Current recommendations in the use of biologics for the treatment of rheumatic diseases in pregnant patients

“...TNF inhibitors are the best studied and appear as low-risk drugs in pregnant patients.”

Biological drugs have revolutionized the treatment of autoimmune rheumatic diseases and are used for an ever increasing proportion of patients. TNF inhibitors were the first to be introduced for the treatment of rheumatoid arthritis (RA), and have subsequently also shown efficacy in other autoimmune diseases. When treatment improves functional capacity and quality of life, patients of both genders wish to live normal lives including procreation. An increasing number of monoclonal antibodies wait for approval by governmental authorities. Many of these drugs will finally be used by female and male patients of fertile age who need to know whether these agents have adverse effects on fertility and reproduction. Since ethical considerations prevent studies of biological agents in pregnant women, knowledge on their effect on the developing fetus, and the newborn are gained only from inadvertent drug exposure. Manufacturers usually discourage use of biological agents in pregnant women because of lack of human data and out of fear of litigation.

Some features of molecule structure are shared by several biologic agents and are presented in the following. Most biological agents are monoclonal antibodies of the IgG1 class targeting cell structures or secreted products that are directly involved in the disease process. Antibodies containing a Fab fragment and the Fc part of IgG (= complete antibody) are actively transferred through the placenta by Fc receptors on the trophoblast. In all animal species used for testing developmental toxicity, fetal exposure to IgG is very low during organogenesis, but placental transfer starts at the beginning of the second trimester and increases until term when maternal and fetal serum levels are equal or higher in cord serum [1,2]. One study could show that discontinuing a complete monoclonal antibody before week 30 of gestation prevented transfer of detectable amounts to the newborn child [3].

By contrast, maternal treatment with a complete monoclonal antibody after gestational week 30 results in high blood levels in the newborns [4,5] and, depending on the nature of the biological agent, can suppress immune function of the infant. This could increase the risk of infection in general and even with live vaccines [6].

Biological agents targeting cytokines

TNF inhibitors

Among the TNF inhibitors presently available, infliximab, adalimumab and golimumab are complete monoclonal antibodies showing increasing transplacental passage throughout pregnancy. Etanercept is a fusion protein directed against the TNF receptor and certolizumab is a pegylated Fab fragment against TNF. Transplacental passage of etanercept is much less than for the complete antibodies [7] and is minimal for certolizumab which lacks the Fc part of immunoglobulin [8].

The human experience with TNF inhibitors from case reports, small series, some controlled studies and drug registries can be summarized as follows: an increased rate of miscarriage in women treated around conception was reported by one registry-based study [9], but has not been confirmed by other registry based or case-control studies. This finding is difficult to reconcile with the reports of successful anti-TNF treatment of infertile women and women with recurrent miscarriage [10,11]. Preliminary data from the Organization of Teratology and Information (OTIS) project, showed no significant increased risk of malformations nor any consistent pattern of congenital abnormalities in exposed compared with non-exposed pregnancies [12–15]. One retrospective and uncontrolled study claimed that the use of infliximab or etanercept in early pregnancy increased the rate of the congenital VACTER association (V: vertebrae malformation; A: anal anomalies; C: cardiac anomalies; ...
T: tracheal problems, E: esophageal problems, R: renal anomalies) inhibitors [16]. However, no controlled or registry-based study has confirmed this observation [9,12,13].

“Most biological agents are monoclonal antibodies of the IgG1 class...”

- Male fertility & therapy with TNF inhibitors
  TNF inhibitors can have an impact on spermatogenesis. Oligoasthenozoospermia has been reported in case reports, but was not increased in 26 patients with spondylarthritics in comparison to healthy controls [17]. Patients on anti-TNF therapy showed significantly better sperm motility and vitality than untreated patients.

- IL-1 receptor antagonist
  Anakinra, a IL-1 receptor antagonist has a half-life of 4–6 h and does not accumulate. Animal studies showed no fetotoxicity even at doses 100-times the therapeutic dose and in spite of detection of anakinra in amniotic fluid. A healthy child was delivered by a patient treated with anakinra throughout pregnancy and lactation [18]. No other reports exist.

- Inhibitor of IL-6 (tocilizumab)
  Embryo-fetal developmental toxicity of tocilizumab, a monoclonal antibody that inhibits IL-6 receptor signaling pathways has been studied in animals without evidence for a teratogenic/dysmorphic effect at any dose. Except for an abstract on the outcome of 33 RA pregnancies no published reports exist [19]. Ten healthy newborns were delivered from RA pregnancies with known outcome that went to term.

- Abatacept
  Abatacept, a CTLA4 and human immunoglobulin fusion protein is a selective co-stimulation modulator inhibiting the activation of T cells. Abatacept crosses the placenta [22]. No human pregnancy experience has been published.

Future research
Transplacental passage of biological agents differs related to their molecular structure. It is most extensive for complete monoclonal antibodies and less for fusion proteins or drugs that do not contain the Fc part of immunoglobulin. Whether the latter drugs confer less risk for the fetus and infant must be proven at a larger scale and with measurements of drug levels and functional assays in neonates and infants. Other aspects at present unknown are effects of monoclonal antibodies against T cells or B cells on the maturation and function of the child’s immune system. An increased susceptibility to infection and an
impaired vaccine response are possible though not proven risks of antenatal exposure to antibodies against immunocompetent cells and cytokines in the second half of pregnancy. Extended follow-up studies of children exposed antenatally to biological agents in order to detect short- or long-term adverse effects of are needed.

“Abatacept, tocilizumab, anakinra, rituximab and belimumab must be discontinued before or at conception...”

Studies on reproductive function and offspring of men treated with biological agents are extremely rare and clearly need investigation.

**Recommendation**

There are no placebo-controlled studies and few prospective, controlled studies on biological agents in pregnancy. The latter comprise only TNF inhibitors. For the other biological agents presented, data on human pregnancy are insufficient and therefore not conclusive. Recommendations will therefore be based on pharmacological properties of the drugs and the view of experts. According to published experience, TNF inhibitors are the best studied and appear as low-risk drugs in pregnancy. The latter comprise only TNF inhibitors. For the other biological agents presented, data on human pregnancy are insufficient and therefore not conclusive. Recommendations will therefore be based on pharmacological properties of the drugs and the view of experts. According to published experience, TNF inhibitors are the best studied and appear as low-risk drugs in pregnancy.

Due to insufficient human experience abatacept, tocilizumab and anakinra must be discontinued before or at conception. Abatacept, tocilizumab, anakinra, rituximab and belimumab must be discontinued before or at conception because experience in human pregnancy is currently very limited. Because of its short half-life, prophylactic discontinuation of anakinra before a planned pregnancy is not necessary, but it should not be continued during pregnancy.

From published reports it appears that rituximab is not strong human teratogen. However, second and third trimester exposure causes B-cell depletion in the fetus with unknown long-term effects in the child. With a maximal elimination half-life of 36 days, discontinuation of rituximab 6 months (five-times the half-life) before conception may be adequate and not expose the baby to deleterious effects. Live vaccines should not be given to infants that have been exposed to TNF inhibitors or rituximab in the second half of pregnancy.

Decision for therapy during pregnancy and especially in the second half of pregnancy must be based on assessment of risks for mother and child and weighed against the benefit expected from disease control in the mother.

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