

Anti-TNF therapy and pregnancy outcomes in women with inflammatory arthritis

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Women suffering from inflammatory arthritis may experience a change in disease activity during and after pregnancy. Although the majority will improve, some women may need to continue therapy throughout pregnancy and/or in the lactation period. Since certain disease-modifying antirheumatic drugs have proven to be human teratogens, treatment is limited in these women. Anti-TNF agents fall within the US FDA category B concerning fetal risk, indicating that no adequate and well-controlled studies have been conducted in pregnant or lactating women. However, in the last decade, numerous case series and case reports of pregnancies exposed to anti-TNF therapy have accumulated in the literature. Since these agents may constitute an important therapeutic alternative in pregnant women facing persistent or increased disease activity, we propose a review of the available information on the safety of anti-TNF agents in pregnancy and lactation.

KEYWORDS: adalimumab • anti-TNF therapy • etanercept • inflammatory arthritis • infliximab • lactation • pregnancy • teratogenicity

Inflammatory arthropathies have variable disease activity during and after pregnancy. Although many women suffering from these conditions will improve during pregnancy, some may require continuation of disease-modifying antirheumatic drugs (DMARDs) throughout pregnancy and in the postpartum. In this critical period, therapeutic options are limited since certain DMARDs, such as methotrexate and leflunomide, have been shown to be teratogenic. Furthermore, anti-TNF agents are not recommended during pregnancy, in the absence of well-controlled studies of their safety. However, in recent years, mounting data on pregnancies exposed to anti-TNF therapy have been published by different investigators. Since pregnant patients facing persistent active disease or disease exacerbation may require treatment with these agents, it is crucial to review the available information on the safety of anti-TNF therapy.

What is known (& unknown)

Anti-TNF agents have demonstrated efficacy in reducing disease activity and joint damage and improving health-related quality of life in patients

with rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and ankylosing spondylitis (AS) [1]. Commonly used anti-TNF agents include infliximab, a chimeric monoclonal IgG1 anti-TNF antibody, adalimumab, a human monoclonal IgG1 anti-TNF antibody, and etanercept, a soluble TNF receptor fusion protein linked to the Fc portion of a human IgG1 [1]. These three agents fall within the US FDA category B concerning fetal risk, which indicates, in this case, that 'animal reproduction studies fail to demonstrate a risk to the fetus but adequate and well-controlled studies of pregnant women have not been conducted' [1]. Furthermore, drug manufacturers currently recommend that anti-TNF therapy be avoided during pregnancy and lactation. However, manufacturers' recommendations often represent legal considerations and may be hard to strictly follow in the clinical setting when facing difficult or refractory cases.

Moreover, a recent survey, questioning rheumatologists in the USA about the safety of anti-TNF agents in pregnancy, showed how clinical practice may depart from official recommendations and reflected the paucity of human

data available to date [2]. Fewer than half of the rheumatologists surveyed agreed that pregnancy is contraindicated with the use of these medications (38.6% for etanercept and 46.5% infliximab). Almost half stated that they were uncertain about pregnancy safety with the use of these agents (49.7% for etanercept and 45.4% for infliximab). Despite this uncertainty, respondents generally recommended effective methods of contraception when prescribing these agents to their female patients (75.4% for etanercept and 73.4% for infliximab). However, markedly fewer were likely to review ongoing contraception with women treated with etanercept or infliximab (41.7 and 43.8%, respectively).

In women of reproductive age suffering from inflammatory arthritis, adequate treatment of their condition may increase their chances of reproduction and pregnancy outcome [1]. Indeed, in the past few years, pregnancies in women with rheumatic diseases have increased and this may be due in part to treatment advances [3]. Although it is still controversial if anti-TNF agents have a positive impact on fertility, anti-TNF therapy may improve reproductive function by decreasing disease activity and increasing functional status in patients with inflammatory arthritis [4]. Furthermore, disease activity in inflammatory arthropathies shows different patterns with pregnancy, and some of these women may require more-aggressive therapy, such as anti-TNF agents.

Inflammatory arthritis in pregnancy

Several rheumatic diseases exhibit a fluctuation in disease activity during and after pregnancy. In the majority of women suffering from RA, the disease improves during pregnancy and flares up in the postpartum period [5,6]. Retrospective and prospective studies have shown that 66–75% of women with RA will improve during pregnancy [6–10]. Also, if remission occurs during one pregnancy, it is likely to occur again in future pregnancies [11]. Improvement in disease activity usually occurs during the first and second trimesters and is due to a shift toward a Th2-subtype immune profile, as occurs in normal pregnancy [12]. In late pregnancy, an increase in IL-1 receptor antagonist (IL-1Ra) and soluble TNF receptor (TNFR) serum levels correlates with low RA disease activity [12]. Elevated levels of IL-1Ra and TNFR in the third trimester may lead to improvement of the disease in patients with RA.

Contrary to RA, in which a Th1 immune response predominates during the nonpregnant state, in AS, a Th2 immune response prevails [12]. While RA improves in most pregnant women, AS demonstrates persistent activity that seems to decrease only in late pregnancy [12,13]. Disease activity in AS may either be unchanged, improved or worsened, each with equal frequency [14,15]. Improvement in disease activity during pregnancy is usually correlated with a history of peripheral arthritis [15]. A postpartum flare is experienced by 60–90% of females affected by AS, generally within 6 months after delivery, most often in women with active disease at conception [14,15].

Similar to patients with RA, patients with PsA improve or experience disease remission in 80% of pregnancies [15]. Approximately 70% of PsA pregnancies have a postpartum flare during the first 3 months after delivery [15]. In addition, in JIA, quiescent disease is usually not reactivated by pregnancy, and

approximately 60% of patients with active disease at conception ameliorate during pregnancy [15]. However, most patients flare in the postpartum period [15,16]. In these women who may face disease exacerbation during or after pregnancy, it is imperative to explore the safety of anti-TNF therapy exposure *in utero* or during lactation.

Role of TNF- α in pregnancy

TNF- α is a pleiotropic cytokine released by activated macrophages, monocytes and T lymphocytes [17], and plays an important role in pregnancy. As demonstrated in animal studies, TNF- α is involved in the control of cell proliferation, pregnancy loss and the development of peripheral lymphoid tissue [18,19]. In TNF- α -knockout mice, very poor formation of the secondary structures of lymphoid organs, such as germinal centers, has been observed [20]. Therefore, exposure to anti-TNF therapy during pregnancy and at the time of immune system development could potentially have adverse effects. Furthermore, TNF- α promotes blastocyst implantation, endometrial vascular permeability and uterine decidualization by inducing COX-2 gene expression in early pregnancy [21]. Although it promotes blastocyst implantation in early pregnancy, TNF- α may mediate recurrent spontaneous abortions at a later stage, and higher concentrations of serum TNF- α and serum soluble TNFR-1 have been observed in women with unexplained early spontaneous abortions [22]. TNF- α is also involved in labour onset by inducing uterine contractions, in conjunction with other inflammatory cytokines [23]. TNF- α levels are elevated in the serum and in the amniotic fluid at the time of labour onset and in adverse conditions such as fetal growth retardation, pre-eclampsia and pathological labor [12,24]. TNF- α levels are low in the first trimester, but increase in the second and third trimesters, peaking at the onset of labor [23].

However, the mechanism by which TNF- α may induce the demise of the implanted embryo remains unclear. It has been suggested that ischemic events within materno-fetal blood vessels trigger death of the embryo [25]. In murine models, TNF- α is thought to upregulate a fibrinogen-related prothrombinase, fgl2, which generates thrombin [25]. Thrombin production through this pathway leads to compromise of the placental circulation. The protein C anticoagulant system is the principal inhibitor of thrombin generation. This anticoagulant system includes protein C, protein S, activated protein C, thrombomodulin and endothelial cell protein C receptor (EPCR) [26–28]. Protein C and thrombin have opposite roles; protein C promotes trophoblast growth and controls excessive fibrin deposition whereas thrombin production inhibits trophoblast growth [29]. At sites of damaged endothelium, there is crosstalk between inflammatory and thrombogenic systems [30]. TNF- α is known to downregulate protein C, thrombomodulin and EPCR, altering the balance between procoagulant and anticoagulant molecules [31].

TNF- α may also promote embryonic death by triggering an apoptotic signal in reaction to embryonic structural defects caused by a detrimental stimulus [1]. A study showed that pregnant mice had markedly increased levels of natural killer (NK) cells producing TNF- α and TGF- β 2, and promoting spontaneous abortions

in the presence of another stimulus [32]. Paradoxically, TNF- α may trigger protective mechanisms if repair of the structural defects is possible.

In addition, during pregnancy, soluble cytokine receptors, such as TNFR, are involved in the regulation of cytokines' activities, such as TNF- α . Soluble cytokine receptors can antagonize cytokine activity by binding them. In healthy pregnant women, levels of soluble cytokine receptors are increased [33]. Indeed, when compared with the levels of nonpregnant women, TNFR has been found to increase significantly in the second and third trimesters of pregnancy [13].

Anti-TNF therapy & infertility

As TNF- α is a pleiotropic cytokine involved in pregnancy, with potential adverse effects, some investigators have proposed a beneficial effect of anti-TNF agents in infertility. As elevated TNF- α levels have been shown to be associated with recurrent spontaneous abortions, it has been hypothesized that lowering TNF- α might prevent this complication. Indeed, it has been demonstrated that the Th2 bias observed in women having a normal pregnancy was significantly increased compared with women with unexplained recurrent pregnancy losses [13]. This suggests that recurrent pregnancy losses may be associated with a Th1 bias. Anecdotal experiences of the use of anti-TNF agents to treat infertility have been reported in patients with inflammatory diseases, such as Crohn's disease and psoriasis [34].

However, the use of anti-TNF agents to treat infertility has raised some concerns about the potential risks and benefits, as well as appropriate attainment of informed consent in patients who may be desperate to give birth and be more inclined to agree to risky therapy [4]. Multiple immune therapies, such as intravenous immunoglobulins (IVIGs) and steroids, have been used with unclear efficacy to treat healthy, asymptomatic women who have difficulty in conceiving and have been diagnosed as having 'subclinical autoimmunity' [4]. Some authors are concerned by the employment of these therapies by noninternists and/or nonreproductive endocrinologists who manage infertility, and pinpoint the lack of recognized standards or board certifications required for a physician to practice as a reproductive immunologist [4]. A potential use of etanercept to treat infertility may relate to its effect on lowering NK-cell levels; however, it is still controversial as to whether increased levels of NK cells cause miscarriages or prevent conception, or whether anti-TNF agents, such as etanercept, prevent this by decreasing the levels of these cells [4].

Although it generates controversy, research assessing the efficacy of anti-TNF therapy in infertile patients has been performed. A recent study by Winger *et al.* retrospectively analyzed patients with a history of recurrent spontaneous abortions (defined as more than three miscarriages) who were treated with combinations of anticoagulants, IVIGs and anti-TNF agents [25]. These investigators aimed to determine if the addition of an anti-TNF agent could increase the success rates of their standard protocol of heparin and IVIG. In total, 75 pregnancies were retrospectively evaluated. Subjects were divided into three groups: group I were treated with heparin alone (21 patients), group II

were treated with heparin and IVIG (37 patients) and group III were treated with heparin, IVIG and etanercept or adalimumab (17 patients). Patient groups were formed partly through self selection and partly through differences in initial work up and history. For example, patients with a more-difficult reproductive history, such as repeated *in vitro* fertilization (IVF) failure, in addition to recurrent miscarriages, were offered the more-aggressive anti-TNF protocol. In group III, either adalimumab 40 mg injected subcutaneously every 1–2 weeks or etanercept 25 mg injected subcutaneously every 84 h was administered. The anti-TNF agent was generally started 1 month before initiating a cycle of conception and was continued until ultrasound evidence of fetal cardiac activity. Subjects from the three groups were relatively homogeneous for age, past miscarriages, inherited thrombophilia and autoimmunity, except that group III had higher levels of NK cells and positivity for antinuclear and antiphospholipid antibodies.

Live birth rates were greater within group III and were as follows: group I: 19% (four out of 21), group II: 54% (20 out of 37) and group III: 71% (12 out of 17) [30]. Fetal outcomes, such as gestational age and birth weight, were similar for the three groups. A 42-year-old woman in group II delivered a baby with Down's syndrome. No other congenital anomaly was reported in this study. It is unclear why patients receiving anti-TNF agents had higher rates of live births. The authors hypothesized that the beneficial effect of the anti-TNF agent may have been mediated by proteins of the protein C anticoagulant system, since TNF- α is known to downregulate some of these proteins.

The impact of anti-TNF therapy on male fertility is also of interest and several studies have investigated this issue. The effect of anti-TNF agents on spermatozoa quantity and quality is debated. Some studies have reported that TNF- α negatively affects spermatozoa motility, morphology and genomic integrity [35–37]. Other studies showed no evidence of an effect of TNF- α on sperm motility or apoptosis [1]. Moreover, in a study performing semen analysis in ten men suffering from Crohn's disease and treated with infliximab, a decrease in spermatozoa motility and quantity was observed [38]; however, this study was quite small. These studies show conflicting results and it is therefore difficult to draw conclusions regarding the effect of anti-TNF therapy on male reproductive function.

Safety of anti-TNF therapy in animal studies

Several studies assessing the safety of anti-TNF therapy have been conducted in animal models. However, because anti-TNF antibodies do not bind with TNF- α in species other than humans and chimpanzees [39], animal studies were not performed with the actual anti-TNF antibodies used in humans. Therefore, an analogous anti-TNF antibody that selectively inhibits murine TNF- α was used to conduct reproductive, developmental and fertility toxicology studies in mice [39]. No evidence of anti-TNF antibody embryotoxicity or teratogenicity has been demonstrated in animal studies. In addition, other animal studies using a soluble TNFR combined with an IgG heavy-chain chimeric protein reported no embryotoxicity or teratogenicity [40].

Anti-TNF agent transfer through the placenta & lactation

The molecular structures of anti-TNF agents, including chimeric and human IgG1 anti-TNF antibodies, and soluble receptor fusion protein linked to the Fc portion of human IgG1, allow minimal placental transfer during the first trimester, but passage through the placenta cannot be ruled out during the second and third trimesters [41]. Although there are no published studies on the ability of engineered molecules such as infliximab, adalimumab and etanercept to cross the placenta, in primates, there is substantial placental transfer of maternal IgG to the fetal circulation before birth, and the IgG1 subtype is readily transported across the placenta with the help of immunoglobulin-binding proteins [41]. Transplacental transfer of maternal IgG starts early during the second trimester and peaks near term [41]. It has been observed that exogenous IVIG administered to immunodeficient mothers crossed over to the offspring [42]. Furthermore, it has been demonstrated that maternally derived IgG antibodies, such as varicella and measles antibodies, can take more than a year to be cleared by the child [43].

Until recently, there was no evidence that engineered therapeutic antibodies administered perinatally to pregnant women crossed the placenta [39,44]. However, a recent study reports that a child exposed to infliximab during pregnancy had therapeutic levels of infliximab at 6 weeks of age [43]. His mother suffered from refractory Crohn's disease and had received five infusions of infliximab at a dosage of 10 mg/kg during her pregnancy. Her last infusion was administered 2 weeks before delivery and infliximab was not detected in her breast milk. The child's serum levels of infliximab slowly declined over the next 6 months and the child's evaluation at 6 months revealed no immunologic abnormality, including normal T- and B-cell levels, normal immunoglobulin concentrations, and normal and protective humoral responses to conjugated polysaccharide vaccines. This case raises some concerns as to whether children exposed to anti-TNF therapy during pregnancy might develop adverse events, such as drug-induced lupus, human antichimeric antibodies (HACA), demyelinating disorders or lymphoma [43].

The amount of IgG1 secreted in breast milk is very small [43]. It would be unlikely that infliximab and adalimumab would be found in breast milk in a clinically significant quantity. The case reported by Vasiliauskas *et al.* is consistent with this, and other investigators have found absent or undetectable levels of infliximab in the breast milk of treated patients [1,44]. However, another case report showed an accumulation of infliximab in breast milk from a woman with RA [45]. Even if infliximab may accumulate in breast milk, the antibody is likely to be digested in the GI tract of the child, in theory minimizing the risk of toxicity through breast feeding exposure [46].

In humans, etanercept is secreted into breast milk and, until more data are available, lactation should be discouraged during etanercept treatment [47]. However, because etanercept is a protein, as is the case for infliximab and adalimumab, it is likely to be digested in the GI tract of the child and not be absorbed systemically [46].

Case series of anti-TNF therapies in human pregnancies *Infliximab*

A large case series has been published of 96 pregnancies in women with Crohn's and rheumatic diseases who were exposed to infliximab at conception and/or during the first trimester [48]. They observed 68 live births, 14 miscarriages and 18 therapeutic abortions. One child born at 24 weeks experienced intracerebral and intrapulmonary bleeding and died. Another child developed respiratory distress and seizures. Two children presented with congenital malformations: one had tetralogy of Fallot and the other an intestinal malrotation. Some of these women were concomitantly exposed to other drugs during pregnancy, such as leflunomide, azathioprine and metronidazole, which may have played a role in the anomalies.

The Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry observed 66 women with Crohn's disease [49]. Of these, 36 were exposed to infliximab. No birth defects were reported. Furthermore, the rates of miscarriage and neonatal complications were not different between infliximab-treated and untreated patients.

Mahadevan *et al.* reported on the intentional use of infliximab during pregnancy for induction or maintenance of remission in ten women with Crohn's disease [44]. Eight women received infliximab throughout pregnancy, one was exposed to infliximab during the first trimester only and one began therapy in the third trimester. All ten pregnancies ended in live births. There were no congenital malformations. There were three premature births, one low-birth-weight child and one child who developed respiratory distress.

Tursi described a woman with Crohn's disease treated with infliximab for induction and maintenance of remission throughout pregnancy. The patient gave birth to a healthy child at 36 weeks of gestation. No adverse events were reported [50]. Two other cases of women with Crohn's disease exposed to infliximab during the first trimester of pregnancy resulted in healthy live births [51,52]. A miscarriage in a woman exposed to infliximab and methotrexate was also reported [53].

Etanercept

A large study assessed pregnancy outcomes in 417 pregnant women with RA exposed to anti-TNF agents [54]. Etanercept was the agent used in 81% of cases. Of the 417 pregnancies, 387 normal deliveries were observed. There were 25 miscarriages, five therapeutic abortions and nine preterm births. The rates of these events were comparable to general population figures [55]. No malformations or neonatal deaths were reported.

The Organization of Teratology Information Services (OTIS) collected information on 33 pregnant RA patients who were exposed to etanercept (29) or infliximab (four), without concomitant methotrexate therapy, during the first trimester [56]. These patients were compared with 77 patients with RA who were treated with various agents, including DMARDs but not with anti-TNF agents, with 50 healthy controls. Preterm delivery was more frequent in patients on anti-TNF agents (28.0% for etanercept) and in the RA control group (23.5%), compared

with the healthy subjects (4.3%). This difference was most likely due to the underlying disease. Spontaneous abortions occurred with both etanercept (three) and infliximab (one). A trisomy 18 chromosomal abnormality, ending in spontaneous abortion, was observed in one etanercept-exposed pregnancy. No difference in the rate of congenital malformations was observed between the three groups.

The British Society of Rheumatology Biologics Register reported 22 pregnancies in women with rheumatic diseases who were exposed to anti-TNF therapy at the time of conception (16 etanercept, three infliximab and three adalimumab) [57]. Nine of these women were on concomitant methotrexate therapy and two were receiving leflunomide. All patients stopped their therapy during the first trimester, except two patients on etanercept who continued treatment throughout pregnancy. This resulted in six first-trimester miscarriages (three in patients also receiving methotrexate and one receiving leflunomide at conception), three elective abortions and 13 live births (one born preterm and one with low birthweight). The two patients exposed to etanercept throughout pregnancy had a Caesarian section (one secondary to fetal distress). No birth defects were observed. One patient treated with adalimumab, which was discontinued during the first trimester, reported recurrent cystitis during pregnancy.

The Spanish registry BIOBADASER observed 14 pregnancies in women with inflammatory arthritis exposed to anti-TNF agents (eight etanercept, four infliximab and two adalimumab) [58,59]. They reported seven live births with no complications in four subjects treated with etanercept and three treated with infliximab. In addition, they reported three therapeutic abortions (two etanercept and one adalimumab) and one spontaneous abortion (infliximab), while three pregnancies had no available outcome. No congenital malformations were reported.

In a study using questionnaires administered to rheumatologists, Chakravarty *et al.* reported 15 pregnancies in women with rheumatic diseases exposed to etanercept and two exposed to infliximab [2]. One pregnancy, in a patient treated with both etanercept and methotrexate, resulted in a miscarriage. The six pregnancies with known outcomes in women exposed to etanercept (without methotrexate) resulted in normal deliveries. Of the two pregnancies exposed to infliximab, one resulted in a full-term healthy baby, while the outcome of the other pregnancy was not stated. No congenital malformations were reported.

In a recently published review article, Skomsvoll *et al.* reported six pregnancies in five women treated with etanercept during the first trimester [1]. These pregnancies resulted in two miscarriages and four full-term healthy babies. Furthermore, five pregnancies in women suffering from RA and JIA were documented by Koskvik *et al.*, and ended in three live births and two miscarriages [60].

Roux *et al.* observed a group of 442 patients treated with anti-TNF agents, in which three women with RA unexpectedly became pregnant [24]. One woman treated with etanercept opted for a therapeutic abortion, despite a normal ultrasound and satisfactory fetal evolution. One patient with adalimumab exposure delivered a healthy baby at 32 weeks gestational age. One patient

with etanercept exposure delivered a baby who suffered from a neonatal urinary infection and adrenal congenital hyperplasia of probable hereditary origin.

In addition, normal deliveries and live births have been reported in women with RA exposed to etanercept during the first trimester and throughout pregnancy [61,62].

Carter *et al.* recently described a woman with PsA who received etanercept 50 mg subcutaneously twice weekly throughout her pregnancy [63]. This patient gave birth to a child with tracheal atresia, tracheoesophageal fistula, oesophageal atresia, unperforated anus, hypospadias, T12 vertebral anomaly, spina bifida occulta and patent foramina ovale. These manifestations were consistent with VATER association (V: vertebrae anomalies; A: anal anomalies; T: tracheal problems; E: esophageal problems; R: radius or renal defects) without renal or limb abnormalities.

Adalimumab

Fewer data on adalimumab exposure during pregnancy are available, since this agent was introduced to the market only relatively recently. In a study of 61 pregnant women with inflammatory arthropathies, four were exposed to adalimumab [64]. No maternal or fetal adverse outcomes were reported.

Furthermore, a woman with refractory Crohn's disease was treated with adalimumab throughout pregnancy. Her pregnancy was uncomplicated and she delivered a healthy child with no congenital malformations [65].

In addition, Coburn *et al.* described a pregnant woman with refractory Crohn's disease who received adalimumab induction and maintenance therapy during the second and third trimesters of pregnancy. This resulted in a normal delivery and no fetal adverse outcomes were reported [66].

Expert commentary

Current available data do not seem to support a large excess risk of adverse pregnancy and/or fetal outcomes in women exposed to anti-TNF therapy at some point during pregnancy. However, evidence is limited by the relatively small number of published case series and case reports, differences in the type and dosage of anti-TNF agents, possible use of concomitant teratogenic drugs (e.g., methotrexate and leflunomide) and the timing of exposure during pregnancy. Indeed, most of the data relate to exposures during the first trimester and few patients have been exposed throughout pregnancy or in the second or third trimester. Furthermore, no long-term follow-up studies are available at this time. As therapeutic levels of anti-TNF agents have been observed in a child exposed to one of these agents late in pregnancy [43], more information is needed regarding adverse outcomes during infancy. In addition, some adverse effects of *in utero* drug exposure might be observed decades later in the offspring, as was the case for *in utero* exposure to diethylstilbestrol (DES) and clear cell adenocarcinoma (CCA) of the vagina and cervix [67], highlighting the importance of long-term follow-up studies.

Few authors have reported congenital malformations after exposure to anti-TNF therapy. However, a recent unpublished report, which analyzed FDA data on adverse events following the use of

anti-TNF agents since they became commercially available until 2005, revealed 41 cases of children with congenital anomalies born to mothers taking these drugs during pregnancy [68]. Nonetheless, no information on the total number of women exposed to these agents during pregnancy could be provided, so an incidence measure could not be estimated. Furthermore, in one study, the overall number of reported malformations was not increased in women exposed to anti-TNF therapy compared with general population figures [52], and no causal relationship has been proven.

Considering this uncertainty, it is clear that each woman requiring disease-modifying drugs during her pregnancy must be evaluated individually. In cases without a therapeutic alternative, anti-TNF therapy has been used in the first trimester of pregnancy. However, during the late second or third trimester, more caution is advised since placental transfer, with therapeutic levels in the newborn, has been documented. Furthermore, in women requiring disease control during the period of attempted conception, which can be prolonged, anti-TNF agents are probably one of the best therapeutic options when compared with other DMARDs, such as methotrexate and leflunomide, which must be stopped several months prior to conception. Finally, the toxicity of anti-TNF therapy exposure during

lactation is theoretically negligible since these agents are likely to be digested in the GI tract of the infant. However, in all situations, it is imperative to provide appropriate information to the patient and family (including admission of what remains unknown), so that the potential risks and benefits can be weighed.

Five-year view

With the emergence of postmarketing surveillance of anti-TNF agents, more prospective data collection is expected over the next 5 years. This will allow for assessment of the adverse events after *in utero* exposure to anti-TNF agents, compared with the general population or other women with inflammatory arthritis not treated with anti-TNF agents. Furthermore, studies linking data from drug and birth registries are underway [1].

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Key issues

- To date, anti-TNF agents fall within the US FDA category B for pregnancy and lactation, indicating that animal studies fail to demonstrate a risk, but adequate and well-controlled studies in pregnant and lactating women have not been conducted.
- Most women with rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis will improve during pregnancy, while only a third of women with ankylosing spondylitis will improve. However, the majority of these diseases will flare in women in the postpartum period.
- TNF- α is an important pleiotropic cytokine involved in pregnancy, promoting blastocyst implantation in early pregnancy, while mediating spontaneous abortion at a later stage.
- Anti-TNF therapy has been used in women suffering from infertility and some investigators report positive results, although data are limited.
- Placental transfer of anti-TNF agents in late pregnancy has been documented, resulting in therapeutic levels in the newborn.
- Although anti-TNF agents can be found in breast milk, they are probably digested in the GI tract of the child.
- No large excess risks of fetal or maternal adverse outcomes have been reported following exposure to anti-TNF therapy during pregnancy compared with general population figures.
- Sporadic cases of congenital malformation have been reported, but do not seem to be in excess of what is expected in the general population.
- More-prospective data collection is needed to better assess the long-term outcomes of children exposed *in utero* or through lactation to anti-TNF therapies.

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