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Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs

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A consensus paper concerning the interaction of anti-rheumatic drugs and reproduction was published in 2006, representing data collected during the year 2004 and 2005. Because of an increasing use of biological agents in women of fertile age, the information was updated for the years 2006 and 2007. Experts disagree whether TNF-inhibitors should be stopped as soon as pregnancy is recognized or may be continued throughout pregnancy. Pregnancy experience with abatacept and rituximab is still too limited to prove their safety for the developing fetus. They must be withdrawn before a planned pregnancy. LEF has not been proven to be a human teratogen. Registries of transplant recipients have shown that cyclosporin (CsA) and tacrolimus do not increase the rate of congenital anomalies, whereas mycophenolate mofetil (MMF) clearly carries a risk for congenital anomalies. Prophylactic withdrawal of drugs before pregnancy is mandatory for abatacept, rituximab, LEF and MMF. Data remain insufficient for gonadal toxicity of immunosuppressive drugs in men and for excretion of these drugs in human breast milk.

Key words: Pregnancy, Biological agents, Immunosuppressive drugs.

Introduction

During the last 20 yrs, several new immunosuppressive drugs have been introduced into the therapy of rheumatic diseases. Given that rheumatic diseases disproportionately affect women of child-bearing age, the safety of new drugs regarding birth defects, miscarriages or pre-term delivery is of concern. A consensus paper concerning the interaction of anti-rheumatic drugs and reproduction was published in 2006 [1], representing data collected during the year 2004 and 2005. Because of an increasing use of biological agents we now update this information for the years 2006 and 2007, using a literature survey performed as reported in 2006.

Biological agents

The manufacturers of the TNF-α inhibitors infliximab, etanercept, adalimumab and the B-cell depleting monoclonal antibody rituximab advise discontinuing these agents prior to a planned pregnancy. However, numerous new pregnancies inadvertently occurring during therapy with biological agents in the first trimester have been reported.

Infliximab

The transplacental passage of infliximab occurs in patients treated with infliximab in the 2nd and 3rd trimester of pregnancy [2]. Serum levels of infliximab in five infants born of mothers with IBD treated with infliximab throughout pregnancy were equal to maternal serum levels and remained detectable up to 6 months of life [2]. Another child had a serum infliximab level of 39.5 μg/ml at 6 weeks of age declining during the following 6 months despite breastfeeding and continued treatment of the mother. No infliximab was detected in breast milk [3].

A healthy child was born after maternal treatment with 5 mg/kg throughout pregnancy. The child was breastfed without adverse effects [4]. Another study reported 14 patients with IBD treated within 3 months of conception. Therapy was continued in 12 women throughout the first and second trimester. The outcome of pregnancy was reported for 10 pregnancies with delivery of seven healthy babies, two premature children and one miscarriage [5]. Continuous treatment with infliximab throughout pregnancy of four women with inflammatory arthritis resulted in the birth of healthy children [6]. In summary, data for all reported pregnancy outcomes under treatment with infliximab showed no increase in miscarriage, prematurity or structural malformations in neonates compared with non-exposed pregnancies.

Etanercept

Experience from 72 pregnancies of RA patients treated with etanercept has been published. Most patients were exposed in the first trimester and three throughout pregnancy [7–9]. The outcome included seven elective terminations of pregnancy, nine miscarriages, 48 live-born children and eight unknown. Two major malformations occurred, one being trisomy 18 in a miscarried child, and the other, being born of a mother treated with 100 mg of etanercept weekly throughout pregnancy, showed multiple anomalies fitting to the so-called VATER (vertebral anomaly, anal atresia, tracheo-oesophageal fistula, oesophageal atresia, renal and radial anomalies) association. The child also had hypospadias and patent foramen ovale [10]. The VATER association is a rare condition that occurs spontaneously. A causal relationship between therapy and event cannot be proven.

Adalimumab

Studies in pregnant cynamologous monkeys at doses up to 100 mg/kg of adalimumab have not revealed harm to the fetuses. Twenty-nine first trimester exposures in pregnant RA patients concluded with 23 live births, one termination, two spontaneous abortions and three unknown [7, 8, 11]. One premature child was born with hip dysplasia. Additionally four pregnancies and treatment throughout pregnancy in patients with Crohn's disease have resulted in healthy live-born children [12, 13]. In the cohort

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study of Chambers *et al.* [11], no increase in the rate of miscarriage, pre-term birth or structural malformations was found compared with non-treated and healthy pregnant controls. The birth weight was within normal range.

Breastfeeding during therapy with TNF-α inhibitors

There are no new reports on the passage of etanercept or adalimumab into human breast milk. Several abstracts and case reports stated that several children were breastfed during maternal treatment with TNF-α inhibitors and showed normal growth and development.

Male fertility and therapy with TNF-α inhibitors

A study of three men with AS and monotherapy with infliximab from 8 to 24 months revealed asthenozoospermia and teratozoospermia [14]. The study lacked a control group of male patients not treated with TNF-α inhibitors.

Conclusion

Experience with TNF inhibitors is still too limited to claim safety during pregnancy. Therefore, experts disagree on their use in pregnant women. Some advocate to stop them after a positive pregnancy test, others will continue them throughout pregnancy. Most reports concern first trimester use of TNF-α inhibitors, but transplacental passage does not occur until week 16 onwards. Long-term effects of intrauterine exposure to TNF-α inhibitors have not been studied.

At present it is not known whether TNF-α inhibitors are secreted into breast milk and can be ingested by the breastfed child. Mothers who wish to breastfeed should be informed that there is insufficient knowledge with which to provide advice. Similarly there is insufficient data to determine whether or not TNF-α inhibitors have an influence on spermatogenesis.

Abatacept

Abatacept, a CTLA4 and human immunoglobulin fusion protein, has been introduced as a selective co-stimulation modulator for the treatment of RA. Abatacept crosses the placenta. Treatment of pregnant rats and rabbits with up to 29 times the dose given to humans did not produce malformations in the offspring. At a dose 11 times the dose given to humans, alterations of immune function was found in the offspring of rats consisting in a 9-fold increase in the T-cell-dependent antibody response in female pups. The manufacturer advises against pregnancy during therapy and recommends contraception until 10 weeks after withdrawal of the drug. No human pregnancy experience has been published; therefore, no statement on the safety of abatacept during pregnancy can be made. Abatacept should not be started or continued during pregnancy.

Rituximab

Reproductive toxicity studies in non-human primates have not shown fetotoxicity of rituximab, a monoclonal, B-cell depleting antibody. Rituximab crosses the placenta from week 16 onwards, like all IgG immunoglobulins, and achieves fetal serum levels similar to maternal levels. Published experience includes three pregnancies in women with lymphomas also treated with CHOP (a combination of cytotoxic drugs and prednisolone), and pregnancy in a woman with autoimmune haemolytic anaemia [15]. Treatment with rituximab was limited to the first trimester in two, to the second and third in two additional pregnancies. In the latter, the serum levels of rituximab were similar in the mother and newborn, and the number of B cells was greatly reduced in these children. Spontaneous recovery of B-cell numbers occurred in both infants. After first trimester exposure, lymphopenia but not B-cell depletion was noted. In all children, IgG levels were normal and they all showed a normal vaccine response.

In an unpublished safety update report of 2005, 24 pregnancies exposed to rituximab 1–8 months prior to conception were registered in patients with malignancies. The 10 pregnancies with known outcome concluded with the delivery of a live infant without congenital malformations or serious neonatal or early childhood infections. Two of the children had low granulocyte counts after birth, and one also had anaemia and lymphopenia.

Conclusion

Experience with rituximab is too limited to allow any statement on safety in pregnancy. When administered in the 2nd and 3rd trimester, B-cell depletion occurs in the fetus. Long-term studies on B cell and immune function of children exposed *in utero* are lacking. Rituximab should be stopped before a planned pregnancy, maternal serum levels measured and pregnancy attempted only after serum levels are negative.

Tacrolimus and mycophenolate mofetil

Recently, tacrolimus and mycophenolate mofetil (MMF) have been successfully used to treat patients with SLE, particularly those with a history of lupus nephritis.

Tacrolimus

Experience of pregnancy exposure to tacrolimus stems mainly from transplant recipients. The studies published in 2006–07 confirm the absence of an increased risk of miscarriage or congenital anomalies [16].

MMF

The new reports of 2006–07 on use of MMF during 28 pregnancies have confirmed that MMF increases the risk for congenital malformations including facial dysmorphia and malformation of the ears (microtia and anotia) [17, 18–20]. Recently, the American Food and Drug Administration (FDA) notified healthcare providers that use of MMF is associated with increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, oesophagus and kidney.

Conclusion

The available data show that the calcineurin inhibitors do not increase the risk for congenital abnormalities. Tacrolimus and cyclosporin (CsA) may therefore be continued during pregnancy when indicated. The risk for intrauterine growth restriction and for prematurity is increased both in transplant recipients and patients with autoimmune diseases regardless of the type of immunosuppressive therapy. However, at present, it is not known whether this is related to the underlying maternal condition, or the frequent use of combinations of immunosuppressive drugs in this patient population. Human experience confirms the increased risk of birth defects during therapy with MMF. Based on data from the United States National Transplantation Pregnancy Registry and additional post-marketing data, the pregnancy category for MMF has been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). Experts disagree as to the time point of withdrawal of MMF before a planned pregnancy, but because of its long half-life it should be discontinued at least 6 weeks before a planned pregnancy.

LEF

A case report described a child exposed to LEF during the first 16 weeks of pregnancy born prematurely with blindness and

TABLE 1. Outcome of 49 pregnancies exposed to biological agents and immnunosuppressive drugs observed by the authors during 2006–07

Diagnosis	Therapy	No. of pregnancies	Time of exposure before/during pregnancy	Premature delivery	Pregnancy outcome	Neonatal health
2 RA, 1 PsA, 2 Oligoarthritis	Infliximab	5	1 st Trimester		4 Terminations, 1 live birth	Healthy neonate
8 RA, 1 AS	Etanercept	9	6 Exposed 1st trimester, 3 throughout pregnancy		1 Termination, 5 live birth, 3 out-come unknown	5 Healthy infants
3 SLE	Rituximab	3	12, 6 and 4 months before pregnancy withdrawn	2	1 Termination, 2 live birth	2 Healthy neonates
10 SLE	AzA	10	9 Throughout pregnancy, 1 transiently stopped	2	1 Miscarriage, 7 live birth, 2 outcome unknown	7 Healthy neonates
10 SLE, 2 PSS, 2 PsA	CsA	14	13 Throughout pregnancy, 1 stopped in 2nd trimester	5	1 Miscarriage, 12 live birth	1 Premature infant with multiple anomalies died
2 SLE	MMF	3	3 Exposed in 1st trimester	1	1 Miscarriage, 1 termination 1 live birth	Healthy neonate
4 RA	LEF	4	4 Exposed 1st trimester	1	1 Miscarriage, 2 live birth, 1 outcome unknown	2 Healthy infants
1 RA	MTX	1	1 Exposed 1st trimester		1 Live birth	1 Healthy infant

PSS: Primary SS.

cerebral palsy [21]. An ongoing study of the Organization of Teratology Information Specialists (OTIS) prospectively collects data on intrauterine exposures to LEF. The preliminary results (Congress abstracts) of 63 RA pregnancies exposed to LEF during the first trimester have not shown an increase in miscarriage or congenital malformations compared with 108 RA pregnancies not exposed to LEF. A slight increase in prematurity was noted in the infants exposed to LEF. The available experience limited to a total of 74 pregnancies leaves the question open whether LEF is a human teratogen. The case report cited above does not prove a causal relationship between LEF and the observed anomalies. Because of the small number of pregnancies studied, LEF should be stopped before a planned pregnancy and conception attempted only after a washout with cholestyramine or active charcoal.

Long-term effects of intrauterine exposure to fluorinated corticosteroids

Several animal studies and a few human studies have raised concern about possible negative long-term effects of betamethasone and dexamethasone given to accelerate fetal lung maturation. It was suspected that antenatal exposure to betamethasone might result in insulin resistance in adult offspring, but a 30-yr follow-up of a randomized controlled trial found no clinical effect on cardiovascular risk factors such as body size, blood lipids, blood pressure, prevalence of diabetes or history of cardiovascular disease [22].

No negative effects on the neuropsychological development of a small cohort of 16 anti-Ro/SSA-positive children exposed *in utero* to very high dosages of dexamethasone (mean total dose 186.6 mg) were found [23]. This dose is much higher than those used to enhance fetal lung maturity, and these findings seem reassuring in view of the large number of infants exposed in the past to repeated antenatal courses of therapy with fluorinated corticosteroids.

Own cases

The authors reported 49 pregnancies that had occurred during therapy with biological agents and immunosuppressive drugs during 2006–07 (Table 1). These cases add to our knowledge, particularly for CsA and AZA where most pregnancy experience stems from transplant recipients. Not unexpectedly, most cases of prematurity occurred in patients with SLE independent of therapy. Except for one prematurely born child that died with multiple cardiac malformations, the other pregnancies with known outcome ended with the delivery of healthy children.

Conclusion

Experience with pregnancy exposure to biological agents and new immunosuppressive drugs is slowly accumulating. In regard to TNF-α inhibitors, safety issues are still under debate. LEF may turn out not to be a human teratogen; however, larger patient cohorts are needed. The safety of tacrolimus during pregnancy is suggested by new data whereas MMF appears to carry a significant teratogenic risk. There remains a substantial lack on studies investigating the transfer of biological agents and immunosuppressive drugs to breast milk and their effect on the nursing child. Likewise, more investigations in regard to immunosuppressive drugs and gonadal function in men are needed. Overall, the new data from the years 2006–07 have not changed the recommendations given in the consensus paper of 2006 [1].

Rheumatology key messages

- TNF-α inhibitors may be continued during pregnancy when strongly indicated.
- MMF must be withdrawn before pregnancy.
- Extent of fetal risk not clarified for exposure to LEF, abatacept and rituximab.

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