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Original Article

Title: Improved pregnancy outcome in patients with Rheumatoid Arthritis who followed an ideal clinical pathway.

Subtitle: Healthcare quality indicators and pregnancy outcome in Rheumatoid Arthritis.

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Abstract

Objective: Among women with rheumatoid arthritis (RA) we aimed to assess the effect of optimal management of pregnancy, on a composite outcome of miscarriage and complicated birth. Methods: Data were extracted from healthcare databases of the Lombardy Region, Italy (2004–2013), as a part of the RECord-linkage On Rheumatic Diseases Study. Analyses included women with RA identified through copayment exemption code (ICD9-CM code 714.0) and controls from the general population aged between 18 and 50. Seven healthcare quality indicators (HCQI) were constructed and summarized in 3 pathways indicators: A) diagnostic; B) therapeutic; C) and prenatal follow-up. The groups of complicated birth or miscarriage identified the adverse pregnancy outcome (APO). The relationship between HCQI and APO was analysed using logistic models and the results presented as odds ratios (OR) and 95% confidence intervals (95%CI). Results: The study cohort included the first pregnancy observed in 443 patients with RA compared with 6097 women belonging to the general population. In RA population, patients who followed the ideal pathway had a reduced risk of overall APO with an OR=0.60 (95%CI 0.39, 0.94) and of miscarriage/perinatal death with an OR=0.40 (95%CI 0.24, 0.69) compared to those who did not. Compared with the general population, patients with RA who met all HCQI during pregnancy displayed a risk of APO with an OR=0.92 (95%CI 0.61, 1.38) and miscarriage/perinatal death with an OR=0.77 (95%CI 0.47,1.29). Conclusions: The adherence to the ideal clinical pathway in women with RA restored the risk of APO to that expected for the general population.

Significance and Innovations

- Women with RA who followed an ideal pathway i.e., stratification of pre-conceptional obstetric risk, modulation of therapy, and prenatal rheumatological follow-up had a reduced risk of complicated birth or miscarriage compared to women with RA who did not follow the ideal pathway.

- In RA, the optimal management of pregnancy restores the risk of adverse pregnancy outcome to that expected for the general population.

- This study proposed, for the first time, seven healthcare quality indicators that need to be validated prospectively in women with RA who wish to become pregnant.

Introduction

The management of pregnancy in women with Rheumatoid Arthritis (RA) has substantially changed in the past few decades, along with the milestones in RA treatment such as biologic and targeted synthetic agents, and treat-to-target strategies (1). With the improvement in the management of RA, patients with severe disease have been able to reach remission more frequently and live normal lives, including starting a family. As a consequence, the paradigm that "RA spontaneously improves during pregnancy" has been defied over years, as nearly half of RA pregnant patients can have disease flares (2). Therefore, it has become critical to provide a tool for risk stratification and develop uniform management plans to improve favourable pregnancy outcomes among women with RA. Preconception counselling should include evaluation of maternal disease activity, modification of treatment, and assessment of general obstetric risk factors as performed in routine obstetric care (3). Patients should be informed about specific wash-out periods for teratogenic medications such as methotrexate (MTX) and leflunomide (LFN) and, conversely, about the fact that several anti-rheumatic drugs are appropriate for use during pregnancy and lactation (4).

This approach to women of childbearing age with RA could be considered as an "ideal" management pathway, however, in the literature, neither data explored the impact of this pathway on pregnancy outcomes nor guidelines specifically aimed at pregnancy management in RA. Whereas it would be suitable to have a systematic approach to the issue of pregnancy in RA, we have identified seven healthcare quality indicators (HCQI) grouped in A) diagnostic; B) therapeutic; C) and prenatal follow-up pathways, partly adopted from recommendations developed in other rheumatic conditions (5). Evidence support that RA patients with an active disease have significantly less chance for spontaneous improvement during pregnancy and are at risk for adverse pregnancy outcome (APO) making appropriate to consider instrumental (e.g. musculoskeletal imaging) and laboratory assessments (e.g. C-reactive protein test) as part of pre-conceptional risk stratification in patient with RA (6,7). In addition, in patients planning a pregnancy, expert's opinion supports the usefulness of a more extensive laboratory assessment including acknowledged potential risk factors for pregnancy complications, firstly anti-Ro/-La antibodies and antiphospholipid (aPL) antibodies (8).

To date, robust data on pregnancy outcomes are very desirable, especially when exploring the impact of different therapeutic approaches or clinical pathways. For this purpose, data from administrative healthcare databases (AHD) are useful due to their virtually complete coverage of the general population.

This study aimed to evaluate the impact of adherence to A) diagnostic; B) therapeutic; C) and prenatal follow-up pathways indicators ("ideal clinical pathway") on pregnancy outcomes, compared with women belonging to the general population and with women with RA who did not adhere, in an unselected population-based dataset.

Patients and Methods

Study design and setting

This is a retrospective observational study on the RECord-linkage On Rheumatic Diseases (RECORD) dataset, including data from AHD of the Lombardy region (>10,000,000 inhabitants), Italy. In detail, the design of the RECORD study includes a database population derived from 115,684 records of potentially RA individuals and 462,736 non-RA individuals matched by sex, age and province of origin (4 non-RA cases for each case of potential RA). As elsewhere described, we developed and validated an algorithm that identified 70,061 'true' cases of RA matched by sex and age with 280,244 non-RA cases within the original population of 462,736 non-RA cases through copayment exemption code 006.714.0 and based on its demonstrated high specificity (96.39%) and good sensitivity (77.08%) for RA (9). Access to data was granted by the General Directorate of Health for the purpose of the RECORD study, a project promoted by the Italian Society for Rheumatology aiming to set up a national surveillance system to monitor the health burden of rheumatic diseases in Italy using AHD. The protocol was approved by the ethical committee of the Pavia University Hospital. Data included were retrieved between 1 January 2004 and 31 December 2013.

Participants

From RECORD dataset, we extracted data of female patients with RA and controls women aged between 18 and 50 (9). Only data for the first pregnancy observed both in patients after the time of diagnosis of RA and in control cases were analyzed. Data included demographics (birthdate), redeemed prescriptions (Anatomic Therapeutic Chemical code, date of drug delivery, quantity), disease certification (code and date), outpatient visits (code and date) and hospital discharge forms including information on the date of delivery or miscarriage. The time of conception has been approximated from the date of delivery or miscarriage. Exposure to glucocorticoids (GCs), aspirin, low molecular weight heparin (LMWH), biological synthetic disease modifying drugs (bDMARDs), conventional synthetic DMARDs (csDMARDs) clustered in not recommended (MTX and LFN) and appropriate (cyclosporine A; hydroxychloroquine, HCQ; sulphasalazine; azathioprine). Concomitant comorbidities including the Charlson comorbidity index, thyroid diseases, chronic kidney failure, pre-gestational diabetes and hypertension were recorded as elsewhere described (10–14).

Variables

Seven healthcare quality indicators (HCQI) were constructed based on fulfillment of the following seven criteria: 1) having at least one blood lab tests (including erythrocyte sedimentation rate and/or C-reactive protein test) performed within 18 months before conceiving and the date of delivery or miscarriage); 2) pre-conception musculoskeletal imaging (including x-ray or ultrasound examinations of hands and feet performed within 18 months before conception and date of delivery or miscarriage) ; 3) pre-pregnancy aPL tests (at least one test performed within 18 months prior to conception, and the date of delivery or miscarriage); 4) ANA test and anti-ENA (anti-Ro/SSA) test (at least one test prescribed within 18 months prior to conception, and the date of delivery or miscarriage) ; 5) no exposure or wash-out from teratogenic drugs (MTX/LEF) indicated by the absence of redemption between 6 months before pre-conception and date of delivery or miscarriage; 6) no exposure to biological drugs (no medical prescriptions for abatacept, tocilizumab, rituximab, anakinra, certolizumab, etanercept, infliximab, adalimumab, golimumab between the presumed date of conception and date of delivery or miscarriage (at the time the study was conducted targeted synthetic DMARDs were not available in Italy and exposure to these drugs was not taken into account); 7) rheumatologic monitoring and follow-up via outpatient visits (at least one outpatient visit at the rheumatology department for women with RA). The 7 indicators were summarized in 3 main pathways indicators: A) diagnostic pathway composed by 1) blood lab tests; 2) musculoskeletal imaging; 3) aPL antibodies tests, 4) ANA and anti-ENA tests); B) therapeutic pathway based on 5) no exposure or wash-out from MTX/LEF or 6) no exposure to biological drugs; C) prenatal follow-up pathway 7) consisting of at least one rheumatological visit. The concomitant presence of all the 3 pathways indicators (A+B+C) defined the ideal clinical pathway.

Statistical methods

The pregnancy outcome was defined on the basis of the Disease-Related Groups (DRG, version 24) of complicated birth, pregnancy losses (miscarriage) or perinatal death collectively defined as APO codes (370: cesarean section due to complications, 372: vaginal delivery with complications, 374 and 375: vaginal delivery with complications requiring surgical intervention, 378: ectopic pregnancy, 379: threatened miscarriage; 380: spontaneous miscarriage, 381: spontaneous miscarriage requiring surgical intervention) and ICD9-CM codes (V271-277: perinatal death) (15). Sub-analysis on miscarriage and perinatal death (DRG 380-381, V271-273-274-276-277) was also performed. Conception date was estimated 42 days before the date of miscarriage for DRG 378-379 and 380 and 84 days before the date of miscarriage for DRG 381.

The relationship between HCQI and outcome variables was analyzed using logistic models crude and adjusted for age, Charlson comorbidity index, thyroid diseases and hypertension when comparing RA

patients versus the general population; adjusting for age, Charlson comorbidity index and thyroid diseases comparing women with RA who followed the ideal pathway versus women that did not. The results are presented as odds ratios (OR) and 95% confidence intervals (95% CI). All the analyses were performed using R statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Results

The study cohort included the first pregnancy observed in 443 patients with RA compared with 6097 control women belonging to the general population. Table 1 summarizes the demographic and therapeutic features of our cohort. The mean maternal age for all sampled mothers was 34 years (RA interquartile range 31-37, general population interquartile range 30-37). RA patients had a significantly higher frequency of thyroid diseases, overall APO and miscarriage/perinatal death as compared to the general population. Patients with RA adherent to the ideal clinical pathway were similar to non-adherent in socio-demographic and disease characteristics (Table 1). Overall, compared to women with RA who did not adhere to the ideal clinical pathway, RA patients in the ideal pathway were more exposed to treatment (no treatment in 56 patients in ideal pathway (39.7%) versus 199 cases not in ideal pathway (65.9%), p <0.001), including GCs (57 RA patients (40.4%) in ideal pathway versus 61 (20.2%) for those not in ideal pathway) and HCQ (58 patients (41.1%) in ideal pathway versus 44 (14.6%) not in ideal pathway, p<0.001) (Table 1).

Patients with RA who followed the ideal clinical pathway had a reduced risk of overall APO with an adjusted OR = 0.6 (95%CI 0.39, 0.94) and of miscarriage/perinatal death with an adjusted OR = 0.4 (95%CI 0.24, 0.69) compared to women with RA who did not adhere (Table 2). Among the three pathways (A, B, C), the multivariate analysis identified the therapeutic pathway as the main factor associated with overall APO with an adjusted OR = 0.28 (95% CI 0.14-0.55) and with miscarriage/perinatal death with an adjusted OR = 0.22 (95%CI 0.11-0.46). Analysing the associations between individual HCQI and APO, in the diagnostic pathway, aPL tests had an adjusted OR = 0.56 (95%CI 0.37, 0.85) and ANA or anti-ENA tests had an adjusted OR = 0.64 (95%CI 0.42, 0.96); in therapeutic pathway no exposure or washout of MTX/LEF had an adjusted OR = 0.22 (95%CI 0.11,0.46) (Table 2). Only two patients had not withdrawn the ongoing treatment with bDMARDs, making a reliable estimation of OR for this item not feasible (Table 2).

Compared with the general population, RA patients who met diagnostic, therapeutic and prenatal follow-up pathways indicators displayed a risk of APO with an adjusted OR = 0.92 (95%CI 0.61, 1.38) and of miscarriage/perinatal death with an adjusted OR = 0.77 (95%CI 0.47,1.29) (Table 3). Additional sensitivity analysis performed excluding ectopic pregnancy, threatened miscarriage and twin pregnancies (DRG D78, DRG 279, V272-273-274-276-277) gave similar results (supplementary Tables 1-4).

Further exploratory analyses evaluated the effect of common anti-rheumatic drugs used during pregnancy and preventative treatments, such as aspirin and LMWH, on outcomes of interest in patients with RA compared to women with RA but without that treatment. The crude RR for APO in the GCs users was =

1.40 (95%CI 1.09, 1.81; p=0.014), the RR for miscarriage and perinatal death in LMWH users was = 0.20 (95%CI 0.03, 1.33; p=0.05), while the use of aspirin had no influence on APO with a RR = 0.99 (95%CI 0.54, 1.82; p=1) and on miscarriage/perinatal death with a RR = 0.46 (0.12, 1.67; p= 0.25). No differences were observed with others csDMARDs (data not shown).

Discussion

This study based on AHD data demonstrated that the optimal management of pregnancy defined as "ideal clinical pathway" in women with RA was associated with a significantly reduced risk of APO restoring it to that expected for the general population.

Overall, we found an increased rate of APO and miscarriage/perinatal death in RA patients as compared to the general population (APO = 157 cases in RA patients versus 1809 cases in the general population, p 0.012; miscarriage/perinatal death = 115 cases versus 1360 cases in the general population, p 0.044). Nearly one-third of pregnant patients (157 cases, 35.4%) with RA experienced APO and one fourth (155 cases, 26%) had a pregnancy loss or miscarriage/perinatal death. Our data agree with some previous studies conducted using AHD. Lin et al. demonstrated that after adjusting for potential confounders, mothers with RA were (OR) 1.47 (95%CI 1.22, 1.78), 1.20 (95%CI 1.05, 1.38), 2.22 (95%CI 1.59, 3.11) and 1.19 (95%CI 1.07 to 1.31) time more likely than unaffected mothers to experience low birth weight, small for gestation age infants, preeclampsia and caesarean sections (7). Similarly, a previous study reported firstborn children of women diagnosed as having chronic inflammatory arthritis were often preterm and they had higher perinatal mortality with an OR = 3.26 (95%CI 1.04, 10.24) (16).

We found that between the three main pathways indicators of the ideal clinical pathway (stratification of pre-conceptional obstetric risk, modulation of therapy, and prenatal rheumatological follow-up) "the ideal therapeutic pathway" comprising no exposure or wash-out from MTX/LEF and no exposure to biological drugs, conferred a significantly reduced odds of APO and miscarriage/perinatal death. If LEF and MTX are not recommended in women planning and during pregnancy and this justifies the choice as HCQI, the item related to bDMARDs discontinuation deserves an additional thought. We identified the HCQI "no exposure to biological DMARDs" as a surrogate marker of maternal disease activity and not because of the assumption of teratogenicity/toxicity of these treatments. In our study only two patients continued bDMARDs , besides, in the period covered by RECORD study (1 January 2004 - 31 December 2013) there were sparse data on bDMARDs use in pregnancy, as well as the European League Against Rheumatism (EULAR) and the British Society for Rheumatology had not yet published guidelines for the prescription of pregnancy-compatible medications. This reflects the attitude at the time the study was conducted, but it is likely that the scenario will change as the use of biologic bDMARDs during pregnancy will consolidate (1).

The significant association between the ideal therapeutic pathway with the outcomes of the study suggests that the women who were not adherent were also not properly treated for their RA. This

reinforces the importance of adjustment of therapy for RA before conception and throughout pregnancy, because medication use could affect pregnancy course not only influencing maternal disease activity but also the gestational outcome. In our study, compared to RA patients not adherent to the ideal pathway, adherent cases were significantly more exposed to treatment, including HCQ and glucocorticoids. The use of steroids during pregnancy has been proved to be an independent risk factor for preterm delivery in women with RA when used at high doses (17,18). Although this is a study conducted on administrative data, we can hypothesize that exposure to therapy represents a marker of high RA disease activity and severity. In our setting, it is possible that the more active the disease the greater the probability of being included in the ideal clinical pathway, but in any case, this resulted in a lower OR of APO and miscarriage/perinatal death. If the diagnostic and prenatal follow-up pathways appear to have a marginal effect in our study, nevertheless, there might also be a residual confounding given that patients properly treated could have appropriate stratification of pre-conceptional obstetric risk and timely prenatal rheumatological follow-up.

Analysing individual HCQI in women with RA, we observed that, especially screening for aPL antibodies, ANA and anti-ENA were associated with a lower OR of APO and miscarriage/perinatal death. Notably, aPL antibodies occur in RA patients with an estimated prevalence up to 30%, more than expected in the general population, and the presence of significant and persistently positive titers increases the risk of APO including unexplained spontaneous miscarriage, premature births, preeclampsia, placental insufficiency with growth restriction, and prematurity, all potential complications of pregnancy that have been described in RA (19). In this view, we have incorporated aPL tests as part of diagnostic HCQI and as advised by EULAR recommendation for the prevention and management of aPL syndrome in adults (20). This study might suggest the value of searching for aPL antibodies in RA patients wishing for a pregnancy. In fact, despite the absence of formal recommendation or validated HCQI focused on stratification of pre-conceptional obstetric risk in patients with RA, we started from the basic and universally accepted assumption that aPL antibodies are pathogenic autoantibodies and therefore recognized risk factors for APO (20). Also, RA pregnancy may have an increased risk of APO, this combined with the increased prevalence of aPL antibodies in RA itself, could have a synergistic effect between RA and aPL antibodies in the determinism of APO (21). RA and aPL antibodies could be two distinct factors that must be individually profiled and the exclusion of one of them it would imply a sub-optimal risk stratification (5,20,21). This is undoubtedly a speculative conclusion, just supported by expert's opinion, but our study could be the first to give indirect evidence of the impact of diagnostic pathway indicators on APO that should be proposed and tested in the future.

To our knowledge, this study demonstrates for the first time that adherence to the ideal clinical pathway and especially the modulation of therapy such as discontinuation of contra-indicated medications such as MTX and LFN associated with a reduced risk of complicated birth or miscarriage in women with RA. This data was confirmed after adjusting for specific comorbidities that can interfere with gestational outcome, such as thyroid diseases, more prevalent and common in patients with RA compared to the general population. The strength of our study lies in the advantage of providing population-based samples representative of the target population, allowing generalizability of findings. This data source avoids potential referral bias reported from multidisciplinary pregnancy clinics where cohorts of subset of patients are offered integrated management of pregnancy that could not be generalizable to the general rheumatic disease population (22).

We acknowledge that our study has limitations which are intrinsic in the administrative data. First, uncomplicated pregnancy losses occurred before 15 weeks did not require hospitalization and may not even be recognized (22). Furthermore, the first pregnancy during the period of data captured is not necessarily the first pregnancy for that woman as enrolment periods in health insurance do not cover the entire reproductive history. Our approach based on AHD did not provide variables including lifestyle (maternal socioeconomic status, smoking, alcohol or body max index), results of laboratory exams and variables on disease activity, although we considered the use of glucocorticoids as proxies of more active disease, as shown in previous works (9,10). In our study only two patients were receiving bDMARDs during pregnancy, in fact, at the time the data were extracted, it was common practice to stop bDMARDs at positive pregnancy index (23). An additional limitation is the lack of data about the new-born (birth weight, length and head circumference, neonatal adverse events). Ultimately, we could not account for all possible confounding factors, and some residuals confounding intrinsic to observational studies may still modify the risk of APO estimation in our cohort.

The concept of preconception counselling and risk stratification, and multidisciplinary management during pregnancy has gained greater importance in the field of Rheumatology though to date many women struggle to find adequate counselling on reproductive issues to guide them on pregnancy planning, lactation, and early parenting in relation to their chronic condition (3,24) In conclusion, our findings suggest the adherence to an ideal clinical pathway should be strived for as much as possible in order to offer the best possible chances for a successful pregnancy to women with RA.

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Table 1. Characteristics and comparison of women with RA and general population and patients with RA adherents or not to the ideal pathway analysed at the time of first pregnancy.

	Rheumatoid Arthritis (N=443)	**General population (N=6097)**	**p-value RA versus general population**	**Rheumatoid Arthritis Ideal Pathway (N=141)**	**Rheumatoid Arthritis Not Ideal Pathway (N=302)**	**p-value RA ideal versus not ideal pathway**
Pregnancies, n (%)	443 (100)	6097 (100)	1	141 (100)	302 (100)	1
Age at conception - Median (IQR)	34 (31-37)	34 (30-37)	0.846	34 (31-37)	34 (30-37)	0.092
Disease duration at conception (years) - Median (IQR)	3.8 (1.8-6.2)	N.A.	---	3.8 (1.7-6.0)	3.9 (1.9-6.3)	0.715
Charlson Index - Mean (SD)	1.1 (0.4)	0.1 (0.4)	<0.001	1.1 (0.6)	1.0 (0.2)	0.120
Charlson Index - Mean (SD)[§]	0.1 (0.4)	0.1 (0.4)	0.544	0.1 (0.6)	0 (0.2)	0.120
Specific comorbidities						
Thyroid diseases, n (%)	24 (5.4)	145 (2.4)	<0.001	5 (3.5)	19 (6.3)	0.335
Hypertension, n (%)	5 (1.1)	39 (0.6)	0.22	2 (1.4)	3 (1)	0.655
Chronic kidney failure, n (%)	0 (0)	1 (0)	1	0 (0)	0 (0)	1
Pre-pregnancy diabetes mellitus, n (%)	13 (2.9)	172 (2.8)	1	8 (5.7)	5 (1.7)	0.031
Treatment						
Glucocorticoids, n (%)	118 (26.6)	0 (0)	---	57 (40.4)	61 (20.2)	<0.001
Hydroxychloroquine, n (%)	102 (23)	0 (0)	---	58 (41.1)	44 (14.6)	<0.001
Aspirin, n (%)	20 (4.5)	0 (0)	---	12 (8.5)	8 (2.6)	0.012
Low molecular weight heparin, n(%)	20 (4.5)	0 (0)	---	9 (6.4)	11 (3.6)	0.294
Allowed csDMARDs, n (%)	48 (10.8)	0 (0)	---	21 (14.9)	27 (8.9)	0.087
No treatment, n (%)*	255 (57.6)	0 (0)	---	56 (39.7)	199 (65.9)	<0.001
«Ideal pathway», n (%)	141 (31.8)	N.A.	---	---	---	---
Ideal diagnostic pathway, n (%)	414 (93.5)	N.A.	---	---	---	---
Ideal therapeutic pathway, n (%)	403 (91)	N.A.	---	---	---	---
Ideal prenatal follow-up pathway, n (%)	172 (38.8)	N.A.	---	---	---	---
Overall APO, n (%)	157 (35.4)	1809 (29.7)	0.012	---	---	---
Miscarriage/perinatal death, n (%)	115 (26)	1360 (22.3)	0.044	---	---	---

List of abbreviations: RA, Rheumatoid Arthritis; IQR, interquartile range; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; APO, adverse pregnancy outcome. [§] Charlson Index calculated excluding rheumatic disease; *no treatment among glucocorticoids, hydroxychloroquine and allowed csDMARds.

Table 2. Odds ratio of overall APO, miscarriage and perinatal death in patients with RA who followed healthcare quality indicators compared to women with RA who did not (reference).

Clinical pathway indicator	Overall APO Adjusted OR (95%CI)	Miscarriage/perinatal death Adjusted OR (95%CI)
1) Diagnostic pathway	**1.05 (0.46-2.38)**	**0.84 (0.36-1.98)**
N° pts adherent/not adherent, 414/29	147/10	106/9
Blood chemistry tests	**0.99 (0.47-2.11)**	**0.78 (0.36-1.70)**
N° pts adherent/not adherent, 409/34	145/12	104/11
Imaging	**1.09 (0.72-1.65)**	**1.14 (0.72-1.81)**
N° pts adherent/not adherent, 163/280	60/97	45/70
Antiphospholipid antibody tests	**0.56 (0.37-0.85)**	**0.34 (0.20-0.56)**
N° pts adherent/not adherent, 188/255	52/105	27/88
ANA or anti-ENA tests	**0.64 (0.42-0.96)**	**0.43 (0.27-0.68)**
N° pts adherent/not adherent,263/180	80/77	48/68
2) Therapeutic pathway	**0.28 (0.14-0.55)**	**0.22 (0.11-0.46)**
N° pts adherent/not adherent, 403/40	132/25	94/21
No exposure or washout of MTX/LEF	**0.31 (0.15-0.62)**	**0.22 (0.11-0.46)**
N° pts adherent/not adherent, 405/38	134/23	94/21
No exposure to biological DMARDs	**Not estimable**	**Not estimable**
N° pts adherent/not adherent, 441/2	155/2	115/0
3) Prenatal follow-up pathway	**0.85 (0.56-1.28)**	**0.65 (0.40-1.04)**
N° pts adherent/not adherent, 172/271	59/98	37/78
Rheumatological visit (at least one)	**0.85 (0.56-1.28)**	**0.65 (0.40-1.04)**
N° pts adherent/not adherent, 172/271	59/98	37/78
Ideal pathway	0.6 (0.39-0.94)	0.4 (0.24-0.69)
N° pts adherent/not adherent, 141/302	41/116	23/92

List of abbreviations: MTX, methotrexate; LFN; leflunomide; DMARDs, disease modifying antirheumatic drugs; APO, adverse pregnancy outcome.

Table 3. Odds ratio of overall APO, miscarriage and perinatal death in patients with RA who followed or not the ideal pathway compared to the general population.

	Overall APO **Adjusted OR (95%CI)**	**Miscarriage/perinatal death** **Adjusted OR (95%CI)**
General population	Ref	Ref
RA patients in ideal pathway	0.92 (0.61-1.38)	0.77 (0.47-1.29)
RA patients not in ideal pathway	1.5 (1.13-2)	1.84 (1.33-2.55)