Prospectively-followed pregnancies in patients with inflammatory arthritis taking biological drugs: an Italian multicentre study

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Abstract

Objective

Information on new drugs does not include their possible effects on pregnancy because pregnant women are excluded from clinical trials. Although not classified as teratogenic in animals, limited data is available on biological anti-rheumatic agents and their safety in human pregnancy. The aim of the study is to evaluate the safety of biological drugs in pregnant patients with chronic arthritis.

Methods

Pregnancy outcome and maternal disease variations were prospectively followed in six Italian Rheumatology Centres. Patients exposed to biological agents during the periconceptional period or during pregnancy were included in the study. The occurrence of congenital malformations as well as the obstetric and neonatal outcomes were assessed.

Results

Between 1999 and 2013 we identified 79 exposed pregnancies in 67 women affected by different rheumatic diseases with peripheral chronic arthritis. At the time of the start of pregnancy, 56 patients were taking etanercept, 13 adalimumab, 3 infliximab, 2 each certolizumab-pegol and rituximab, 1 each golimumab, anakinra and abatacept. Biological treatment was stopped after a mean of 41 days since documented pregnancy. Live births were reported in 66% of pregnancies. The rate of spontaneous pregnancy loss was 20%. Only one congenital malformation was reported.

Conclusion

TNF-alpha inhibitors can be considered safe in the periconception period, representing a possible therapeutic choice also in young women affected by an aggressive form of chronic arthritis and hoping for a pregnancy. Reports of exposure during 2nd/3rd trimester are still limited and suggest caution. Experience with abatacept, tocilizumab, anakinra and rituximab in pregnancy is insufficient.

Key words

pregnancy, chronic arthritis, biologic anti-rheumatic drugs

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Received on November 14, 2014; accepted in revised form on March 23, 2015.

Competing interests: none declared.

Introduction

The widespread use of biological agents has greatly ameliorated patients' quality of life and has led to a better perception of social needs such as family planning. Indeed, more and more women today ask their rheumatologists about the possibility to fall pregnant and the potential risks of anti-rheumatic treatment (biological or not) before and during gestation. Many patients with inflammatory arthritis in fact are women in their reproductive age and with a generally normal fertility. The gestational course of patients with rheumatic diseases may vary greatly, but clinical observations suggest that arthritis with peripheral joint involvement frequently improves during pregnancy (1). In spite of this, many patients fail to stop treatment during gestation or before conception without suffering disease relapses. On the other hand, some effective and well-known anti-rheumatic drugs, such as methotrexate and leflunomide, are not indicated in patients planning a pregnancy because of their potential teratogenicity (2, 3). Even if published data about safety of more recent biologic anti-rheumatic treatment in pregnant patients is still limited, biological drugs, essentially antibodies or antibody derived proteins directed to pro-inflammatory cytokines or cytokines receptors, are not considered fetotoxic. For ethical issues, well-conducted studies have not been performed in pregnant women, and the published experiences mainly consist of preclinical/animal reproduction studies, single case reports and registries of pregnant patients with arthritis or inflammatory bowel disease. The experience with some biologic drugs (anakinra (4, 5), rituximab (6), abatacept (7), tocilizumab (8)) is now insufficient to claim their safety during gestation (9, 10), whereas human and animal data on anti-TNF-alpha agents exposed pregnancies seem to be reassuring (11). Whilst most of the available data come from retrospective studies, here we present our prospectively collected data on pregnancy course and outcome in women with inflammatory arthritis taking biological drugs immediately before or during gestation, particularly focusing on obstetrical and foetal outcomes.

Methods

We conducted a multicentre, observational, prospective study involving six referral Rheumatology centres in Italy (Brescia, Pavia, Rome, Bari and 2 centres in Milan). The study was approved by the institutional ethics committee and informed consent was obtained from all the mothers. Starting from 1999 and until 2013, we registered in a computerised electronically-filled form all consecutive female patients with pregnancies exposed during peri-conception period and/or during gestation to biological agents approved to treat chronic inflammatory rheumatic diseases: etanercept, infliximab, adalimumab, golimumab, certolizumab-pegol, anakinra, rituximab, abatacept and tocilizumab. The availability of complete clinical information during gestation as well as 6 months before and after pregnancy was considered as an essential inclusion criterion. Not directly exposed pregnancies (from women treated with biological therapies only before conception) were excluded, except for 2 rituximab-exposed pregnancies. These cases were included in order to evaluate the effect of B lymphocyte depletion on pregnancy and babies' health. Data collected in our database included patients' medical history (tobacco and alcohol intake, comorbidity), underlying rheumatic disease-related features (diagnosis, disease duration, disease activity before, during and after pregnancy, extra-articular manifestations, treatment, laboratory tests). Obstetrical history (parity, infertility, prior pregnancy, previous obstetric complications), current pregnancy details (maternal and foetal disease, complications during gestation, obstetric outcomes, kind of labour), newborn health (gestational age, birth weight, Apgar score, postnatal illnesses) and lactation. Disease activity was determined using DAS28-CRP score. The primary outcome measure was the occurrence of congenital malformations. Secondary outcome measures were the rate of: live birth, spontaneous abortion (defined as <10 weeks gestation), foetal death (defined as ≥10 weeks gestation), elective termination, premature birth (defined as birth less than 37 weeks of gestation),

very-low-birth weight (defined as birth weight less than 1500 g), small-for-gestational age (defined as birth weight less than the 10th percentile for their gestational age), foetal/neonatal complications, and Caesarean sections.

Statistical analysis

All data were expressed as mean (or median) ± standard deviation (or range). Differences between continuous variables were evaluated using Student's *t*-test or Mann-Whitney test, whereas the χ^2 test or Fisher's exact test were used to analyse the categorical variables. A *p*-value <0.05 was considered statistically significant.

Results

Study population

We observed 79 exposed pregnancies in 67 women affected by rheumatic diseases, mainly chronic inflammatory arthritis such as rheumatoid arthritis, spondyloarthropathies, including psoriatic arthritis, and juvenile idiopathic arthritis. Three women received biological drugs off-label because of musculoskeletal symptoms complicating their underlying condition: one patient had a Behçet disease and 2 had dermatomyositis without systemic involvement. Among the recruited patients, we observed 2 cases of Sjögren's syndrome, 2 cases of inflammatory bowel disease and an overlap syndrome (rheumatoid arthritis and systemic lupus erythematosus). None of the patients had an associated antiphospholipid syndrome, although 14 (out of the 53 studied; 26.4%) were positive for the presence of antiphospholipid (aPL) antibodies in 1 or 2 tests, while triple positivity was not found. A previous history of unexplained infertility was present in 3 patients (aged 33, 35 and 43 years, respectively), who underwent ovarian stimulation with clomiphene citrate. The main features of patients enrolled are shown in Table I. Disease activity scores before, during and after pregnancy are presented in Figure 1. At the time of pregnancy start, 56 patients were taking etanercept, 13 adalimumab, 3 infliximab, 2 each certolizumab-pegol and rituximab, 1 each golimumab, anakinra and abatacept. The mean time of biological exposure before pregnancy was 23 months (range 1-88). Biological treatment was stopped after a mean of 41 days (range 13-259) since the last menstrual period. Seventy-four patients out of the 75 treated with anti TNF-alpha agents stopped the drug at the time of the first positive pregnancy test. One patient with rheumatoid arthritis first started etanercept at pregnancy week 23 because of the occurrence of a severe arthritis with systemic inflammation. The drug was stopped at week 37 of gestation, 1 week before delivery. Another patient affected by rheumatoid arthritis decided to take etanercept throughout gestation due to a severe articular involvement. Four patients (3 with spondyloarthritis and 1 with juvenile idiopathic arthritis), received etanercept during the third trimester (3 during the second as well), due to a disease flare. In this group, 1 patient delivered at 34 weeks (when she was still on treatment with etanercept 25 mg every week); the others stopped the drug 1-3 weeks before delivery (1 at week 34 and 2 at week 37). Concomitant treatment at conception included: prednisone (48%; ≤5 mg/day), folic acid (35%), NSAIDs (26%), hydroxychloroquine (20%), sulphasalazine (8%), cyclosporine A (1%), azathioprine (1%). In the first trimester folic acid was taken by 70% of the patients. Furthermore, 6 mothers were being treated with methotrexate (1 received 7.5 mg/week, 3 10 mg/week, 1 12.5 mg/week and 1 15 mg/week). The drug was stopped 20-39 days after conception. Two other patients stopped methotrexate before the 3 month wash-out period currently recommended in case of pregnancy (8 and 9 days before their first positive pregnancy test, respectively). Finally, 2 women stopped leflunomide 15 and 26 days after the estimated pregnancy onset and received the wash-out procedure with cholestyramine. No difference was found in the steroid dosage either before or after conception between patients treated with biological agents during the 2nd/3rd trimester and untreated patients.

Table I. Patient characteristics at time of conception.

	Exposed pregnancies: 79
Maternal age at conception, yrs (mean ± SD)	33 ± 5
Disease duration, yrs (mean ± SD)	13 ± 9
Maternal rheumatic disease	
Rheumatoid arthritis, n (%)	37 (47)
Spondyloarthropathies, n (%)	13 (16)
Psoriatic arthritis, n (%)	13 (16)
Juvenile idiopathic arthritis, n (%)	13 (16)
Dermatomyositis, n (%)	2 (2)
Behçet's disease, n (%)	1 (1)
Comorbidities, n (%)	13/79 (16)
Previous pregnancy complications, n (%)	11/79 (14)
Laboratory tests	
RF pos, n (%)	12/53 (23)
ACPA pos, n (%)	13/43 (30)
RF or ACPA pos, n (%)	16/53 (30)
C3 mg/dl (mean ± SD)	110 ± 30
C4 mg/dl (mean ± SD)	20 ± 8
ANA pos, n (%)	27/58 (46)
Anti-ENA antibodies pos, n (%)	3/58 (5)
DAS28 (mean ± SD)	2,12 ± 1.2
CRP mg/dl (mean ± SD)	2.5 ± 5

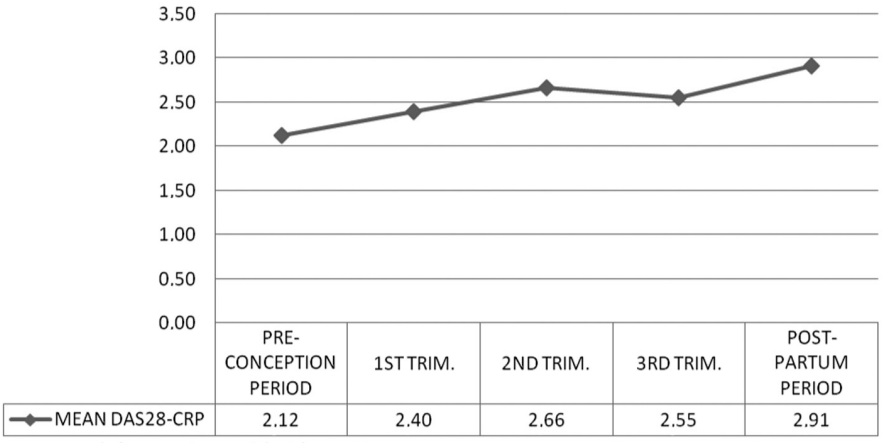

Fig. 1. Disease activity measured with DAS28-CRP pre, during and post pregnancy.

Table II. Overview of pregnancy outcomes.

	Exposed pregnancies: 79
Liveborn infant, n (%)	52 (66)
Spontaneous abortion, n (%)	11 (14)
Intrauterine death, n (%)	5 (6)
Elective termination, n (%)	9 (11)
Ectopic pregnancy, n (%)	2 (2)
Among live births:	
Male sex, n (%)	16/52 (31)
Twin gestation, n (%)	0
Birth defects, n (%)	1/52 (2)
Delivery by Caesarean section, n (%)	25/52 (48)
Pre-term delivery (<37w)	12/52 (23)
Pre-term delivery (<34 w)	6/52 (12)

Pregnancy outcome

As shown in Table II, 52 live births in a total of 79 pregnancies were reported (66%). Caesarean section was performed in 25/52 cases (48%). Only 10 women (19%) had an emergency Caesarean delivery due to obstetric complications: premature rupture of membranes (PROM) (3), maternal high blood pressure (3), labour dystocia (2), pre-eclampsia (1) and foetal distress (1). The rate of spontaneous abortion/foetal death was 20% (11/79 and 5/79, respectively). Spontaneous abortions occurred during the first 8 weeks of gestation, while all the observed intrauterine deaths occurred at pregnancy week 10. Overall, 2 ectopic pregnancies (2.5%) and 9 terminations (11%) were observed. The mean (± SD) maternal age in the group of patients that decided for an elective termination was 29 ± 7 yrs, significantly lower than in mothers who decided to continue with the pregnancy (34±5 yrs, p=0.01). Three of the 9 women who underwent voluntary abortion were on methotrexate (drug dosages: 7.5 mg/week, 10 mg/week and 15 mg/week), 1 on abatacept. No significant differences about maternal age, tobacco and alcohol intake, comorbidity, previous pregnancy complications, rheumatic disease activity, immunological laboratory tests and drug exposure were noted between the group of patients ending in pregnancy loss and the group ending in live birth. The occurrence of pregnancy loss was not related to the presence of aPL antibodies as detailed in Table III.

Table III. Pregnancy loss and antiphospholipid antibodies (aPL). Pregnancy loss in 53 pregnancies with available aPL antibody-profile. Four out of the 11 pregnancies ending in early miscarriages were not evaluated for presence of aPL antibody.

	aPL antibody-positive pregnancies (n=14)	aPL antibody-negative pregnancies (n=39)	Fisher's exact test
Intrauterine deaths (n=5)	1/14 (7%)	4/39 (10%)	P 1.000
Spontaneous abortions (n=11)	2/14 (14%)	5/39 (12.8%)	P 0.646

Neonatal outcome

Of 52 live births, 12 babies (23%) were born prematurely at less than 37 weeks of gestation and 6 of them (12%) were born at less than 34 weeks of gestation. A very pre-term labour (31 weeks) occurred in a woman with pre-eclampsia. Mean (± SD) gestational age at birth was 37.8±2 weeks. Mean (± SD) birth weight was 3000±676 g. One pre-term baby had a very low birth weight and 2 small for gestational age babies were observed. There were 3 neonatal complications in newborns exposed to etanercept only in the first trimester: 2 respiratory distress syndrome (one in a baby with intrauterine growth restriction born at week 31 from a mother affected by pre-eclampsia) and a pneumothorax in a pre-term baby born at 34 weeks of gestational age. One congenital malformation (cleft palate, micrognathia, myopia, glaucoma, oesophageal motility disorder) was reported in a baby exposed to adalimumab during the first 31 days of gestation whose mother was treated only with low-dose prednisone (less than 5 mg per day) throughout pregnancy.

Pregnancy and neonatal outcome of cases exposed to particular drugs

Ten pregnancies were exposed to an 'X' category drug (methotrexate, n=8 and leflunomide, n=2) in addition to the biological agent. In these pregnancies we observed 5/10 live births (50%), 3 voluntary abortions (30%), 1 spontaneous abortion (10%) and 1 foetal death (10%). All 6 pregnancies exposed to biological agent during second/third trimester (from women treated with etanercept in monotherapy) ended in live births. The only complication noted in this group of pregnancies was a pre-term premature rupture of the membranes (PPROM) in a mother treated between 28 and 34 weeks of gestation, who was not taking any additional drug including glucocorticoids. In our study, only 4/79 pregnancies (5%) were exposed to biological agents other than TNF-alpha inhibitors. Among these, 2 (1 exposed to anakinra plus methotrexate and 1 to abatacept) ended in voluntary abortion; 2 live births were observed after rituximab treatment, which was discontinued 6 and 11 months before conception, respectively.

Thirty-four babies (61%) were breastfed. Lactating women didn't receive any biological agent nor 'X' category drugs during breastfeeding. Fifteen mothers (44%) took prednisone (less than 10 mg/day) and 8 (25%) hydroxychloroquine (200 mg/day).

Discussion

Our study describes the prospective analysis of 79 pregnancies occurred in women affected by chronic arthritis and treated with IgG monoclonal antibodies or fusion proteins, in most of the cases TNF-alpha inhibitors (95%). In this study the observed rate of malformations was similar to that expected in the general population (1.5–2.5%) (12, 13). The critical reappraisal of the only case of neonatal malformation observed in our study did not reveal any relationship between intrauterine drug exposure and birth defect. The time of exposure to biological agents was very short in this case (31 days), as well as in the majority of observed pregnancies. Indeed, in 74/79 cases (94%), the mean time of exposure was 41 days after the last menstrual period, a situation considered safe because the active transplacental transport of IgG only starts after the first trimester (14). Although biological agents should be discontinued after the first positive pregnancy test, severe maternal rheumatic flares can require treatment to be started again during gestation (10). Conversely, in the last part of it, transplacental

passage significantly changes, also depending on the different structural features of biological compounds. The active transport is particularly effective for IgG molecules: while their levels in the maternal circulation decrease during pregnancy, IgG of maternal origin exponentially increase in the foetal circulation over the course of weeks and can exceed maternal concentration at term (15). In order to avoid an impaired immune response and a higher infective risk in the babies, TNF-alpha inhibitors should be discontinued before gestational week 30, especially if they are complete monoclonal antibodies. In our cohort, 6 pregnancies were exposed to the fusion protein etanercept beyond this period, because of high maternal disease activity. All these cases ended in live births and only a PPROM with a pre-term delivery was observed in a mother treated between 28 and 34 weeks. No foetal/neonatal complications were noted in this group of pregnancies and in particular no infectious events were reported in the newborns. In our cohort, spontaneous abortion and foetal death rate was 14 and 6%, respectively. The same proportion was observed in retrospective studies about TNF-alpha use in pregnancy (16) and in the general population, too. The rate of early pregnancy loss in the general obstetric population aged 30-34 years (17), including clinically undetectable pregnancies, is estimated to be about 20-25% (17, 18). On the other hand, in the British Society for Rheumatology Biologics Register a slight increase in spontaneous abortion rate was observed in women exposed to TNF-alpha inhibitors at conception (24%), mainly in those also receiving concomitant methotrexate or leflunomide (33%) (16). We cannot confirm this observation because in the subgroup of 10 patients receiving both "X" category drugs and biological agents only 2 early miscarriages (20%) were observed with the same rate of our study population. Elective termination was performed in 9/79 women (12%), with a higher rate in the group of patients exposed to biological agent plus methotrexate or leflunomide (30%) and with lower maternal age. This data is in contrast with a recent paper reporting that women with RA taking methotrexate seemed to have a lower rate of unwanted pregnancies ending in elective terminations (19). On the other hand, we observed 5 voluntary abortions in mothers taking medications not classified as fetotoxic. These cases testify the overall urgent need of performing a proper counselling for all the women taking anti-rheumatic drugs, not only at the beginning, but also during the course of treatment.

We observed a high prevalence of Caesarean sections (48%) and pre-term deliveries (23%). However, only 10 women had an emergency Caesarean section (19%) due to obstetrical complications; in 8/52 deliveries (15%) the surgical solution was adopted by the treating physician in the absence of medical problems in mothers or babies. Pre-term delivery occurred in 12/52 women (23%), and in 6 cases (11%) it was performed before week 34. This frequency is higher than that of the general obstetric population (5-13%) (20), but is quite similar to that of RA mothers exposed and not exposed to biological agents (16). As reported in other papers, pregnancy in rheumatic diseases is generally related to a higher risk of primary Caesarean section and pre-term delivery (21, 22). In our study, few neonatal complications (6%) were noted, in accordance with previous reports (23). In particular, we did not observe any infectious event nor post-vaccine complications in children despite the antenatal exposure to immunosuppressive agents. Even if the number of observed pregnancies was relatively small, this multicentre study supports the safety of TNF-alpha inhibitors during the early stage of pregnancy. Indeed, we observed neither a high rate of malformations nor any relevant obstetric or neonatal adverse events. In agreement with the already published data (24), we can conclude that women who inadvertently become pregnant while taking TNF-alpha inhibitors should be reassured that continuation of pregnancy does not represent a risk for obstetric outcomes. On the contrary, these drugs could be very useful in the critical phase just before conception, when adjustment of therapy is often needed, allowing the withdrawal of "X category" drugs. In periconceptional period and during early pregnancy an adequate medication will not only improve maternal health, but could also create a more favourable health profile for the foetal growth (25).

Even if reports of exposure during second/third trimester are too limited to make recommendations, TNF-alpha inhibitors could be considered in the second part of gestation also in patients with very active disease. Till now, experience of pregnancy exposure to abatacept, tocilizumab, anakinra and rituximab in women with rheumatologic conditions has largely been limited to conference abstracts or simple case reports (26). In our opinion, it is extremely important to collect data about all the pregnancies exposed to new biological drugs in order to enlarge our knowledge about their safety profile and, in this case, large-scale national and international pregnancy registries are needed. In addition, only the long-term follow-up of the babies will allow to confirm the safety of gestational drug exposure. In fact, little data is now available on health, development, immune competence and infection susceptibility of the exposed infants.

In summary, the safety of anti-rheumatic medications during pregnancy is a difficult topic. For each woman, the decision about pharmacological treatment in preconception period and during pregnancy will depend upon many variables. For this reason an appropriate preconception counselling and an interdisciplinary collaboration with the co-operation of rheumatologists, obstetrics, gynaecologists and neonatologists represent the most effective way of improving obstetric outcomes and promoting neonatal health. Finally, a more effective physician-patient communication about family planning and desire of pregnancy is necessary to overcome a clear unmet need of young women affected by rheumatic diseases.

Acknowledgments

We would like to thank Giovanna Mazza and Enrico Colombo for their help in compiling study data and Mrs Sara Lord for the English revision of the manuscript.

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