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Vroom, Fokaline; de Walle, Hermien E. K.; van de Laar, Mart A. J. F.; Brouwers, Jacobus R. B. J.; de Jong-van den Berg, Lolkje T. W.

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Disease-Modifying Antirheumatic Drugs in Pregnancy

Current Status and Implications for the Future

Fokaline Vroom,¹ Hermien E.K. de Walle,² Mart A.J.F van de Laar,^{3,4}
Jacobus R.B.J. Brouwers^{1,5} and Lolkje T.W. de Jong-van den Berg¹

- 1 Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration (GUIDE), Groningen, The Netherlands
- 2 Department of Medical Genetics, EUROCAT Registration Northern Netherlands, University Medical Centre Groningen, Groningen, The Netherlands
- 3 Department of Rheumatology, Medisch Spectrum Twente, Enschede, The Netherlands
- 4 University Twente, Enschede, The Netherlands
- 5 Department of Clinical Pharmacy & Clinical Pharmacology, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands

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Abstract

Drug use during pregnancy is sometimes unavoidable, especially in chronic inflammatory diseases such as rheumatoid arthritis (RA). The use of disease-modifying antirheumatic drugs (DMARDs) often starts in the early stage of RA; therefore, women of reproductive age are at risk for exposure to a DMARD at time of conception as well as during pregnancy. The aim of this paper was to review recent literature about DMARDs used for rheumatic diseases in pregnancy and to describe the type of study designs and results reported.

Twenty-nine studies; eight on hydroxychloroquine/chloroquine, thirteen on methotrexate, three on sulfasalazine and six on azathioprine were identified. With respect to hydroxychloroquine, most studies concluded that it could be safely used

in systemic lupus erythematosus or RA. The same conclusions were drawn from the azathioprine studies, but the available evidence is scarce. Although the evidence regarding the safety of methotrexate during pregnancy is conflicting, a high rate of pregnancy losses indicates a risk to the fetus. For each individual case it must be decided whether the benefits outweigh the potential risks. No major teratogenic effects of sulfasalazine were seen although teratogenic effects still can not be excluded. For all other DMARDs, the information on their use in pregnancy was limited.

This review underscores the gross absence of data on safety and risks of DMARD use during conception and pregnancy. While young women use these drugs in pregnancy, this review stresses the importance of good monitoring and further research.

A chronic disease requires continual attention on behalf of the patient and the attending physician. In the case of a progressive chronic inflammatory disease such as rheumatoid arthritis (RA), continuous medication is often inevitable. Because of a change in the objective of pharmacotherapy, i.e. to include disease control as well as symptom control, treatment with disease-modifying antirheumatic drugs (DMARDs) is commenced in the early stages of rheumatic diseases.^[1,2] Therefore, women who are at the reproductive age and who have RA are at risk for exposure to a DMARD or other antirheumatic drugs at the time of conception as well as during pregnancy. Although many women will experience a spontaneous remission of their disease during pregnancy, and therefore continuation of medication might not be necessary, the risk of drug exposure during conception, as well as in the first stage of the pregnancy, remains.

For those who do require medication during their pregnancy, clinical decisions considering the mother as well as the child have to be made with respect to pharmacotherapy. Ideally, these decisions will be based on evidence-based information. However, for obvious reasons, randomised controlled trials (RCTs) hardly ever include pregnant women. As a consequence, decisions in daily practice with respect to the use of DMARDs in pregnancy will be based on animal experiments, observation studies in humans and expert opinion, rather than analytical epidemiological studies such as case-control surveillances or follow-up studies. Mitchell^[3] recom-

mended these kinds of studies as the best available evidence for identifying teratogens.

This article reviews the recent literature on the use of DMARDs in rheumatic diseases in pregnancy and describes the type of study designs employed and the results reported.

A search, using EMBASE, the Cochrane Library and MEDLINE, was conducted of original manuscripts in the medical and pharmacological literature published in English between 1990 and 2004. The generic (adalimumab, anakinra, auranofin, sodium aurothiomalate, aurothioglucose, azathioprine, mercaptopurine, hydroxychloroquine, ciclosporin, cyclophosphamide, etanercept, infliximab, leflunomide, methotrexate, penicillamine and sulfasalazine) or brand names of all DMARDs and biologicals were used at the start of the search, and this search was refined with one of the following keywords or variations: 'pregnant', 'pregnancy outcome', 'birth defects', 'malformations' and 'adverse outcome'. In addition, the reference lists of appropriate articles, related books, guidelines and prescribing information were used.

Primarily, the search was restricted to human studies describing original data; reviews were thereby excluded. If no information could be found on human studies, results from animal studies were considered (briefly discussed in this review). The search was also restricted to the use of monotherapy in rheumatic diseases (i.e. RA and systemic lupus erythematosus [SLE]). Studies describing the use of

Table I. Disease-modifying antirheumatic drugs, their indications, US FDA pregnancy-risk category and dosage regimen in rheumatoid arthritis (RA)^[4,5]

Drug	Pregnancy-risk category ^a	Indications	Dosage
Adalimumab		RA	40 mg/wk sc
Anakinra	B	RA	100 mg/day sc
Auranofin	C	RA	3mg twice daily
Gold sodium thiomalate	C	RA	50mg weekly im (for 20 weeks)
Aurothioglucose	C	RA, JIA, psoriatic arthritis	50mg weekly im
Azathioprine	D	RA, CD, organ transplantation, chronic active hepatitis	1–2.5 mg/kg/day
Chloroquine	C	Malaria prophylaxis, liver amoebiasis, RA, SLE	150–300 mg/day (7–10 weeks), 100–200mg (maintenance treatment)
Ciclosporin	C	Prophylaxis after organ transplantation, psoriasis, RA	2.5 mg/kg (2 doses/day) 3–4 mg/kg/day (maintenance treatment)
Cyclophosphamide	D	Chronic lymphatic leukaemia, autoimmune diseases such as SLE	50–200 mg/day orally
Etanercept	B	RA, polyarticular JIA, psoriatic arthritis	25mg twice weekly
Hydroxychloroquine	C	Malaria prophylaxis, RA, SLE, DLE, photodermatoses	400 mg/day
Infliximab	C	CD, RA, AS	3 mg/kg iv
Leflunomide	X	RA	100 mg/day (3 days), 10–20 mg/day (maintenance treatment)
Methotrexate	X	Cancer, psoriasis, RA	7.5–10 mg/wk or 2.5–5mg thrice weekly
Penicillamine	D	RA, metal intoxication	150 mg/day (start)
Sulfasalazine	B	CD, RA, PU, UC	1000mg twice daily, orally

a See table II for definitions.

AS = ankylosing spondylitis; **CD** = Crohn's disease; **DLE** = discoid lupus erythematosus; **im** = intramuscular; **iv** = intravenous; **JIA** = juvenile idiopathic arthritis; **PU** = proctitis ulcerosa; **RA** = rheumatoid arthritis; **sc** = subcutaneous; **SLE** = systemic lupus erythematosus; **UC** = ulcerative colitis.

antirheumatic drugs in other indications (e.g. azathioprine post-transplantation) were not included.

All eligible publications were systematically scored for information on specific study design (e.g. case report, cohort study or RCT) and outcome of the pregnancies (e.g. number of live births, birth defects and miscarriages or abortions). Comments were noted regarding: (i) the type of birth defect; (ii) the indication for which the medication was taken; (iii) the follow-up time after pregnancy; (iv) the use of co-medication; (v) the exposure time or period of the drug; and (vi) miscellaneous findings.

1. General Issues

Currently, 16 drugs (including four biologicals) are approved by the US FDA for disease modification of RA (table I). In addition to their beneficial

effect on the course of RA, the majority are also labelled for other indications (table I). The dosage regimen varies between DMARDs and also per indication; the dose in RA therapy is shown in table I.

According to the FDA classification, leflunomide and methotrexate (pregnancy-risk category X) should not be used in pregnancy. Cyclophosphamide, azathioprine and penicillamine are in pregnancy-risk category D, meaning that their use during pregnancy may outweigh the teratogenic risks. Most drugs are in pregnancy-risk category or B or C (table II), indicating that adequate and well controlled studies in pregnant women have either not been performed or showed no risk. No drug is in pregnancy-risk category A. Adalimumab is the only agent which has not yet been assigned a pregnancy-risk category.

Table II. Pregnancy-risk categories according to the US FDA^[6]

Category	Criteria
A	Adequate and well controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during the later trimesters)
B	Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well controlled studies of pregnant women have not been conducted
C	Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus
D	Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
X	Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any positive benefit

Thirty studies were identified in the search: hydroxychloroquine/chloroquine (eight studies); methotrexate (13); sulfasalazine (3); azathioprine (6). Hereafter, other DMARDs are only briefly discussed in this article, because of a lack of information.

1.1 Hydroxychloroquine

The use of hydroxychloroquine and chloroquine during pregnancy in small doses has shown to be safe.^[7] However, when larger doses are used for the treatment of acute malaria, oculotoxicity and cochlear toxicity have been reported.^[7]

Since 1990, several studies have investigated the safety of hydroxychloroquine and chloroquine during pregnancy (table III), most describing its use in SLE. One study was performed in a randomised clinical setting,^[11] two studies describe a cohort comparing an exposed group to a non-exposed group.^[9,14] The remaining studies^[7,8,10,12,13] described a cohort exposed to hydroxychloroquine or chloroquine without a comparative group.

None of the studies found an increased risk of congenital malformations. Most studies looked in detail for visual and hearing abnormalities, based on

the suspicion of oculotoxicity and cochlear toxicity, but none of them found an increased association of these specific abnormalities with the use of hydroxychloroquine or chloroquine during pregnancy after a follow-up time varying from 9 months to 19 years.

Five studies^[9-11,13,14] concluded that hydroxychloroquine could be safely used during pregnancy in the treatment of SLE and advised the continuation of therapy during pregnancy rather than discontinuation. However, it must be noted that there is no evidence to suggest any benefit from initiating hydroxychloroquine therapy during pregnancy.

1.2 Methotrexate

The use of methotrexate during pregnancy is described primarily in case reports, although a few studies described an exposed cohort. Kozłowski et al.^[15] found no congenital anomalies among five live-born children in a cohort of ten pregnancies, but the rate of spontaneous abortions was rather high (three of ten pregnancies). Østensen et al.^[22] reviewed four cases of methotrexate use during pregnancy. They found three live-born children without congenital malformations, and one woman had a miscarriage. Lewden et al.^[27] described 28 pregnancies exposed to methotrexate and found 19 live births, of which one had minor neonatal anomalies, five were elective abortions and four were spontaneous abortions.

Donnenfeld et al.^[17] showed, in a series of case reports, ten healthy live births and four first trimester spontaneous abortions (it was not reported if an autopsy was performed). The remaining case reports all reported fetuses with minor or major anomalies^[18-21,23-26] (table IV) except for Feldkamp and Carey^[16] who described a healthy live birth. Feldkamp and Carey^[16] considered that a critical period of exposure to methotrexate (>10mg weekly) exists at 6–8 weeks after conception.

Regarding the high rate of spontaneous abortions seen in the studies mentioned previously,^[15,17,22,27] it must be noted that methotrexate occasionally is used as an abortifacient in the management of an ectopic or unwanted pregnancy.^[20] The guidelines of the American College of Rheumatology advise a female

Table III. Disease-modifying antirheumatic drugs and pregnancy: studies of hydroxychloroquine (HCQ) and chloroquine (CQ)

Study (country, year)	Design	Pregnancy outcome	Comments
Levy et al. ^[7] (Canada, 1991)	Exposed cohort to HCQ and CQ	27 pregnancies: 14 live births, with no congenital abnormalities; six induced abortions; four spontaneous abortions; three stillbirths	<p>Birth defects: all children are physically and developmentally normal, with no clinical evidence of eye or hearing defects</p> <p>Indication: SLE (n = 11), RA (n = 3) or malaria prophylaxis (n = 4)</p> <p>Follow-up: between 9mo and 19y (mean 5.3y)</p> <p>Co-medication: prednisone, aspirin (acetylsalicylic acid), ibuprofen, azathioprine, phenytoin, levothyroxine sodium and penicillamine</p> <p>Exposure: only in first trimester</p> <p>Miscellaneous: more patients were on CQ (n = 16) than on HCQ (n = 8). For 18 women, representing 21 pregnancies, detailed information was reported; further information for the six pregnancies with an induced abortion was not available</p>
Buchanan et al. ^[8] (UK, 1992)	Exposed cohort to HCQ (from larger cohort)	Eight pregnancies: five live births with two additional live births with neonatal SLE; one fetal loss	<p>Birth defects: none presented fetal malformations</p> <p>Indication: SLE (n = 8); arthritis (n = 7)</p> <p>Follow-up: a 4-year period for 76 patients; no detailed information on these eight pregnancies</p> <p>Co-medication: azathioprine, prednisolone and aspirin</p> <p>Exposure: mean 20wk (range 1–39); 200 mg/day (n = 6) or 400 mg/day (n = 2)</p> <p>Miscellaneous: larger cohort included 100 consecutive pregnancies in 76 women, of which eight received HCQ</p>
Buchanan et al. ^[9] (UK, 1996)	Controlled cohort receiving HCQ	<p>Exposed: 32 live births (1 twin); one Down's syndrome; two spontaneous abortions; three stillbirths</p> <p>Control: 44 live births, one with an extra finger; four spontaneous abortions; five stillbirths</p>	<p>Birth defects: no evidence of visual disturbance was observed</p> <p>Indication: cutaneous rash (n = 33) arthritis (n = 18) and serositis (n = 1) in SLE (n = 31) and DLE (n = 2) patients</p> <p>Follow-up: no information</p> <p>Co-medication: azathioprine and prednisolone</p> <p>Exposure: mean 24.4mo (antenatal) and 28.4wk (pregnancy); 200 mg/day (n = 22) or 400mg/day (n = 14) at some point during gestation</p> <p>Miscellaneous: HCQ continuation is probably safe during pregnancy in patients with SLE, but there is no obvious advantage in commencing treatment</p>
Parke and West ^[10] (USA, 1996)	Exposed cohort to HCQ	Nine pregnancies: nine live births	<p>Birth defects: to date, no visual or hearing abnormalities have been reported and development appears normal</p> <p>Indication: SLE</p> <p>Follow-up: mean 33mo; routine examinations have not been done in all children</p> <p>Co-medication: prednisone, subcutaneous heparin and aspirin</p> <p>Exposure: throughout pregnancy; 200 mg/day or 200mg every other day</p> <p>Miscellaneous: it is safer to continue HCQ rather than to discontinue because of pregnancy</p>

Continued next page

Table III. Contd

Study (country, year)	Design	Pregnancy outcome	Comments
Levy <i>et al.</i> ^[11] (Brazil, 2001)	Randomised controlled study; HCQ or PL	20 pregnancies Receiving HCQ: ten live births Receiving PL: nine live births; one died after delivery at 25 wks of gestation	Birth defects: clinical examination was normal and no auditory deficit occurred. Examination of eyes was normal in all children Indication: HCQ (eight with SLE; two with DLE); PL (nine with SLE; one with DLE) Follow-up: examination at age 1.5–3 years Co-medication: prednisone and aspirin Exposure: mean 11wk (start) to 12wk after delivery Miscellaneous: HCQ is safe in pregnancy with SLE; final prednisone dosage was decreased in HCQ recipients and increased in PL recipients
Klinger <i>et al.</i> ^[12] (Canada, 2001)	Exposed cohort to HCQ (14) or CQ (7)	21 pregnancies: 20 live births (one twin), one with congenital birth defect; one spontaneous abortion	Birth defects: no visual or ophthalmological abnormalities in any of the exposed children Indication: SLE or RA Follow-up: ophthalmological examination at mean 2.8 ± (SD) 2.9y Co-medication: no information Exposure: mean: 7.2 ± 2.9mo; 317 ± 109 mg/day (HCQ) and 332 ± 116 mg/day (CQ) Miscellaneous: recruited through the Mother Risk Programme (Canada); inclusion criteria: ≥1mo of daily CQ or HCQ during pregnancy
Motta <i>et al.</i> ^[13] (Italy, 2002)	Exposed cohort to HCQ	35 pregnancies: 35 live births, with no congenital malformations	Birth defects: no baby had ocular symptoms or complications because of maternal treatment Indication: SLE (n = 19); scleroderma (n = 3); undifferentiated CTD (n = 2); mixed CTD (n = 4); dermatomyositis (n = 1); primary antiphospholipid syndrome (n = 4); and RA (n = 1) Follow-up: an ophthalmological assessment was done at birth and again at 1y in 16 infants Co-medication: no information Exposure: 200 mg/day for ≥1 year before pregnancy and throughout gestation Miscellaneous: data seem to confirm safety of HCQ treatment during pregnancy
Costedoat-Chalumeau <i>et al.</i> ^[14] (France, 2003)	HCQ cohort	Exposed (n = 133): 117 live births, with three malformations; 15 spontaneous abortions; one fetal death; no induced abortions Control (n = 70): 59 live births, with four malformations; seven spontaneous abortions; two fetal deaths; two induced abortions	Birth defects: no visual, hearing, growth or developmental abnormalities were reported Indication: SLE (n = 69 exposed; n = 41 control); miscellaneous/unclassified CTD (n = 13/4); primary Sjögren's syndrome (n = 8/8) Follow-up: mean age 26mo (range 12–108mo) Co-medication: prednisone (n = 108/56); aspirin (n = 112/54); low molecular weight heparin (n = 35/13); azathioprine (n = 2/2); intravenous immunoglobulin (n = 2/0) Exposure: HCQ ≥6mo prior to pregnancy and continued throughout gestation; 200mg twice daily (n = 122); 200 mg/day (n = 11) Miscellaneous: findings support preliminary evidence for the safety of HCQ during pregnancy

HCQ = chloroquine; CTD = connective tissue disease; DLE = discoid lupus erythematosus; PL = placebo; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

patient, using methotrexate to wait at least one ovulatory cycle after discontinuation of methotrexate therapy before attempting to conceive because of its teratogenic potential.^[1]

The evidence regarding safety of methotrexate during pregnancy is conflicting, although a critical period and dose for exposure are proposed. The high rate of pregnancy losses indicates a risk to the fetus and, therefore, in each individual patient, consideration regarding the use of methotrexate before, as well as during, pregnancy has to be made. However, some situations, such as exposure after the first trimester in a severe case of RA, may lead to the conclusion that the benefits of using methotrexate to control disease activity may outweigh the potential risks. Although some healthy pregnancies have occurred after early methotrexate exposure, recommendations to stop methotrexate as soon as a pregnancy is discovered are in order. Clinical research is warranted to determine the delay between cessation of methotrexate and safe conception.

1.3 Sulfasalazine

A population-based case control study (based on 22 865 malformed offspring and 38 151 healthy controls) by Nørgård et al.^[29] showed no increased prevalence of congenital malformations among children born to women treated with sulfasalazine during pregnancy. The reported use of sulfasalazine during pregnancy was low (0.07%).

Källén^[30] studied children with orofacial clefting (n = 1044) extracted from a large birth registry (n = 576, 873) and observed three cases of sulfasalazine use during pregnancy (risk ratio [RR] = 3.0; 95% CI 0.62, 8.77). Among the total population, he found 515 users of sulfasalazine.

In contrast, Koyama et al.^[28] described a case of a neonate with holoprosencephaly, born to a woman with continuous sulfasalazine treatment before and during pregnancy. It was the first case report of this type of malformation after sulfasalazine use.

The above described sulfasalazine studies (summarised in table V) are in accordance with its FDA pregnancy-risk category B; no major teratogenic

effects of were seen, although the risk teratogenic events can not be excluded.

1.4 Azathioprine and Mercaptopurine

One case report by Oefflerbauer-Ernst et al.^[36] showed one healthy child after exposure to azathioprine *in utero*. Francella et al.^[35] studied mercaptopurine, an active metabolite of azathioprine, and found no statistically significant increase in major malformations and some other outcomes. The authors concluded that before conception, at conception or during pregnancy this drug appeared to be safe. Ramsey-Goldman et al.^[32] reported on several immunosuppressive drugs being used before or during pregnancy; azathioprine was the only drug administered during pregnancy. Although they found that the overall survival of women using immunosuppressive drugs prior to or during pregnancy encouraging, they questioned their safety and long-term mutagenic effects. Heneghan et al.^[33] and Alstead et al.^[31] studied an exposed cohort, selected from a larger cohort, and concluded that the use of azathioprine during pregnancy appeared to be generally safe. Nørgård et al.^[34] reported the only study which showed an increased risk of malformations, although this could be confounded by disease activity. The above studies are summarised in table VI.

1.5 Miscellaneous Disease-Modifying Antirheumatic Drugs

1.5.1 Biologicals

Adalimumab

Information on the effects of adalimumab (approved by the FDA in 2003) in human pregnancy were not found during the search. The product leaflet declared that there was no indication from an animal study of maternal toxicity, embryo toxicity or teratogenicity.^[37]

Infliximab

Information from a database maintained by the manufacturer showed 131 women exposed to infliximab during pregnancy,^[38] and outcome data were available for 96 women. Sixty-four pregnancies delivered a live-born child, miscarriage occurred in 14

Table IV. Disease-modifying antirheumatic drugs and pregnancy: studies of methotrexate (MTX)

Study (country, year)	Design	Pregnancy outcome	Comments
Kozlowski et al. ^[15] (USA, 1990)	Exposed cohort	10 pregnancies: five live-born infants; three spontaneous abortions; two elective abortions	Birth defects: none of the children exhibited congenital abnormalities Indication: definite or classical adult RA (n = 6); polyarticular juvenile RA (n = 1); allergic angiitis (n = 1) Follow-up: mean 11.5y (range 3.7–16.7y) Co-medication: aspirin, NSAIDs, HCQ, gold preparations and cytotoxics Exposure: 7.5 or 10 mg/wk orally. All patients stopped MTX within first trimester; one was exposed until 15th week of gestation Miscellaneous: data extracted from patients who unknowingly became pregnant; details gathered by telephone interview; selection criteria: receiving MTX from January 1961 to July 1986
Feldkamp and Carey ^[16] (USA, 1993)	Case report	One healthy live birth	Birth defects: a healthy full-term male infant was born Indication: RA Follow-up: examination at age 12wk Co-medication: ibuprofen, misoprostol, cimetidine or sucralfate (chronic), cefaclor, oxycodone and aspirin Exposure: time from conception to discontinuation of MTX was minimal 3d to maximal 39d gestation; 7.5 mg/wk Miscellaneous: this case report was followed by a literature review

Continued next page

Table IV. Contd

Study (country, year)	Design	Pregnancy outcome	Comments
Donnenfeld et al. ^[17] (USA, 1994)	Case reports	14 pregnancies: ten healthy live births, one with cavernous haemangioma; four first trimester spontaneous losses	Birth defects: one child with cavernous haemangioma Indication: RA (n = 7); cancer (n = 2); bacterial infection (n = 1); psoriasis (n = 1); unknown (n = 3) Follow-up: no information Co-medication: aspirin, plaquenil, prednisone, dactinomycin and other chemotherapeutic agents Exposure: within 1y of conception or during pregnancy Miscellaneous: the small number of patients in this sample precluded any conclusions regarding whether an association exists between preconceptional MTX exposure and spontaneous pregnancy loss; data obtained through questionnaires using data from the teratogen information services (OTIS and ENTIS)
Buckley et al. ^[18] (USA, 1997)	Case report	One live-birth infant with multiple congenital anomalies	Birth defects: the congenital abnormalities described are typically seen with exposure to an antifolate and include facial, skeletal and cardiac abnormalities Indication: polyarticular juvenile RA Follow-up: infant died at age 6mo Co-medication: folic acid, NSAIDs and gold preparations Exposure: total dose of ~100mg over a period of 8wk Miscellaneous: an autopsy was not performed
Del Campo et al. ^[19] (USA, 1997)	Case report	One live birth with structural anomalies typical of maternal MTX exposure	Birth defects: fetal aminopterin/MTX syndrome and developmental delay Indication: chronic severe psoriasis Follow-up: 2y and 10mo Co-medication: none taken Exposure: 12.5mg three times weekly throughout the first 8wk post-conception Miscellaneous: no information

Continued next page

Table IV. Contd

Study (country, year)	Design	Pregnancy outcome	Comments
Bawle et al. ^[20] (USA, 1998)	Case reports	Three pregnancies: three live births, all with anomalies	Birth defects: fetal MTX syndrome (case 1); mild manifestation of fetal MTX syndrome (cases 2 and 3) Indication: termination of pregnancy (cases 1 and 3); cancer (case 2) Follow-up: 26y (case 1); 9y (case 2); 3.5y (case 3) Co-medication: fluorouracil and radiation therapy (case 2) Exposure: 6wk post-conception (case 1); 7.5wk till 28.5wk post-conception (case 2); 11–23 wk post-conception (case 3) Miscellaneous: early psychomotor development was normal (cases 1 and 3); 'mentally deficient' to low 'borderline' limits of intelligence compared with other students his age (case 2)
Giannakopoulou et al. ^[21] (Greece, 2000)	Case report	One live birth with only minor malformation	Birth defects: an inguinal hernia was diagnosed Indication: cancer Follow-up: growth and development, up to the 22nd month, are normal Co-medication: cyclophosphamide and fluorouracil Exposure: during first and second trimester Miscellaneous: no information
Østensen et al. ^[22] (Norway, 2000)	Exposed cohort	Four pregnancies: three live births, with no congenital malformations; one miscarriage	Birth defects: children have developed physically and mentally according to their present age Indication: psoriatic arthritis; juvenile chronic arthritis; RA Follow-up: 1mo, 8mo and 5y Co-medication: naproxen, folic acid (at time of conception) Exposure: median 4y; between 5mg and 15mg weekly Miscellaneous: miscarriage at wk 8, congenital malformations not investigated

Continued next page

Table IV. Contd

Study (country, year)	Design	Pregnancy outcome	Comments
Krähenmann et al. ^[23] (Switzerland, 2002)	Case report	One terminated pregnancy; fetus had multiple malformations	Birth defects: fetus was diagnosed with complete AVSD and left-sided diaphragmatic hernia Indication: RA Follow-up: pregnancy was terminated at 19wk Co-medication: folic acid (irregularly) Exposure: at wk 4+6d and wk 5+6d of gestation: two 10mg injections Miscellaneous: no information
Nguyen et al. ^[24] (USA, 2002)	Case report	One terminated pregnancy; fetus had multiple internal and external malformations	Birth defects: multiple internal and external malformations Indication: psoriasis Follow-up: elected termination at 20wk Co-medication: sertraline Exposure: 7.5 mg/day orally for 2d at 3.5wk post-conception Miscellaneous: autopsy revealed craniofacial, axial skeletal, cardiopulmonary and gastrointestinal abnormalities
Granzow et al. ^[25] (USA, 2003)	Case report	One live birth with an incomplete cleft palate and associated asymmetric deformities of the toes on both feet	Birth defects: incomplete cleft palate and associated asymmetric deformities of the toes on both feet Indication: management of a molar pregnancy Follow-up: at 38d Co-medication: no information Exposure: approximately the 8th wk of gestation Miscellaneous: no information
Chapa et al. ^[26] (USA, 2003)	Case report	One terminated pregnancy, with fetal anomalies	Birth defects: absent or markedly shortened long bones; abnormal positioning of the hands; micrognathia; echogenic bowel and two-vessel umbilical cord Indication: failed pregnancy termination Follow-up: pregnancy termination at 26wk Co-medication: misoprostol Exposure: at 6wk; 75mg intramuscular Miscellaneous: no information

Continued next page

Table IV. Contd

Study (country, year)	Design	Pregnancy outcome	Comments
Lewden et al. ^[27] (France, 2004)	Exposed cohort	28 pregnancies; 19 live births, one with minor neonatal anomalies; five elective abortions; four spontaneous abortions	<p>Birth defects: one child with minor anomalies; metatarsus varus and eyelid angioma</p> <p>Indication: RA; Takayasu's arthritis; psoriatic arthritis and dermatomyositis or ankylosing spondylitis</p> <p>Follow-up: exposure between 1993 and 2001</p> <p>Co-medication: NSAIDs and corticosteroids</p> <p>Exposure: mean 10.5 mg/wk; discontinuation during first 4wk (n = 16); still treated between 5 and 8wk (n = 10); stopped after 8wk (n = 1); from wk 6 to 11 (n = 1)</p> <p>Miscellaneous: no strong teratogenic risk associated with low-dose MTX, provided that the drug is discontinued as early as possible in pregnant women; information gathered via pharmacovigilance network and teratology information services</p>

AVSD = atrioventricular septal defect; **ENTIS** = European Network of Teratology Information Services; **HCCQ** = hydroxychloroquine; **OTIS** = Organization of Teratology Services; **RA** = rheumatoid arthritis.

pregnancies and 18 pregnancies underwent elective abortion.

Srinivasan^[39] reported on an exposed cohort of 27 women exposed to infliximab immediately prior to or during the first trimester of pregnancy. Data were available for ten women; six women had live-born children, of whom one died a few days after birth, three reported a miscarriage and one underwent an elective abortion.

Burt et al.^[40] reported one case of a woman receiving infliximab shortly after becoming pregnant; a healthy child was born and no neonatal abnormality was noted.

Chakravarty et al.^[41] reported two pregnancies exposed to infliximab; one healthy baby was born, and one outcome was not stated.

Etanercept

Exposure to etanercept occurred in 15 pregnancies reported by Chakravarty et al.^[41] Six healthy children were born, four were still pregnant at the time of the report, one had an elective abortion and one had a spontaneous abortion.

Anakinra

No information about the use of anakinra in pregnancy was found in literature. The prescribing information declared that no effect on early development, embryo-fetal development or peri- and postnatal development was observed.^[42]

1.5.2 Leflunomide

The active metabolite of leflunomide is teratogenic in rats and rabbits and may cause fetal harm in humans.^[43] Therefore, leflunomide must not be administered to pregnant women or women who wish to become pregnant. A safety update by the manufacturer of leflunomide^[44] involving 310 exposures during pregnancy reported 164 cases of which the outcome was known. Forty-three pregnancies were terminated, 36 women had miscarriages and 85 ended in live births (seven of whom were born with congenital malformations).

1.5.3 Ciclosporin

Although ciclosporin is a pregnancy-risk category C drug (meaning that animal studies either showed an adverse effect or have not been conduct-

ed and that there are no adequate and well controlled studies in pregnant women), a meta-analysis has been conducted by Bar et al.^[45] The authors concluded that the use of ciclosporin did not appear to be a major human teratogen. They found a non-significant odds ratio for malformations of 3.83 (95% CI 0.75, 19.6).

1.5.4 Cyclophosphamide

Since 1990, only a few cases have been reported on the use of cyclophosphamide during pregnancy.^[46-48] Cyclophosphamide is considered to be teratogenic and is classified as D in the pregnancy-risk category. Two cases reported a live-born child,^[46,48] one case reported a child who died 12 days after birth and was diagnosed with a pattern of malformations referred to as cyclophosphamide embryopathy^[47] and one case reported an unknown outcome. In addition to their own case report, Vaux et al.^[47] give an overview of all cases reported in the literature between 1964 and 2003. In particular, they described craniofacial and limb defects and showed that all reported cases had similar patterns of malformations.

1.5.5 Gold Preparations

No reports about the use of gold preparations in pregnancy could be found after 1990. According to the product leaflets of aurothioglucose,^[49] auranofin^[50] and sodium aurothiomalate,^[51] all showed teratogenic effects in animal studies. The product leaflet of aurothioglucose was thought to be teratogenic in early human studies but later studies indicate that it might not be harmful. (This information could not be confirmed by this literature search). Despite this, gold preparations are not recommended for use in pregnancy.^[49]

1.5.6 Penicillamine

Since 1990, several case reports have been published on the use of penicillamine in human pregnancy.^[52-61] Penicillamine is in the D pregnancy-risk category. All reported cases described the use of penicillamine in Wilson's disease, an inheritable autosomal recessive disorder of copper accumulation.^[56] The results of the case reports are ambig-

uous, both healthy children and children with anomalies were born.

2. Discussion

This review underscores the gross absence of data on the safety and risks of DMARD use during conception and pregnancy. Regulatory authorities, scientific societies and rheumatologists and other specialists are obliged to dissuade the continuation of most DMARDs if pregnancy is desired. Nevertheless, RA patients do become pregnant and sometimes continue drug use of DMARDs.

Since 1990, a limited number of studies on DMARD use during pregnancy were found. Apart from two large case-control studies (22 865 cases vs 38 151 controls^[29] and 1044 cases vs 576 873 controls^[30]) and one large cohort (19 430 women),^[34] most studies are either small cohorts ranging between 4 and 515 (exposed) women or case reports ranging between 1 and 14 cases.

According to Mitchell,^[3] two main study approaches have been developed, with the purpose of identifying teratogens after marketing approval of a drug, i.e. follow-up studies and case-control surveillances. In follow-up studies, small numbers are sufficient to identify high-risk teratogens. But for drugs which have a moderate or low teratogenic potential, large numbers of exposed persons are needed, especially when the outcome is rare. Case-control studies have more substantial statistical power and are therefore more appropriate to identify moderate teratogenic drugs. Case-control studies can provide safety and risk estimates that become more precise as data accumulate.

The results for the use of methotrexate in pregnancy reconfirm the category X of the FDA categorisation, stating that the possible risk clearly outweighs any positive benefit. The advice to wait at least one ovulatory cycle after discontinuation of methotrexate before attempting to conceive remains valid. In contrast to the FDA categorisation, this review suggests that hydroxychloroquine in moderate doses can be safely used during pregnancy in the treatment of SLE or RA. However, these conclusions are based on small exposed cohorts.

Table V. Disease-modifying antirheumatic drugs and pregnancy: studies of sulfasalazine (SSZ)

Study (country, year)	Study design	Pregnancy outcome	Comments
Koyama <i>et al.</i> ^[28] (Japan, 1996)	Case report	One neonate with holoprosencephaly	Birth defects: dysmorphic features: microcephaly; flat nose; median clefts of lip and palate and hypotelorism Indication: CD Follow-up: child died at 6mo Co-medication: ferostatin; kernac (plant) and protective drug for gastritis or gastric ulcer Exposure: treatment before and during pregnancy; 3 g/day Miscellaneous: an autopsy was not undertaken; pregnancy occurred after treatment with human menopausal gonadotropin and human chorionic gonadotropin and artificial insemination
Nørgård <i>et al.</i> ^[29] (Hungary, 2001)	Case control (population based)	22 865 malformed offspring; 38 151 healthy controls. Exposed to SSZ: 17 cases; 26 controls	Birth defects: no significant increased prevalence of selected congenital abnormalities Indication: CD or UC (except one control) Follow-up: 1980–1996 Co-medication: concomitant drug use was not analysed separately because of insufficient numbers of women without co-medication Exposure: first, second and third trimester; 4–8 g/day orally Miscellaneous: based on self-reported use or logbook information; autopsy was obligatory for all infant deaths and was usual in still-born fetuses during the study period
Källén ^[30] (Sweden, 2003)	Case control	Population: 576 873 (Medical Birth Registry) Identified orofacial cleft: 1044 SSZ exposure in population: 515 SSZ exposure among orofacial cleft: three (observed)	Birth defects: in Sweden, maternal drug use is not a major contributor to orofacial clefts Indication: UC and CD (for three cases) Follow-up: July 1995 through December 2001 Co-medication: glucocorticoids and naproxen (for 1 of 3 cases) Exposure: first trimester Miscellaneous: risk ratio (observed/expected) 3.0 (95% CI 0.62, 8.77); orofacial cleft rate 18.1 per 10 000 births (1044/576 873); data were collected prospectively

CD = Crohn's disease; **UC** = ulcerative colitis.

Azathioprine is categorised as a drug that, despite indications of fetal risks, can be considered during pregnancy if the benefits of therapy outweigh the potential risks. The results of this review are in line with this advice and conclude that azathioprine seems to be generally safe in pregnancy. Only one large cohort was conducted, which found an increased risk for malformations, which could be confounded by disease activity.^[34] It must be realised that for some drugs (e.g. sulfasalazine and azathioprine), information is limited to their use in rheumatic diseases; studies describing the use of these drugs in other indications may broaden the discussion, but are not likely to change the conclusions found in this review.

Meijer et al.^[62] and Hernandez-Diaz et al.^[63] described the use of folic acid antagonists, but neither study reported a protective effect of folic acid when methotrexate or sulfasalazine is used. Hernandez-Diaz et al.^[63] showed a reduction of the OR of having an infant with a neural tube defect when carbamazepine or trimethoprim, both folic acid antagonists, were administered in combination with folic acid compared with women who received the drugs without folic acid.

Information about other DMARDs is even more limited; studies are mostly based on case reports or small exposed cohorts. A recent study with respect to cyclophosphamide by Clowse et al.^[64] showed that all four pregnancies exposed to cyclophosphamide resulted in first trimester miscarriage thus confirming its category D pregnancy-risk status.

It must be noted that small studies are not powered to detect any moderate or low risk for birth defects. If, for example, a certain birth defect occurred in 1 of 1000 births, a sample size of approximately 600 can detect approximately a 20-fold or higher increase of that birth defect. However, none of the cohorts in this review had sample sizes >600 and are by definition too small to detect a small or moderate increase in the prevalence of specific birth defects.

Albrecht et al.^[65] conducted a study evaluating the impact of case series and case reports describing

innovative treatment. They concluded that case series and reports can be well received and have significant influence on subsequent literature and possibly on clinical practice. They reported that the case reports and case series they found in *The Lancet* were followed by a clinical trial in 17% and 33% of cases, respectively. Because pregnant women are usually excluded from clinical trials, case reports and case series are the first signals in clinical practice of an adverse effect or outcome after exposure to a drug. Ideally, these should be followed by a case-control surveillance or follow-up study. This overview of the literature showed that although many case reports, case series and small exposed cohorts did function as a signal for a possible adverse outcome, they were almost never followed by a case-control surveillance or follow-up study. Perhaps more time is needed to collect enough data to conduct proper case-control surveillances or large cohort studies.

This review focused on recent literature, assuming that older information is taken into account by the construction of the pregnancy-risk categorisation. Recent information on the influence of DMARDs on pregnancy and pregnancy outcomes is limited. This might be explained by the focus on the use of DMARDs in rheumatic disease and the use of the drugs as monotherapy. Another reason might be the timing of the approval for a particular drug on the market. Drugs recently approved, such as etanercept and infliximab, are used for a selected group to whom existing therapy is not effective anymore. Clinical trials exclude pregnant women; therefore, it is to be expected that the information on these drugs after drug approval is limited.

None of the studies reported on the relationship between exposure to the drug, genetic variability and the effects of these genetic factors. This might not have been an issue when these studies were conducted; however, this will be an important factor in the future and therefore has to be considered.

Despite limited information on the influence of DMARDs in pregnant women with a rheumatic disease, these drugs are used in practice and despite the advice to avoid pregnancy patients become preg-

Table VI. Disease-modifying antirheumatic drugs and pregnancy: studies of azathioprine/mercaptopurine (AZA/MP)

Study (country, year)	Design	Pregnancy outcome	Comments
Alstead et al. ^[31] (UK, 1990)	Exposed cohort to AZA	16 pregnancies: 15 live births (one twin), with no congenital abnormalities; two terminations	Birth defects: all alive and well Indication: CD (n = 14) or UC (n = 2) Follow-up: 6mo to 16y Co-medication: prednisolone (n = 12), sulfasalazine (n = 6), mesalazine (n = 1) and codeine phosphate (n = 1) Exposure: seven women continued AZA throughout pregnancy; five stopped before 16wk gestation Miscellaneous: AZA appears not to be harmful to the fetus in early or late pregnancy in humans in doses used in IBD
Ramsey-Goldman et al. ^[32] (USA, 1993)	Exposed cohort to AZA (from larger cohort)	Nine pregnancies: eight live births (one twin), with no congenital malformations; one neonatal death; one miscarriage	Birth defects: there were no congenital malformations in the infants exposed to AZA during pregnancy Indication: SLE Follow-up: mean 6.1y (range 1.5–13y) Co-medication: no information Exposure: prior to pregnancy (n = 5) and prior, as well as during, pregnancy (n = 9) Miscellaneous: final study group consisted of 334 women; 14 patients (23 pregnancies) were exposed before or during pregnancy to AZA (n = 9) or ciclosporin (n = 3) or methotrexate (n = 1) or combined AZA and ciclosporin (n = 1); only AZA was administered during pregnancy
Heneghan et al. ^[33] (UK, 2001)	Exposed cohort to AZA, prednisolone and ciclosporin (from larger cohort)	31 live births, with two abnormalities; one fetal death (25wk); one fetal loss (20wk); one termination; two miscarriages	Birth defects: Perthes' disease; severe mental and physical handicap (neither mother received AZA) Indication: AIH Follow-up: median 10y (range 1.5–16y) Co-medication: prednisolone and ciclosporin Exposure: (at conception) AZA 1 mg/kg/day (n = 2) or 2 mg/kg/day (n = 4); AZA 1 mg/kg/day (n = 8) or 2 mg/kg/day (n = 1) plus prednisolone; prednisolone alone (n = 7) and ciclosporin (n = 1) Miscellaneous: AZA appeared to be generally safe and without adverse outcomes
Nørgård et al. ^[34] (Denmark, 2003)	Cohort AZA (or MP)	Exposed: 11 live births; two malformations (one died). Control: 19 418 live births; 711 malformations	Birth defects: aphakia and multiple malformations Indication: UC; CD; myasthenia gravis; vasculitis; IgA nephritis; AIH; glomerulonephritis; and renal transplant Follow-up: no information Co-medication: prednisolone, ciclosporin, ursodeoxycholic acid and antihypertensive drugs Exposure: (variable) 30d before conception to third trimester Miscellaneous: odds ratio for malformation = 6.7 (95% CI 1.4, 32.4); the data indicate an increased risk of malformations; associations could be confounded by disease activity; study period was 1 January 1991 to 31 December 2000

Continued next page

Table VI. Contd

Study (country, year)	Design	Pregnancy outcome	Comments
Francella et al. ⁽³⁵⁾ (USA, 2003)	Exposed cohort to MP (from larger cohort)	39 pregnancies: 32 live births, with one major birth defect; three minor birth defects; five spontaneous abortions; one elective abortion; one miscarriage	Birth defects: there was no statistical difference in major congenital malformations among male or female patients taking MP compared with controls Indication: IBD Follow-up: minimum 18mo from birth Co-medication: Antibacterials, sulfasalazine, mesalazine, systemic and local corticosteroids, anti diarrhoeals and antispasmodics Exposure: cohort exists of females (f) and males (m), divided into 4 groups: (A) MP before conception (f/m); (B1) MP at time of conception (f/m); (B2) during entire pregnancy (f); (C) pregnancies before MP treatment (f/m) Miscellaneous: MP use before or at conception or during pregnancy appeared to be safe
Oefflerbauer-Ernst et al. ⁽³⁶⁾ (Austria, 2004)	Case report (AZA)	One healthy baby	Birth defects: healthy baby Indication: CD Follow-up: no information Co-medication: no information Exposure: therapy at conception and throughout pregnancy Miscellaneous: discontinuation of AZA and MP treatment seems to be no longer indicated if planning a pregnancy

AIH = autoimmune hepatitis; **CD** = Crohn's disease; **IBD** = inflammatory bowel disease; **SLE** = systemic lupus erythematosus; **UC** = ulcerative colitis.

nant while receiving DMARDs. Therefore, we suggest that a good monitoring system for DMARD use during pregnancy, which reports all pregnancies irrespective of pregnancy outcome, could be of great help to contribute to the research of possible teratogenicity of DMARDs. In addition, it could help to provide more solid information to patients and healthcare professionals in RA treatment.

3. Conclusion

In conclusion, this review underscores the gross absence of data on safety and risks of DMARD use during conception and pregnancy. Clinicians working with young patients using DMARDs are obliged to dissuade the continuation of most DMARDs in case pregnancy is desired. Nevertheless, this review shows that RA patients become pregnant and sometimes continue drug use and; therefore, further research on the safety and risks of these drugs during pregnancy is necessary.

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Correspondence and offprints: Dr *Lolkje T.W. de Jong-van den Berg*, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.

E-mail: lt.w.de.jong-van.den.berg@rug.nl

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