Table 1 Characteristics of our patients and controls

	No	Age (years) Mean (SD)	Sex	Disease duration (years) Mean (SD)	IgM RF positive No (%)	IgG anti-CCP positive No (%)
EOA	32	59.3 (11.4)	26F; 6M	8.3 (3.6)	0	0
NOA	35	61.5 (9.2)	21F; 14M	9.1 (3.2)	0	0
RA	45	52 (16)	32F; 13M	10.6 (6.5)	28 (62)	31 (69)
Healthy subjects	50	54.4 (18.2)	39F; 11M	–	2 (4)	0

peptide antibodies (anti-CCP) are highly specific for RA and good predictors of radiographic joint damage[9]; for that reason this study aimed at detecting these autoantibodies in serum samples of patients with EOA, in order to ascertain their clinical usefulness and, possibly, to contribute to the clarification of the relationship of EOA with classical OA and RA. On the one hand, positive results may support the hypothesis that EOA is an interface between OA and RA, but, on the other hand, negative results may support the hypothesis that EOA is one end of the spectrum of OA.

We evaluated 32 patients with EOA showing typical EOA radiographic findings.[6] The control group included 35 patients affected by nodal OA of the hands (NOA) fulfilling American College of Rheumatology criteria[10] and 50 healthy subjects. All the patients were examined for exclusion of psoriatic arthritis, RA, undifferentiated spondyloarthropathies, gout, and pseudogout. In addition, 45 patients with RA were examined to test the sensitivity and specificity of our anti-CCP enzyme linked immunosorbent assay (ELISA) kit (table 1).

The second generation of anti-CCP antibodies was tested with an ELISA commercial kit (Axis-Shield, UK). All groups were assayed for IgM rheumatoid factor (RF), with ELISA methodology (Orgentec, Germany). Patients with EOA and the control group were negative for anti-CCP, whereas two healthy subjects were IgM RF positive. Of 45 patients with RA, 23 were positive for RF and anti-CCP, 5 for RF, 8 for anti-CCP, and 9 negative for both. The specificity of anti-CCP in diagnosing RA is well known,[9] and in our study it was 100%. For this reason the detection of anti-CCP has a higher diagnostic performance than RF, by virtue of its higher specificity. The sensitivity of anti-CCP was 69%, but becomes 80%, if calculated in conjunction with RF.

In our opinion, the absence of anti-CCP antibodies in EOA as opposed to their high prevalence in RA is a further difference between EOA and RA, supporting the hypothesis that EOA represents a subset of OA, as suggested by other authors.[2–4 7] Therefore, the anti-CCP assay can be considered a further useful test to help to discriminate between EOA and RA in the early stage of the disease. The conjunction of both a negative RF test and a negative anti-CCP test make the diagnosis of RA unlikely and argue for the diagnosis of EOA.

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Paternal and maternal exposure to leflunomide: pregnancy and neonatal outcome

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Leflunomide is a pyrimidine synthesis inhibitor with proven teratogenic and fetotoxic effects in animal studies, and its active metabolite is detectable in plasma up to 2 years after discontinuation of the drug.[1–3] For this reason the fetus could have in utero exposure to leflunomide up to 2 years after the end of treatment unless an oral cholestyramine regimen, 8 g three times daily for 11 days, is administered to obtain undetectable plasmatic levels.[1–3]

Table 1 Outcome in exposed cases

Case No	Maternal age	Exposure period	Washout procedure	Pregnancy outcome	Neonatal follow up
1 Maternal	35	Until 6½ months before conception	No	Caesarean section at 39 weeks	Normal male, 2600 g
2 Maternal	34	Until 1½ months before conception	No	Voluntary abortion	
3 Maternal	30	Until 9 weeks of gestation	No	Voluntary abortion	
4 Maternal	37	Until 5 weeks	No	Voluntary abortion	
5 Maternal	35	Until 9 weeks	No	Caesarean section at 36 weeks	Normal male, 2200 g
6 Paternal	31	Throughout pregnancy	No	Caesarean section at 38 weeks	Normal male, 3350 g

Leflunomide has been classified as pregnancy category X by the Federal Drug Administration and the manufacturer recommends that for women of childbearing age ''treatment with leflunomide must not be started until pregnancy is excluded and it has been confirmed that reliable contraception is being used''.[1 4] Label instructions about paternal exposure recommend a washout procedure to minimise any possible risk.[1 4] To date, there have been no epidemiological human studies of pregnancies after or during paternal or maternal leflunomide exposure, and current knowledge is restricted to a few cases.[2 4]

CASE REPORTS

We report on five cases of women who conceived within 2 years after the discontinuation of, or during, leflunomide treatment, and one case of pregnancy during paternal exposure (table 1). They were referred to our teratogen information service between July 2002 and January 2004.

Four women were exposed in the first trimester and one conceived 6½ months after stopping the treatment. Despite our recommendation, none of the women performed the washout procedure, resulting, therefore, in fetal exposure to therapeutic drug levels during organogenesis. In the case of paternal exposure, leflunomide was taken from 6 months before conception and during the whole pregnancy with intercourse without a condom during the gestation.

Three women had voluntary abortions owing to the fear of malformation and three women had live births with healthy babies (two maternal and one paternal exposure). In one of the two cases of maternal exposure the leflunomide treatment was given until 6½ months before the conception, in the other until the 9th week of gestation. They delivered their babies at 39 and 36 weeks, both by caesarean section, weighing 2600 and 2200 g respectively, with normal neonatal outcome. These cases increase the number of previously reported cases, bringing to four the number of live birth normal babies with complete follow up. To date there has been no report of human congenital malformation after prenatal leflunomide exposure. In the case of paternal treatment, a normal baby of 3350 g was delivered by caesarean section at 38 weeks—the first reported case.

DISCUSSION

Seven cases of babies born with congenital malformations were reported by Ostensen referring to a manufacturer's safety update to 2003 about 164 pregnancies followed up completely in 310 women exposed. Of these 164 cases, 85 were full term pregnancies, 43 were voluntary abortions, and 36 miscarried.[5]

Chakravarty *et al* reported 10 pregnancies in patients taking leflunomide: two cases lost at follow up, two continuing pregnancies, two legal abortions, one spontaneous abortion, two full term healthy babies, and one preterm infant without detailed follow up.[4]

The scarcity of published data about human pregnancy and neonatal outcome justifies the collection of as many cases as possible because in teratological counselling it is mandatory to consider all known human cases once a drug has been indicated as a potential teratogen in experimental studies. A post-marketing surveillance study has been established by the manufacturer to monitor the outcome of pregnancies, including first trimester exposures.[2 6]

At present the possible fetal and neonatal side effects of leflunomide exposure are being investigated by a Canadian OTIS (Organisation of Teratology Information Service) in a prospective study.[5]

We consider it advisable to warn couples that no controlled or adequate study is available and for inadvertent exposure during pregnancy it is necessary to inform them about the theoretical reproductive risk reported in animal studies and to recommend the washout procedure and accurate fetal ultrasound examinations.

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