Review
Anti-inflammatory and immunosuppressive drugs and reproduction

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Abstract

Rheumatic diseases in women of childbearing years may necessitate drug treatment during a pregnancy, to control maternal disease activity and to ensure a successful pregnancy outcome. This survey is based on a consensus workshop of international experts discussing effects of anti-inflammatory, immunosuppressive and biological drugs during pregnancy and lactation. In addition, effects of these drugs on male and female fertility and possible long-term effects on infants exposed to drugs antenatally are discussed where data were available. Recommendations for drug treatment during pregnancy and lactation are given.

6-MP = 6-mercaptopurine; AAP = American Academy of Pediatrics; CI = confidence interval; COX = cyclo-oxygenase; CQ = chloroquine; CsA = cyclosporin A; CYC = cyclophosphamide; FDA = United States Food and Drug Administration; HCQ = hydroxychloroquine; IBD = inflammatory bowel disease; LDA = low-dose aspirin; MMF = mycophenolate mofetil; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drugs; OR = odds ratio; RR = relative risk; SLE = systemic lupus erythematosus; SSZ = sulphasalazine.

Introduction

The pregnancy categories of the United States Food and Drug Administration (FDA) in their present form are often not helpful for the clinician treating patients with active chronic disease during pregnancy and lactation. They combine risk assessment and benefit, and are for most products based on animal data. There is no requirement to update categories with human experience. Drug trials in pregnant or lactating mothers are not performed with new drugs. Therefore the only information on the safety of drugs during pregnancy and lactation is derived from experimental and preclinical animal studies. Human experience accumulates in most cases from inadvertent drug exposure during pregnancy and lactation. Because only drugs considered safe can be studied in pregnant or lactating women, the number of controlled studies is small. In the absence of controlled studies, reporting bias favours the reporting of negative experiences, particularly in case reports and small case series.

An important aspect of exposure *in utero* to drugs is possible long-term effects that will become manifest later in life. Because a follow-up several decades after antenatal exposure is not easily performed, information on late harmful effects in offspring is not available for most drugs. However, as a result of increasing awareness, studies are planned or in progress addressing these important questions.

Gonadotoxic effects of anti-inflammatory and immuno-suppressive drugs have only seldom been studied except for cytotoxic drugs and, in men, salazopyrine. However, there is an increasing awareness among patients that drugs may impair fertility or be mutagenic. Again, available information concerns mostly experimental and preclinical animal studies.

Information on the excretion of drugs into breast milk is based mostly on single-dose or short-term treatment. Studies enrolling a large number of lactating women have not been performed. The effect of the drug on the nursing infant has in many cases not been studied. Investigations studying an influence of chronic drug ingestion on child behaviour and development are also lacking. In general, drug concentrations in breast milk that expose the suckling infant to 0.1% of the maternal dose are regarded as fairly safe, whereas an ingestion of about 10% of the mother's dose requires caution. Recommendations given for drugs for which no reports or only single case reports exist are based on theoretical considerations. This is the case for many immunosuppressive drugs and the biologicals. In view of the substantial benefits of breastfeeding, denying it unnecessarily is a serious concern.

Recommendations on prescribing during pregnancy differ, sometimes considerably, in articles and textbooks. Even the recommendations given by the producer of a given drug can vary in different countries. This situation is unsatisfying for both the patient and the treating physician.

For this reason an international workshop of experts with experience in drug therapy of pregnant and lactating women was arranged. The aim was to reach a consensus on anti-inflammatory and immunosuppressive drugs during pregnancy and lactation with a focus on patients with rheumatic disease.

Methods

A panel of 29 international experts including 17 specialists of internal medicine and rheumatology, 8 obstetricians, 3 paediatricians and 1 specialist in genetics agreed to participate in a consensus workshop on antirheumatic drugs during pregnancy and lactation held in connection with the 4th International Conference on Sex Hormones, Pregnancy and Rheumatic Diseases, held in Stresa, Italy, on 20 to 22 September 2004. Four categories of drugs were discussed in separate working groups: anti-inflammatory drugs, corticosteroids, immunosuppressive drugs and biological agents. Current practice of prescribing during pregnancy and lactation was evaluated by questionnaires for the four drug categories under discussion. The results of these questionnaires revealed which issues needed special attention because of diverging practice of the specialists.

Before the workshop, members of the four working groups searched the databases Medline and Cochrane for the period 1960 to 2004 under the following terms: each drug, fertility, gonadal toxicity, pregnancy, teratogenicity, lactation, and children of mothers treated during pregnancy. Because of the scarcity of data, all types of original observations in humans were accepted provided they were published in English, Italian, French, German or Spanish. It was acknowledged that causality between observed fetal or neonatal effects and a given drug was often not documented, and that the possibility for chromosomal aberrations or effects of the underlying maternal disease were frequently not taken into account in published experience.

The data from the available scientific literature were summarized in the form of surveys, which were sent to the participants before the workshop. The data were then presented and discussed in workshops devoted to the above-mentioned groups of drugs. Finally the conclusions and recommendations of the working groups were discussed by all participants in a plenary session.

If no consensus could be reached for a given drug, the reason for diverging opinions is stated in the recommendations. Consensus was reached for most drugs. When clinical evidence was lacking, consideration of legal issues has necessitated recommendations based on theoretical risks for several drugs. The level of evidence for the recommendations are presented in accordance with the classification by Miyakis and colleagues [1], as follows: Class I is a prospective study in a broad spectrum of the representative population or meta-analysis of randomized

controlled trials; Class II is a prospective study in a narrow spectrum of the representative population or well-designed cohort or case-control analytic study or retrospective study in a broad spectrum of the representative population; Class III is a retrospective study in a narrow spectrum of the representative population; and Class IV is a study design in which predictor is not applied in a blinded fashion or a descriptive case series or an expert opinion. The application of this classification has its problems because, in the field of drugs during pregnancy and lactation, randomized controlled studies are simply a minority. As a result the level of evidence for the teratogenicity of methotrexate and cyclophosphamide is only III. The low level of evidence for drugs during breastfeeding is likewise due to the scanty documentation and total absence of controlled studies. In contrast, the classification reveals the low level of evidence on which many of the recommendations are based. This opens for clinical decisions weighing risk and benefit of therapy in the individual patient.

Note
Data on breastfeeding or fertility are presented in the text only when studied in humans. Otherwise the information is given exclusively in the tables. With regard to biological drugs, sufficient data on which to base recommendations exist only for etanercept and infliximab. Other biological drugs are therefore not included in this survey.

Non-steroidal anti-inflammatory drugs (NSAID)
NSAID and outcome of pregnancy
A Danish case-control study showed a link between the use of NSAID during pregnancy and miscarriage [2]. Odds ratios ranged from 1.3 for NSAID use 10 to 12 weeks before miscarriage to 7.0 for use 1 week before miscarriage. Potential bias and confounders of the study were the validity of the registry variables, confounding by indication for treatment, and the fact that prescription and not drug consumption had been recorded [3]. A second population-based cohort study including 1,063 women confirmed an increased risk of miscarriage for the use of NSAID (including aspirin) but not of paracetamol during pregnancy [4]. The odds ratio (OR) was 1.8, but increased to 5.6 when taken around conception and to 8.1 when used for more than 1 week. Interference of NSAID with implantation and placental circulation was suspected as the explanation for the findings. By contrast, a meta-analysis of low-dose aspirin during the first trimester did not find an increase in miscarriage [5]. The risk for miscarriage did not differ between women treated with aspirin or placebo (relative risk (RR) 0.92; 95% confidence interval (CI) 0.71 to 119).

By stimulating uterine contractions and enhancing cervical ripening, prostaglandins are important mediators in parturition. Inhibitors of cyclo-oxygenases (COX) can prolong gestation and labour. Indomethacin, aspirin, ibuprofen, sulindac, diclofenac and ketoprofen [6-8] as well as the preferential COX-2 inhibitors nimesulide and meloxicam [8,9] have been used successfully for the inhibition of premature labour. Similarly, celecoxib has been found to be as effective as indomethacin as a tocolytic agent [10].

Potential mutagenic and teratogenic effects
Animal studies
In rats and rabbits, the incidence of diaphragmatic hernia, ventricular septum defect and gastroschisis/midline defects is increased in fetuses exposed to NSAID when compared with non-exposed controls [11,12]. The incidences of the three defects are higher in aspirin-treated animals than in non-aspirin NSAID-treated animals. This indicates that irreversible inhibition of COX-1 and COX-2 is more toxic than reversible inhibition. It was also shown that inhibition of COX-1 mediates these developmental anomalies [12].

Human studies
Several population-based cohort and case-control studies have assessed the teratogenic risks of first-trimester use of non-selective COX inhibitors, including aspirin. Neither the American Collaborative Perinatal Project [13,14], the Michigan Medicaid surveillance study [15], the Swedish National Project [16], nor the recent Danish population-based study [3] together comprising several hundred thousand pregnancies have found an increased risk of congenital malformations. First-trimester use of selective COX-2 inhibitors has not been reported in human pregnancy.

A meta-analysis of published reports on use of aspirin (doses not specified) during the first trimester found no increased risk for congenital anomalies including renal anomalies and congenital heart defects. However, a significantly higher risk of gastroschisis was detected in infants born to women using aspirin in the first trimester compared with non-aspirin users (OR 2.37; 95% CI 1.44 to 3.88) [17]. The Spanish Collaborative study of Congenital Malformations confirmed an increased risk of gastroschisis at first-trimester prenatal exposure to salicylates (OR 3.47, $p = 0.015$) after controlling for maternal age and maternal smoking in a case-control study [18].

Effects on the ductus arteriosus
Both COX-1 and COX-2 are expressed in endothelial and smooth muscle cells of the ductus arteriosus [19] and hence the constriction or premature closure of the ductus is a risk with all NSAID. No constriction of the ductus arteriosus occurred in the only human study of 12 pregnancies exposed to celecoxib [10]. Effects on ductal blood flow have been shown for most of the non-selective COX inhibitors occurring as early as 4 hours after administration of the drug [20,21]. Several studies with fetal echocardiography found an increasing rate of constriction of the ductus arteriosus from 0 before gestational week 27 to 43% in the period 27 to 30 weeks of gestation and 61% between 31 to 34 weeks of gestation during treatment with indomethacin independently

of the fetal serum concentration [22-24]. The constriction frequently reversed within 24 to 48 hours after the cessation of therapy. However, several studies have shown a significant association between pulmonary hypertension in newborn infants and antenatal exposure to aspirin, naproxen or ibuprofen in the third trimester. The severity of pulmonary hypertension was dose related [24,25].

Effects on fetal and neonatal renal function
COX-1 is expressed in renal tubuli and COX-2 in renal medulla [19]. The blockade of prostaglandin synthesis by NSAID and the decreased activation of prostaglandin receptors cause reduced renal perfusion and oligo-hydramnios. Adverse effects on fetal renal function have been reported for non-selective and selective COX inhibitors [24,26-28]. A marked decline in fetal urine output has been observed within 5 hours of indomethacin ingestion, and oligohydramnios developed in 70 to 82% of pregnancies during the first week of treatment, but disappeared after discontinuation of the drug. Development of oligohydramnios has been shown to be dose dependent [26]. Short-term treatment with celecoxib reduced fetal urine production, but less than indomethacin [10]. Transient anuria, but also fatal persistent anuria and irreversible end-stage renal failure, has been reported in newborn infants exposed to indomethacin or nimesulide [27-29].

Other fetal/neonatal effects
High-dose aspirin and indomethacin given close to delivery have been shown to cause bleeding tendencies and haemorrhage in the central nervous system in the newborn infant [24,30]. Clotting abnormalities have also been detected in newborn infants exposed to 325 to 650 mg of aspirin within 1 week before delivery [15].

Low-dose aspirin (LDA)
Adverse effects of LDA (less than 325 mg/day) on pregnancy outcome were studied in a meta-analysis [5]. Women who took aspirin had a significantly lower risk of preterm delivery than did those treated with placebo (RR 0.92; 95% CI 0.86 to 0.98). There was no significant difference in perinatal mortality (RR 0.92; 95% CI 0.81 to 1.05) and in the rate of small-for-gestational-age infants (12 studies; RR 0.96; 95% CI 0.87 to 1.07) among offspring of mothers treated with aspirin and those of mothers treated with a placebo [5]. More than 10,000 pregnancies exposed to aspirin at 60 to 80 mg/day during the second and third trimester up to term have been reported without any increase in impaired renal function, pulmonary hypertension or clotting ability of the newborn infant [31]. Doppler investigation of fetuses aged 15 to 40 weeks exposed to 60 mg of aspirin daily during the second and third trimesters did not reveal any effect on the ductus arteriosus [32]. One study found that LDA (less than 100 mg) given to the mother could suppress platelet thromboxane A_2 formation in the newborn infant that recovered within 2 days after discontinuation of the drug [33].

There are some reports on epidural haematoma in patients who, while on LDA, underwent epidural anaesthesia; however, prospective studies have not found an increased risk for this complication [34].

Effects of NSAID on fertility
COX-1 and COX-2 are involved in ovulation and implantation [34,35]. Several case reports and small series have described transient infertility after treatment with non-aspirin NSAIDs such as indomethacin, diclofenac, piroxicam and naproxen [36-38]. Studies in animals and humans have shown that NSAID can inhibit the rupture of the luteinized follicle and thereby cause transient infertility. A prospective, randomized trial of ibuprofen in 12 women detected a delay of 2 days or more in follicle rupture in a small number of treated women [38]. However, no alterations of serum progesterone or luteinizing hormone levels were observed. In a study of 13 healthy women, 6 of whom were given the selective COX-2 inhibitor rofecoxib, delayed follicle rupture was observed in 4 of them [39].

A study of men attending an infertility clinic found a decrease in sperm count and quality in non-prescription, chronic users of NSAID (mostly aspirin) at low or moderate doses [40].

Breastfeeding
Most NSAID are excreted in very small quantities into human breast milk [41,42]. The American Academy of Pediatrics (AAP) considers flufenamic acid, ibuprofen, indomethacin, diclofenac, mefenamic acid, naproxen, piroxicam and tolmetin to be compatible with breastfeeding [43]. Aspirin at more than 100 mg/day should be used cautiously because of potential adverse effects in the nursing infant [43]. Feeding immediately before a dose can help to minimize infant exposure to NSAID.

Conclusion and recommendation (Tables 1 and 2)
- Non-selective and selective COX inhibitors can prevent or retard ovulation. The frequency of ovulation inhibition is unknown (evidence level IV).
- Non-selective COX inhibitors are not teratogenic and can be continued during the first and second trimester (evidence level I).
- At present there are no reliable data on selective COX-2 inhibitors; they should therefore be avoided during pregnancy (evidence level IV).
- After gestational week 20, all NSAID (except aspirin at less than 100 mg/day) can cause constriction of the ductus arteriosus and impair fetal renal function (evidence level I).
- All NSAID except LDA should be withdrawn at gestational week 32 (evidence level IV).
- There is no consensus on when to stop LDA before delivery. Some advise cessation of LDA treatment 1 week before a planned delivery with epidural anaesthesia (evidence level IV). Other experts do not stop LDA in

Table 1

Effect of non-steroidal anti-inflammatory drugs, glucocorticosteroids and bisphosphonates on human pregnancy and fertility

Drug	FDA risk[a]	Transplacental passage	Human teratogenicity	Fetal/neonatal adverse effects	Long-term effects in offspring	Impairment of fertility
Non-steroidal anti-inflammatory drugs	B/D	Yes	No	In late pregnancy, constriction of the ductus arteriosus, reduction of renal blood flow	Not studied	Cases of inhibition of follicle rupture
Prednisone	B	Limited	Increase in oral clefts	Rare (cataract, adrenal insufficiency, infection)	Not studied	Not studied
Dexamethasone	C	Yes	Not reported[b]	Neurodevelopmental abnormalities	Not studied	Not studied
Betamethasone	C	Yes	Not reported[b]	Neurodevelopmental abnormalities ?	Not studied	Not studied
Bisphosphonates	C	Not studied	Not reported	Two cases of hypocalcaemia in the newborn infant	Not studied	Not studied

Details and references are given in the text. [a]The United States Food and Drug Administration (FDA) pregnancy risk categories are as follows: A, no risk in controlled clinical studies in humans; B, human data reassuring or when absent, animal studies show no risk; C, human data are lacking; animal studies show risk or are not done; D, positive evidence of risk, benefit may outweigh; X, contraindicated during pregnancy. [b]No indication for maternal use in the first trimester.

Table 2

Non-steroidal anti-inflammatory drugs, corticosteroids and bisphosphonates during lactation

Drug	Secretion into breast milk	Effect on nursing infant	Breastfeeding allowed
Non-steroidal anti-inflammatory drugs	In low concentrations	No adverse effects	Diclofenac, flufenamic acid, ibuprofen, indomethacin, ketorolac, mefenamic acid, naproxen and piroxicam are compatible with breastfeeding [41-43]
Prednisone	0.025% of maternal dose	No adverse effects	Compatible with breastfeeding [84,85]
Dexamethasone	Not studied	Not known	Avoid
Betamethasone	Not studied	Not known	Avoid
Bisphosphonates	Pamidronate not detected, no reports on other bisphosphonates	No adverse effect in one case [91]	Insufficient data. Risk-benefit must be weighed before breastfeeding

pregnant patients with antiphospholipid syndrome, regarding the benefit of LDA as being greater than the small risk of haematoma connected with epidural anaesthesia (evidence level II).

• Breastfeeding immediately before a dose can help to minimize infant exposure to NSAID (evidence level IV).

New anticoagulant drugs

Currently, the most widely used drugs for treatment and secondary prevention of thromboembolic manifestations and pregnancy morbidity caused by antiphospholipid syndrome are LDA, heparin (unfractionated or of low molecular mass) and oral anticoagulants. Their optimal use in pregnant patients with APS has been described [44,45].

Current developments target potent drugs with a predictable mode of action, easy mode of administration and minimal requirements for blood control. For platelet inhibition, effective

oral preparations that directly block the glycoprotein IIb/IIIa receptor on platelets (the binding site for fibrinogen) are to be expected on the market soon [46]. Pentasaccharides, which are molecules that induce a conformational change in the antithrombin molecule so that this can bind and inactivate activated coagulation factor X, are logical alternatives for low-molecular-mass heparin. The pentasaccharide fondoparinux can be administered once daily subcutaneously in a fixed dose and has proven efficacy for the treatment and prophylaxis of venous thromboembolic manifestations [47,48]. Fondoparinux crosses the placenta, and cord blood samples contain levels about one-tenth of those in maternal blood [49]. Ximegalatran is a derivate from hirudin, a direct thrombin inhibitor, that can be given orally in two fixed daily doses, does not need monitoring and is at least as effective as conventional treatment in non-valvular atrial fibrillation [50] and for the treatment and prophylaxis of venous thrombo-embolic events [51,52]. Its effect is not influenced by food,

drugs or P450 enzymes. Because of hepatic toxicity, however, it has not been approved by the FDA. Currently, little is known about the safety of the new anticoagulants during pregnancy and lactation.

Conclusion and recommendation
• At the present state of knowledge, the new antiplatelet and anticoagulant drugs cannot be recommended for use in pregnant or lactating women. The pentasaccharide fondoparinux can cross the placenta, suggesting that it is less safe than heparin or low-molecular-mass heparin during pregnancy (evidence level IV).

Corticosteroids

11β-Hydroxysteroid dehydrogenase in the placenta converts cortisol and corticosterone to the relatively inactive 11-keto forms, leaving no more than 10% of the active drug to reach the fetus [53]. Glucocorticoids with fluorine at the 9α position, like betamethasone and dexamethasone, are considerably less well metabolized by the placenta.

Side effects with special relevance to pregnancy
Corticosteroid side effects in pregnant women include all that are present in non-pregnant subjects taking corticosteroids. Side effects such as increased blood pressure, osteopenia, osteonecrosis and susceptibility to infection are of special relevance in pregnancy. Pregnancy induces insulin resistance at later stages, and the resulting glucose intolerance is further enhanced by exogenous glucocorticoids with an increased risk of gestational diabetes. Pregnancy-specific complications are premature rupture of the membranes, frequently reported in corticosteroid-treated patients with systemic lupus erythematosus (SLE) and in one controlled study comparing treatment with corticosteroids with treatment with heparin in pregnant antiphospholipid-antibody-positive patients [54].

Potential mutagenic and teratogenic effects
Hydrocortisone produces dose-related teratogenic and toxic effects in genetically susceptible experimental animals, with increased rates of cleft palate, cataract, fetal loss and fetal growth restriction [55,56].

In the human, results from case-control and prospective studies indicate that exposure to hydrocortisone and prednisone during the first trimester can lead to a small increase in oral clefts [57-61]. A meta-analysis found a 3.3-fold increased OR of oral clefts after first-trimester exposure to corticosteroids [62]. Similar results were reported by the Spanish Collaborative Study of Congenital Malformations [57] and by two additional studies [59,61], but a reporting bias might exist because several large studies found no statistically increased rate of oral clefts [60,63]. Available data do not allow a conclusion to be drawn about the specific oral cleft phenotype associated with glucocorticoid exposure in humans (cleft lip, cleft palate or both). Since oral clefts occur at about 1:1,000 births in the general population, the

possible increase to 3 or 4 for every 1,000 births after embryonic exposure to corticosteroids is minimal [62]. On the whole, corticosteroids do not seem to increase the risk of congenital abnormalities noticeably in humans.

The influence of corticosteroids on intrauterine growth has been controversial. Some authors have demonstrated an increased incidence of low-birthweight babies in mothers on corticosteroids [56,64], whereas others have not [65]. Infections in newborn infants after antepartum exposure to corticosteroids occur rather infrequently [66] and maternal corticosteroid therapy does not induce general immuno-suppression in the newborn infant [67]. The possible induction of hypertension in adult life by antenatal exposure to corticosteroids has not been proven in humans [68]. Other rare adverse events reported for antenatal exposure to corticosteroids are neonatal cataract [69] and adrenal suppression in children born to women taking high doses of steroids during pregnancy [70,71].

Antenatal exposure to synthetic fluorinated corticosteroids betamethasone and dexamethasone
A single course of fluorinated corticosteroids (betamethasone or dexamethasone, 24 mg) to pregnant women at risk for preterm delivery, between 24 and 34 weeks of gestational age, clearly reduced the risk of death, respiratory distress syndrome and cerebral haemorrhage in their preterm infants [72]. In the meantime, however, evidence has accumulated on the potential harm of repeated courses of steroids for the mother and the fetus. Findings in animals widely suggest that repeated antenatal steroid doses can interfere with the growth and development of the immature brain [73,74], and observations on humans suggest that antenatal and postnatal dexamethasone may negatively affect the child's neuro-psychological development [75-78]. In view of this concern, a further NIH consensus conference in 2000 confirmed the previous statement of the advantages of one course of antenatal corticosteroids but also made it clear that, in view of their potential hazard, repeated courses should not be given routinely but be reserved for patients in randomized controlled clinical trials [79].

The possible negative effects seem linked more to dexamethasone than to betamethasone [80]. In addition, a separate meta-analysis of the data in the Cochrane review showed that only betamethasone, and not dexamethasone, significantly reduces neonatal mortality [81]. For these two reasons it has been suggested that betamethasone should be preferred when available [82]. Adverse effects on neuropsychological development in children have not been observed after exposure to steroids that are inactivated by placental enzymes [83].

Breastfeeding
Only trace amounts of hydrocortisone are excreted into human breast milk [84]. In six lactating women, prednisolone

doses of 10 to 80 mg/day resulted in milk concentrations ranging from 5% to 25% of maternal serum levels [85]. Even at a maternal dose of 80 mg/day, the nursing infant would ingest only 10 µg/kg which corresponds to <10% of the infant's endogenous cortisol production. No data are available for dexamethasone or betamethasone in lactating women [43].

Conclusion and recommendation (Tables 1 and 2)
- Maternal indications: prednisone, prednisolone and methyl prednisolone.
- Fluorinated corticosteroids for antenatal treatment: betamethasone should be preferred when available rather than dexamethasone (evidence level II).
- Stress doses of hydrocortisone at delivery are recommended in patients on long-term therapy (evidence level IV).
- Corticosteroids do not seem to increase the risk of congenital abnormalities noticeably in humans (evidence level II).
- In case of *in utero* exposure to fluorinated steroids, consider postnatal steroids for the baby only if adrenal insufficiency is documented (neonatologist advice is warranted) (evidence level IV).
- Breastfeeding is allowed with moderate doses of steroids (evidence level II). At doses >40 mg consider breastfeeding timing 4 hours after the dose (evidence level IV).

Osteoporosis prevention
For women treated either with corticosteroids or with heparin throughout pregnancy, prevention of osteoporosis is important [86]. Bisphosphonates accumulate in bone for long periods. In mice and rats, gestational exposure to bisphosphonates was associated with decreased fetal bone growth and decreased fetal weight [87]. Three case reports have described the use of bisphosphonates in pregnant women. Two of the children born had transient hypocalcaemia, the third had normal laboratory values and developed normally to 1 year of age [88-91].

- Because of insufficient data, pregnancy should be postponed for 6 months after withdrawal of bisphosphonates (evidence level IV).
- The routine use of oral calcium and vitamin D supplements is recommended in pregnancy and lactation (evidence level IV).

Antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ)
Potential mutagenic and teratogenic effects
CQ was embryotoxic and fetotoxic in high doses (250 to 1,500 mg/kg) in experimental animals. Eye malformations occurred in 45% of animals at 1,000 mg/kg [92]. CQ accumulated preferentially in melanin-containing structures in the fetal uveal tract and inner ear when given during pregnancy [92].

CQ and HCQ cross the placenta with no significant difference in the mean concentration in maternal and cord blood [93]. Weekly malaria prophylaxis with 300 mg of CQ throughout gestation did not increase the congenital malformation rate [94]. In the rheumatism literature, reports on several hundred pregnancies exposed to CQ 250 mg daily or HCQ 200 to 400 mg daily during the first trimester did not find an increase in congenital malformations or cardiac conduction disturbances in children exposed antenatally to antimalarials [88,95-100]. Malformations of the inner ear and other abnormalities after treatment with higher than the recommended dose of CQ throughout pregnancy were reported after intrauterine exposure to 500 mg daily of CQ in three siblings born to a mother with SLE [101]. HCQ has not been associated with congenital malformations.

Breastfeeding
Three studies examined the presence of CQ after the administration of single doses (5 mg/kg and 600 mg) in lactating women [100,102]. Daily ingestion of CQ by a nursing child was calculated as 2.2 to 4.2% of the maternal dose. Two case reports measured the secretion of HCQ during lactation and found 0.35% and 0.0005% of the maternal dose in human breast milk [103,104].

Long-term effects in children
Several studies have investigated long-term effects in children exposed *in utero* or during lactation to HCQ. No decrease in visual acuity, visual field or colour vision, or alterations in electroretinogram and electro-oculogram or hearing impairment, were detected in children studied during the first year of life or up to 4 years of age [105-108]. A case-control study of 133 pregnancies exposed to HCQ found no visual, hearing, growth or developmental abnormalities in children followed up for 108 months. Electrocardiograms of exposed children were normal [99].

Conclusion and recommendation (Tables 3 and 4)
- When indicated, continue antimalarials during pregnancy and lactation (evidence level II).
- HCQ is the antimalarial of choice in fertile women in need of treatment (evidence level IV).
- CQ and HCQ are compatible with breastfeeding (evidence level IV).

Sulphasalazine (SSZ)
Potential mutagenic and teratogenic effects
Reproduction studies with SSZ in rats and rabbits at doses up to six times the human dose have not shown impaired female fertility or harm to the fetus.

A population-based case-control study demonstrated no significant increase in selected congenital abnormalities in the children of women treated with SSZ during pregnancy [109]. A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease

Table 3

Effect of immunosuppressive, cytotoxic and biological drugs on human pregnancy and reproduction

Drug	FDA risk[a]	Transplacental passage	Human teratogenicity	Fetal/neonatal adverse effects	Long-term effects in offspring	Impairment of fertility
Chloroquine/ hydroxychloroquine	C/C	Yes	No	Not at recommended doses	No impairment of vision or hearing	Not studied
Sulphasalazine	B	Fetal like maternal serum concentration	No	Case reports of aplastic anaemia and neutropenia at >2g maternal dose	Not studied	In men: oligospermia, decreased sperm motility, abnormal forms
Leflunomide	X	No data	Data not conclusive	None published	Not studied	Not studied
Azathioprine Mercaptopurine	D[b]	Yes	No	Sporadic congenital anomalies. Transient immune alterations in newborn infants	Normal immune responses in childhood. One case report of late development of autoimmunity.	No
Methotrexate	X	Methotrexate + polyglutamates	Yes	Cytopenia	None reported	Oligospermia at high doses
Cyclophosphamide	D	Yes – animal data	Yes	Chromosomal abnormalities. Cytopenia	Anecdotal	In males and females
Cyclosporine	C	10–50% of maternal plasma concentration	No	Transient immune alterations	None reported	No
Tacrolimus	C	Yes	Not reported	Hyperkalaemia, renal impairment	Not studied	Not studied
Mycophenolate mofetil	C	Yes	3 reports of congenital abnormalities	Not reported	Not studied	Not studied
Intravenous immunoglobulin	C	Yes	No	No fetal effects reported	Not studied	Not studied
Etanercept	B	Yes	Not reported	Not reported	Not studied	Not studied
Infliximab	B	Not reported	Not reported	Not reported	Not studied	Data not conclusive

Details and references are given in the text. [a]The United States Food and Drug Administration (FDA) pregnancy risk categories are as follows: A, no risk in controlled clinical studies in humans; B, human data reassuring or when absent, animal studies show no risk; C, human data are lacking; animal studies show risk or are not done; D, positive evidence of risk, benefit may outweigh; X, contraindicated during pregnancy. [b]Accumulated experience indicates that azathioprine can be used throughout pregnancy without increase in congenital abnormalities.

(IBD). In 186 pregnancies of women treated with SSZ alone or with concomitant steroid therapy, the incidence of fetal morbidity and mortality was comparable both with that of 245 untreated IBD pregnancies and with pregnancies in the general population [110]. Additional studies of pregnancies in women with IBD confirmed these results [111-114]. There have been isolated reports on children born with congenital malformations to mothers treated with SSZ during pregnancy [115]. A study comparing fertility rates and fetal abnormalities of patients with IBD with the general population found a higher rate of malformations among offspring (particularly of men) in patients treated with SSZ [115]. Because SSZ

inhibits the gastrointestinal and cellular uptake of folate, a possible role of folate deficiency cannot be ruled out [116].

Some experts have advised the cessation of SSZ in the last trimester, fearing it could displace bilirubin from albumin and thus induce neonatal pathological jaundice. Yet the bilirubin-displacing capacity of sulphapyridine and SSZ at the low concentrations measured in cord blood is negligible [117]. Kernicterus in the newborn infant after exposure to SSZ *in utero* has not been reported. Aplastic anaemia was found in an aborted fetus exposed during the first trimester to SSZ [118], and another case reported congenital severe

Table 4

Immunosuppressive, cytotoxic and biological drugs during lactation

Drug	Secretion into breast milk	Effect on nursing infant	Breastfeeding allowed
Chloroquine	0.55% of maternal dose [100,102]	No adverse effects	Compatible with breastfeeding
Hydroxychloroquine	0.35% of maternal dose [103,104]	No adverse effects	Compatible with breastfeeding
Sulphasalazine	Sulphasalazine and sulphapyridine secreted at 5.9% of maternal dose [120]	Well tolerated, 1 case of bloody diarrhoea [121]	Allowed in the healthy full-term infant
Leflunomide	No data published	No data published	Avoid because of theoretical risk
Azathioprine (AZA)/ 6-mercaptopurine (6-MP)	AZA and its metabolites detected in milk [135]	9 children nursed (AZA) without adverse effects, 1 child (6-MP) well	Avoid because of theoretical risk
Methotrexate	Excreted in low concentrations. Milk:plasma ratio of 0.08 [155]	Not known	Avoid because of theoretical risk
Cyclophosphamide	Secreted (amount unknown) [172]	Suppression of haematopoiesis reported in one nursing child [169]	Contraindicated during lactation
Cyclosporine	Milk:plasma concentration < 1; wide variability in drug disposition [188]	No adverse effects observed in 9 breastfed children [188]	No consensus, weigh risk/benefit
Tacrolimus	Minute amounts secreted, nursing infant exposed to 0.06% of mother's dose [197]	1 child nursed without side effects [197]	Breastfeeding probably possible
Mycophenolate mofetil	No human studies	Not known	Avoid because of theoretical risk
Intravenous immunoglobulin	No data published	Not known	Breastfeeding probably possible
Etanercept	Secreted at 0.04% of maternal dose [207]	Not known	Data inconclusive, weigh risk/benefit
Infliximab	Secreted in small amount [211]	Not known	Avoid because of theoretical risk

neutropenia in an infant whose mother was taking 3 g of SSZ daily throughout pregnancy [119].

Breastfeeding
Insignificant amounts of uncleaved SSZ have been found in milk, whereas the sulphapyridine levels in milk were about 30 to 60% of those in maternal serum [120]. Diarrhoea and rash were reported in a breastfed infant whose mother was receiving SSZ [121]. Exposure to sulphonamides through breast milk apparently does not pose a significant risk for the healthy, full-term newborn infant, but it should be avoided in ill, stressed or premature infants and in infants with hyper-bilirubinaemia or glucose-6-phosphate dehydrogenase deficiency [43].

Fertility
SSZ does not impair fertility in women. Treatment with SSZ leads to oligospermia, reduced sperm motility, an increased proportion of abnormal forms, and infertility in men and rats [122]. The effect is due to sulphapyridine and cannot be abrogated by folate supplementation. Spermatogenesis recovers at about 2 months after withdrawal of the drug [122].

Conclusion and recommendation (Tables 3 and 4)
- Continuation of SSZ during pregnancy is unlikely to cause fetal harm (evidence level II).
- Folate supplementation is necessary before and throughout pregnancy (evidence level I).
- To prevent neutropenia in the newborn infant, maternal doses of SSZ should not exceed 2 g daily (evidence level IV).
- Male infertility caused by SSZ recovers after discontinuation of the drug. Men should stop SSZ 3 months before attempting to father a child (evidence level IV).
- Breastfeeding is allowed in the healthy, full-term infant (evidence level IV).

Leflunomide
Potential mutagenic and teratogenic effect
Leflunomide given to pregnant rats and rabbits in doses equivalent to human doses induced malformations of the skeleton and central nervous system in the offspring. Prenatal exposure to about 1% of the human dose resulted in decreased birthweight and increased perinatal mortality in the offspring [123].

In a retrospective study, 10 pregnancies occurred in RA patients treated with leflunomide. No congenital malformation occurred in the five pregnancies with known outcome [124]. An unpublished safety update of the manufacturer in September 2004 reported 428 exposures during pregnancy, with known outcome for 165 pregnancies. Twenty-one pregnancies occurred while the male partner was receiving leflunomide. Termination was performed in 44 cases, miscarriage occurred in 36 cases and 85 pregnancies went to term. Congenital malformations occurred in seven children. A Canadian prospective cohort study is currently in progress to investigate possible fetal and neonatal side effects of leflunomide exposure during pregnancy. At present, the study includes a total of 246 pregnancies with known outcome. No significant differences between exposed and non-exposed pregnancies were noted with regard to spontaneous abortion or major structural defects in newborn infants.

Conclusions and recommendations (Tables 3 and 4)

- Leflunomide is contraindicated during pregnancy. Safe contraception during therapy in both women and men is recommended by the manufacturer (evidence level IV).
- When a pregnancy is being planned, leflunomide must be withdrawn. Because the active metabolite of leflunomide is detectable in plasma until 2 years after discontinuation of the drug, cholestyramine must be given to enhance elimination from the body until plasma levels of leflunomide are undetectable (evidence level IV).
- No data exist on excretion into breast milk; breastfeeding is therefore not recommended (evidence level IV).

Azathioprine and 6-mercaptopurine (6-MP)

Azathioprine is a prodrug that after absorption is cleaved to 6-MP, its active metabolite.

Potential mutagenic and teratogenic effect

The fetal liver lacks the enzyme inosinatopyrophosphorylase, which converts azathioprine to its active form and therefore should be theoretically protected from azathioprine crossing the placenta [125].

Azathioprine injected intraperitoneally in doses equivalent to 4 to 13 times the therapeutic human dose caused skeletal defects and multiple malformations in mice and rabbits exposed during gestation [125]. In rodents exposed *in utero* to 1 to 62.5 times the human dose of 6-MP, cleft palate, dilatation of cerebral ventricles and hydrocephalus were observed. Female and male offspring of mice receiving 6-MP in pregnancy had a decreased number of germ cells in the gonads, with resulting decreased fertility [126].

Studies in pregnant transplant recipients receiving azathioprine and prednisone and in pregnant patients treated for IBD with azathioprine or 6MP showed no increase in pregnancy complications or congenital malformations [127-129]. Intrauterine growth restriction has been reported in

40% of renal graft recipient mothers taking both cortico-steroids and azathioprine [64]. Anecdotal experience has associated prenatal exposure to azathioprine with different congenital anomalies, but none of them were clearly linked to the drug. Other reported events after antenatal exposure to azathioprine were transient chromosomal anomalies in clinically normal infants [130], transient lymphopenia [130,131], severe immune deficiency and cytomegalovirus infection [131], and depressed haematopoiesis in infants whose mothers were treated with more than 2 mg/kg azathioprine daily [132].

One group reported an increased incidence of spontaneous abortions and congenital malformations in pregnancies fathered by 13 men treated with 6-MP for IBD at conception or in the 3 months previously [133]. However, it is uncertain whether the control group of untreated IBD male patients was comparable. In addition the overall rate of congenital malformations was within the baseline incidence. Another study did not find any increase in adverse outcomes in men and women treated for IBD with 6-MP before or during the first trimester [134].

Breastfeeding

Azathioprine and its metabolites were found in milk, exposing the child to 0.1% of the maternal dose [135]. Nine children were nursed without side effects.

Fertility

Azathioprine does not adversely affect the fertility of women. A recent study in men found semen quality and quantity to be normal despite long-term treatment with azathioprine [136].

Long-term effects in offspring

Postnatal enhancement of T cell maturation, but otherwise normal immunological development, was detected in children exposed to azathioprine *in utero* [137]. A recent case report found the development of autoimmunity in a daughter of a patient with SLE who had received azathioprine during pregnancy and regarded this as a possible long-term effect of exposure *in utero* [138]. However, a genetic predisposition as the cause of the daughter's SLE cannot be ruled out.

Conclusion and recommendations (Tables 3 and 4)

- When indicated, azathioprine can be used during pregnancy at a daily dose not exceeding 2 mg/kg per day (evidence level II).
- There is no consensus on the use of 6-MP, the active metabolite of azathioprine during pregnancy. Some experts recommend the avoidance of its use during pregnancy (evidence level IV).
- No consensus on nursing exists among experts. The AAP does not recommend breastfeeding because of the theoretical risk of immunosuppression, carcinogenesis and growth restriction in the child (evidence level IV).

Methotrexate (MTX)

Potential mutagenic and teratogenic effect

MTX is a methyl derivative of the folate antagonist aminopterin. Active metabolites of MTX remain in cells or tissues for several months after the cessation of therapy [139]. Closure of the neural tube takes place during week 5; the embryo is therefore probably most vulnerable to anti-folate drugs at this time. The congenital anomalies observed in animals and humans exposed to MTX *in utero* usually involved the central nervous system, cranial ossification, the limbs and the palate and growth retardation [140-142].

Experience with MTX in human pregnancy has been derived mainly from patients treated for cancer with multiagent therapy or when MTX or aminopterin was used unsuccess-fully as an abortifacient to terminate a pregnancy [143,144]. In most of these reports, doses of MTX exceeded the low-dose weekly pulses (5 to 20 mg) applied in rheumatology. Three infants exposed to MTX during the first trimester had multiple cranial anomalies [143-145]. Chromosomal aberra-tions were detected in a healthy newborn infant exposed to MTX and other cytotoxic drugs during pregnancy [144]. In seven cases, MTX had been given during the second and third trimester; six normal children were born and one child had pancytopenia [145].

Reviewing the rheumatology literature of first-trimester exposure to once-weekly doses of 20 mg of MTX or less, disclosed 63 pregnancies [124,146-151]. In the pregnancies not terminated electively, 11 (17%) ended in miscarriage, and of the 33 that proceeded to delivery, four children (12%) had congenital anomalies, including one child with multiple skeletal abnormalities [149]. Birthweights of the full-term infants were within normal range. Previous treatment of women with MTX has no harmful effect on subsequent pregnancy outcomes [152,153]. So far there are no reports of adverse pregnancy outcomes among men exposed to MTX before conception [154].

Breastfeeding

MTX is excreted into breast milk in low concentrations, with a milk:plasma ratio of 0.08 [155]. The significance of this small amount for the nursing child is unknown.

Fertility

MTX does not impair female fertility. There is no indication that monotherapy with MTX induces infertility in men [156], although a case report has described oligospermia in a male patient treated with MTX for psoriasis [157].

Long-term effects in children

A follow-up study of children exposed antenatally to cytotoxic drugs including MTX showed physical, neurological, psychological, haematological, immune function and cytogenetics to be normal after 3 to 19 years [158]. A follow-up ranging from 0.1 to 16.7 years of an additional seven children revealed no developmental or other serious health problems [146].

Conclusions and recommendations (Tables 3 and 4)

- MTX is contraindicated during pregnancy and should be prescribed to fertile women only under the cover of safe contraception (evidence level III).
- MTX must be withdrawn prophylactically 3 months before a planned pregnancy (evidence level IV).
- Folate supplementation should be continued antenatally and throughout pregnancy (evidence level I).
- It is not known whether once-weekly administration of MTX has any significance for the nursing child, given the minute amounts excreted into breast milk. The AAP does not recommend breastfeeding because of theoretical risks (evidence level IV).

Cyclophosphamide (CYC)

Potential mutagenic and teratogenic effect

CYC is teratogenic in all animal species studied, including mice, rats, rabbits and monkeys [159]. Abnormalities induced in animals by specific dose ranges and at specific periods of gestation showed a rather consistent pattern of brain malformation, defective limbs and facial abnormalities.

CYC has an unpredictable effect on the human fetus because it does not always cause malformations when given during the first trimester [160-163]. CYC embryopathy has been reported in nine cases, including defects of the calvaria, anomalies of craniofacial structures, ears and limbs, visceral organs, growth retardation and developmental delay during childhood [160-168]. CYC given in the second and third trimester does not result in structural abnormalities but it may cause growth restriction, impair neurological development and suppress haematopoiesis in the infant [164,169]. Therapy with CYC completed before pregnancy does not increase the rate of miscarriage or congenital abnormalities in offspring [170].

Little information is available about the outcome of children born to men taking CYC. Isolated reports of congenital abnormalities have been associated with paternal use of CYC, but a direct relationship is difficult to prove [171].

Breastfeeding

CYC is excreted into human breast milk [172]. Suppression of haematopoiesis has been reported in a breastfed infant nursed by a mother who received CYC [169].

Fertility

CYC is gonadotoxic in both women and men, depending on the cumulative dose and the age of the patient. Impairment of fertility follows both daily oral and intermittent pulse therapy [173]. In women, sustained amenorrhoea after a total dose of 3.5 to 7 g of CYC was rare under the age of 25 years, increased to 12% for patients aged 26 to 30 years and to

25% for patients aged 31 years or older [174]. Women older than 32 years have a substantial risk for amenorrhoea at 8 g/m^2, which increases to sustained amenorrhoea for 90% of women at 12 g/m^2 [175]. In men, gonadotoxicity of CYC is present even before puberty [176]. There is no safe threshold of the cumulative dose, and it is not possible to predict which patients will become sterile and which will recover testicular function [177].

Preservation of gonadal function during CYC therapy in women is best done by concomitant treatment with a gonadotrophin-releasing hormone agonist, as a case-control study has shown [178]. Cryopreservation of sperm and sperm banking is the method of choice in men who have no children or have not completed their families.

Long-term effects in children
A case of a papillary thyroid cancer at the age of 11 years and a neuroblastoma at age 14 years in a male twin exposed to CYC *in utero* has been reported. The female twin was unaffected [164]. A population-based study did not find any increase in chromosomal abnormalities in offspring of childhood cancer survivors in Denmark treated with cytotoxic drugs including CYC, nor an increase in Down syndrome or Turner syndrome [179].

Conclusion and recommendation (Tables 3 and 4)
- CYC is a human teratogen (evidence level III).
- CYC is gonadotoxic in men and women (II).
- Intravenous CYC therapy should be started only after a negative pregnancy test (evidence level IV).
- Measures for preservation of fertility must be taken (evidence level IV).
- Safe contraception is necessary when fertile women are treated with CYC (evidence level IV).
- Attempts at conception should be delayed until 3 months after the cessation of therapy (evidence level IV).
- Breastfeeding is not recommended (evidence level IV).

Cyclosporin A (CsA)
Potential mutagenic and teratogenic effect
CsA was not toxic to the exposed fetuses at the maternal dosage of 10 mg/kg per day, whereas it was embryotoxic at dosages of 25 to 100 mg/kg per day [180].

More than 800 pregnancies receiving CsA have been reported, mainly in transplant recipients [181-185]. The observed rate of 3% of congenital malformations has not exceeded the rate reported in the general population, nor has any particular pattern of abnormalities emerged. Renal and liver function were normal in 166 newborn infants exposed to CsA *in utero* [186]. A meta-analysis evaluated the risk of congenital malformations, preterm delivery or low birthweight from CsA treatment during pregnancy [187]. The calculated OR of 3.83 for malformations did not achieve statistical significance. The overall prevalence of 4.1% of malformations

in the study population did not vary substantially from that reported in the general population. The OR for prematurity did not reach statistical significance, although the overall prevalence rate was 56.3%. It is not clear whether maternal therapy with CsA or the underlying maternal disease was associated with increased rates of prematurity and low birthweight (less than 2,500 g).

Breastfeeding
Small amounts of CsA are excreted in breast milk. Successful breastfeeding without side effects has been reported in 15 children [188].

Long-term follow-up of children
Follow-up for 1 to 12 years of 175 children registered in the National Transplantation Pregnancy Register (USA) found normal development in 84% of offspring exposed to CsA *in utero* [189]. The high incidence of prematurity was suspected to be involved in the mental developmental delay observed in 16% of the children. Because CsA can induce autoimmunity in rodents after exposure *in utero*, several studies have addressed this issue in children of transplant recipients. The maturation and development of T cells, B cells and NK cells can be impaired during the first year of life [137], and transient B cell depletion has been described in several infants [190]. A case-control study of the immune function of children born to mothers with connective tissue diseases found normal blood cell counts, immunoglobulin levels and lymphocyte subpopulations in offspring of mothers treated with immunosuppressive drugs (including CsA) [191]. All children responded satisfactorily to hepatitis B vaccination. A paediatric follow-up ranging from 3 months to 11 years of age found three cases with long-term developmental difficulties, but no learning disability (mental retardation) among 31 children exposed to CsA during pregnancy [192].

Conclusion and recommendation (Tables 3 and 4)
- CsA can be maintained in pregnancy at the lowest effective dose (evidence level I).
- Control maternal blood pressure and renal function during therapy (evidence level II).
- There is no consensus among experts on nursing. Safety during breastfeeding is not proven (evidence level IV). The AAP does not recommend breastfeeding because of theoretical risks.

Tacrolimus
Potential mutagenic and teratogenic effect
Tacrolimus is fetotoxic in animals, causing increased late fetal loss and decreased live birth rate.

No controlled human studies are available. Two studies from the same centre, one retrospective, the other prospective, examined the outcome of a total of 70 pregnancies under tacrolimus after kidney transplantation, simultaneous kidney–

pancreas transplantation, or liver transplantation [193,194]. About 50% of the babies were either preterm or premature; one was born with congenital anomalies [194].

A retrospective analysis recorded 100 pregnancies in 84 mothers treated with a mean daily dose of tacrolimus of 12 mg/day during 1992 to 1998 [195]. Of the pregnancies with known outcome, 71 progressed to delivery (68 live births, 2 neonatal deaths and 1 stillbirth) and 24 were terminated (12 spontaneous and 12 induced). The mean duration of gestation was 35 weeks, with 59% of deliveries being premature, but with appropriate birthweight in 90% of cases. The most common complications in the newborn infant were transient hypoxia, hyperkalaemia and renal dysfunction. Four newborn infants presented with malformations, without any consistent pattern of affected organs. An additional study found no increase in congenital anomalies in newborn infants born to tacrolimus-treated kidney recipients [196].

Breastfeeding

According to one case report, only 0.02% of the mother's dose of tacrolimus is transmitted to the breastfed baby [197].

Conclusion and recommendation (Tables 3 and 4)

- Tacrolimus may be maintained during pregnancy at the lowest possible dose (evidence level III).
- Breastfeeding is possible (evidence level IV).

Mycophenolate mofetil (MMF)

Potential mutagenic and teratogenic effect

Treatment of pregnant rats and rabbits with 30 to 50% of the human dose has resulted in birth defects in the offspring, comprising the central nervous system, cardiovascular and renal system [198].

No controlled studies on pregnancy during treatment with MMF are available, but data exist in drug company files (Roche Pharma, safety update). By April 2005, 119 pregnancies under maternal treatment with MMF had been reported; however, the outcome is known for only 76 of these. Twenty miscarriages and 13 terminations of pregnancy were reported. Twenty-two deliveries resulted in healthy newborn infants. Abnormalities at birth were observed in 10 newborn infants, yet a causative role for MMF could not be established. Sixty-nine pregnancies occurred after paternal exposure, with a known outcome for 45 of these. Six congenital anomalies such as foot malformation, hand malformation, bladder anomaly and chromosomal abnormality were reported; 36 newborn infants were healthy.

Two newborn infants with structural congenital anomalies were reported from the National Transplantation Pregnancy Registry after *in utero* exposure to MMF [199,200]. One child had hypoplastic nails and short fifth fingers, normal chromosomes, and normal growth and development [199]. A

terminated pregnancy of a patient treated with MMF before conception and during the first trimester of pregnancy disclosed multiple fetal malformations, specifically facial dysmorphology and midline anomalies, including agenesis of the corpus callosum [198].

Conclusion and recommendation (Tables 3 and 4)

- MMF is contraindicated during pregnancy and should be given to women of fertile years only under cover of reliable contraception (evidence level III).
- Because of enterohepatic recirculation and a long half-life, treatment with MMF should be stopped at least 6 weeks before a planned pregnancy (evidence level IV).
- No data exist on excretion into breast milk; breastfeeding is therefore not recommended (evidence level IV).

Intravenous immunoglobulin

Placental transfer of IgG is dependent on the dose and gestational age. It crosses the placenta in significant amounts after 32 weeks of gestation. Studies on pregnant patients with haematological and autoimmune diseases have focused on fetal survival but not on neonatal health. No fetal adverse effects of intravenous immunoglobulin have been reported. Randomized trials with regard to immune function in the newborn infant or in response to vaccination in childhood have not been performed. Normal percentages of T cells, B cells, NK cells and monocytes were found in 20 infants born after maternal immunoglobulin treatment for fetal alloimmune thrombocytopenia [201]. No data are available with regard to fertility or breastfeeding, but harmful effects seem unlikely.

Conclusion and recommendation (Tables 3 and 4)

- Intravenous immunoglobulin can be used in pregnancy (evidence level II).
- Breastfeeding is allowed (evidence level IV).

Biological drugs

At the present stage of knowledge, there is no evidence implicating tumour necrosis factor-α antagonists with embryotoxicity, teratogenicity or increased pregnancy loss (Table 3). Except for a few case reports on successful pregnancies [202-205], no data on fertility or breastfeeding are available for adalimumab (human monoclonal antibody against TNF-α), anakinra (the interleukin-1 receptor antagonist) or rituximab (the monoclonal antibody against CD20). For the latter drugs no recommendations with regard to reproduction are given.

Etanercept

Potential mutagenic and teratogenic effect

Soluble TNF-R crosses the placenta and gains access to the fetal circulation in mice but does not interrupt pregnancy or impair fetal development. Pregnancy studies in rats and rabbits using 60 to 100 times the human dose of etanercept did not show any teratogenicity or fetotoxicity [206].

Experience from 32 pregnancies treated with etanercept has been reported without an increased risk of congenital abnormalities or other adverse effects [124,207].

Breastfeeding
A case report showed that etanercept is excreted into human breast milk. The effect on the nursing child is not known [208].

Conclusion and recommendation (Tables 3 and 4)
- Etanercept should not be continued during pregnancy because of a lack of much information (evidence level IV).
- Because the effect on the nursing child is not known, breastfeeding is not recommended (evidence level IV).

Infliximab
Potential mutagenic and teratogenic effect
A developmental toxicity study conducted in mice using an analogous murine anti-TNF-α antibody showed no evidence of maternal toxicity, embryotoxicity, or teratogenicity [209].

Several case reports and small series have reported an absence of adverse fetal or maternal outcomes after treatment with infliximab during pregnancy [124,207,210]. Data from the infliximab safety database, including 146 pregnancies of women affected by Crohn's disease and rheumatoid arthritis collected from October 1998 to April 2003, found that 131 pregnant women were exposed directly to the drug, 15 indirectly through their partners [211]. Outcome data were available for 106 of these patients. Live births occurred in 67% (64 of 96), miscarriages in 15% (14 of 96), and therapeutic termination in 19% (18 of 96) of the pregnancies. The study suggests that infliximab exposure during pregnancy results in outcomes that do not differ from those in the United States population of pregnant women with or without Crohn's disease not exposed to the drug.

Breastfeeding
Passage of infliximab into human breast milk in one patient with RA was demonstrated [212].

Fertility
Semen quality was studied in eight men receiving infliximab for IBD [213]. Semen samples showed no statistical difference between pre-infusion and post-infusion values. Motility and the percentage of normal oval forms were below normal both before and after infusion, probably reflecting the underlying disease process or previous therapy. The results of the study suggest that semen quality is not seriously affected by infliximab treatment.

Conclusion and recommendation (Tables 3 and 4)
- The safety of infliximab during pregnancy has not been sufficiently documented (evidence level III). It should therefore be stopped when pregnancy is recognized (evidence level IV).

- Because the effect on the nursing child is not known, breastfeeding is not recommended (evidence level IV).

Conclusion
In an area in which controlled studies are lacking for the most part, uncertainty about the magnitude of risk demands a cautious approach to the therapy of pregnant and lactating women. Data accumulate slowly and in an uncontrolled way regarding immunosuppressive drugs and pregnancy. Information continues to be insufficient with regard to lactation, to gonadotoxic effects, and to long-term effects in children exposed to immunosuppressive drugs *in utero* or by breastfeeding. Studies of these issues are urgently needed. The updating of available information at regular intervals and adjustment of recommendations on the use of drugs during pregnancy and lactation is warranted.

Competing interests
The authors declare that they have no competing interests.

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References
1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G: **International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS).** *J Thromb Haemost* 2006, **4:**295-306.
2. Nielsen GL, Sorensen HT, Larsen H, Pedersen L: **Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study.** *Br Med J* 2001, **322:**266-270.
3. Chan LY, Yuen PM: **Risk of miscarriage in pregnant users of NSAIDs. More information is needed to be able to interpret study's results.** *Br Med J* 2001, **322:**1365-1366.
4. Li DK, Liu L, Odouli R: **Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study.** *Br Med J* 2003, **327:**368-373.
5. Kozer E, Moldovan Costei A, Boskovic R, Nulman I, Nikfar S, Koren G: **Effects of aspirin consumption during pregnancy on pregnancy outcomes: meta-analysis.** *Birth Defects Res B Dev Reprod Toxicol* 2003, **68:**70-84.
6. Yussoff Dawood M: **Nonsteroidal antiinflammatory drugs and reproduction.** *Am J Obstet Gynecol* 1993, **169:**1255-1265.
7. Lewis RB, Schulman JD: **Influence of acetylicsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labour.** *Lancet* 1973, **ii:**1159-1161.
8. Sawdy RJ, Lye S, Fisk NM, Bennett PR: **A double-blind randomised study of fetal side effects during and after short-term maternal administration of indomethacin, sulindac, and nimesulide for therapy of preterm labor.** *Am J Obstet Gynecol* 2003, **188:**1046-1051.
9. Locatelli A, Vergani P, Bellini P, Strobelt N, Ghidini A: **Can a cyclooxygenase type-2 selective tocolytic agent avoid the fetal side effects of indomethacin?** *BJOG* 2001, **108:**325-326.
10. Stika CS, Gross GA, Leguizamon G, Gerber S, Levy R, Mathur A, Bernhard LM, Nelson DM, Sadovsky Y: **A prospective randomized safety trial of celecoxib for treatment of preterm labor.** *Am J Obstet Gynecol* 2002, **187:**653-660.
11. Cook JC, Jacobson CF, Gao F, Tassinari MS, Hurtt ME, DeSesso JM: **Analysis of the nonsteroidal anti-inflammatory drug literature for potential developmental toxicity in rats and rabbits.** *Birth Defects Res B Dev Reprod Toxicol* 2003, **68:**5-26.

12. Cappon GD, Cook JC, Hurtt ME: **Relationship between cyclooxygenase 1 and 2 selective inhibitors and fetal development when administered to rats and rabbits during the sensitive periods for heart development and midline closure.** *Birth Defects Res B Dev Reprod Toxicol* 2003, **68:**47-56.

13. Heinonen OP, Slone D, Shapiro S: *Birth Defects and Drugs in Pregnancy.* Littleton, MA: Littleton Publishing Sciences Group; 1977:286-295.

14. Slone D, Heinonen OP, Kaufman DW, Siskind V, Monson RR, Shapiro S: **Aspirin and congenital malformations.** *Lancet* 1976, **ii:**1373-1375.

15. Briggs GG, Freeman RK, Yaffe SJ (eds) *Drugs in Pregnancy and Lactation.* 6th edition. Philadelphia: Lippincott Williams & Wilkins; 2002.

16. Källèn B: **The teratogenicity of antirheumatic drugs – what is the evidence?** *Scand J Rheumatol* 1998, **27(Suppl 107):**119-124.

17. Kozer E, Shekoufeh N, Costei A, Boskovic R, Nulman I, Koren G: **Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis.** *Am J Obstet Gynecol* 2002, **187:**1623-1630.

18. Martinez-Frias ML, Rodriguez-Pinilla E, Prieto L: **Prenatal exposure to salicylates and gastroschisis: a case-control study.** *Teratology* 1997, **56:**241-243.

19. Stanfield KM, Bell RR, Lisowski AR, English ML, Saldeen SS, Khan KN: **Expression of cyclooxygenase-2 in embryonic and fetal tissues during organogenesis and late pregnancy.** *Birth Defects Res A Clin Mol Teratol* 2003, **67:**54-58.

20. Momma K, Takeuchi H: **Constriction of the ductus arteriosus by non-steroidal anti-inflammatory drugs.** *Prostaglandins* 1983, **26:**631-643.

21. Norton ME, Merril J, Cooper BAB, Kuller JA, Clyman RI: **Neonatal complications after the administration of indomethacin for preterm labor.** *N Engl J Med* 1993, **329:**1602-1607.

22. Vermillion ST, Scardo JA, Lashus AG, Wiles HB: **The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age.** *Am J Obstet Gynecol* 1997, **177:**256-261.

23. Van den Veyver IB, Moise KJ Jr, Ou CN, Carpenter RJ Jr: **The effect of gestational age and fetal indomethacin levels on the incidence of constriction of the fetal ductus arteriosus.** *Obstet Gynecol* 1993, **82:**500-503.

24. Norton ME: **Fetal effects of indomethacin administration during pregnancy.** *Teratology* 1997, **56:**282-292.

25. Alano MA, Ngougmna E, Ostrea EM Jr, Konduri GG: **Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn.** *Pediatrics* 2001, **107:**519-513.

26. Hickok DE, Hollenbach KA, Reilley SF, Nyberg DA: **The association between decreased amniotic fluid volume and treatment with nonsteroidal anti-inflammatory agents for preterm labor.** *Am J Obstet Gynecol* 1989, **160:**1525-1531.

27. van der Heijden B, Gubler MC: **Renal failure in the neonate associated with in utero exposure to non-steroidal anti-inflammatory agents.** *Pediatr Nephrol* 1995, **9:**675.

28. Llanas B, Cavert MH, Apere H, Demarquez JL: **Les effets secondaires du ketoprofène après exposition intra-utérine. Intérêt du dosage plasmatique.** *Arch Pediatr* 1996, **3:**248-253.

29. Peruzzi L, Gianooglio B, Porcellini G, Conti G, Amoro A, Coppo R: **Neonatal chronic kidney failure associated with cyclooxygenase-2 inhibitors administered during pregnancy.** *Minerva Uro Nefrol* 2001, **53:**113-116.

30. Stuart MJ, Gross SJ, Elrad H, Graeber JE: **Effects of acetylsalicylic-acid ingestion on maternal and neonatal hemostasis.** *N Engl J Med* 1982, **307:**909-912.

31. Hertz-Picciotto I, Hopenhayn-Rich C, Golub M, Hooper K: **The risks and benefit of taking aspirin during pregnancy.** *Epidemiol Rev* 1990, **12:**108-148.

32. Di Sessa TG, Moretti ML, Khoury A, Pulliam DA, Arheart KL, Sibai BM: **Cardiac function in fetuses and newborns exposed to low-dose aspirin during pregnancy.** *Am J Obstet Gynecol* 1994, **171:**892-900.

33. Leonhardt A, Bernert S, Watzer B, Schmitz-Ziegler G, Seyberth HW: **Low-dose aspirin in pregnancy: maternal and neonatal aspirin concentrations and neonatal prostanoid formation.** *Pediatrics* 2003, **111:** e77-e81.

34. Horlocker TT, Bajwa ZH, Ashraf Z, Khan S, Wilson JL, Sami N, Peeters-Asdourian C, Powers CA, Schroeder DR, Decker PA, *et al.*: **Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection.** *Anesth Analg* 2002, **95:**1691-1697.

35. Reese J, Zhao X, Ma WG, Brown N, Maziasz TJ, Dey SK: **Comparative analysis of pharmacologic and/or genetic disruption of cyclooxygenase-1 and cyclooxygenase-2 function in female reproduction in mice.** *Endocrinology* 2001, **142:**3198-3206.

36. Sookvanichsilp N, Pulbutr P: **Anti-implantation effects of indomethacin and celecoxib in rats.** *Contraception* 2002, **65:** 373-378.

37. Mendonca LLF, Khamashta MA, Nelson-Piercy C, Hughes GRV: **Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility.** *Rheumatology* 2000, **39:**880-882.

38. Uhler ML, Hsu JW, Fisher SG, Zinaman MJ: **The effect of nonsteroidal antiinflammatory drugs on ovulation: a prospective, randomized clinical trial.** *Fertil Steril* 2001, **76:**957-961.

39. Pall M, Friden BE, Brannstrom M: **Induction of delayed follicular rupture in the human by the selective COX-2 inhibitor rofecoxib: a randomized double blind study.** *Hum Reprod* 2001, **16:**1323-1328.

40. Martini AC, Molina RI, Tissera AD, Ruiz RD, De Cuneo MF: **Analysis of semen from patients chronically treated with low or moderate doses of aspirin like drugs.** *Fertil Steril* 2003, **80:** 221-222.

41. Østensen M: **Safety of non-steroidal anti-inflammatory drugs during pregnancy and lactation.** *Inflammopharmacology* 1996, **4:**31-41.

42. Spigset O, Hägg S: **Analgesics and breast-feeding. Safety considerations.** *Paediatr Drugs* 2000, **2:**223-238.

43. Committee on Drugs. American Academy of Pediatrics: **The transfer of drugs and other chemicals into human milk.** *Pediatrics* 2001, **108:**776-789.

44. Derksen RHW, Khamashta MA, Branch DW: **Management of the obstetric antiphospholipid syndrome.** *Arthritis Rheum* 2004, **50:**1028-1039.

45. Empson M, Lassere M, Craig J, Scott J: **Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant [review].** *Cochrane Database Syst Rev* 2005, **2:**CD002859.

46. Nguyen CM, Harrington RA: **Glycoprotein IIb/IIIa receptor antagonists: a comparative review of their use in percutaneous coronary intervention.** *Am J Cardiovasc Drugs* 2003, **3:** 23.

47. The Matisse Investigators: **Subcutaneous Fondoparinux versus intravenous unfractioned heparin in the initial treatment of pulmonary embolism.** *N Engl J Med* 2003, **349:**1695-1702.

48. Turpie AG, Eriksson BI, Bauer KA, Lassen MR: **New pentasaccharides for the prophylaxis of venous thromboembolism.** *Chest* 2003, **124:**371S-378S.

49. Dempfle CEH: **Minor transplacental passage of fondoparinux in vivo.** *N Engl J Med* 2004, **350:**1914-1915.

50. Olsson SB Executive Steering Committee on behalf of the SPORTIF III investigators: **Stroke prevention with the oral direct thrombion inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial.** *Lancet* 2003, **362:**1691-1698.

51. Fiessinger JN, Huisman MV, Davidson BL, Bounameaux H, Francis CW, Eriksson H, and THRIVE Treatment Study Investigators: **Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial.** *JAMA* 2005, **293:**681-689.

52. Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, and EXULT A Study Group: **Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement.** *N Engl J Med* 2003, **349:**1703-1712.

53. Benediktsson R, Calder AA, Edwards CRW, Seckl JR: **Placental 11b-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure.** *Clin Endocrinol* 1997, **46:**161-166.

54. Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L: **Repeated fetal losses associated with antiphospholipid antibodies; a collaborative randomized trial comparing prednisone with low-dose heparin treatment.** *Am J Obstet Gynecol* 1992, **166:**1318-1323.

55. Pinsky L, DiGeorge AM: **Cleft palate in the mouse: a teratogenic index of glucocorticoid potency.** *Science* 1965, **147:**402-403.

56. Reinisch JM, Simon NG: **Prenatal exposure to prednisone in humans and animals retards intrauterine growth.** *Science* 1978, **202**:436-438.

57. Rodriguez-Pinilla E, Martinez-Frias ML: **Corticosteroids during pregnancy and oral clefts: a case-control study.** *Teratology* 1998, **58**:2-5.

58. Carmichael SL, Shaw GM: **Maternal corticosteroid use and risk of selected congenital anomalies.** *Teratology* 1999, **86**:242-244.

59. Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P, Contributors to the MADRE database: **First trimester exposure to corticosteroids and oral clefts.** *Birth Defects Res A Clin Mol Teratol* 2003, **67**:968-970.

60. Czeizel AE, Rockenbauer M: **Population-based case-control study of teratogenic potential of corticosteroids.** *Teratology* 1997, **56**:335-340.

61. Fraser FC, Sajoo A: **Teratogenic potential of corticosteroids in humans.** *Teratology* 1995, **51**:45-46.

62. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, *et al.*: **Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies.** *Teratology* 2000, **62**:385-392.

63. Källén B: **Maternal drug use and infant cleft lip/palate with special reference to corticoids.** *Cleft Pal Craniofacial J* 2003, **40**:624-628.

64. Scott JR: **Fetal growth retardation associated with maternal administration of immunosuppressives.** *Am J Obstet Gynecol* 1977, **128**:668-676.

65. Czeizel AE, Toth M: **Birth weight, gestational age and medications during pregnancy.** *Int J Gynaecol Obstet* 1998, **60**:245-249.

66. Schmidt PL, Sims ME, Strassner HT, Paul RH, Mueller E, McCart D: **Effect of antepartum glucorticoid administration upon neonatal respiratory distress syndrome and perinatal infection.** *Am J Obstet Gynecol* 1984, **178**:178-186.

67. Cederqvist LL, Merkatz IR, Litwin SD: **Fetal immunoglobin synthesis following maternal immunosuppression.** *Am J Obstet Gynecol* 1977, **129**:687-690.

68. Benediktsson R, Lindsay RS, Noble J, Seckl JR, Edwards CRW: **Glucocorticoid exposure *in utero*: new model for adult hypertension.** *Lancet* 1993, **341**:339-341.

69. Kraus AM: **Congenital cataract and maternal steroid injection.** *J Pediatr Ophthalmol Strabismus* 1975, **12**:107-108.

70. Coté CJ, Meuwissen HG, Pickering RJ: **Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy.** *J Pediatrics* 1974, **85**:324-328.

71. Price HV, Salaman JR, Laurence KM, Langmaid H: **Immunusuppressive drugs and the fetus.** *Transplantation* 1976, **21**:294-298.

72. National Institutes of Health: *Report of the Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcome. NIH Publication no. 95-3784.* Bethesda, MD: National Institute of Child Health and Human Development; 1994.

73. Huang WL, Haper CG, Evans SF, Newnham JP, Dunlop SA: **Repeated prenatal corticosteroid administration delays astrocyte and capillary tight junction maturation in fetal sheep.** *Int J Dev Neurosci* 2000, **19**:487-493.

74. Matthews SG: **Antenatal glucocorticoids and programming of the developing CNS.** *Pediatr Res* 2000, **47**:291-300.

75. Jobe AH, Wada N, Berry LM, Ikegami M, Ervin MG: **Single and repetitive maternal glucocorticoid exposures reduce fetal growth in sheep.** *Am J Obstet Gynecol* 1998, **178**:880-885.

76. French NP, Hagan R, Evans SF, Godfrey M, Newnham JP: **Repeated antenatal corticosteroids: size at birth and subsequent development.** *Am J Obstet Gynecol* 1999, **180**:114-121.

77. Abbasi S, Hirsch D, Davis J, Stouffer N, Debbs R, Gerdes JS: **Effect of single versus multiple courses of antenatal corticosteroids on maternal and neonatal outcome.** *Am J Obstet Gynecol* 2000, **182**:1243-1249.

78. Spinillo A, Viazzo F, Colleoni R, Chiara A, Cerbo RA, Fazzi E: **Two-year infant neurodevelopmental outcome after single or multiple antenatal courses of corticosteroids to prevent complications of prematurity.** *Am J Obstet Gynecol* 2004, **191**:217-224.

79. National Institutes of Health: **Antenatal corticosteroid revisited: repeat courses.** *NIH Consensus Statement* 2000, **17**:1-18.

80. Urban R, Lemancewicz A, Przepiesc J, Urban J, Kretowska M: **Antenatal corticosteroid therapy: a comparative study of dexamethasone and betamethasone effects on fetal Doppler flow velocity waveforms.** *Eur J Obstet Gynecol Reprod Biol* 2005, **120**:170-174.

81. Crowley P: **Prophylactic corticosteroids for preterm delivery.** *Cochrane Database Syst Rev* 2000, **2**:CD000065.

82. Jobe AH, Soll RF: **Choice and dose of corticosteroid for antenatal treatments.** *Am J Obstet Gynecol* 2004, **190**:871-885.

83. Lodygensky GA, Rademaker K, Zimine S, Gex-Fabry M, Lieftink AF, Lazeyras F, Groenendaal F, de Vries LS, Huppi PS: **Structural and functional brain development after hydrocortisone treatment for neonatal chronic lung disease.** *Pediatrics* 2005, **116**:1-7.

84. Katz FH, Duncan BR: **Entry of prednisone into human milk.** *N Engl J Med* 1975, **293**:1154.

85. Öst L, Wettrell G, Bjorkhem I, Rane A: **Prednisolone excretion in human milk.** *J Pediatrics* 1985, **106**:1008-1011.

86. Ruiz-Irastorza G, Khamashta MA, Hughes GR: **Heparin and osteoporosis during pregnancy: 2002 update.** *Lupus* 2002, **11**:680-682.

87. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A: **Transplacental effcts of bisphosphonates on fetal skeletal ossification and mineralization in rats.** *Teratology* 1999, **60**:68-73.

88. Dunlop DJ, Soukop M, McEwan HP: **Antenatal administration of aminopropylidene diphosphonate.** *Ann Rheum Dis* 1990, **49**:955.

89. Illidge TM, Hussey M, Godden CW: **Malignant hypercalciaemia in pregnancy and antenatal administration of intravenous pamidronate.** *Clin Oncol* 1996, **8**:257-258.

90. Rutgers-Verhage AR, de Vries TW, Torringa MJL: **No effects of bisphosphonates on the human fetus.** *Birth Defects Res A* 2003, **67**:203-204.

91. Siminoski K, Fitzgerald AA, Flesch G, Gross MS: **Intravenous pamidronate for treatment of reflex sympathetic dystrophy during breast feeding.** *J Bone Miner Res* 2000, **15**:2052-2055.

92. Phillips-Howard PA, Wood D: **The safety of antimalarial drugs in pregnancy.** *Drug Safety* 1996, **14**:131-145.

93. Costedoat-Chalumeau N, Amoura Z, Aymard G, Huong DLT, Wechsler B, Vauthier D, Dermer ME, Darbois Y, Piette JC: **Evidence of transplacental passage of hydroxychloroquine in humans.** *Arthritis Rheum* 2002, **46**:1123-1124.

94. Wolfe MS, Cordero J: **Safety of chloroquine in chemosuppression of malaria during pregnancy.** *Br Med J* 1985, **290**:1466-1467.

95. Levy M, Buskila D, Gladman DD, Urowitz MB, Koren G: **Pregnancy outcome following first trimester exposure to chloroquine.** *Am J Perinatol* 1991, **8**:174-178.

96. Parke AL: **Antimalarial drugs, systemic lupus erythematosus and pregnancy.** *J Rheumatol* 1988, **15**:607-610.

97. Parke AL, West B: **Hydoxychloroquine in pregnant patients with systemic lupus erythematosus.** *J Rheumatol* 1996, **23**:1715-1718.

98. Buchanan NMM, Toubi E, Khamashta KE, Lima F, Kerslake S, Hughes GRV: **Hydoxychloroquine and lupus pregnancy: review of a series of 36 cases.** *Ann Rheum Dis* 1996, **55**:486-488.

99. Costedoat-Chalumeau N, Amoura Z, Duhaut P, Huong DLT, Sebbough D, Wechsler B, Vauthier D, Denjoy I Lupoglazoff JM, Piette JC: **Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group.** *Arthritis Rheum* 2003, **48**:3207-3211.

100. Borden MB, Parke AL: **Antimalarial drugs in systemic lupus erythematosus. Use in pregnancy.** *Drug Safety* 2001, **24**:1055-1063.

101. Hart CN, Naunton RF: **The ototoxicity of chloroquine phosphate.** *Arch Otolaryngol Head Neck Surg* 1964, **80**:407-412.

102. Akintonwa A, Gbajumo SA, Mabadeje AFB: **Placental and milk transfer of chloroquine in humans.** *Ther Drug Monit* 1988, **10**:147-149.

103. Nation RL, Hackett LP, Dusci LJ, Ilett KF: **Excretion of hydroxychloroquine in human milk.** *Br J Clin Pharmacol* 1984, **17**:368-369.

104. Østensen M, Brown ND, Chiang PK, Aarbakke J: **Hydroxychloroquine in human breast milk.** *Br J Clin Pharmacol* 1985, **28**:357.

105. Klinger G, Morad Y, Westall CA, Laskin C, Spitzer KA, Koren G, Ito S, Buncic RJ: **Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases.** *Lancet* 2001, **358:**813-814.

106. Motta M, Tincani A, Faden D, Zinzini E, Lojacono A, Marchesi A, Frassi M, Biasini C, Zatti S, Chirico G: **Follow-up of infants exposed to hydroxychloroquine given to mothers during pregnancy and lactation.** *J Perinatol* 2005, **25:**86-89.

107. Cimaz R, Brucato A, Meregalli E, Muscarà M, Sergi P: **Electroretinograms of children born to mothers treated with hydroxychloroquine (HCQ) during pregnancy and breastfeeding.** *Arthritis Rheum* 2004, **50:**3056-3057.

108. Borba EF, Turrini-Filho JR, Kuruma KA, Bertola C, Pedalini ME, Lorenzi MC, Bonfa E: **Chloroquine gestational use in systemic lupus erythematosus: assessing the risk of child ototoxicity by pure tone audiometry.** *Lupus* 2004, **13:**223-227.

109. Norgard B, Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT: **Population based case control study of the safety of sulphasalazine used during pregnancy.** *Aliment Pharmacol Ther* 2001, **15:**483-486.

110. Mogadam M, Dobbins WO, Korelitz BI, Ahmed SW: **Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome.** *Gastroenterology* 1981, **80:**72-76.

111. Järnerot G: **Fertility, sterility and pregnancy in chronic inflammatory bowel disease.** *Scand J Gastroenterol* 1982, **17:**1-4.

112. Nielsen OH, Andreasson B, Bondesen S, Jarnum S: **Pregnancy in ulcerative colitis.** *Scand J Gastroenterol* 1993, **18:**735-742.

113. Baocco PJ, Korelitz BI: **The influence of inflammatory bowel disease and its treatment on pregnancy and on fetal outcome.** *J Clin Gastroenterol* 1984, **6:**211-216.

114. Willoughby CP, Truelobe SC: **Ulcerative colitis and pregnancy.** *Gut* 1980, **21:**469-474.

115. Moody GA, Probert C, Jayanthi V, Mayberry JF: **The effects of chronic ill health and treatment with sulphasalazine on fertility amongst men and women with inflammatory bowel disease in Leicestershire.** *Int J Colorect Dis* 1997, **12:**220-224.

116. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA: **Folic acid antagonists during pregnancy and the risk of birth defects.** *N Engl J Med* 2000, **343:**1608-1614.

117. Järnerot G, Anderson S, Esbjörner E, Sandström B, Brodersen R: **Albumin reserve for binding of bilirubin in maternal and cord serum under treatment with sulphasalazine.** *Scand J Gastroenterol* 1981, **16:**1049-1055.

118. Zwi LJ, Becroft DM: **Intrauterine aplastic anemia and fetal hydrops: a case report.** *Pediatr Pathol* 1986, **5:**199-205.

119. Levi S, Libermann M, Levi AJ, Bjarnason I: **Reversible congenital neutropenia associated with maternal sulphasalazine therapy.** *Eur J Pediat* 1988, **148:**174-175.

120. Esbjörner E, Järnerot G, Wranne L: **Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation.** *Acta Paediatr Scand* 1987, **76:**137-142.

121. Branski D, Kerem E, Gross-Kieselstein E, Hurvitz H, Litt R, Abrahmav A: **Bloody diarrhoea – a possible complication of sulphasalazine transferred through human breast milk.** *J Pediat Gastroenterol Nutr* 1986, **5:**316-317.

122. O'Morain C, Smethurst P, Doré CJ, Levi AJ: **Reversible male infertility due to sulphasalazine: studies in man and rat.** *Gut* 1984, **25:**1078-1084.

123. Brent RL: **Teratogen update: reproductive risks of leflunomide (Arava). A pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child.** *Teratology* 2001, **63:**106-112.

124. Chakravarty EF, Sanchez-Yamamoto D, Bush TM: **The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcome.** *J Rheumatol* 2003, **30:**241-246.

125. Polifka JE, Friedman JM: **Teratogen update: azathioprine and 6-mercaptopurine.** *Teratology* 2002, **65:**240-261.

126. Reimers TJ, Sluss PM: **6-Mercaptopurine treatment of pregnant mice: effect on second and third generation.** *Science* 1978, **201:**65-67.

127. The Registration Committee of the European Dialysis and Transplant Association: **Successful pregnancies in women treated by dialysis and kidney transplantation.** *Br J Obstet Gynaecol* 1980, **87:**839-845.

128. Alstead EM, Ritchie JK, Leonard-Jones JE, Farthing MJG: **Safety of azathioprine in pregnancy in inflammatory bowel disease.** *Gastroenterology* 1990, **99:**443-446.

129. Moskovitz DN, Bodian C, Chapman ML, Marion JF, Rubin PH, Scherl E, Present DH: **The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients.** *Am J Gastroenterol* 2004, **99:**656-661.

130. Price HV, Salaman JR, Laurence KM, Langmaid H: **Immunusuppressive drugs and the fetus.** *Transplantation* 1976, **21:**294-298.

131. Coté CJ, Meuwissen HG, Pickering RJ: **Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy.** *J Pediatrics* 1974, **85:**324-328.

132. Davison JM, Dellagrammatikas H, Parkin JM: **Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients.** *Br J Obstet Gynaecol* 1985, **92:**233-239.

133. Rajapakse RO, Korelitz BI, Zlatank I, Baiocco PJ, Gleim GW: **Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease.** *Am J Gastroenterol* 2000, **95:**684-688.

134. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH: **The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study.** *Gastroenterology* 2003, **124:**9-17.

135. Bennett PN: **Azathioprine.** In *Drugs and Human Lactation*. Edited by Bennett PN. Amsterdam: Elsevier; 1988:286-287.

136. Dejaco C, Mittermaier C, Reinisch W, Gasche C, Waldhoer T, Moser H Stroemer G: **Azathioprine treatment and male infertility in inflammatory bowel disease.** *Gastroenterology* 2001, **121:**1048-1053.

137. Pilarski LM, Yacyshyn BR, Lazarovits AI: **Analysis of peripheral blood lymphocyte populations and immune function from children exposed to cyclosporine or to azathioprine *in utero*.** *Transplantation* 1994, **57:**133-144.

138. Scott JR, Branch WD, Holman J: **Autoimmune and pregnancy complications in the daughter of a kidney transplant patient.** *Transplantation* 2002, **73:**815-816.

139. Schröder H, Fogh K: **Methotrexate and its polyglutamate derivates in erythrocytes during and after weekly low-dose oral methotrexate therapy of children with acute lymphoblastic leukaemia.** *Cancer Chemother Pharmacol* 1988, **21:**145-149.

140. Wilson JG, Scott WJ, Ritter EJ, Fradkin R: **Comparative distribution and embryo toxicity of methotrexate in pregnant rats and rhesus monkeys.** *Teratology* 1979, **19:**71-98.

141. Milunsky A, Graef JW, Gaynor MF: **Methotrexate-induced congenital malformations.** *J Pediatrics* 1968, **72:**790-795.

142. Chapa JB, Hibbard JU, Weber EM, Abramowicz JS, Verp MS: **Prenatal diagnosis of methotrexate embryopathy.** *Obstet Gynecol* 2003, **101:**1104-1107.

143. Powell HR, Eckert H: **Methotrexate-induced congenital malformations.** *Med J Aust* 1971, **2:**1076-1077.

144. Schleuning M, Clemm C: **Chromosomal aberrations in a newborn whose mother received cytotoxic treatment during pregnancy.** *N Engl J Med* 1987, **317:**1666-1667.

145. Pizzuto J, Aviles A, Noriega L, Niz J, Morales M, Romero F: **Treatment of acute leukemia during pregnancy: presentation of nine cases.** *Cancer Treat Rep* 1980, **64:**679-683.

146. Kozlowski RD, Steinbrunner JV, MacKenzie AH, Clough JD, Wilke WS, Segal AM: **Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease.** *Am J Med* 1990, **88:**589-592.

147. Feldkamp M, Carey JC: **Clinical teratology counseling and consultation case report: low dose methotrexate exposure in early weeks of pregnancy.** *Teratology* 1993, **47:**533-539.

148. Donnenfeld AE, Pastuszak A, Salkoff Noah J, Schick B, Rose NC, Koren G: **Methotrexate exposure prior to and during pregnancy.** *Teratology* 1994, **49:**79-81.

149. Buckley LM, Bullaboy CA, Leichtman L, Marquez M: **Multiple congenital anomalies associated with weekly low-dose methotrexate treatment of the mother.** *Arthritis Rheum* 1997, **40:**971-973.

150. Østensen M, Hartmann H, Salvesen K: **Low dose weekly methotrexate in early pregnancy. A case series and review of the literature.** *J Rheumatol* 2000, **27:**1872-1875.

151. Krähenmann F, Østensen M, Stallmach Th, Huch A, Chaoui R: *In utero* **first trimester exposure to low-dose methotrexate with increased fetal nuchal translucency and associated malformations.** *Prenat Diagn* 2002, **22:**489-490.

152. Rustin GJS, Booth M, Dent J, Salt S, Rustin F, Bagshawe KD: **Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours.** *Br Med J* 1984, **288:**103-106.

153. Gervaise A, Masson L, de Tayrac R, Frydman R, Fernandez H: **Reproductive outcome after methotrexate treatment of tubal pregnancies.** *Obstet Gynecol Surv* 2005, **60:**175-176.

154. Green DM, Zevon MA, Lowrie G, Seigelstein N, Hall B: **Congenital anomalies in children of patients who received chemotherapy for cancer in childhood and adolescence.** *N Engl J Med* 1991, **325:**141-146.

155. Johns DG, Rutherford LD, Keighton PC, Vogel CL: **Secretion of methotrexate into human milk.** *Am J Obstet Gynecol* 1972, **112:**978-980.

156. Morris LF, Harrod MJ, Menter MA, Silverman AK: **Methotrexate and reproduction in men: Case report and recommendations.** *J Am Acad Dermatol* 1993, **29:**913-916.

157. Sussman A, Leonard JM: **Psoriasis, methotrexate, and oligospermia.** *Arch Dermatol* 1980, **116:**215-217.

158. Aviles A, Diaz-Maqueo JC, Talavera A, Guzman R, Garcia EL: **Growth and development of children of mothers treated with chemotherapy during pregnancy: current status of 43 children.** *Am J Hematol* 1991, **36:**243-248.

159. Mirkes PE: **Cyclophosphamide teratogenesis. A review.** *Teratogen Carcinogen Mutagen* 1985, **5:**75-88.

160. Greenberg LH, Tanaka KR: **Congenital anomalies probably induced by cyclophosphamide.** *JAMA* 1964, **188:**423-426.

161. ToledoTM, Harper RC, Moser RH: **Fetal effects during cyclophosphamide and irradiation therapy.** *Ann Intern Med* 1971, **74:**87-91.

162. Murray CL, Reichert JA, Anderson J, Twiggs LB: **Multimodal cancer therapy for breast cancer in the first trimester of pregnancy. A case report.** *JAMA* 1984, **252:**2607-2608.

163. Kirshon B, Wasserstrum N, Willis R, Herman GE, McCabe ER: **Teratogenic effects of first-trimester cyclophosphamide therapy.** *Obstet Gynecol* 1988, **72:**462-464.

164. Zemlickis D, Lishner M, Erlich R, Koren G: **Teratogenicity and carcinogenicity in a twin exposed in utero to cyclophosphamide.** *Teratogen Carcinogen Mutagen* 1993, **13:**139-143.

165. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G: **Fetal outcome after *in utero* exposure to cancer chemotherapy.** *Arch Intern Med* 1992, **152:**573-576.

166. Enns GM, Roeder E, Chan RT, Ali-Khan Catts Z, Cox VA, Golabi M: **Apparent cyclophosphamide (cytoxan) embryopathy: a distinct phenotype?** *Am J Med Genet* 1999, **86:**237-241.

167. Paladini D, Vassallo M, D'Armiento MR, Cianciaruso B, Martinelli P: **Prenatal detection of multiple fetal anomalies following inadvertent exposure to cyclophosphamide in the first trimester of pregnancy.** *Birth Defects Res A Clin Mol Teratol* 2004, **70:**99-100.

168. Vaux KK, Kahole NC, Jones KL: **Cyclophosphamide, methotrexate, and cytarabine embropathy: is apoptosis the common pathway?** *Birth Defects Res A Clin Mol Teratol* 2003, **67:**403-408.

169. Durodola JI: **Administration of cyclophosphamide during late pregnancy and early lactation: a case report.** *J Nat Med Ass* 1979, **71:**165-166.

170. Gershenson DM: **Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumors.** *J Clin Oncol* 1988, **6:**270-275.

171. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, Pendergrass TW, Robison LL: **Pregnancy outcome of partners of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.** *J Clin Oncol.* 2003, **21:**716-721.

172. Wiernik PH, Duncan JH: **Cyclophosphamide in human milk.** *Lancet* 1971, **i:**912.

173. Waxman J: **Chemotherapy and the adult gonad: a review.** *J R Soc Med* 1983, **76:**144-148.

174. Boumpas DT, Austin HA, Vaughan EM, Yarboro CH, Klippel JH, Balow JE: **Risk of sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy.** *Ann Intern Med* 1993, **119:**366-369.

175. Huong DLT, Amoura Z, Duhaut P, Sbai A, Costedoat N, Wechsler B, Piette JC: **Risk of ovarian failure and fertility after intra-venous cyclophosphamide. A study in 84 patients.** *J Rheumatol* 2002 ;29:2571-2576.

176. Silva CAA, Hallak J, Pasqualotto FF, Barba MF, Saito MI, Kiss MHB: **Gonadal function in male adolescents and young males with juvenile onset systemic lupus erythematosus.** *J Rheumatol* 2002, **29:**2000-2005.

177. Kenney LB, Laufer MR, Grant FD, Grier H, Diller L: **High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood.** *Cancer* 2001, **91:**613-621.

178. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ: **Use of a gonadotropin-releasing hormone analog against premature ovarian failure during cyclophosphamide therapy in women with severe lupus.** *Arthritis Rheum* 2005, **52:**2761-2767.

179. Winter JF, Boice JD, Mulvihill JJ, Stovall M, Frederiksen K, Tawn EJ, Olsen JH: **Chromosomal abnormalities among offspring of child-cancer survivors in Denmark: a population based study.** *Am J Hum Genet* 2004, **74:**1282-1285.

180. Mason RJ, Thomson AW, Whiting PH, Gray ES, Brown PA, Catto GRD, Simpson JG: **Cyclosporine-induced fetotoxicity in the rat.** *Transplantation* 1985, **39:**9-12.

181. Cockburn I, Krupp P, Monka C: **Present experience of Sandimmun in pregnancy.** *Transplant Proc* 1989, **21:**3730-3732.

182. Hussein MM, Mooij JMV, Roujouleh H: **Cyclosporine in the treatment of lupus nephritis including 2 patients treated during pregnancy.** *Clin Nephrol* 1993, **40:**160-163.

183. Armenti VT, Ahlswede KM, Ahlswede BA, Jarrell BE, Moritz MJ, Burke JF: **National transplantation pregnancy registry: outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant recipients.** *Transplantation* 1994, **57:**502-506.

184. Lamarque V, Leleu MF, Monka C, Krupp P: **Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun.** *Transplant Proc* 1997, **29:**2480.

185. Barrou BM, Gruessner AC, Sutherland DE, Gruessner RW: **Pregnancy after pancreas transplantation in the cyclosporin era: report from the International Pancreas Transplant Registry.** *Transplantation* 1998, **65:**524-527.

186. Shaheen FAM, Al-Sulaiman MH, Al-Khader AA: **Long-term nephrotoxicity after exposure to CsA *in utero*.** *Transplantation* 1993, **56:**224-225.

187. Bar Oz B, Hackman R, Einarson T, Koren G: **Pregnancy outcome after CsA therapy during pregnancy: a meta-analysis.** *Transplantation* 2001, **71:**1051-1055.

188. Moretti ME, Sgro M, Johnson DW, Sauve RS, Woolgar MJ, Taddio A, Verjee Z, Giesbrecht E, Koren G, Ito S: **Cyclosporine excretion into breast milk.** *Transplantation* 2003, **75:**2144-2146.

189. Stanley CW, Gottlieb R, Zager R Eisenberg J, Richmond R, Moritz MJ, Armenti VT: **Developmental well-being in offspring of women receiving post-renal transplant.** *Transplant Proc* 1999, **31:**241-242.

190. Di Paolo S, Schena A, Morrone LF, Manfredi G, Stallone G, Derosa C, Procino A, Schena FP: **Immunologic evaluation during the first year of life of infants born to cyclosporine treated female kidney transplant recipients.** *Transplantation* 2000, **69:**2049-2054.

191. Cimaz R, Meregalli E, Biggioggero M, Borghi O, Tincani A, Motta M, Airo P, Meroni PL: **Alterations in the immune system of children from mothers treated with immunosuppressive agents during pregnancy.** *Toxicol Lett* 2004, **149:**155-162.

192. Sgro MD, Barrozino T, Mirghani HM, Sermer M, Moscato L, Akoury H, Koren G, Chitayat D: **Pregnancy outcome post renal transplantation.** *Teratology* 2002, **65:**5-9.

193. Jain AB, Shapiro R, Scantlebury VP, Potdar S, Jordan ML, Flohr J, Marcos A, Fung JJ: **Pregnancy after kidney and kidney-pancreas transplantation under tacrolimus: a single center's experience.** *Transplantation* 2004, **77:**897-902.

194. Jain AB, Reyes J, Marcos A, Mazariegos G, Eghtesad B, Fontes PA, Cacciarelli TV, Marsh JW, de Vera ME, Rafail A, *et al.*: **Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years.** *Transplantation* 2003, **76:**827-832.

195. Kainz A, Harabacz I, Cowlrick IS, Gadgil SD, Hagiwara D: **Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus.** *Transplantation* 2000, **70:**1718-1721.

196. Miniero R, Tardivo I, Curtoni ES, Segoloni GP, La Rocca E, Nino A, Todeschini P, Tregnaghi C, Rosati A, Zanelli P, Dall'Omo AM: **Pregnancy after renal transplantation in Italian patients: focus on fetal outcome.** *J Nephrol* 2002, **15:**626-632.

197. French AE, Soldin SJ, Soldin OP, Koren G: **Milk transfer and neonatal safety of tacrolimus.** *Ann Pharmacother* 2003, **37:** 815-818.

198. Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F: **Mycophenolate mofetil in pregnancy after renal transplantation: a case of major foetal malformations.** *Obstet Gynecol* 2004, **103:**1091-1094.

199. Pergola PE, Kancharla A, Riley DJ: **Kidney transplantation during the first trimester of pregnancy: immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone.** *Transplantation* 2001, **71:**994-997.

200. Armenti VT, Radomski JS, Gaughan WJ, Philips LZ, McGrory CH, Coscia LA; National Transplantation Registry: **Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation.** *Clin Transpl* 2003, **17:**131-141.

201. Radder CM, Roelen DL, van de Meer-Prins, Claas FH, Kanhai HH, Brand A: **The immunologic profile of infants born after maternal immunoglobulin treatment and intrauterine platelet transfusions for fetal/neonatal alloimmune thrombocytopenia.** *Am J Obstet Gynecol* 2004, **191:**815-820.

202. Vesga L, Terdiman JP, Mahadevan U: **Adalimumab use in pregnancy.** *Gut* 2005, **54:**890.

203. Sanchez Munoz D, Hoyas Pablos E, Ramirez Martin Del Campo M, Nunez Hospital D, Guerrero Jimenez P: **Term pregnancy in a patient with Crohn's disease under treatment with adalimumab.** *Gastroenterol Hepatol* 2005, **28:**435.

204. Herold M, Schnohr S, Bittrich H: **Efficacy and safety of a combined rituximab chemotherapy during pregnancy.** *J Clin Oncol.* 2001, **19:**3439.

205. Kimby E, Sverrisdottir A, Elinder G: **Safety of rituximab therapy during the first trimester of pregnancy: a case history.** *Eur J Haematol* 2004, **72:**292-295.

206. Goroir BP, Peppel K, Silva M, Beutler B: **The biosynthesis of tumor necrosis factor during pregnancy: studies with a CAT reporter transgene and TNF inhibitors.** *Eur Cytokine Netw* 1992, **3:**533-537.

207. Hyrich K, Symmons D, Watson K, Silman A: **Pregnancy outcome in women who were exposed to anti-TNF agents: Results from a national population register.** *Arthritis Rheum*, in press.

208. Østensen M, Eigenmann GO: **Etanercept in breast milk.** *J Rheumatol* 2004, **31:**1017-1018.

209. Treacy G: **Using an analogous monoclonal antibody to evaluate the reproductive and chronic toxicity potential for a humanized anti-TNF-α monoclonal antibody.** *Hum Exp Toxicol* 2000, **19:**226-228.

210. Mahadevan U, Kane S, Sandborn WJ, Cohen RD, Hanson K, Terdiman JP, Binion DG: **Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease.** *Aliment Pharmacol Ther.* 2005, **21:**733-738.

211. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR: **Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis.** *Am J Gastroenterol* 2004, **99:**2385-2392.

212. Förger F, Matthias T, Oppermann M, Østensen M, Helmke K: **Infliximab in breast milk.** *Lupus* 2004, **13:**753.

213. Mahadevan U, Terdiman JP, Aron J, Jacobsohn S, Turek P: **Infliximab and semen quality in men with inflammatory bowel disease.** *Inflamm Bowel Dis* 2005, **11:**395-399.