - 14 days
- etanercept - 102 ± 30 hours.

These numbers for adults only provide part of the picture. In actuality, the drugs are measurable for many weeks in the neonate. Infliximab is detectable for 3-6 months in infants²⁻⁶ and

adalimumab was shown to remain detectable in infants for at least 11 weeks postpartum.³

There is a case report that describes a healthy baby born to a mother treated throughout her pregnancy with infliximab for Crohn’s disease.⁷ At age 3 month the infant received a BCG vaccine. The infant died at 4.5 months as a result of disseminated BCG. This case report raised a question regarding the safety of childhood vaccination with live vaccine for infants exposed to biologic medications in utero. The World Congress of Gastroenterology addresses this question in their position statement: “Vaccination of infants exposed to biological therapy in utero should be given at standard schedules, *except for live-virus vaccines*, which are best not given if circulating biologic agents are detectable in the infant.”⁸

The New Biologics

A review of a number of biologic drugs that have been used during pregnancy is presented below.

Abatacept (Orencia®)

Abatacept is a selective costimulation modulator that selectively modulates a key costimulatory signal required for full activation of T-lymphocytes expressing CD28. It is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 linked to the modified Fc portion of human immunoglobulin G1. It is indicated for the treatment of adult and juvenile rheumatoid arthritis, and juvenile idiopathic arthritis.

There have been 7 reported cases of fetal exposure to abatacept.⁹ Four were during the double-blind period of the drug's rheumatoid arthritis trials, where methotrexate was added to abatacept. Of these, three women suffered spontaneous abortions and one had an elective termination. Two more cases occurred during the AGREE trial, also involving cotreatment with methotrexate; both were electively terminated.⁹ The seventh reported case was of a 33-year-old woman with rheumatoid arthritis who was treated with abatacept (10 mg/kg every 4 weeks) and methotrexate (15 mg per week).¹⁰ Both drugs were stopped when the pregnancy was established. The last dose of abatacept was taken at 2.5 weeks' gestation. At 40 weeks, a healthy infant was delivered and follow-up at 3.5 years showed that the child was doing well.

Tocilizumab (Actemra®)

Tocilizumab is a humanized anti-human interleukin 6 receptor monoclonal immunoglobulin G1 (IgG1), with an H2L2 polypeptide structure. It is used to treat rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis.

Early clinical trials with tocilizumab reported 33 pregnancies.¹¹ Twenty-six of these cases involved combination treatment with methotrexate. The outcomes are known for 31 of the pregnancies: 13 therapeutic terminations, 7 spontaneous miscarriages, 10 healthy term

newborns, and 1 neonatal death due to acute respiratory distress syndrome.

Anakinra (Kineret®)

Anakinra is a recombinant, non-glycosylated version of the human interleukin 1 receptor antagonist. It is indicated for treatment of rheumatoid arthritis.

There are three case reports of anakinra exposure in pregnancy (2 included treatment during the first trimester).^{12,13} All delivered healthy babies, with no complications reported during available follow-up. There are as yet no studies on whether anakinra crosses the placenta.

Rituximab (Rituxan®)

Rituximab is a genetically engineered chimeric murine/human IgG1 monoclonal antibody that binds CD20 antigen on B-lymphocytes. Indications include B-cell non-Hodgkin's lymphoma, B-cell chronic lymphocytic leukemia, rheumatoid arthritis, and Wegener's Granulomatosis.

By November 2009, the rituximab global drug safety database had reports of 231 women becoming pregnant while on rituximab.¹⁴ The outcomes are known for 153 of the pregnancies. There were 90 live births, 33 spontaneous abortions, 28 elective terminations, 1 stillbirth at 20 weeks due to umbilical cord knot, and 1 maternal death due to cerebral haemorrhage (patient had idiopathic thrombocytopenic purpura). Of the live births, there were 16 premature deliveries, 3 congenital abnormalities (club foot in a twin, VSD/PFO/PDA, Turner syndrome diagnosed prior to rituximab administration), and 11 infants had haematological abnormalities at birth. Three infants who had undetectable B-cell counts had rituximab levels tested and found to be detectable in cord or infant blood.

Tumour Necrosis Factor-Alpha (TNF α) Inhibitors

Adalimumab (Humira®)

Adalimumab is a recombinant human IgG1 monoclonal antibody that binds to soluble TNF α with high affinity and specificity, thus interfering

with its interaction with cell surface receptors. Indications are rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and psoriasis. The drug has also been used off-label for treatment of infertility.

An analysis from the OTIS (Organisation of Teratology Information Specialists) database in 2011 included 161 exposed pregnancies, 79 women as the disease comparison group, and 134 women as the healthy comparison group.¹⁵ There was no evidence of an association between adalimumab exposure and major birth defects, or a specific pattern of malformation.

Delivery outcomes were studied in subfertile women who had been treated with adalimumab within an *in vitro* fertilization (IVF) cycle and compared to women undergoing IVF without immunologic therapy.¹⁶ No increase in birth defect rates was observed in 41 infants of subfertile women, compared to 95 infants of 69 mothers with no exposure to the drug.

Based on the limited data currently available, adalimumab does not appear to increase the risk of major congenital malformations above the baseline risk in the general population. The World Congress of Gastroenterology on Biological Therapy (WCOG) in its position statement suggests that adalimumab be considered as low risk and compatible with use during conception and pregnancy in at least the 1st and 2nd trimesters.⁸ Benefits of treatment for the mother should be weighed against the unknown risks to the fetus when considering adalimumab use during pregnancy.

Infliximab (Remicade®)

Infliximab is a chimeric IgG1 κ monoclonal antibody to human TNF α . It binds specifically to soluble and transmembrane forms of human TNF α . Indications are rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

Based on currently available data on over 200 exposed pregnancies, infliximab does not appear to increase the risk of major congenital malformations above the baseline risk in the general population. Exposed infants are reported to have a normal response to non-live vaccines.^{4,17} The WCOG position statement notes that

infliximab is considered to be low risk and compatible with use during conception and pregnancy in at least the 1st and 2nd trimesters.⁸ Benefits of treatment for the mother should be weighed against the unknown risks to the fetus when considering the use of this drug during pregnancy.

Certolizumab Pegol (Cimzia®)

Certolizumab "is a recombinant, humanized antibody Fab' fragment, with specificity for human TNF- α ".¹⁸ It selectively neutralizes membrane-associated and soluble human TNF α . Indications are rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease. As mentioned above, placental transfer has been shown to be minimal with this drug.³

Reports on known outcomes of 253 exposed pregnancies from the UCB Pharma global safety database did not raise concerns of adverse pregnancy outcomes.¹⁹ 191/253 (75.5%) pregnancies resulted in live births, 37/253 (14.6%) had spontaneous miscarriages, and 25/253 (9.9%) elected to terminate their pregnancy. In the live birth group, 3 infants had congenital malformations: 1 vesicoureteric reflux, 1 congenital morbus hirschsprung and club feet, and 1 high aortic arch with aberrant left subclavian vein. There was no apparent impact on pregnancy outcomes, but the authors caution that additional data from large numbers of pregnant women are needed.

The limited information available to date on exposure to certolizumab, combined with its low placental transfer, suggest no increased risk for major congenital malformations above the baseline risk in the general population. The WCOG position statement notes that certolizumab is considered to be low risk and compatible with use during conception and pregnancy, in at least the 1st and 2nd trimesters.⁸ Benefits of treatment for the mother should be weighed against the unknown risks to the fetus when considering certolizumab use during pregnancy.

Golimumab (Simponi®)

Golimumab is a human IgG1 monoclonal antibody that forms high affinity, stable complexes with both the soluble and

transmembrane bioactive forms of human TNF. Indications are rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

There are currently no human data in pregnancy. However, animal data from cynomolgus monkeys shows that the drug crosses the placenta, but no developmental effects were caused by gestational exposure.²⁰

Etanercept (Enbrel®)

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1. It binds specifically to soluble and cell surface tumour TNF, blocking its interaction with cell surface TNF receptors. Indications are rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.

In 2008, OTIS reported on 138 pregnancies exposed to etanercept in the first trimester for treatment of rheumatoid arthritis.²¹ There were 6 spontaneous miscarriages and 2 terminations (unspecified heart defect and Turner syndrome), 130 live births (11 had birth defects with no specific pattern of malformation).

There are reports on over 85 additional first trimester exposures to etanercept which did not raise concerns for adverse pregnancy outcomes.

Based on the limited available data, etanercept does not appear to increase the risk for major congenital malformations above the baseline risk in general population. Benefits of treatment for the mother should be weighed against the unknown risks to the fetus when considering etanercept use during pregnancy.

REGISTRIES

There are also several registries looking at the safety of biological treatments during pregnancy.

PIANO Registry²²

The PIANO registry is a 1000 patient prospective registry that was established to examine pregnancy outcomes of women with Crohn's and Ulcerative Colitis treated with immunomodulators (azathioprine, 6-mercaptopurine) or biologic therapy (anti-TNF) during pregnancy.²³ Women

from 30 US treatment centres for inflammatory bowel disease were prospectively enrolled to be contacted at regular intervals during their pregnancy and postpartum. There are four groups in the registry: unexposed women, women on thiopurines, women on anti-TNF drugs, and women on combination therapy (thiopurines plus anti-TNF). Over 1000 patients with inflammatory bowel disease have been registered and, as of 2012, outcomes are available for 797 completed pregnancies (102 exposed to infliximab, adalimumab, and certolizumab alone; 59 exposed to combination with azathioprine or 6-mercaptopurine; 265 exposed to azathioprine or 6-mercaptopurine alone; and 337 unexposed). Anti-TNF agents were not associated with spontaneous abortion, congenital anomalies, preterm birth, intrauterine growth retardation, C-section, or NICU stays. It was noted, however, that infants of mothers who had been on combination therapy had an increased risk of infections at age 12 months compared to non-exposed children (RR = 1.50; 95% CI 1.08-2.09).

OTIS Autoimmune Diseases in Pregnancy Studies²⁴

The Organization of Teratology Information Specialists, is a nonprofit organisation dedicated to providing evidence-based information to mothers, health care professionals, and the general public about medications and other exposures during pregnancy and while breastfeeding. OTIS is researching the effects of immune modulators and autoimmune diseases on pregnancy. The diseases that are being looked at include Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, and multiple sclerosis. Drug exposures include the following drugs: abatacept (Orencia®), certolizumab (Cimzia®), tocilizumab (Actemra®), tofacitinib (Xeljanz®), ustekinumab (Stelara®), adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®), leflunomide, methotrexate, and teriflunomide (Aubagio®).

SUMMARY

As mentioned above, the position of the WCOG is that anti-TNF drugs are considered to be low risk and compatible with use during conception and

pregnancy in at least the 1st and 2nd trimesters.⁸ On the other hand, a consensus statement on biological agents for the treatment of rheumatic diseases, prepared at 13th Annual Workshop on Advances in Targeted Therapies in March 2012, notes “Since a lack of association is extremely difficult to prove, no biological agents can be assumed to be safe.”²⁵

In general, although case reports and registry findings show a generally good profile in pregnancy, the safety of anti-TNF treatment during pregnancy is still unknown. Experts disagree about whether TNF α inhibitors should be stopped when pregnancy is being considered or whether they can be continued throughout pregnancy. Studies and analyses currently underway may shed some light on the safety profile of these agents in pregnancy and their effect on the fetus and infant. Based on currently available data, however, these agents do not appear to increase the risk of major congenital malformations above the baseline risk in the general population and of adverse pregnancy outcomes compared to women with same baseline disorders. Benefits of treatment for the mother, and the importance of good control of her disease, should be weighed carefully against the unknown risks to the fetus when considering use of the new biologics during pregnancy.

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