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ORIGINAL ARTICLE

Catch me if you can: a national survey of rheumatologists and obstetricians on the use of DMARDs during pregnancy

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Abstract The use of disease-modifying anti-rheumatic drugs and biological therapy is variable throughout pregnancy. This questionnaire-based study was undertaken to explore and compare the current practice amongst rheumatologists and obstetricians across the UK, regarding the use of drugs during pregnancy. A questionnaire was devised to address issues regarding individual drugs used during preconception, pregnancy and lactation. Members of the British Society of Rheumatology, Midlands Rheumatology Society and the British Maternal Fetal Medicine Society were emailed. Results were analysed by the online survey software and Fisher's exact testing. Our results show differences between rheumatologists and obstetricians. A total of 500 members of each society were emailed. There were 102 (20 %) versus 33 (7 %) respondents. With regard to medication, in relation to advice given before conception, hydroxychloroquine 80 versus 61 % continue, 19 versus 15 % discontinue ($p = 1.0$); sulphasalazine 59 versus 70 % continue, 41 versus 6 % discontinue ($p = 0.002$); azathioprine 62 versus 58 % continue, 36 versus 21 % discontinue ($p = 0.37$); methotrexate 0 versus 3 % continue, 100 versus 76 % discontinue ($p = 0.2$); leflunomide 0 versus 0 % continue, 98 versus 42 % discontinue ($p = 1.0$); anti-TNF therapy 7 versus 15 % continue, 54 versus 54 % discontinue ($p = 0.05$); and rituximab 2 versus 12 % continue, 95 versus 52 % ($p = 0.01$) would discontinue prior to conception. This survey is the first of its nature amongst rheumatologists and obstetricians. Most would give advice to continue with sulphasalazine, azathioprine and stop methotrexate and leflunomide. We observed no uniform practice and therefore recommend guidelines.

Keywords Reproductive · Pregnancy and rheumatic disease · Biological therapies · DMARDs · Immunosuppressants · NSAIDs · Education (patients) · Attitude of health professionals · Medical education · Education research

Introduction

The use of disease-modifying anti-rheumatic drugs (DMARDs) in pregnancy has been variable, and until about the mid-1980s, there was little published about the safety of such medications [1, 2]. As a result, a number of patients preferred to manage without medication, even though it may have meant experiencing a flare of their disease or an exacerbation of symptoms [3]. This has been of particular concern given that rheumatic diseases tend to affect women of childbearing age to a greater degree, and therefore the safety (or otherwise) of DMARDs is of particular importance. Cessation of medication in itself is not an answer as uncontrolled disease may have detrimental maternal and foetal effects.

In 2006 [4], a seminal paper was produced reviewing anti-inflammatory and immunosuppressive drugs in relation to pregnancy and lactation. This was based on a consensus opinion of a number of international experts, including specialists in rheumatology and internal medicine, obstetrics, paediatrics and genetics. A separate working group has discussed four categories of drugs, namely anti-inflammatory drugs, corticosteroids, immunosuppressive (DMARDs) and biological agents. Prescribing practice was assessed through questionnaires; databases (Medline

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and Cochrane for the period of 1960–2004) were searched for potential toxicity and the above data were summarised, discussed and distilled into conclusions and recommendations. An update on the safety of biological agents was formulated more recently [5].

Two large-scale respective studies have shown that improvement in disease activity during pregnancy is limited to between 48 and 63 %, when validated measurements of disease activity are used [6, 7]. As a result, some form of drug therapy will be required in approximately 50 % of patients with RA during pregnancy. On the basis of the consensus opinion, corticosteroids and analgesics such as paracetamol can be used throughout pregnancy; NSAIDs can be administered safely until week 32 of gestation; antimalarials, sulphasalazine, azathioprine and ciclosporin are compatible with pregnancy; and methotrexate, leflunomide and biologics should be withdrawn before a planned pregnancy [8]. To date, there are no studies within the UK that have evaluated whether such guidance is accepted and followed. The purpose of the present study was to establish through a questionnaire-based survey the perceptions and prescribing practices of rheumatologists and obstetricians in the UK with regard to the use of DMARDs during pregnancy.

Methods

In order to determine prescribing practices in relation to DMARDs during pregnancy, a questionnaire-based survey was undertaken. A group of experienced clinicians (rheumatologists and obstetricians) participated in an initial workshop to discuss and debate the current practices in relation to DMARD prescription in pregnancy, based upon individual experience. The results of this discussion then formed the basis of designing a questionnaire that was aimed at determining the following factors: pre-pregnancy counselling, continuation and discontinuation of specific DMARDs, period of discontinuation in relation to conception, the time at which DMARDs were restarted and the existence of local guidelines in this area. Face validity of the questionnaire was established by testing this amongst a number of experienced colleagues. The initial questionnaire was then piloted for user acceptability, and the results of the pilot study were used to modify and refine the questionnaire.

Discussion between experts, general physicians and general practitioners established that the prime prescribers of DMARD therapy during pregnancy would be specialists, either rheumatologists or obstetricians. It was highly unlikely that DMARD therapy would be either initiated or continued during pregnancy by general practitioners, general physicians or non-rheumatology specialist physicians without consultation with rheumatologists or obstetricians (including materno-foetal physicians). It was therefore decided that the questionnaire would be circulated to rheumatologists and obstetricians working within this area.

The questionnaire was sent out to all members of the British Society for Rheumatology (BSR), the Midlands Rheumatology Society (MRS) and British Materno-Fetal Medical Society (BMFMS). Each questionnaire that was sent out was marked with a unique identifier to which the investigators of the study were blinded. The purpose of the identifier was purely administrative in order to send out a reminder to non-responders. A single reminder was sent out to non-responders as it was felt that further reminders would be unnecessarily intrusive. Data from returned questionnaires would then be used to provide the results as expressed as percentage proportions of respondents. Statistical analysis (where appropriate) was carried out using Fisher's exact test.

Results

A total number of 500 rheumatologists and 500 obstetricians were emailed the questionnaire in the first instance. Following an initial mailing, responses received were 68 from rheumatologists and 25 from obstetricians. After a period of 6 weeks from the initial mailing, non-responders were sent a reminder. Following this further 34 responses were received from rheumatologists and 8 responses were received from obstetricians. In total, 102 responses (20 %) were received from rheumatologists and 33 (7 %) from obstetricians.

Demographics

Of the responses received from rheumatologists and obstetricians, 52 and 94 % respectively were from consultants, 37 and 3 % respectively were from specialist registrars, and 2 and 3 % respectively were from associate specialists. In total, 6 % of responses from rheumatologists were from nurse practitioners.

51 and 58 % of responses respectively from rheumatologists and obstetricians were from teaching hospitals or an academic unit, and 46 and 39 % respectively were from a district general hospital.

Of the respondent rheumatologists and obstetricians, 32 and 79 % respectively had over 15 years of clinical experience, 20 and 15 % respectively had eleven to 15 years of clinical experience and 39 and 3 % respectively had 6–10 years of clinical experience. In total, 9 % of rheumatologists and 3 % of obstetricians declared clinical experience of <5 years.

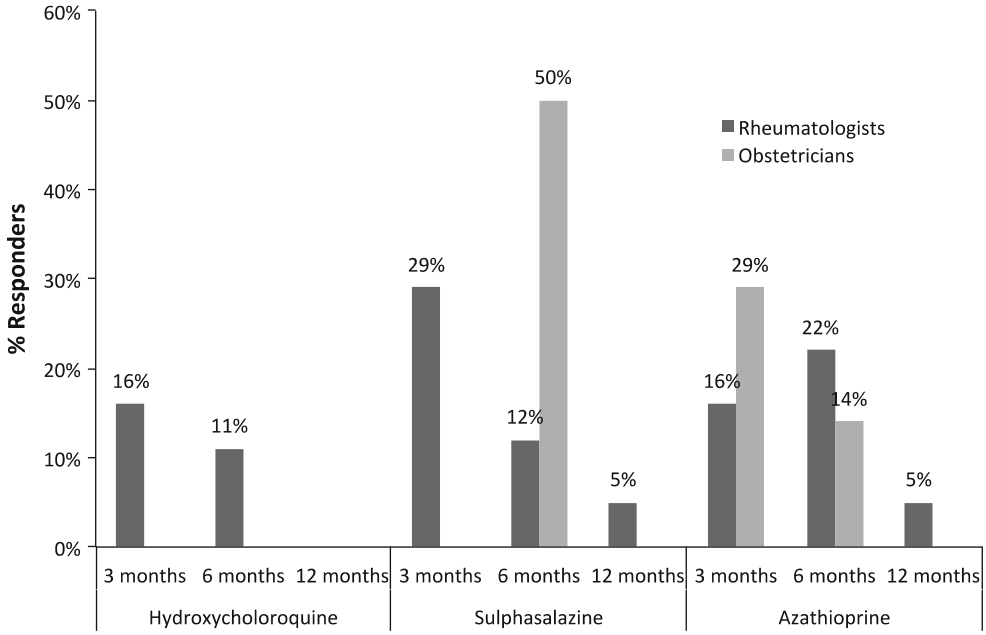

Fig. 1 Preconception discontinuation of sulphasalazine, hydroxychloroquine and azathioprine

Preconception education and counselling, local guidelines

A total of 62 and 39 % rheumatologists and obstetricians respectively stated that they always offered education and counselling with regard to DMARD therapy in pregnancy, and 37 and 61 % respectively 'sometimes' offered this. In total, 55 % of rheumatologists compared to 58 % of obstetricians always documented advice regarding education and counselling.

A total of 75 % of rheumatologists stated that they had no local guidelines in place with regard to DMARD therapy in pregnancy, compared to 94 % of obstetricians who declared an absence of local guidelines.

Significant differences were noted between rheumatologists and obstetricians with regard to those who always offered patient education and advice (63 vs. 39 %, $p = 0.0001$), and the use of local guidelines (25 vs. 6 %, $p = 0.02$).

Preconception advice regarding NSAIDs, DMARDs and Biologics

Table 1 demonstrates the advice given by rheumatologists and obstetricians prior to conception regarding treatment. Figures 1, 2 and 3 illustrate the time period of discontinuation before conception if advised to discontinue.

Table 2 illustrates the time intervals at which respondents would suggest restarting DMARD therapy. It is apparent that the majority of rheumatologists and obstetricians would base this on individual reasons, type of DMARD and patient preference.

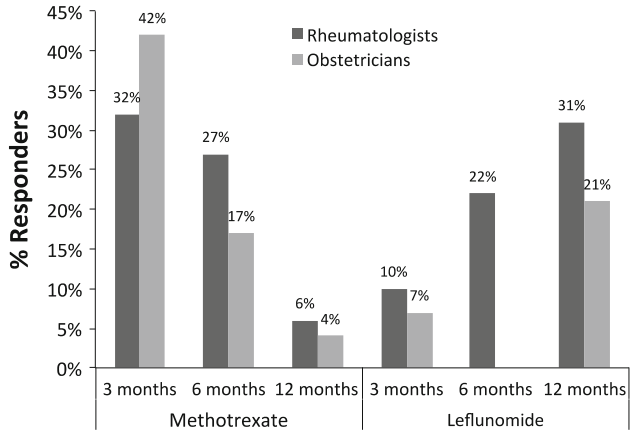

Fig. 2 Preconception discontinuation of methotrexate and leflunomide

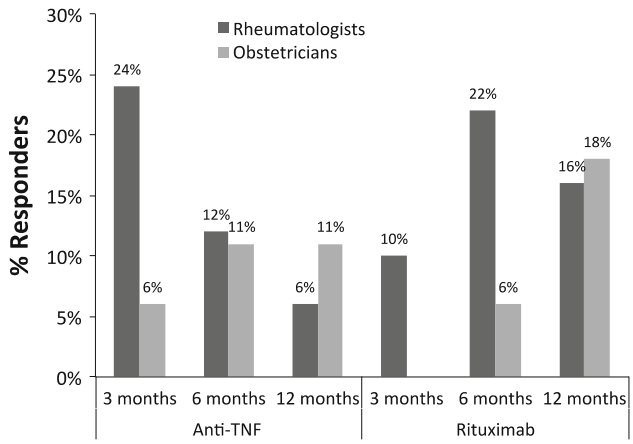

Fig. 3 Preconception discontinuation of anti-TNF and rituximab

Table 1 Advice given before conception regarding NSAIDs, DMARDs and Biologics

Medications		Rheumatologists (%)	Obstetricians (%)	*p* value
NSAIDs	Continue	32	18	0.63
	Discontinue	67	39	
Hydroxychloroquine	Continue	80	61	1.00
	Discontinue	19	15	
Sulphasalazine	Continue	59	70	0.002
	Discontinue	41	6	
Azathioprine	Continue	62	58	0.37
	Discontinue	36	21	
Methotrexate	Continue	0	3	0.20
	Discontinue	100	76	
Leflunomide	Continue	0	0	1.00
	Discontinue	98	42	
Anti-TNF Therapy	Continue	7	15	0.05
	Discontinue	92	54	
Rituximab	Continue	2	12	0.01
	Discontinue	95	52	

Table 2 Reasons for restarting DMARDs

Reasons	Rheumatologists (%)	Obstetricians (%)
Immediately post conception	0	3
Immediately post child birth	26	18
3 months post child birth	8	6
6 months post child birth	7	0
Other	59	73

Discussion

A number of rheumatological diseases, of which RA is a prototype, may occur in women during the childbearing age. There is a natural inclination to stop all medication during pregnancy because of concerns about the possible detrimental effect on the foetus. However, the disease needs to be adequately controlled because active disease in itself may have serious materno-foetal consequences. A tension exists between balancing the side effects of DMARDs and controlling disease. In clinical practice, each case must be managed on an individual basis to provide the least possible risk to the mother and the foetus, but at the same time minimising adverse events due to disease flare [9]. High-powered medical evidence is unlikely to be forthcoming in this area due to the inherent ethical difficulties in conducting randomised controlled trials using DMARDs in pregnancy. Clinical practice therefore would inevitably be guided by experience, as well as the evidence base that has accumulated through the use of DMARDs over time. Recently, there have been a number of learned publications that provide guidance on the use of DMARDs in pregnancy based upon the existing evidence [4, 5, 9, 10], and therefore there is a reasonable expectation that routine clinical practice will be in accordance with such guidance and reflect uniformity.

In this study, we have asked the question as to whether there is conformity in practice in relation to the use of DMARDs in pregnancy, thereby exploring what actually happens at the clinician–patient interface. We have approached this through a national questionnaire survey directed at all rheumatologists and obstetricians practising materno-foetal medicine. We selected these groups because of their involvement in this area of clinical practice, and through our discussions with other peers it emerged that it would be highly unlikely for other practitioners (general physicians, primary care physicians, specialist physicians, general obstetricians) to either initiate or continue DMARD therapy during pregnancy without consulting a rheumatologist or a specialist in materno-foetal medicine. In essence, our results show that there is no consistency of practice amongst rheumatologists and obstetricians, or between these two groups. Clinical practice in this area would seem to be individualistically driven. There were also wide variations observed in the use of specific DMARDs.

Pre-pregnancy counselling has been strongly recommended and should include the risks of disease flare, the consequences of this for the mother and foetus, as well as advice and risks about appropriate drug therapy. In our survey, only 62 % of rheumatologists and 39 % of obstetricians always offered some form of education and counselling. Surprisingly, documentation of this was far less, being just above 50 % in both groups. Furthermore, only a

minority of rheumatologists and obstetricians declared that they had local guidelines to help in their decision-making.

A number of studies have been conducted on anti-malarials, sulphasalazine and azathioprine during pregnancy. Hydroxychloroquine in a dose of 200–400 mg daily did not confer an increase in any adverse outcome on the foetus when taken in the first trimester [11–13]. Similarly, the use of sulphasalazine during pregnancy found no increase in birth defects [14, 15] or an adverse foetal outcome [16]. A prospective case–control study of azathioprine showed no increase in the rate of birth defects [17]. In relation to the use of hydroxychloroquine, sulphasalazine and azathioprine, colleagues have summarised the evidence that anti-malarials, sulphasalazine and azathioprine (not exceeding a daily dose of more than 2 mg per kg) can be used during pregnancy with no adverse foetal outcome (evidence level 2) [4]. In our survey, however, 19, 41 and 36 % of rheumatologists discontinued hydroxychloroquine, sulphasalazine and azathioprine respectively compared to 15, 6 and 21 % of obstetricians. Of the rheumatologists, 16 % stated that they discontinued hydroxychloroquine 3 months prior to conception and 11 % would discontinue this for 6 months before. Respondents also stated that they would withdraw sulphasalazine and azathioprine between three and 12 months prior to conception. In relation to azathioprine, for example, 16 % of rheumatologists would withdraw this 3 months before conception compared to 29 % of obstetricians and 5 % of rheumatologists would withdraw this 12 months before conception.

Methotrexate and leflunomide are contraindicated during pregnancy. Methotrexate is a teratogenic in humans and can lead to a number of congenital abnormalities [18, 19]. Likewise, animal studies with leflunomide have demonstrated an increased risk of teratogenicity [20], although the only prospective control study of leflunomide exposure during pregnancy in women did not show an increased rate of major birth defects [21]. In our survey, virtually all the respondents stated that they would discontinue methotrexate and leflunomide during pregnancy except for one respondent obstetrician, who stated that methotrexate would be continued. However, there was no consistency in terms of when these drugs would be discontinued. Thirty-two and 10 % of rheumatologists compared to 42 and 7 % of obstetricians stated that they would discontinue methotrexate and leflunomide respectively 3 months before conception. Six and 31 % of rheumatologists compared to and 21 % of obstetricians stated that they would discontinue methotrexate and leflunomide respectively 12 months prior to conception.

With regard to the biologics, abatacept [22] and rituximab [23] should both be discontinued before conception as per the manufacturer's advice. There is emerging evidence that anti-TNF therapy can be continued until conception [5, 8, 24]. In our survey, 2 % of rheumatologists and 12 % of obstetricians stated that they would continue rituximab during pregnancy. In total, 92 % of rheumatologists and 54 % of obstetricians stated that they would discontinue anti-TNF therapy prior to conception. The discontinuation period varied from 3 months (24 % of rheumatologists and 6 % of obstetricians) to 12 months (6 % of rheumatologists and 11 % of obstetricians).

Our study has shown that there are wide variations in the way rheumatologists and specialist obstetricians in materno-foetal medicine use DMARDs in patients with rheumatic diseases during pregnancy. A *prima facie* evaluation of the results would suggest that there is a lack of consistency in clinical practice within this area and that clinical practice reflects a conglomeration of individualistic approaches. These results, however, must be considered within the limitations of this study and other confounding factors. First, the response rate that we achieved was relatively modest despite two mailings. A large proportion of the target population did not respond and therefore their practice remains unknown. It is arguable that practice within the non-respondent group could be more aligned towards current guidance. Whilst it might have been possible to select a number of non-responders and focus on them in order to determine a sample of views from this group, we did not pursue this route as we felt that this would be unnecessarily intrusive. Second, we have pooled the results from all the respondents. The respondents in themselves reflect a heterogeneous group of physicians with more than 15 years of clinical experience and some who have less than 5 years of clinical experience. It remains unknown as to whether there might be differences depending upon the level of experience of the clinician, or alternatively whether there may be differences depending upon whether the respondent might be medically qualified or another healthcare professional, such as a nurse practitioner. Our study was not designed to examine this. Third, although we have shown that clinical practice within this area reflects wide variation, the questionnaire was not designed to examine why this might be so. We are therefore unable to comment upon causality in terms of why DMARDs were discontinued or not, as the case might be, as well as in relation to the time of the discontinuation. Fourth, the questionnaire did not cover the whole range of DMARDs, nor did it distinguish between individual TNF blocker agents. Whilst this was considered in the initial stages of the questionnaire development, it was decided to be selective in terms of the agents that the questionnaire focused upon in order to maintain brevity and user acceptability. Fifth, whilst the questionnaire asked about what happens in practice, it did not actually test whether what is proclaimed to happen actually happens. There is therefore the possibility that the results

might be reflective of attitudes rather than actual practice although we feel (on the basis of other questionnaire studies) that attitudes correlate well with actual practice. In order to confirm the individual clinicians' attitudes with what they do in practice would be outside the scope of this study and could disproportionately infringe upon patient confidentiality.

Despite the limitations as cited, we would put forward the view that this study is the first of its kind and explores at a national level the use of DMARDs during pregnancy for the treatment of rheumatic diseases, and reflects what happens in clinical practice. It is now accepted that a number of DMARDs are safe and there are some that are unsafe [4, 8–10]. Discontinuation of safe DMARDs runs the risk of a flare of the underlying rheumatological condition with its consequent maternal and foetal effects. Continuation of unsafe DMARDs runs the risk of damage to the foetus. If a DMARD needs to be discontinued, then premature cessation of therapy also runs the risk of a flare of the underlying disease. The clinical management of inflammatory rheumatological conditions during pregnancy is finely balanced and rests upon a careful risk/benefit analysis. Some have very properly drawn attention to the fact that variations in prescribing during pregnancy could lead to a situation that is unsatisfying both for the patient and for the treating physician [4, 8]. They also point out that recommendations for prescribing anti-rheumatic medication during pregnancy may differ in different regions and should be supported by national specialist endorsement. To the best of our knowledge, there are currently no national guidelines addressing the use of DMARDs in pregnancy.

We propose that the results of our current study should act as a catalyst to those empowered to shape clinical policy and should spur the development of guidelines within this area at a national level. It would be an expectation that such guidelines are produced by a consensus between relevant stakeholders (which would include rheumatologists, specialist obstetricians, specialists in maternal–foetal medicine and other healthcare professionals, amongst others) as well as a clear patient voice, in order to develop a product that has patient-centred relevance. We would urge that this should be an ideal that is not just aspirational but realistic. If this is not achieved, then in our view, on the basis of the results of this study, clinical practice within this area will remain at a level of evidence-based reductivism.

Rheumatology key messages

- Our study illustrates the variability in advice given to patients
- There is a great need for consistency amongst clinicians to achieve quality patient care
- Development of a consensus with all key stakeholders would provide a baseline for clinicians

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Conflict of interest The authors have declared no conflicts of interest.

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