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Birth Outcomes in Women Who Have Taken Leflunomide During Pregnancy

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Abstract

Objective—In preclinical reproductive studies, leflunomide was found to be embryotoxic and teratogenic. Women treated with leflunomide are advised to avoid pregnancy; those who become pregnant are advised to reduce fetal exposure through a cholestyramine drug elimination procedure. The present study was undertaken to investigate pregnancy outcomes in women who received leflunomide and were treated with cholestyramine during pregnancy.

Methods—Sixty-four pregnant women with rheumatoid arthritis (RA) who were treated with leflunomide during pregnancy (95.3% of whom received cholestyramine), 108 pregnant women with RA not treated with leflunomide, and 78 healthy pregnant women were enrolled in a prospective cohort study between 1999 and 2009. Information was collected via interview of the mothers, review of medical records, and specialized physical examination of infants.

Results—There were no significant differences in the overall rate of major structural defects in the exposed group (3 of 56 live births [5.4%]) relative to either comparison group (each 4.2%)(P = 0.13). The rate was similar to the 3–4% expected in the general population. There was no specific pattern of major or minor anomalies. Infants in both the leflunomide-exposed and non–leflunomide-exposed RA groups were born smaller and earlier relative to infants of healthy mothers; however, after adjustment for confounding factors, there were no significant differences between the leflunomide-exposed and non–leflunomide-exposed RA groups.

Conclusion—Although the sample size is small, these data do not support the notion that there is a substantial increased risk of adverse pregnancy outcomes due to leflunomide exposure among

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Chambers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Chambers, Robinson, Braddock, Jones.

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women who undergo cholestyramine elimination procedure early in pregnancy. These findings can provide some reassurance to women who inadvertently become pregnant while taking leflunomide and undergo the washout procedure.

Leflunomide, marketed in the US since 1998, is a disease-modifying antirheumatic drug that helps to improve rheumatoid arthritis (RA) symptoms such as joint swelling and tenderness, as well as to slow the progression of joint damage caused by the disease. Leflunomide is an isoxazole immunomodulatory agent with antiproliferative activity. Its mechanism of action is mediated through inhibition of the de novo synthesis of pyrimidine nucleotides as well as reduction of the activity of protein tyrosine kinase (1).

Preclinical reproductive studies in rats and rabbits demonstrated that leflunomide was both embryotoxic (associated with growth restriction and embryolethality) and teratogenic. In rats, malformations of the head, rump, vertebral column, ribs, and limbs were noted. Similarly, malformations of the head and bilateral dysplasia of the spine and of the scapula were found in rabbits (1). Subsequent studies in mice have shown that leflunomide can induce craniofacial, axial skeleton, heart, and great vessel malformations. In the mouse model, with leflunomide administered at a dose of 30 mg/kg, externally observable skeletal and visceral malformations were seen in an average of 77% of exposed pups (2).

Based on the no-effect level for embryotoxicity or teratogenicity in rats and rabbits, a blood level of leflunomide in humans of 0.03 μg/ml has been regarded as safe. This value is extrapolated from the no-effect maximum concentration level in rats and rabbits that is 123–136 times higher, and a no-effect area under the curve in animals that is 25–72 times higher than the blood level limit set for humans. Because the pharmacodynamic effects of leflunomide are species-specific, i.e., the inhibitory and antiproliferative effects of the drug are substantially stronger in rats than in humans, the recommended safety margins may be even more conservative than these calculations suggest (1–6).

Based on these data, leflunomide has been classified as a pregnancy category X medication in the current US Food and Drug Administration system, indicating that studies in animals have demonstrated fetal abnormalities and that the risks involved in use of the drug by pregnant women clearly outweigh potential benefits (3). Women of reproductive potential are advised to avoid pregnancy while being treated with leflunomide, and if planning pregnancy, to document blood levels of the leflunomide metabolite of <0.02 μg/ml before attempting to conceive. Due to the potentially long half-life of the active metabolite of leflunomide, women who are planning pregnancy or who are taking the medication and inadvertently become pregnant are advised to undergo a drug elimination procedure. This is accomplished with one or more courses of cholestyramine until maternal blood levels are brought below the 0.02 μg/ml limit and maintained below that level for 14 days (4).

However, there are scant data on humans with which to counsel pregnant women about fetal risks in the event of an unplanned but wanted pregnancy. In one report, rheumatologists noted no malformations among the offspring of 10 women who were prescribed leflunomide during pregnancy (5). An additional 4 case reports of pregnancy outcome following first-trimester exposure to leflunomide have been published. Two of these pregnancies ended in elective termination, and a third in a normal live birth (6). The fourth resulted in an infant born 9 weeks preterm, with cerebral palsy and blindness in 1 eye (7).

Given the limited data on humans available to date, it has not been possible to determine if the animal developmental toxicity data are predictive of human developmental concerns. This study was undertaken to evaluate the effects of leflunomide treatment in the first trimester of pregnancy on the frequency of major and minor structural defects in infants, preterm delivery, birth size, and postnatal growth up to 1 year of age.

PATIENTS AND METHODS

Study design

From 1999 through 2009, the Organization of Teratology Information Specialists (OTIS) Collaborative Research Group conducted a pregnancy outcome prospective cohort study to address the fetal safety of exposure to leflunomide for any length of time during the first trimester of pregnancy. OTIS Collaborative Research Group members who contributed to the study are listed in Appendix A. The OTIS Collaborative Research Group study design has been described in detail elsewhere (8). Briefly, the study is intended to evaluate a spectrum of adverse pregnancy outcomes in exposed pregnancies relative to unexposed pregnancies, and specifically to identify or rule out a specific pattern of minor and/or major structural anomalies that might occur in prenatally exposed infants but not in comparison infants.

Participants in the study were recruited from among the annual pool of ~70,000 pregnant callers to OTIS counseling services throughout the US and Canada who initiated contact with an OTIS service with questions about any exposure in pregnancy, and from direct marketing to rheumatologists through mail, professional meetings, and the OTIS Web site. In addition, Sanofi-Aventis, the manufacturer of Arava (leflunomide), encouraged referrals to the study by publishing the OTIS study toll-free telephone number in the package insert and providing information on the OTIS study on the product Web site. Potentially eligible subjects were referred to a central OTIS study coordinating center located at the University of California, San Diego, where all screening, enrollment, and followup procedures were subsequently carried out.

Participants were recruited into 1 of 3 groups: 1) pregnant women with a diagnosis of rheumatoid arthritis (RA) or juvenile rheumatoid arthritis (JRA) who took at least one dose of leflunomide on or after the estimated date of conception, 2) a disease-matched comparison group of pregnant women with a diagnosis of RA or JRA who did not take leflunomide at any time during pregnancy and did not have exposure to any other known teratogenic agent, and 3) a comparison group of healthy pregnant women without a diagnosis of RA, JRA, or any other autoimmune disease, including type 1 or type 2 diabetes mellitus, and without exposure to any known human teratogen, including isotretinoin, anticonvulsants, and large quantities of alcohol. The women in this third group were selected from among callers to OTIS services who had questions about nonteratogenic exposures such as antibiotics, selected over-the-counter pain medications, or dental x-rays.

Women who were exposed to methotrexate or cyclophosphamide at any time during pregnancy were ineligible for any of the study groups. In the disease-matched comparison group, women who had previously been treated with leflunomide were ineligible if they had received any dose of the drug within 2 years prior to the index pregnancy, unless they had documented blood levels below 0.02 μg/ml prior to pregnancy. Enrollment in the cohort study was completed prior to week 21 of gestation, and before the known outcome of that pregnancy, including knowledge of major structural defects that were prenatally diagnosed.

In addition to the cohort study, women who did not meet the criteria for enrollment in the cohort (due to, e.g., retrospective reports, late gestational age at enrollment, indication for treatment other than RA or JRA) were recruited as part of a case series of leflunomide-exposed pregnancies and followed up using similar methods as for the cohort participants. All women in the study provided oral consent for participation, and subsequently signed written consent. The study was approved by the University of California, San Diego Institutional Review Board.

Data collection on exposure, outcome, and potential confounders

Each woman enrolled in the cohort study completed 2 or 3 structured telephone interviews during pregnancy that addressed history of previous pregnancies, family medical history, prepregnancy body mass index, socioeconomic and demographic information on the woman and her partner, and exposures during the current pregnancy. The exposure history included dosages, dates, and indications for all medications; use of caffeine; use of supplemental vitamins; occupational exposures; infectious or chronic disease; prenatal testing or other medical procedures; and use of recreational drugs, tobacco, and alcohol.

Each woman was provided with a diary in which she was asked to keep a record of any additional exposures that might occur before delivery. This information was supplemented with telephone interviews to update information on exposures and events. In addition, women with RA or JRA were asked to respond to questions about disease activity or symptoms at the time of enrollment. Functional status was determined using the Health Assessment Questionnaire (9). Pain and patient's perception of global severity of the disease (over the last week) were evaluated with the use of a 0–100 visual analog scale modified for telephone administration.

Birth outcome was recorded on a standard interview form completed by telephone shortly after delivery or the end of pregnancy. Measures included the outcome of pregnancy (live birth, stillbirth, elective termination, or spontaneous abortion), the presence or absence of major structural defects, gestational age at delivery, mode of delivery, length and type of hospital stay, maternal or newborn complications, maternal weight gain, infant Apgar scores, and infant birth weight, length, and head circumference.

Medical records from the prenatal care provider, the hospital of delivery, the rheumatologist, and the pediatrician were examined for additional exposure and outcome data. In addition, the infant's physician was asked to return a form reporting postnatal growth measures and the presence or absence of any major structural defect noted up to that point. Major structural anomaly was defined as a defect that has cosmetic or functional importance.

Liveborn infants were also examined by a member of a team of 3 pediatric dysmorphologists (KLJ, LKR, and SRB) who traveled to see these infants in their homes. These evaluations were completed for both major and minor structural anomalies; the latter were defined as structural defects that have no cosmetic or functional importance and that are known to occur in <4% of the general population (10). Examples of these frequently subtle minor structural defects include a missing crease on one or more of the digits, a broad nasal bridge, protruding earlobes, or a relatively indistinct philtrum of the upper lip. Infants who received this dysmorphologic examination were evaluated using a standard checklist itemizing 132 such anomalies (8). Photographs were taken of each infant to aid in addressing possible issues of interrater reliability among multiple examiners. The examiner in each case was blinded with regard to the exposure status of the mother.

Evaluation of outcomes

Major structural defects were defined according to the Metropolitan Atlanta Congenital Defects Program classification system (11). In addition to those defects noted in the physical examination or medical record or reported by the mother, information on "functional" abnormalities was collected. These were defined as developmental abnormalities that did not represent clearly defined congenital defects in structure. Included in this group of functional problems were infants with hydronephrosis first identified on prenatal ultrasound leading to more extensive postnatal diagnostic procedures, but of unknown clinical significance.

Based on the suspected predictive value of 3 or more minor structural defects for a major abnormality (12), the number of minor anomalies among infants who received the dymorphologic examination was compared across groups. In addition, because of the known association of a pattern of specific minor anomalies with prenatal exposure to many known human teratogens, clustering of specific minor structural defects in leflunomide-exposed infants was evaluated for evidence of a pattern (defined as at least 3 specific minor anomalies occurring in at least 2 children) that could subsequently be compared with prevalence of the same pattern in infants from the disease-matched and healthy comparison groups.

Prematurity was defined as spontaneous delivery at <37 completed weeks' gestation. Small for gestational age or for prematurity-adjusted chronological age was defined as ≤10th centile for sex and age, determined using standard National Center for Health Statistics 2000 growth curves (13) for full-term infants and Lubchenko curves (14) for preterm infants.

Sample size and power

The initial target sample size for the cohort study was set at 100 pregnancies per group, projected to yield a sample of 75 live births per group. This sample size was selected to provide ~75% power at $\alpha = 0.05$ (1-tailed) to detect at least a 10% incidence of a specific pattern of 3 or more minor malformations in the exposed group relative to either of the comparison groups, and 89% power to detect a 10% incidence in the exposed group if the comparison groups could be combined. This effect size is similar in magnitude to that seen in children prenatally exposed to various known human teratogens, such as the older anticonvulsants (15,16).

Statistical analysis

Univariate categorical analyses were conducted, comparing the 3 cohort groups using chi-square or Fisher's exact test. Analysis of variance was used for assessment of continuous variables. For those outcomes with significant differences, subsequent pairwise comparisons were made between the leflunomide-exposed and disease-matched comparison groups. Significant pairwise comparisons were further analyzed using multivariable linear or logistic regression. In regression models, a confounding factor was included if it changed the estimate of the effect of exposure by >10%. Maternal age was forced into the model whether or not it met the criteria for confounders. All statistical tests were performed using R open source software with 2-tailed tests, with α levels of 0.05 judged as significant.

RESULTS

A total of 250 participants from the US and Canada were enrolled in the cohort study: 64 in the leflunomide-exposed group, 108 in the disease-matched comparison group, and 78 in the normal healthy comparison group. The rate of enrollment of women who had taken leflunomide during pregnancy declined steeply in the latter years of the study after generic and other treatment options became available, and it was determined that study conclusions would be unlikely to change based on the very limited number of additional subjects likely to be recruited; enrollment therefore was discontinued in 2008.

Characteristics of the mothers in the cohort study are shown in Table 1. Groups were similar with regard to most characteristics; however, women in the leflunomide-exposed group were more likely to have been enrolled earlier in gestation, to have lower socioeconomic status, to have not started multivitamin or folic acid supplements by the time of conception, and to be smokers. In addition, women in the leflunomide and disease-matched groups were more likely than the healthy comparison group to have taken prednisone or nonsteroidal

antiinflammatory medications during pregnancy. Gestational timing of the last dose of leflunomide was on average 3.1 weeks after conception, with the latest exposure ending at 8.6 weeks after conception. Although women who did not undergo any washout procedure were eligible for enrollment, nearly all women in the leflunomide group (95.3%) underwent at least one course of the cholestyramine washout procedure early in pregnancy immediately following discontinuation of leflunomide, and 12 women (18.8%) reported receiving >1 course of cholestyramine (range 2–6 courses). Among the 31 women for whom there was documentation available to indicate when the leflunomide metabolite levels were <0.02 μg/ml, this was demonstrated at a mean (±SD) of 10.7 ± 4.4 weeks after conception (range of 5–19 weeks).

Birth outcomes were similar across groups (Table 2). Women in the leflunomide-exposed group were more likely to deliver by cesarean section than women in either of the comparison groups. The overall proportion of major structural anomalies did not differ significantly between groups (Table 3) ($P = 0.13$ among live births, $P = 0.73$ excluding lost to followup.). The 3 defects reported in the leflunomide-exposed group were occult spinal dysraphism (tethered cord) which was surgically repaired, unilateral uretero pelvic junction obstruction leading to multicystic kidney disease, and microcephaly (defined as head circumference below the 3rd centile on at least 2 measurements following birth).

A total of 206 liveborn infants (92%) received the dysmorphologic examination (at a mean age of 4 months [range 2 weeks–16 months]). Among these infants, a higher proportion of children in the leflunomide-exposed group had 3 or more minor anomalies than children in the other 2 groups ($P = 0.10$), however, there was no evidence of a specific pattern of 3 or more anomalies noted in the leflunomide-exposed children (Table 3).

Univariate 3-group comparisons demonstrated that birth weight, birth length, birth weight or length ≤10th centile, preterm delivery, gestational age at delivery, and postnatal weight ≤10th centile differed between groups ($P \leq 0.04$) (Table 4). However, in post hoc pairwise comparisons between the leflunomide-exposed group and the disease-matched comparison group only gestational age at delivery ($P < 0.01$) and birth weight exhibited a significant difference ($P = 0.02$).

Adjusted effects on mean gestational age at delivery in liveborn infants and mean birth weight in full-term infants for the leflunomide-exposed group relative to the disease-matched group were calculated using linear regression (Table 5). After adjustment for maternal age, maternal race/ethnicity, socioeconomic status, timing and duration of prednisone, tobacco use, and preeclampsia, leflunomide exposure was no longer a significant predictor of gestational age ($P = 0.17$). Similarly, after adjustment for maternal age, socioeconomic status, tobacco use, gestational age at delivery, and timing and duration of prednisone use, leflunomide exposure was no longer a significant predictor of birth weight ($P = 0.68$).

Among 19 liveborn infants in the case series whose mothers were not eligible for the cohort study, 2 malformations were reported: a case of aplasia cutis congenita in the surviving member of a twin pair, and multiple malformations including Pierre Robin sequence, cleft of the soft palate, and chondrodysplasia punctata in an infant born to a mother who was treated with leflunomide for systemic lupus erythematosus. In addition to structural defects, 2 functional problems were reported: 1 child had bilateral sensorineural hearing loss, and the other had infantile seizures of unknown etiology.

DISCUSSION

In the present study there were no significant differences in the overall rate of major structural defects in the leflunomide-exposed cohort group relative to either of the comparison groups, and rates noted in all 3 groups were similar to the 3–4% expected in the general population. In addition, the 3 major defects that were noted in the leflunomide-exposed cohort group were neither similar to each other nor consistent with the defects noted in animal studies. The 2 structural defects noted in the case series, although not directly comparable with the cohort study results, were not consistent with any defects reported in the cohort group, and were attributable to alternative factors. Aplasia cutis is known to occur with increased frequency in the surviving member of a monozygotic twin pair (17), and chondrodysplasia punctata has been reported, from a case series, to be a fetal complication related to maternal lupus (18). Finally, there was no evidence of a specific pattern of 3 or more minor anomalies among those children with prenatal leflunomide exposure who underwent the dys-morphologic examination.

Although shortened gestational age and reduced birth weight were noted more frequently in the leflunomide-exposed group, the adjusted means were similar to those in the disease-matched comparison group, indicating that these excess risks were attributable to confounding, and perhaps to the more severe underlying disease necessitating more frequent and higher-dose treatment with corticosteroids. Increased risks of preterm delivery and reduced birth weight in both the leflunomide-treated and disease-matched groups relative to the healthy comparison group might be attributed to the underlying inflammatory arthritis. This interpretation is consistent with the findings of a 2006 birth certificate study that demonstrated elevated relative risks of preterm delivery, lower birth weight, cesarean section delivery, and preeclampsia in women with RA compared with women without RA (19).

The lack of concordance between these data on humans and the animal findings might be explained by species differences in susceptibility to leflunomide’s teratogenic effects. However, the inhibitory and antiproliferative effects of the drug are substantially stronger in rats than in humans. Therefore, although the typical dose for humans may result in blood levels similar to those in the rat, this dose may be insufficient to cause effects in the human embryo (1). Since the last dose of leflunomide was taken by women in this sample almost exclusively within the first 3–4 weeks after conception, it is possible that there were too few women in the study with exposure during a later, but potentially more critical, window of embryonic development. Finally, with a sample of this size, power to detect increased risks of specific major birth defects is very limited.

The initial target sample size for the cohort study was selected to provide sufficient power to detect at least a 10% incidence of a specific pattern of minor anomalies in the leflunomide-exposed group relative to the comparison groups. Based on the actual sample size achieved, we had 65% power to detect at least a 10% incidence of a pattern of minor anomalies relative to none in the disease-matched comparison group, and 79% power to detect this effect size if the 2 comparison groups were combined. However, importantly, we did not see any evidence of a specific pattern of minor anomalies in any children in the leflunomide-exposed group, i.e., no 2 children among the 51 leflunomide-exposed children who had the dysmorphologic examination had the same 3 minor anomalies. Therefore, despite the smaller-than-projected sample size, it is unlikely that conclusions regarding this outcome would differ had additional exposed subjects been recruited.

A possible limitation of this study is the use of a volunteer sample, which may limit generalizability. This is common to virtually all pregnancy registry studies, and is an

unavoidable limitation of studies involving relatively rare exposures in pregnancy. The extent to which women who contacted OTIS and agreed to participate are representative of the groups of exposed and unexposed pregnancies from which they were drawn is not known. However, the fact that women in all 3 cohorts were recruited prospectively prior to the known abnormal or normal outcome of pregnancy eliminates the potential for a volunteer bias based on prior knowledge of outcome. In addition, because of the comprehensive data collection from multiple sources about covariates, several important potential confounders with respect to differences between groups could be addressed.

Another limitation of this study is that, due to the contraindication for leflunomide in pregnancy, all participants in the leflunomide-exposed group discontinued the medication upon recognition of pregnancy, and nearly all underwent 1 or more drug elimination procedures, with a wide range of gestational weeks before leflunomide metabolite levels were below the recommended limit. As a result, the window of exposure timing varied, and only a small subset of the sample was exposed to full doses of the drug beyond 3 weeks postconception. Therefore, in this study it was not possible to address possible risks associated with use of leflunomide over the entire period of embryonic development. However, the first 3 weeks of embryonic development represent a critical window of sensitivity during which many of the specific malformations noted in the animal models might have been initiated in humans.

Strengths of this study include the detailed and comprehensive data collected on exposures and confounders including disease symptoms, the use of concurrently followed up disease-matched as well as a healthy comparison groups, and the dysmorphologic examinations performed on >92% of infants to rule out a subtle pattern of structural differences that might be missed on a routine clinical examination.

While women are advised to avoid pregnancy when being treated with leflunomide, unplanned pregnancies are not uncommon (20). The findings of this study can be reassuring to women who inadvertently become pregnant while taking this medication and who undergo the recommended cholestyramine washout procedure. Due to the infrequent use of this medication in the general population of women of reproductive age, it is unlikely that sufficient numbers of exposed pregnancies could be recruited to rule out more moderate increased risks of specific major defects. However, the data from this study suggest that if leflunomide is a human teratogen, the risks are not high, i.e., on the order of the ≥20% risks seen with some other category X medications such as isotretinoin and thalidomide. Continued monitoring of outcomes following exposed pregnancies and longer-term followup of the children’s development could help confirm and expand on these findings for women and their health care providers in the event of inadvertent pregnancy exposure.

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Sanofi-Aventis had no role in the study design, data collection, data analysis, or writing of the manuscript. This was an investigator designed, initiated, and independently conducted, analyzed, and interpreted study. The only role of Sanofi-Aventis was financial support and encouraging referral of exposed patients from health care providers. As per the contract with the authors, Sanofi-Aventis was given the opportunity to review the manuscript prior to submission for publication but did not have any role in approving the content, nor was submission contingent on their comments or approval.

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References

1. 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; 63:106–12. [PubMed: 11241434]
2. Fukushima R, Kanamori S, Hirashiba M, Hishikawa A, Muranaka RI, Kaneto M, et al. Teratogenicity study of the dihydroorotate-dehydrogenase inhibitor and protein tyrosine kinase inhibitor Leflunomide in mice. Reprod Toxicol. 2007; 24:310–6. [PubMed: 17604599]
3. Boothby LA, Doering PL. FDA labeling system for drugs in pregnancy. Ann Pharmacother. 2001; 35:1485–9. [PubMed: 11724104]
4. Sanofi-Aventis. Arava prescribing information. URL: http://www.sanofi-aventis.us
5. 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 pattern and pregnancy outcomes. J Rheumatol. 2003; 30:241–6. [PubMed: 12563675]
6. De Santis M, Straface G, Cavaliere A, Carducci B, Caruso A. Paternal and maternal exposure to leflunomide: pregnancy and neonatal outcome. Ann Rheum Dis. 2005; 64:1096–7. [PubMed: 15958772]
7. Neville CE, McNally J. Maternal exposure to leflunomide associated with blindness and cerebral palsy. Rheumatology (Oxford). 2007; 46:1506. [PubMed: 17602201]
8. Chambers CD, Braddock S, Briggs GG, Einarson A, Johnson YR, Miller RK, et al. Postmarketing surveillance for human teratogenicity: a model approach. Teratology. 2001; 64:252–61. [PubMed: 11745831]
9. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980; 23:137–45. [PubMed: 7362664]
10. Marden PM, Smith DW, McDonald MJ. Congenital anomalies in the newborn infant, including minor variations: a study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. J Pediatr. 1964; 64:357–71. [PubMed: 14130709]
11. Centers for Disease Control and Prevention. Metropolitan Atlanta Congenital Defects Program (MACDP). URL: http://www.cdc.gov/ncbddd/bd/macdp_resources.htm
12. Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies. I Association with major malformations. J Pediatr. 1987; 110:531–7. [PubMed: 3559800]
13. Centers for Disease Control and Prevention. National Center for Health Statistics Pediatric Growth Curves. 2000. http://www.cdc.gov/growthcharts
14. Hall, JG.; Allanson, JE.; Gripp, KW.; Slavotinek, AM. Handbook of physical measurements. 2. Oxford: Oxford University Press; 2007.
15. Jones KL, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N Engl J Med. 1989; 320:1661–6. [PubMed: 2725616]
16. Gladstone DJ, Bologa M, Maguire C, Pastuszak A, Koren G. Course of pregnancy and fetal outcome following maternal exposure to carbamazepine and phenytoin: a prospective study. Reprod Toxicol. 1992; 6:257–61. [PubMed: 1591483]
17. Cambiaghi S, Schiera A, Tasin L, Gelmetti C. Aplasia cutis congenita in surviving co-twins: four unrelated cases. Pediatr Dermatol. 2001; 18:511–5. [PubMed: 11841641]
18. Chitayat D, Keating S, Zand DJ, Costa T, Zackai EH, Silverman E, et al. Chondrodysplasia punctata associated with maternal autoimmune diseases: expanding the spectrum from systemic lupus erythematosus (SLE) to mixed connective tissue disease (MCTD) and scleroderma report of eight cases. Am J Med Genet A. 2008; 146A:3038–53. [PubMed: 19006208]
19. Reed SD, Vollan TA, Svec MA. Pregnancy outcomes in women with rheumatoid arthritis in Washington State. Matern Child Health J. 2006; 10:361–6. [PubMed: 16649008]
20. Henshaw K. Unintended pregnancy in the United States. Fam Plann Perspect. 1998; 30:24–9. 46. [PubMed: 9494812]

APPENDIX A: MEMBERS OF THE OTIS COLLABORATIVE RESEARCH GROUP

The following members of the OTIS Collaborative Research Group contributed to this study: Arizona Teratology Information Program, University of Arizona, Tucson: D. Quinn, S. Riordan; California Teratogen Information Service Pregnancy Risk Line, University of California, San Diego: K. Kao; Connecticut Pregnancy Exposure Information Service, University of Connecticut Health Center, Farmington: J. Brochu, S. LaVigne; Nebraska Teratogen Project, University of Nebraska Medical Center, Omaha: E. Conover; New York Pregnancy Risk Network, Ferre Institute, Binghamton: M. Roth; Perinatal Environmental and Drug Exposure Consultation Service, University of Rochester Medical Center, Rochester, New York: R. Miller; Texas Teratogen Information Service, University of North Texas, Denton: B. Debus, L. Wolfe; Utah Pregnancy Risk Line, Utah Department of Health, Salt Lake City: J. Carey, J. Robertson; Hospital for Sick Children, Toronto, Ontario, Canada: N. Djokanovic, A. Einarson, G. Koren; Long Beach Memorial Hospital, Long Beach, California: G. Briggs; University of Washington, Seattle: J. Polifka; Washington, DC: S. Lamm; Georgetown University Medical Center, Washington, DC: O. Soldin; University of Montreal, Montreal, Quebec, Canada: A. Berard; University of California, Irvine: C. Lyons Gaffaney; University of Pittsburgh, Pittsburgh, Pennsylvania: K. Wisner.

Table 1

Characteristics of the women taking leflunomide and the women in the comparison groups*

Characteristic	Leflunomide group (n = 64)	Disease-matched comparison group (n = 108)	Healthy comparison group (n = 78)	P†
Age, mean ± SD years	31.7 ± 6.1	31.6 ± 5.1	30.4 ± 5.1	0.22
Race/ethnicity				0.06
White/non-Hispanic	47 (73.4)	88 (81.5)	53 (68.0)	
Hispanic	8 (12.5)	14 (13.0)	12 (15.4)	
Black	6 (9.4)	5 (4.6)	3 (3.9)	
Asian	3 (4.7)	1 (1.0)	8 (10.3)	
Other	0	0	1 (1.3)	
Unknown	0	0	1 (1.3)	
Low socioeconomic status‡	16 (25.0)	11 (10.2)	13 (16.7)	0.04
Primigravid	18 (28.1)	38 (35.2)	24 (30.8)	0.64
Primiparous	23 (35.9)	51 (47.2)	36 (46.2)	0.32
Any previous spontaneous abortion	15 (23.4)	24 (22.2)	21 (26.9)	0.76
Any previous elective termination	10 (15.6)	14 (13.0)	11 (14.1)	0.85
Prepregnancy BMI, mean ± SD kg/m^2	25.1 ± 6.4	23.4 ± 5.4	25.0 ± 6.0	0.10
Multivitamins or folate at conception	14 (21.9)	79 (73.2)	52 (66.7)	<0.01
Any alcohol during pregnancy	24 (37.5)	48 (44.4)	37 (47.4)	0.49
Any tobacco use during pregnancy	16 (25.0)	9 (8.3)	8 (10.3)	<0.01
Gestation at time of enrollment, mean ± SD weeks	9.8 ± 6.0	11.8 ± 4.6	13.0 ± 4.6	<0.01
Diagnosis			–	0.56
Rheumatoid arthritis	53 (82.8)	84 (77.8)		
Juvenile rheumatoid arthritis	11 (17.2)	24 (22.2)		
Symptom score, mean ± SD			–	
Pain, 0–100 points	35.5 ± 28.2	33.0 ± 27.0		0.56
Activity, 0–60 points	8.5 ± 8.6	9.3 ± 9.3		0.58
Global, 0–100 points	27.9 ± 25.2	29.5 ± 25.6		0.69
Dosage leflunomide, mg/day§		–	–	–
Mean ± SD	17.6 ± 5.1			
Range	2.5–100.0			
Weeks postconception last dose of leflunomide		–	–	–
Mean ± SD	3.1 ± 1.8			
Range	0–8.6			
Cholestryramine washout procedure	61 (95.3)	–	–	–
Systemic steroid use	44 (68.8)	69 (63.9)	2 (2.6)	<0.01
NSAID use	38 (59.4)	42 (38.9)	11 (14.1)	<0.01
Weight gain in pregnancy for live births, mean ± SD kg	14.6 ± 7.3	12.7 ± 4.4	15.8 ± 6.6	<0.01
≥1 prenatal ultrasound >14 weeks gestation for live births	54 (96.4)	92 (96.8)	67 (93.1)	0.47

* Except where indicated otherwise, values are the number (%). In some cases, numbers do not sum to total, due to missing values. BMI = body mass index; NSAID = nonsteroidal antiinflammatory drug.

† Three-group comparisons, by chi-square or Fisher's exact test for categorical variables and analysis of variance for continuous variables.

‡ Based on Hollingshead categories derived from maternal and paternal occupation and education (categories 1–5, with 1 being the highest; low socioeconomic status defined as category 4 or 5).

§ Daily dose averaged over weeks postconception before discontinuation of the medication, including loading dose (data available on 58 subjects).

Table 2

Birth outcomes in the women taking leflunomide and the women in the comparison groups*

	Leflunomide group (n = 64)	Disease-matched comparison group (n = 108)	Healthy comparison group (n = 78)
Liveborn infant	56 (87.5)	95 (88.0)†	72 (92.3)
Spontaneous abortion	5 (7.8)	8 (7.4)	3 (3.9)
Stillbirth	0	1 (0.9)	0
Blighted ovum	1 (1.6)	0	0
Elective termination	1 (1.6)	2 (1.9)	0
Lost to followup	1 (1.6)	2 (1.9)	3 (3.8)
Among live births			
Male sex	24 (42.9)	51 (53.7)	37 (51.4)
Twin gestation‡	4 (7.1)	2 (2.1)	1 (1.4)
Delivery by cesarean section§	27 (48.2)	27 (28.7)	18 (25.0)
Preeclampsia	6 (10.7)	3 (3.2)	4 (5.6)
Diabetes any	3 (5.4)	2 (2.1)	4 (5.6)
Source of information on presence or absence of major malformations among live births			
Dysmorphologic examination	51 (91.1)	90 (94.7)	65 (90.3)
Child's physician	2 (3.6)	0	4 (5.6)
Maternal report	3 (5.3)	5 (5.3)	3 (4.2)

*Values are the number (%).

†There was 1 neonatal death, which was due to necrotizing enterocolitis.

‡One twin of each twin pair was randomly selected for analysis.

§$P = 0.01$ for 3-group comparison, by chi-square test.

Table 3

Major and minor structural anomalies in infants of women in the leflunomide-treated and comparison groups*

Anomaly	Leflunomide group	Disease-matched comparison group	Healthy comparison group
Major structural defects in live births, no. (%) and diagnoses	3/56 (5.4): 1 occult spinal dysraphism; 1 unilateral uretero pelvic junction obstruction and multicystic kidney disease; 1 microcephaly	4/95 (4.2): 1 PFO with peripheral pulmonic stenosis; 1 ASD with pulmonic valve stenosis; 1 bilateral inguinal hernia and microcephaly; 1 eye defect of posterior chamber†	3/72 (4.2): 1 unilateral cryptorchidism;‡ 1 Klippel-Trenaunay-Weber syndrome; 1 vocal cord paralysis§
Major structural defects in pregnancy losses, no. (%)and diagnoses	0/7	3/11 (27.3): 2 trisomy 18; 1 chromosomal anomaly NOS	0/3
Major structural defects in all pregnancies, no. (%)¶	3/63 (4.8)	7/106 (6.6)	3/75 (4.0)
Functional problems, diagnoses	1 hydronephrosis grade 2; 1 bilateral vesicoureteral reflux	1 unilateral hydronephrosis; 1 vesicoureteral reflux with unilateral duplicated collecting system	1 congenital esotropia; 1 neonatal encephalopathy and seizures secondary to subarachnoid bleed; 1 tracheomalacia
Minor structural anomalies, no. (%)#			
0–1	12/51 (23.5)	39/90 (43.3)	33/65 (50.8)
2	15/51 (29.4)	22/90 (24.4)	13/65 (20.0)
≥3	24/51 (47.1)	29/90 (32.2)	19/65 (29.2)
Pattern of minor anomalies	0	0	0

* One twin of each liveborn twin pair was randomly selected for analysis; however, no twin was malformed. PFO = patent foramen ovale and pulmonic valve stenosis (in a full-term infant), persisting beyond 6 weeks of life; ASD = atrial septal defect; NOS = not otherwise specified.

† Reported by mother.

‡ Reported by mother; inguinal hernia in a full-term infant, requiring surgery.

§ Persistent and not due to trauma.

¶ All pregnancies excluding loss to followup.

$P = 0.05$ for 3-group overall comparison; $P = 0.10$ for 3-group comparison of infants with ≥3 minor structural anomalies, by chi-square test.

Table 4

Gestational age, birth size, and postnatal growth in liveborn infants of women in the leflunomide-treated and comparison groups*

	Leflunomide group (56 live births)	Disease-matched comparison group (95 live births)	Healthy comparison group (72 live births)	*P*†	*P*, leflunomide group vs. disease-matched group‡
Gestational weeks					
Mean ± SD	36.9 ± 3.2	38.2 ± 2.4	39.3 ± 1.5	<0.01	<0.01
Range	24.1–41.7	26.4–41.4	33.9–41.6		
Preterm delivery (<37 weeks)§	20 (35.7)	23 (24.5)	5 (6.9)	<0.01	0.19
Full-term infants					
Weight, mean ± SD gm	3,116 ± 457	3,310 ± 391	3,580 ± 420	<0.01	0.02
Length, mean ± SD cm	50.0 ± 2.4	50.4 ± 2.6	51.2 ± 2.3	0.04	0.45
Head circumference, mean ± SD cm	34.1 ± 1.6	34.3 ± 1.6	34.6 ± 1.4	0.22	–
Infants ≤10th centile at birth					
Weight	9 (16.4)	8 (8.5)	1 (1.4)	<0.01	0.15
Length	2 (3.6)	8 (8.5)	0	0.02	0.27
Head circumference	5 (10.2)	13 (15.3)	5 (8.0)	0.39	–
Infants ≤10th centile postnatal					
Weight	8 (16.0)	13 (15.1)	0	<0.01	0.95
Length	7 (14.0)	5 (6.0)	2 (3.4)	0.11	–
Head circumference	5 (10.2)	9 (10.8)	2 (3.4)	0.24	–

*Except where otherwise indicated, values are the number (%). In some cases, numbers do not sum to total, due to missing values (data on gestational age at delivery missing for 1 infant from the disease-matched group; data on head circumference at birth missing for 7 infants from the leflunomide-treated group, 10 infants from the disease-matched group, and 9 infants from the healthy comparison group).

†Three-group comparisons, by Fisher's exact test for categorical variables and analysis of variance for continuous variables.

‡Pairwise comparison of leflunomide-treated group and disease-matched comparison group, performed on variables for which the *P* value in the 3-group comparison was <0.05.

§Of preterm infants, 4 were very preterm (<30 weeks gestation) (2 infants from the leflunomide-exposed group [3.6%] and 2 infants from the disease-matched comparison group [2.1%]).

Table 5

Multivariate analysis of gestational age and birth size in infants of women in the leflunomide-treated and disease-matched comparison groups

Model, variable	β estimate	Standard error	P
Gestational weeks (liveborn infants) *			
Leflunomide (no vs. yes)	0.68	0.49	0.17
Maternal age (years)	−0.07	0.04	0.13
Prednisone timing (vs. none)			
First or second or third trimester	0.30	0.88	0.74
First and second trimesters	−0.90	1.20	0.45
Second and third trimesters	−0.50	0.92	0.58
First and second and third trimesters	−0.51	0.48	0.29
Maternal race/ethnicity (vs. white)			
Black	−4.65	1.03	<0.01
Hispanic	−0.75	0.73	0.31
Asian/Pacific Islander	1.11	1.35	0.41
Socioeconomic status (category vs. 1 [highest])			
2	0.40	0.56	0.48
3	0.60	0.66	0.36
4	0.27	0.92	0.77
5	1.87	1.12	0.10
Tobacco use during pregnancy (yes vs. no)	−0.67	0.67	0.31
Preeclampsia (yes vs. no)	−0.99	0.89	0.27
Birth weight (full-term liveborn infants) †			
Leflunomide (no vs. yes)	32.79	78.10	0.68
Maternal age (yrs)	8.00	6.91	0.25
Tobacco use during pregnancy (yes vs. no)	−111.53	102.73	0.28
Gestational age (weeks)	133.13	31.30	<0.01
Prednisone timing (vs. none)			
First or second or third trimester	−196.24	124.36	0.12
First and second trimesters	−44.33	244.30	0.86
Second and third trimesters	−522.12	143.21	<0.01
First and second and third trimesters	−350.59	75.43	<0.01
Socioeconomic status (category vs. 1 [highest])			
2	222.79	86.90	0.01
3	111.09	102.40	0.28
4	179.18	146.69	0.23
5	−135.92	349.16	0.70

* Multiple linear regression adjusted $R^2 = 0.20$.

† Multiple linear regression adjusted $R^2 = 0.37$.