The Use of Disease Modifying Antirheumatic Drugs in Women with Rheumatoid Arthritis of Childbearing Age: A Survey of Practice Patterns and Pregnancy Outcomes

ELIZA F. CHAKRAVARTY, DEANNA SANCHEZ-YAMAMOTO, and THOMAS M. BUSH

ABSTRACT. ***Objective.*** To describe the practices of rheumatologists when prescribing the disease modifying antirheumatic drugs (DMARD) methotrexate (MTX), leflunomide (LF), etanercept (ET), and infliximab (IN) to women of childbearing age with rheumatoid arthritis (RA) and the pregnancy outcomes of patients who become pregnant while taking these medications.

Methods. A questionnaire was mailed to 600 members of the American College of Rheumatology inquiring about their perception of fetal risk, their recommendations regarding the use of birth control in women of childbearing age taking DMARD, and the pregnancy outcomes of women with DMARD exposure.

Results. One hundred seventy-five rheumatologists (29%) returned completed surveys. Respondents were more likely to agree that pregnancy is contraindicated in women taking MTX (95%) or LF (92.7%) than for women taking ET (38.6%) or IN (46.5%). Accordingly, most required birth control for women taking MTX (95.7%) and LF (97.3%), and fewer for women taking ET (75.4%) or IN (73.4%). A total of 65 pregnancies exposed to these DMARD were reported (MTX 38, LF 10, ET 14, IN 2, MTX and ET 1). Only 3 congenital malformations, all in the MTX group, were reported among the 52 pregnancies with known outcomes.

Conclusion. Rheumatologists agree that there is a risk of teratogenicity with MTX and LF and usually require the use of reliable methods of birth control in women taking these medications. There is no consensus about ET and IN; however, physicians still tend to discuss reliable birth control methods with their female patients. We have confirmed there is a risk of congenital malformations with *in utero* exposure to MTX. No malformations were reported in infants exposed to LF, ET, or IN, but the number of reported pregnancy outcomes was small. (J Rheumatol 2003;30:241–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PREGNANCY CONGENITAL MALFORMATIONS
METHOTREXATE ETANERCEPT LEFLUNOMIDE INFLIXIMAB

There may be a risk of teratogenicity with the use of methotrexate (MTX) in the treatment of rheumatoid arthritis (RA). The fetal aminopterin/MTX syndrome has been described in the offspring of women taking MTX for the treatment of malignancies or as an abortifacient[1]. Features of this syndrome include skeletal abnormalities of the skull and limbs, microcephaly, and hydrocephalus. Patients treated for malignancies have generally been exposed to higher doses of MTX than are commonly used to treat RA. A small number of case reports have been published describing the outcomes of pregnancies with exposure to low dose weekly MTX[2-9]. Although a few infants exposed to low dose MTX early in pregnancy have manifested features of the fetal aminopterin/MTX syndrome, most of the reported pregnancies have resulted in births of full term healthy infants.

The recent introductions of a disease modifying antirheumatic drug (DMARD) with suspected teratogenicity, leflunomide (LF)[10], and 2 with unknown risk to the fetus, etanercept (ET)[11] and infliximab (IN)[12], raise the issue of how diligent rheumatologists should be in requiring reliable birth control in their female patients of childbearing age who are taking DMARD. There are no reports of the outcomes of pregnancies in women with RA with *in utero* exposure to LF or ET, and only one report of pregnancies exposed to IN[13]. Hence current guidelines for the use of these medications in women of childbearing age are based almost exclusively on extrapolation of data from animal experiments[14].

From the Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, Stanford, California; and Division of Rheumatology, Santa Clara Valley Medical Center, San Jose, California, USA.

E.F. Chakravarty, MD, Fellow, Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine; D. Sanchez-Yamamoto, RNP, Nurse Practitioner; T.M. Bush, MD, Chief, Division of Rheumatology, Department of Medicine, Santa Clara Valley Medical Center.

Address reprint requests to Dr. T.M. Bush, Division of Rheumatology, Santa Clara Valley Medical Center, 751 S. Bascom Avenue, San Jose, CA 95128.

Submitted April 2, 2002; revision accepted August 14, 2002.

We investigated prescribing practices of rheumatologists with respect to the treatment of RA in women of childbearing age. We hope to expand the collective experience of pregnancy outcomes in women receiving MTX, LF, ET, and IN for the treatment of RA.

MATERIALS AND METHODS

A 4 page anonymous survey was sent to a systematic sample of 600 physician members of the American College of Rheumatology (ACR). Questionnaires were sent by mail to every sixth physician member listed in the *2001 Directory* of the ACR. Selected members had identified adult rheumatology as their primary specialty and were practicing within the United States. International members, trainee members, and emeritus members were excluded.

The survey contained general questions about the respondent and their practice including age, sex, practice type, geographic setting, and the number of patients with RA seen. For each medication, specific questions were asked about the use in female patients with RA of childbearing age. Respondents were asked how often they prescribed each medication to women of childbearing age, how often they required the use of effective methods of birth control when prescribing each medication to these patients, and how often they reviewed continued use of birth control with patients at subsequent visits. Answers were recorded using a scale of "always," "usually," "sometimes," or "never." Respondents were then asked about whether they agreed with the statement that pregnancy is contraindicated in women receiving each medication using a 5 point Likert scale ("strongly agree," "agree," "not sure," "disagree," and "strongly disagree"). Respondents were asked to list the number of pregnancies that occurred in patients taking each medication, how the patient was counseled with respect to the pregnancy, and the pregnancy outcome (if known). Pregnancy outcomes were identified as "term delivery of healthy infant," "therapeutic abortion," "spontaneous abortion," "premature delivery," "congenital malformations," or "other complications." Congenital malformations were not further defined. To increase response rates, the questionnaire did not require respondents to review records to specify doses of medications or approximate times of exposure. The survey was anonymous, but respondents were given the option of identifying themselves for further followup. Answers to questions about use of and opinions about specific medications were not included in the analysis if the respondent indicated that they never prescribed the medication to women of childbearing age.

Physicians' prescribing practices were analyzed in a dichotomous fashion according to whether they answered "always" or "usually" versus "sometimes" or "never." Opinions about the contraindication of pregnancy in patients taking these medications were similarly analyzed according to whether they answered "strongly agree" or "agree" versus "not sure," "disagree," or "strongly disagree." The numbers of reported pregnancies and their outcomes were tallied. If the outcomes were not reported or the patients were still pregnant at the time the survey was completed, the outcomes were reported as unknown.

This study was approved by the Investigational Review Board at Santa Clara Valley Medical Center.

RESULTS

Of the 600 surveys that were mailed, 4 were returned unopened and 175 (29%) were returned completed. The demographics of the respondents are shown in Table 1. Seventy-one percent of respondents were male and the average age was 49.9 years. The types of practices of respondents were well distributed, with 25.9% practicing in academic settings or teaching hospitals, 25.9% in large group practices, and 48.2% in small group or solo practices.

Table 1. Respondent demographics. Percentage of respondents marking specific responses.

Average age, yrs	49.9
Male, %	71.4
Type of practice, %	
Academic/teaching hospital	25.9
Large group	25.9
Small group/solo	48.2
Practice setting, %	
Urban/large city	42
Suburban/medium city	50.3
Rural/small town	7.7
No. of RA patients in practice, %	
> 200	47.6
50–200	38.8
< 50	13.6

The practice settings were predominately urban or suburban, with 42% of respondents working in urban areas or large cities, 50.3% in suburban settings, and only 7.7% in rural areas. The majority of respondents had at least 50 patients with RA in their practice: 47.6% reported more than 200 patients; 38.8% reported 50–200 patients; and only 13.6% had fewer than 50 patients in their practice. The demographics of respondents reporting pregnancies were similar to those of the entire group (data not shown).

Rheumatologists almost uniformly agreed that pregnancy is contraindicated in women taking either MTX or LF, and accordingly required the use of reliable methods of birth control for patients treated with these medications (Table 2). Ninety-five percent and 92.7% of respondents agreed that pregnancy is contraindicated in patients taking MTX and LF, respectively. Consistent with these concerns, rheumatologists required the use of effective methods of birth control when prescribing these medications to women of childbearing age at similar rates (95.7% MTX and 97.3% LF). However, they were less diligent in reviewing continued use of birth control with patients at subsequent visits (55% MTX and 66.2% LF).

Respondents were less certain about the risk of either ET or IN exposure to the developing fetus. Fewer than half of the respondents agreed that pregnancy is contraindicated with use of these medications (38.6% ET and 46.5% IN). An almost equal number indicated that they were uncertain about the safety of pregnancy with the use of these medications (49.7% ET and 45.4% IN). Despite this uncertainty, respondents generally required effective methods of birth control when prescribing these medications to their female patients (75.4% ET and 73.4% IN). Respondents were even less likely to review ongoing birth control with women treated with ET or IN (41.7% and 43.8%, respectively).

Forty-one respondents (23%) reported a total of 65 pregnancies in patients who were taking MTX, LF, ET, or IN at conception (Table 3). Twenty-seven respondents reported

Table 2. Physician practice patterns and opinions about contraindication of pregnancy for patients using each medication. Percentage of respondents using Likert scales.

	Methotrexate	Leflunomide	Etanercept	Infliximab
Agree that pregnancy is contraindicated*	95	92.7	38.6	46.5
Require birth control**	95.7	97.3	75.4	73.4
Review continued use of birth control**	55	66.2	41.7	43.8

*Responded "strongly agree" or "agree." **Responded "always" or "usually.")

Table 3. Number of pregnancies and reported outcomes.

	Methotrexate	Leflunomide	Etanercept	Infliximab
Total number of pregnancies*	39	10	15	2
Fullterm healthy deliveries, n	21	2	6	1
Congenital malformations (no. deliveries)†	3	0	0	0
Preterm delivery, n	0	1	0	0
Elective abortions, n	8	2	1	0
Spontaneous abortions, n*†	7	1	1	0
Patients still pregnant, n	1	2	4	0
Outcome not stated, n	0	2	3	1

*One pregnancy resulted in spontaneous abortion after exposure to MTX and ET at conception.
†One pregnancy (taking MTX) resulted in a spontaneous abortion; the fetus had a congenital malformation.

one pregnancy, 9 reported 2 pregnancies, and 5 reported 3 or more pregnancies.

Thirty-nine pregnancies were reported in patients taking MTX. Twenty-one of these pregnancies resulted in the delivery of fullterm, healthy infants. Seven patients had spontaneous abortions, including one in which the fetus was found to have a congenital malformation. Eight patients underwent elective abortions, 4 of whom were counseled by their rheumatologist to consider termination. Three pregnancies resulted in congenital malformations of the offspring: 2 live births and one spontaneous abortion. No further information was supplied about the nature of the malformations or whether they were attributed to MTX exposure. Only one patient was still pregnant at the time of the survey.

There were fewer pregnancies reported with the use of LF, ET, or IN. Ten pregnancies were reported in patients taking LF. Only 2 respondents stated that they prescribed cholestyramine to their patients, but almost all patients were referred for high risk obstetric evaluation and cholestyramine may have been prescribed by the obstetrician. Of the 6 pregnancies with known outcomes, 2 resulted in the delivery of fullterm healthy infants and one in preterm delivery. Further information about the infant delivered prematurely was not detailed. Two patients underwent elective abortions upon recommendation by their rheumatologist and one patient had a miscarriage.

Fifteen pregnancies were reported in patients taking ET. Of the 8 pregnancies for which outcomes are known, 6 resulted in the delivery of fullterm healthy infants, and one patient elected to terminate the pregnancy. One patient who was taking both ET and MTX had a spontaneous abortion. Only 2 pregnancies were reported in patients taking IN for RA. One patient had a fullterm healthy baby and the outcome of the other pregnancy was not stated.

DISCUSSION

RA is a chronic disease that commonly affects women of childbearing age. Treatment of RA generally requires prolonged therapy with DMARD to achieve and maintain remission from active disease. MTX has been one of the mainstays of treatment of RA because of its efficacy, general tolerability, and relative ease of administration[15]. More recently new DMARD such as LF, ET, and IN have been introduced for the treatment of RA, both singly and in combination with conventional therapies. Relatively few data are available about longterm adverse events associated with the use of these newer medications.

MTX is an antimetabolite that has been used in high doses to induce elective abortions when administered during the first trimester[16]. The risks of teratogenicity with MTX have been a subject of considerable concern since its early use for cancer chemotherapy and failed attempts of medical abortion. The aminopterin/MTX syndrome has been well described by a series of case reports since the 1950s. Features of this syndrome include prenatal growth retardation, skeletal abnormalities of the skull and digits, anencephaly, microcephaly, and hydrocephalus[1]. MTX has been

given a pregnancy rating of X by the US Food and Drug Administration (FDA), indicating that pregnancy is contraindicated[17]. Therefore it is recommended that rheumatologists counsel women who are taking MTX for the treatment of RA to avoid pregnancy[14,15]. Folic acid or folinic acid supplementation is recommended in patients taking MTX to reduce the incidence of other adverse effects associated with folate deficiency[15]. If pregnancy is desired, it is recommended that MTX be discontinued at least 3 months prior to conception[6].

Our study indicates that rheumatologists are concerned about the teratogenicity of MTX. Ninety-five percent of respondents agreed that pregnancy is contraindicated while patients are taking this medication, and are equally diligent about requiring effective methods of birth control when prescribing it to women of childbearing age. Further, a number of respondents recommended termination of pregnancies that occurred while patients were taking the medication.

Despite recommendations for birth control, women do occasionally become pregnant while taking MTX and the fetus is exposed to the drug during early fetal life. To our knowledge, there have been 23 pregnancies in patients using MTX for autoimmune diseases reported in the literature (Table 4). In all but 2 reports, standard low dose weekly MTX was used. In one report the patient was taking daily MTX (5 mg/day) for the treatment of psoriasis[3]. We included an additional report of an attempted medical abortion because the weekly dose of MTX was similar to that used for the treatment of RA[2].

The previously reported pregnancies with MTX exposure resulted in 13 healthy fullterm births and only 4 infants with congenital malformations. Two patients elected to terminate the pregnancies, and 4 had spontaneous abortions. The reported malformations resembled those of the fetal aminopterin/MTX syndrome. Two occurred in patients taking weekly low dose MTX for psoriasis and juvenile RA. One occurred in a woman taking daily MTX (5 mg/day) for the treatment of psoriasis, and one in a patient taking daily MTX (2.5 mg/day for 5 days) to induce abortion.

In our study, 39 patients were exposed to MTX during pregnancy. More than half of the pregnancies had favorable outcomes with the delivery of fullterm healthy infants. A similar proportion of pregnancies in our study as compared to previous reports resulted in spontaneous abortions (7/39 and 4/23, respectively). Three pregnancies resulted in congenital malformations. No further information was provided about the nature of these abnormalities and the anonymous format of the survey precluded further case review. We do not know whether the malformations were manifestations of the aminopterin/MTX syndrome. Assuming no overlap of cases reported in our study with previous publications, the combined rate of reported congenital malformations in infants with known outcomes who were exposed to MTX *in utero* is 17%. The rate of congenital abnormalities in the general population was reported as 2–3% in a study of 1.6 million infants born in Calfornia[18].

Leflunomide, ET, and IN are DMARD that have been more recently been approved by the FDA for treatment of RA. Since they have been available for use for a much shorter time and have therefore been prescribed to fewer patients, there is little to no published experience with outcomes of pregnancies with *in utero* exposure to these medications.

Leflunomide is a pyrimidine synthesis inhibitor that has been shown to have teratogenic and fetotoxic properties in animal studies[10,19]. It additionally poses unique concerns in regard to teratogenicity because of its extremely long half-life. The active metabolite of LF can be detectable in plasma

Table 4. Reports of pregnancy outcomes in patients taking MTX for the treatment of autoimmune diseases (RA, juvenile RA, and psoriasis).

Reference	No. of Pregnancies	Indication for MTX	Exposure, Weeks of Gestation	Average Dose, mg/week	Outcome
2	1	Attempted abortion	8–10 wks	2.5 qD × 5d	Skeletal abnormalities of skull and extremities
3	1	Psoriasis	8 wks	35 mg/week (5 mg/day)	Skeletal abnormalities of skull
4	10	RA, JRA, "allergic angiitis"	2–15 wks	7.5–10	5 fullterm healthy infants, 3 spontaneous abortions, 2 elective abortions
5	1	RA	10 days	7.5	Fullterm healthy infant
6	4	RA	2–6 wks	7.5–12.5	4 fullterm healthy infants
7	1	JRA	8 wks	10–12.5	Delivery at 36 weeks, skeletal abnormalities, cardiac abnormalities, developmental delay, death at 6 months from RSV
8	1	Psoriasis	8 wks	12.5	Skeletal abnormalities, low birth weight, developmental delay
9	4	RA, JRA, PsA	2–6 wks	2.5–15	3 fullterm healthy infants, 1 spontaneous abortion (2.5 mg/week)
Total	23				13 fullterm healthy infants, 4 spontaneous abortions, 2 elective abortions, 4 congenital malformations

RSV: respiratory syncytial virus.

for up to 2 years after discontinuation of the drug. A regimen of oral cholestyramine every 8 hours for 11 days is necessary to reduce plasma levels below detection. Hence, unless cholestyramine is employed, a fetus could have significant *in utero* exposure to LF up to 2 years after its discontinuation. Leflunomide has been labeled pregnancy class X by the FDA[10]. Further, female patients of childbearing age should be counseled to use effective forms of contraception and have a negative pregnancy test before beginning the drug[10,15].

About 30 women have been reported to have become pregnant while taking LF[20]. All but 3 women elected to terminate the pregnancies because of the risk of teratogenicity to the fetus. The remaining 3 women were still pregnant at the time of publication. There are no known reports in the literature of the outcomes of pregnancies in women while taking this drug. Despite the paucity of data on human pregnancies exposed to LF, we have found that rheumatologists agree that pregnancy is contraindicated in patients taking this medication and are rigorous about requiring birth control before prescribing it to patients of childbearing age. Again, there appears to be less diligence about reviewing birth control methods at followup visits with patients taking LF.

In our survey, 10 pregnancies occurred while the mother was taking LF. Of the 6 pregnancies with known outcomes, 2 resulted in the delivery of fullterm healthy infants, one infant was born prematurely, and one resulted in spontaneous abortion. Two patients elected to terminate the pregnancies.

Etanercept and IN are members of a new class of medications for RA that inhibit tumor necrosis factor alpha (TNF-α). Etanercept is a soluble TNF receptor and IN is a chimeric monoclonal antibody against TNF. The FDA has labeled both medications Pregnancy Category B: no evidence of risk in humans. Animal studies have not revealed fetotoxicity or teratogenicity, but studies on human pregnancy are not available[11,12,21]. There are no reports of pregnancies exposed to ET. There is one abstract report of outcomes of pregnancies exposed to IN[13]. The outcomes of pregnancy in patients taking IN for the treatment of Crohn's disease (45 patients) as well as RA (4 patients) and juvenile RA (one patient) were reported collectively, without delineation of specific pregnancy outcome by indication for IN. Although 2 infants were born with complications (one infant born prematurely at 23 weeks, and one infant born with tetralogy of Fallot), pregnancy outcomes overall did not differ from that of a national cohort of healthy women.

The opinions of respondents about the safety of pregnancy for patients taking either ET or IN reflect the paucity of human data available to date. Almost half of respondents were uncertain about whether pregnancy is contraindicated in patients who are taking these medications. However, respondents were still likely to require birth control while women are using these medications, although less likely than with DMARD that have higher perceived risks of teratogenicity.

We report a total of 15 pregnancies exposed to ET and 2 exposed to IN. One pregnancy, in a patient taking both ET and MTX, ended in spontaneous abortion. The 6 pregnancies with known outcomes in patients exposed to ET (without MTX) resulted in delivery of fullterm healthy infants. No congenital malformations or other adverse outcomes were reported. Of the 2 reported pregnancies exposed to IN, one resulted in a fullterm healthy infant and the outcome of the other pregnancy was not stated.

There are a few limitations of this study. First, the response rate is lower than the average physician response rate reported for mailed surveys of 52–61%[22-24]. However, it does fall within the range of physician response rates in published studies (11–100%)[24]. It is possible that the sensitive nature of the subject matter accounts for a reluctance among survey recipients to complete and return the questionnaire. This may lead to bias in reporting. For example, physicians with patients with poor pregnancy outcomes may be more likely to answer a survey addressing this subject. We designed our study to be anonymous, given concerns for privacy and protection of both respondents and their patients. Because of respondents' anonymity, we were precluded from obtaining further details of reported pregnancies or outcomes of pregnancies at the time the survey was completed. Therefore, we do not have data on the congenital malformations reported by respondents, nor can we ascertain if there is any overlap of the pregnancies reported in our study and those previously reported in the literature.

A second limitation of the study is that respondents might exhibit bias when self-reporting their prescribing practices. For example, respondents may overestimate the actual frequency they discuss birth control with patients to approximate an ideal practice style rather than their actual performance.

To our knowledge, we report the largest experience with pregnancy in patients treated with MTX for RA, and the first experience of pregnancy outcomes in patients with *in utero* exposure to LF and ET. We found that rheumatologists' prescribing patterns are generally consistent with recommendations outlined in the literature for MTX and LF. However, there was less diligence about reviewing ongoing use of effective methods of birth control with women taking any of the studied DMARD. In a 1994 national survey, 49% of pregnancies were unintended and 48% of women aged 15–44 had at least one unintended pregnancy[25]. Although the risk of unintended pregnancy was highest among young, single, poor women with a low education level there was still a substantial risk in women in a New York survey that were older than 35 (27%), married (30%), with a good income (32%), or with higher levels of education (34%)[26].

Contraception is very effective but not always used appropriately. In one study half of women with unintended pregnancies were using some form of contraception[27], and 27% of women in another study missed doses of their oral contraceptives and were at risk of pregnancy[28]. Rheumatologists may further reduce the risk of pregnancies with *in utero* exposure to these medications by increasing the frequency with which continuing birth control use is discussed with patients over the course of treatment.

Our data confirm a risk of congenital malformations with *in utero* exposure to MTX: 3/24 pregnancies resulted in congenital malformations. We report preliminary data of pregnancy outcomes of infants exposed to LF, ET, and IN. With the exception of one preterm delivery, there were no congenital malformations or adverse events reported with these DMARD. Prospective studies about the outcomes of pregnancies with exposure to these medications are needed for better understanding of the risks to the developing fetus.

REFERENCES

1. Reich EW, Cox RP, Becker MH, Genieser NB, McCarthy JG, Converse JM. Recognition in adult patients of malformations induced by folic-acid antagonists. Birth Defects 1978;14:139-60.
2. Milunsky A, Graef JW, Gaynor MF. Methotrexate-induced congenital malformations. J Pediatr 1968;72:790-5.
3. Powell HR, Ekert H. Methotrexate-induced congenital malformations. Med J Aust 1971;2:1076-7.
4. Kozlowski RD, Steinbrunner JV, MacKenzie AH, Clough JD, Wilkie WS, Segal AM. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. Am J Med 1990;88:589-92.
5. Feldkamp M, Carey JC. Clinical teratology counseling and consultation case report: low dose methotrexate exposure in the early weeks of pregnancy. Teratology 1993;47:533-9.
6. Donnenfeld AE, Pastuszak A, Noah JS, Schick B, Rose NC, Koren G. Methotrexate exposure prior to and during pregnancy. Teratology 1994;49:79-81.
7. Buckley LM, Bullaboy CA, Leichtman L, Marquez M. Multiple congenital anomalies associated with weekly low-dose methotrexate treatment of the mother. Arthritis Rheum 1997;40:971-3.
8. Del Campo M, Kosaki K, Bennett FC, Jones KL. Developmental delay in fetal aminopterin/methotrexate syndrome. Teratology 1999;60:10-2.
9. Ostensen M, Hartmann H, Salvesen K. Low dose weekly methotrexate in early pregnancy. A case series and review of the literature. J Rheumatol 2000;27:1872-5.
10. Leflunomide package insert. Kansas City, MO: Aventis Pharmaceuticals Inc; 2000.
11. Enbrel package insert. Seattle, WA: Immunex Corporation; 2001.
12. Infliximab package insert. Malvern, PA: Centocor, Inc.; 2000.
13. Antoni CE, Furst D, Manger B, et al. Outcome of pregnancy in women receiving Remicade (infliximab) for the treatment of Crohn's disease or rheumatoid arthritis [abstract]. Arthritis Rheum 2001;44 Suppl:S153.
14. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med 2000;160:610-9.
15. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of RA, 2002 update. Arthritis Rheum 2002;46:328-46.
16. Hausknecht RU. Methotrexate and misoprostol to terminate early pregnancy. N Engl J Med 1995;333:537-40.
17. Schuna AA. Update on treatment of rheumatoid arthritis. J Am Pharm Assoc 1998;38:728-35.
18. California Birth Defects Monitoring Program. Birth defects in California: 1983-1990. Emeryville, CA: California Birth Defects Monitoring Program; 1994.
19. Prakash A, Jarvis B. Leflunomide: a review of its use in active rheumatoid arthritis. Drugs 1999;58:1137-64.
20. Brent RL. Teratogen update: reproductive risks of leflunomide (Arava); a pyramiding synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. Teratology 2001;63:106-12.
21. Jarvis B, Faulds D. Etanercept: a review of its use in rheumatoid arthritis. Drugs 1999;57:945-66.
22. Asch DA, Jedrziewski MK, Christakis NA. Response rates to mail surveys published in medical journals. J Clin Epidemiol 1997;50:1129-36.
23. Kellerman SE, Herold J. Physician response to surveys. Am J Prev Med 2001;20:61-7.
24. Cummings SM, Savitz LA, Konrad TR. Reported response rates to mailed physician questionnaires. Health Serv Res 2001;35:1347-55.
25. Henshaw SK. Unintended pregnancy in the United States. Fam Plann Perspect 1998;30:24-9.
26. Centers for Disease Control. Unintended pregnancy — New York, 1988–1989. MMWR 1991;40:723-5.
27. Mishell DR. Prevention of unplanned pregnancy in U.S. women. J Reprod Med 2000;45:867-71.
28. Oakley D, Potter L, de Leon-Wong E, Visness C. Oral contraceptive use and protective behavior after missed pills. Fam Plann Perspect 1997;29:277-9.