Rheumatic diseases and pregnancy: a national survey about practice patterns among rheumatologists and obstetricians

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Abstract

Objective

Management of rheumatic diseases (RD) is often problematic in pregnant patients, hence the need for guideline implementation. This survey-based study aimed to assess beliefs among obstetricians and rheumatologists about managing RD in pregnant Lebanese patients.

Methods

Questionnaires were completed by a representative sample of rheumatologists and obstetricians practicing throughout Lebanon. Collected data included physicians' information, opinion on pregnancy in RD patients, compatible drugs with fertility, pregnancy and breastfeeding, references used in their clinical management, referral to specialists, and knowledge about guidelines. Qualitative variables were analysed using Chi-square or Fisher's exact tests, and quantitative variables using Wilcoxon or Student t-tests. Results were matched against a scoring system based on the EULAR/BSR guidelines. p-value <0.05 indicated statistical significance.

Results

Analysis showed high response rates of physicians, especially among rheumatologists. Overall, physicians practice was in concordance with international guidelines and only few misconceptions were reported. Systemic lupus erythematosus (SLE) was associated with risk on fertility, foetal malformation and eclampsia while anti-phospholipid (APL) syndrome was associated with miscarriage and vasculitis with eclampsia. Spondyloarthritis was considered 'safe' in pregnancy. Most physicians think that cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil and azathioprine compromise fertility, pregnancy, and breastfeeding.

Conclusion

Our data showed relatively good concordance of the physicians' beliefs with the current literature and recommendations. However, we identified misconceptions about anti-rheumatic drugs safety in pregnancy and discrepancy between rheumatologists and obstetricians practices; hence the need for promoting collaboration between both specialties and disseminating knowledge to physicians and patients in the Middle East region.

Key words

pregnancy, rheumatic diseases, disease management, rheumatologists, obstetricians

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Introduction

Women represent 78% of all patients with autoimmune diseases (1), which might be attributed to enhanced immunoreactivity with higher antibody production in response to antigen stimulation (2). The predisposition of women to rheumatic diseases (RD) is also associated with the influence of sex hormones and genetic factors (3). RD thus often affect women of childbearing age. For years, pregnancy was not considered safe in women with potentially serious systemic autoimmune diseases, not only due to the risk of deterioration in their condition, but also the potential risk of RD medications to the unborn child. Active RD is indeed associated with adverse pregnancy outcomes (4). Moreover, studies have shown that women affected by RD have smaller families due to psychological effects, their disease manifestations, and their exposure to RD medications (5). However, recent evidence suggests that, with careful medical and obstetric management, most of these women can have successful pregnancies (6, 7).

In an attempt for better management of RD and other diseases during pregnancy, the United States Food and Drug Administration (FDA) classified drugs in different pregnancy categories, according to their relative safety to the mother and child. Several studies analysed the safety of RD drugs in pregnancy and identified discrepancies between the FDA recommendations and the clinical experience, especially when taking into consideration the variability of a woman's biology from conception to delivery and breastfeeding, and the different foetal outcomes (7). It became therefore clear that unified guidelines are needed for safe pregnancies with favorable outcomes in RD patients. The British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) have elaborated new guidelines that provide evidence-based non-legally binding recommendations for clinicians to prescribe anti-rheumatic medications at the preconception, pregnancy and postpartum (breastfeeding) stages (8). Similarly, the EUropean League Against Rheumatism (EULAR) has designated a task force in charge of identifying specific points that modulate decisions on the use of anti-rheumatic drugs in the periconceptional and post-partum periods (9).

In the Middle East region, despite the considerable negative impact of RD on pregnancy outcomes (10), studies evaluating the management of RD in pregnant women remain scarce. In Saudi Arabia, a study showed that pregnancies starting after the onset of systemic lupus erythematosus (SLE) resulted in higher stillbirth, preterm birth and perinatal death rates, compared to pregnancies occurring before SLE onset (11). In Egypt, studies have shown that SLE in pregnant women was associated with problematic pregnancies, spontaneous miscarriages, and major complications in live births (12, 13). Moreover, cultural and traditional factors in the Middle East region may affect the clinical management of pregnant women with RD, emphasising the need for collaboration between specialists and the dissemination of knowledge to all stakeholders (14).

This survey-based study aimed to assess the beliefs of obstetricians and rheumatologists about the relationship between RD, pregnancy and their management in Lebanese pregnant patients.

Methods

Participants

In order to determine practice patterns and identify unmet needs in the management of RD and pregnancy in Lebanon, rheumatologists and obstetricians practicing throughout the Lebanese territories, whose names were provided by their respective scientific Societies, were solicited for participation in this survey. Physicians were approached during their annual meetings and the data collection was completed by visits at their offices.

Questionnaires

The questionnaires were filled out anonymously by the physicians. They addressed the following parameters: pre-conception status of RD and counseling, duration of remission or disease control before allowing pregnancy, medications with potential harm-

Table I. Potential effect of RD on fertility and pregnancy outcomes, according to rheumatologists and obstetricians.

	Fertility and pregnancy outcomes, n (%)							
	Fertility		Miscarriage		Eclampsia		Foetal malformation	
	Rheum	Obst	Rheum	Obst	Rheum	Obst	Rheum	Obst
RA	8 (20.5%)	27 (28.7%)	6 (15.4%)	42* (44.7%)	2 (5.1%)	17 (18.1%)	1 (2.6%)	6 (6.4%)
SpA	2 (5.1%)	21* (22.3%)	2 (5.1%)	24* (25.5%)	1 (2.6%)	8 (8.5%)	2 (5.1%)	6 (6.4%)
SLE	16 (41.0%)	40 (42.6%)	25 (64.1%)	76* (80.8%)	27 (69.2%)	54 (57.4%)	14 (35.9%)	22 (23.4%)
Systemic sclerosis	9 (23.1%)	36 (38.3%)	15 (38.5%)	44 (46.8%)	14 (35.9%)	25 (26.6%)	9* (23.1%)	7 (7.4%)
APL syndrome	12 (30.8%)	44 (46.8%)	31 (79.5%)	80 (85.1%)	24 (61.5%)	50 (53.2%)	9* (23.1%)	7 (7.4%)
Vasculitis	12 (30.8%)	37 (39.4%)	21 (53.8%)	52 (55.3%)	13 (33.3%)	57* (60.6%)	8 (20.5%)	16 (17.0%)

Thirty-nine rheumatologists and 94 obstetricians participated in this survey. Results are given as numbers and (%).
APL: anti-phospholipid; Obst: obstetricians; RA: rheumatoid arthritis; RD: rheumatic diseases, Rheum: rheumatologists; SLE: systemic lupus erythematosus, SpA: spondyloarthritis; SS: systemic sclerosis.
*A significantly greater proportion of obstetricians associated RA with miscarriage, SpA with infertility or miscarriage, SLE with miscarriage, and vasculitis with eclampsia. On the other hand, a significantly higher percentage of rheumatologists associated APL syndrome and SS with foetal malformation.

ful impact on fertility, pregnancy and breastfeeding, references consulted for management and drug discontinuation, effects of RD on pregnancy outcome, effect of pregnancy on RD course, and suggested means to improve the management of pregnancy in the context of RD. The investigated diseases were rheumatoid arthritis (RA), spondyloarthritis (SpA), SLE, systemic sclerosis (SS), anti-phospholipid syndrome (APL) and vasculitis. Answers concerning potentially detrimental medications on pregnancy and breastfeeding were matched against a binary scoring system based on the EULAR/BSR guidelines; 'correct' answers counted as '1' and 'incorrect' answers as '0'. Averages of correct answers per medication were calculated, for all participating physicians.

Statistical analysis

Analysis of results was undertaken using the SAS 9.4. For inter-group comparison, Chi square or Fisher's exact tests were used to test hypotheses involving qualitative variables and Student *t*-test or Wilcoxon test were used to test the hypotheses involving quantitative variables. The scoring system was tested for reliability using the Cronbach's alpha coefficient test and a reliability coefficient of 0.60 or higher was considered acceptable. A *p*-value below 0.05 was considered as statistically significant in subgroup analyses comparing responses given by rheumatologists and obstetricians. Significant results were subjected to univariate and multivariate analyses.

Results

Physicians' characteristics and practice

Thirty-nine out of 43 (90.7%) rheumatologists and 94 out of 227 (41.4%) obstetricians completed the questionnaires. All 5 geographical provinces in Lebanon were covered in the scope of this study.

Among participating rheumatologists, 20 (51.3%) worked in a central teaching hospital, while the rest worked in peripheral hospitals or in 'other' practices. Rheumatologists had been practicing for an average of 22.2±11.6 years (range: 4–48 years). The number of pregnant patients with RD seen per month was 1.8±2.0 and the number of RD-complicated pregnancies seen per year varied from 0 to 50, with a mean of 3.8±8.9 pregnancies. When asked about the frequency of discussing and planning the pregnancy with their RD patient, 25 (65.8%) rheumatologists said they always do, while 12 (31.6%) said they sometimes do, one rheumatologist never does and one chose not to answer.

Among participating obstetricians, 44 (46.8%) worked in a central teaching hospital, while the rest worked in peripheral hospitals or in 'other' practices. Obstetricians had been practicing for an average of 26.0±12.8 years, (range: 2–61 years). Sixty-one (66.3%) obstetricians see less than 5 pregnant patients with RD per year, 21.7% see 5 to 10 pregnant patients with RD per year and the others see over 10 cases per year. Eighty (86.0%) obstetricians see less than 5 complicated pregnancy cases due to RD per year. Half of the obstetricians (48 [52.2%]) always discuss pregnancy planning with their RD patients, while 38 (41.3%) said they sometimes do, and 6 (6.5%) never do.

Effect of RD on fertility and pregnancy outcome

Physicians were asked about the potential effect of several RD (RA, SpA, SLE, SS, APL and vasculitis) on fertility and the risk of miscarriage, eclampsia and foetal malformation. The answers are reported in Table I. The greatest risk on fertility was attributed to SLE by 16 (41%) rheumatologists and to APL syndrome by 44 (46.8%) obstetricians. The majority of rheumatologists and obstetricians agreed that the APL syndrome presented the highest risk for miscarriage (31 [79.5%] rheumatologists and 80 [85.1%] obstetricians). The risk of eclampsia was mostly associated with SLE by 27 (69.2%) rheumatologists and with vasculitis by 57 (60.6%) obstetricians. SLE was the worst RD in terms of foetal malformation according to 14 (35.9%) rheumatologists and 22 (23.4%) obstetricians. The majority of participating physicians considered SpA as the 'safest' RD on fertility and pregnancy outcomes. However, differences in responses were substantial only for few diseases. A greater proportion of obstetricians associated RA with miscarriage (p=0.001), SpA with miscarriage (p=0.007), SLE with miscarriage (p=0.040), and vasculitis with eclampsia (p=0.004). On the other hand, a higher percentage of rheumatologists associated APL syndrome and

Table II. Impact of pregnancy on RD course, according to rheumatologists and obstetricians.

	Pregnancy effect on RD course, n (%)					
	Remission during pregnancy		Flare during pregnancy		Flare in post-partum	
	Rheum	Obst	Rheum	Obst	Rheum	Obst
RA	33 (84.6)	54 (57.4)*	5 (12.8)	23 (24.5)	23 (59.0)*	25 (26.6)
SpA	7 (17.9)	20 (21.3)	9 (23.1)	23 (24.5)	8 (20.5)	17 (18.1)
SLE	6 (15.4)	21 (22.3)	32 (82.0)*	53 (56.4)	13 (33.3)	25 (26.6)
SS	6 (15.4)	14 (14.9)	13 (33.3)	31 (33.0)	8 (20.5)	18 (19.1)
APL syndrome	3 (7.7)	12 (12.8)	26 (66.7)*	37 (39.4)	9 (23.1)	22 (23.4)
Vasculitis	5 (12.8)	19 (20.2)	21 (53.8)	34 (36.2)	10 (25.6)	25 (26.6)

Thirty-nine rheumatologists and 94 obstetricians participated in this survey. Results are given as numbers and (%).
APL: anti-phospholipid; Obst: obstetricians; RA: rheumatoid arthritis; RD: rheumatic diseases, Rheum: rheumatologists; SLE: systemic lupus erythematosus, SpA: spondyloarthritis; SS: systemic sclerosis.

SS with foetal malformation (p=0.018 and p=0.018, respectively). Differences observed between the rest of the answers in both specialties were not statistically significant.

Pregnancy impact on the course of RD

Physicians were asked about their opinion on the modulatory effect of pregnancy on RD course. Physicians' answers are reported in Table II. Both specialties, though rheumatologists to a greater extent, considered RA patients likely to be in remission during pregnancy (33 [84.6%] rheumatologists and 54 [57.4%] obstetricians, p=0.003), while flare-ups during pregnancy seemed most probable in SLE patients (32 [82.0%] rheumatologists and 53 [56.4%] obstetricians, p=0.005), APL syndrome (26 [66.7%] rheumatologists and 37 [39.4%] obstetricians, p=0.004), and vasculitis (21 [53.8%] rheumatologists and 34 [36.2%] obstetricians, p>0.05). Highest risk of post-partum flare-ups was attributed to RA by 23 (59.0%) rheumatologists (p<0.001), compared with 25 (26.6%) obstetricians considering RA, SLE and vasculitis patients at highest risk for post-partum relapse.

Impact of RD medications on fertility, pregnancy and breastfeeding

The physicians were asked to select from a list medications that negatively affect fertility, pregnancy and breastfeeding. The list included medications from different therapeutic classes such as analgesics and anti-inflammatory agents, biological agents, anticoagulants, immunosuppressive agents and disease-modifying agents.

• *Fertility*

Figure 1 shows side-by-side the participants' opinions in terms of fertility-challenging RD medications. Medications reported by over 50% of rheumatologists as impairing fertility included cyclophosphamide (28 [71.8%]), leflunomide (23 [59.0%]), methotrexate (21 [53.8]) and mycophenolate mofetil (20 [51.3%]). According to obstetricians, cyclophosphamide and methotrexate topped the list of RD medications compromising fertility by over 75% of the responders, followed by azathioprine, anti-TNF alpha, cyclosporine, mycophenolate mofetil, leflunomide and other biologics. The significant differences between specialties were as follows: a higher proportion of obstetricians thought that fertility is worst affected by methotrexate (p=0.014), anti-TNF alpha (p=0.021) and azathioprine (p<0.001) while a greater proportion of rheumatologists compared to obstetricians, believed that fertility is worst affected by NSAIDs (p=0.003), paracetamol (p=0.027) and low molecular weight heparin (p=0.040).

• *Pregnancy and breastfeeding*

Figure 2 displays side-by-side the par-

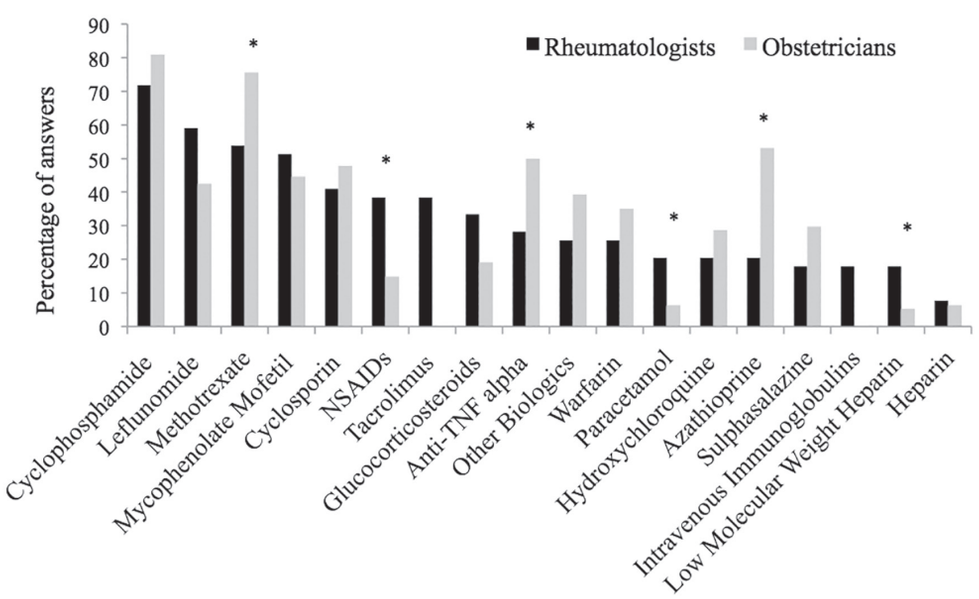

Fig. 1. Percentage of participants who consider the medications detrimental to fertility.
NSAIDs: non-steroidal anti-inflammatory drugs; TNF-alpha: tumour necrosis factor alpha
*p<0.05

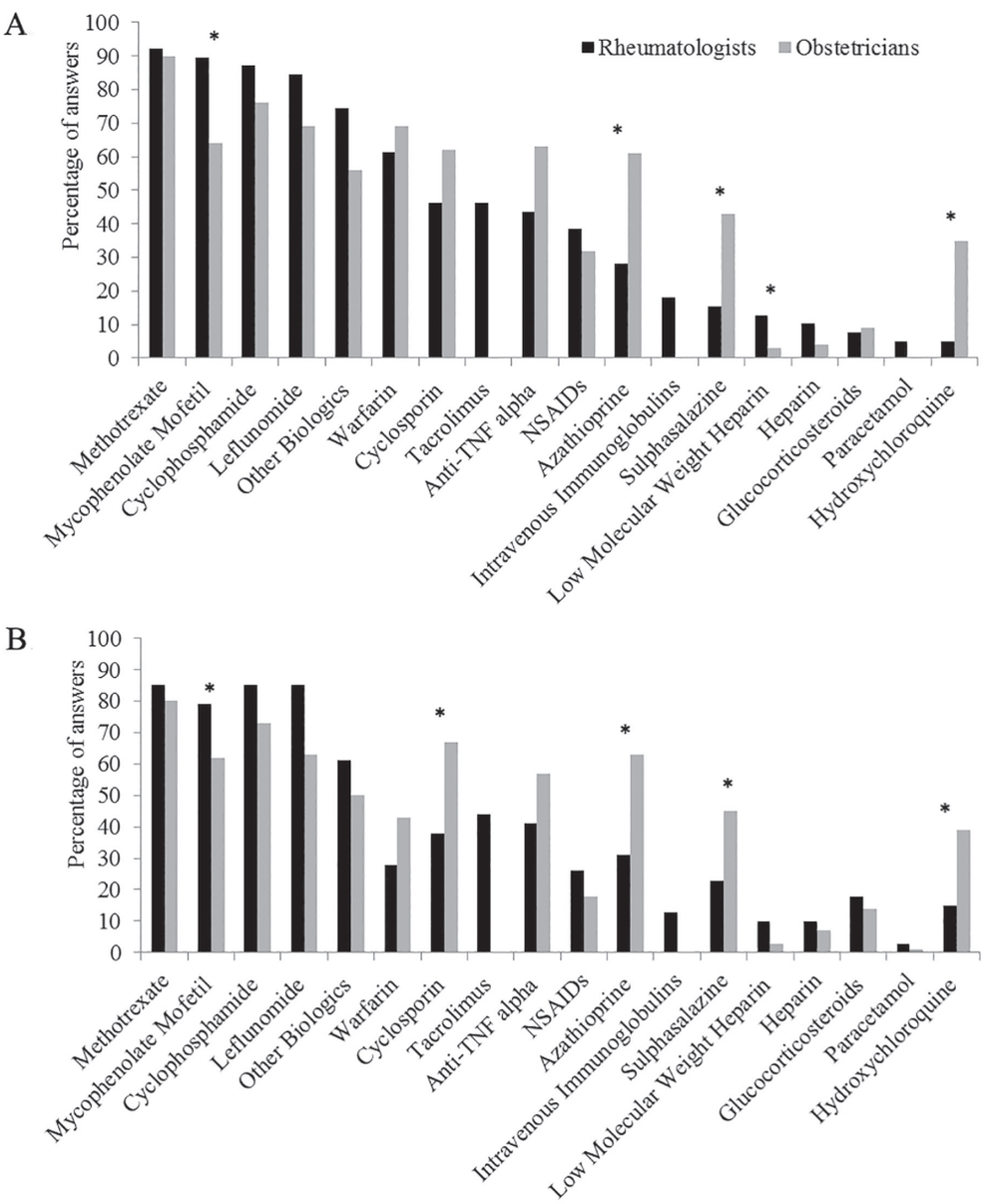

Fig. 2. Percentage of participants who consider the medications incompatible with pregnancy (**A**) and breastfeeding (**B**).
NSAIDs: non-steroidal anti-inflammatory drugs; TNF-alpha: tumour necrosis factor alpha
*$p<0.05$

ticipants' opinions on the compatibility of RD medications with pregnancy (panel A) and breastfeeding (panel B). Medications not allowed during pregnancy, as reported by over 50% of rheumatologists, included methotrexate (36 [92.3%]), followed by mycophenolate mofetil (35 [89.7%]), cyclophosphamide (34 [87.2%]), leflunomide (33 [84.6%]), other biologics (29 [74.4%]) and warfarin (24 [61.5%]. Following a similar trend, rheumatologists considered breastfeeding unsafe during treatment with methotrexate, leflunomide, cyclophosphamide, mycophenolate mofetil and drugs pertaining to the 'other' biologics category. Anti-TNF alpha medications and tacrolimus followed next, with 40–45% of rheumatologists banning them during breastfeeding (Fig. 2B).

With the exception of heparins, paracetamol, glucocorticosteroids and NSAIDs, obstetricians consider the discussed medications incompatible with favourable pregnancy outcomes (Fig. 2A) or safe breastfeeding (Fig. 2B).

A higher percentage of rheumatologists consider mycophenolate mofetil noxious to pregnancy and, similarly to leflunomide, to breastfeeding; while a significantly higher percentage of obstetricians ban azathioprine, sulphasalazine and hydroxychloroquine during pregnancy and, in addition to cyclosporine, during breastfeeding.

Pregnancy planning in women treated for RD

Major discordance occurred in terms of length of washout periods before allowing a pregnancy. While obstetricians recommend a washout period of 6-12 months for patients on methotrexate, leflunomide and anti-TNF alpha medications, rheumatologists would allow earlier conception. In addition, duration of remission and RD control plays a key role in pregnancy planning. Most participants agreed that 1- to 3-month remission duration was too short for a safe pregnancy. Remission duration of 3 to 6 months is advised by 8 (21.6%) rheumatologists and 37 (40.2%) obstetricians and of 6 to 12 months by

Table III. Proportion of answers in accordance with the EULAR/BSR guidelines.

	Binary score average ± SD			
	Rheumatologists		Obstetricians	
	Pregnancy	Breastfeeding	Pregnancy	Breastfeeding
Compatible medications				
Glucocorticosteroids	0.9 ± 0.3	0.8 ± 0.4	0.9 ± 0.3	0.9 ± 0.3
Hydroxychloroquine	0.9 ± 0.2	0.8 ± 0.4	0.6 ± 0.5	0.6 ± 0.5
Sulphasalazine	0.8 ± 0.4	0.8 ± 0.4	0.6 ± 0.5	0.6 ± 0.5
Azathioprine	0.7 ± 0.5	0.7 ± 0.5	0.4 ± 0.5	0.4 ± 0.5
Cyclosporine	0.5 ± 0.5	0.6 ± 0.5	0.4 ± 0.5	0.3 ± 0.5
Anti-TNF-alpha	0.6 ± 0.5	0.6 ± 0.5	0.4 ± 0.5	0.4 ± 0.5
Incompatible medications				
Methotrexate	0.9 ± 0.3	0.8 ± 0.4	0.9 ± 0.3	0.8 ± 0.4
Leflunomide	0.8 ± 0.4	0.8 ± 0.4	0.7 ± 0.5	0.6 ± 0.5
Cyclophosphamide	0.9 ± 0.3	0.8 ± 0.4	0.8 ± 0.4	0.7 ± 0.4
Mycophenolate mofetil	0.9 ± 0.3	0.8 ± 0.4	0.6 ± 0.5	0.6 ± 0.5
Other biologics	0.7 ± 0.4	0.6 ± 0.5	0.6 ± 0.5	0.5 ± 0.5
Total score per specialty	0.777 ± 0.152*		0.603 ± 0.124*	

SD: standard deviation; TNF-alpha: tumour necrosis factor alpha; *p<0.001

22 (59.5%) rheumatologists and 32 (34.8%) obstetricians. Importantly, 16 (17.4%) obstetricians *versus* 2 [5.4%] rheumatologists would not recommend a pregnancy within a year of RD remission or control.

Participants' use of references

Physicians were asked about the resources they turn to when making decisions on the discontinuation of RD medications before/during pregnancy and breastfeeding. About 75% of rheumatologists said to abide by the society recommendations, followed by PubMed search by 14 (35.9%) rheumatologists, and textbook use by 10 (25.6%). Few rheumatologists asked their colleagues for advice or checked material published on the Internet. Obstetricians, on the other hand, almost equally observed the society recommendations (54 [57.4%]) or would consult with a rheumatologist (49 [52.1%]). PubMed is searched by 37 (39.4%) obstetricians, while textbooks and the Internet were the least common information sources among obstetricians. Obstetricians were also asked about the triggers that would compel them to refer their pregnant patient to a rheumatologist, and the four main reasons were a known case of RD, the occurrence of multiple systemic manifestations, moderate-to-severe joint pain and autoantibody seropositivity.

Concordance with the EULAR/BSR guidelines

Answers given by rheumatologists and obstetricians around the compatibility of RD medications with pregnancy and breastfeeding were matched against a binary scoring system based on the EULAR/BSR guidelines. Table III shows proportions of answers in accordance with the guidelines. Most participants correctly considered glucocorticosteroids compatible with pregnancy (average score of 0.9±0.3) and breastfeeding (average score of 0.8±0.4), and methotrexate and cyclophosphamide incompatible with pregnancy (average score of 0.9±0.3 and 0.8±0.4, respectively) and breastfeeding (average score of 0.8±0.4). Further multivariate analysis showed that the physician's specialty and RD patient load correlated closely with the number of answers matching the EULAR/BSR guidelines since rheumatologists had an overall score higher than obstetricians (p<0.001). We then investigated whether working in central teaching hospitals or in peripheral hospitals affected the rheumatologists' knowledge of the guidelines. Twenty physicians practiced at central teaching hospitals and scored 0.78±0.13, slightly higher than the 13 physicians working in peripheral hospitals, who scored 0.76±0.18. However, the difference between these scores was not significant (p=0.702).

Discussion

This study has shown that obstetricians and rheumatologists practicing in Lebanon have sometimes different beliefs and strategies in managing RD and pregnancy. Rheumatologists consider that SLE has the worst effect on fertility, whereas obstetricians would argue that the APL syndrome most seriously impairs conception. Both opinions are in disagreement with medical recommendations, as many studies have failed to show any direct effect of the diseases themselves on fertility (15-17). In fact, aspects of RD that could impair female fertility include disease activity, use of immunosuppressive drugs, flares accompanied by amenorrhea, and renal insufficiency (18).

Eclampsia was mostly associated to SLE by rheumatologists and to vasculitis by obstetricians; rheumatologists were in closer agreement with the medical experience, as a meta-analysis of studies published between 2001 and 2006 reported that women with SLE are at higher risk for eclampsia compared to their healthy counterparts (19), while studies on the effects of vasculitis on pregnancy are limited since vasculitis prevails in women beyond their reproductive age (20). However, a recent study has identified signs of pre-eclampsia in patients with vasculitis, whereby infiltration of placental tissue by vasculitis-associated neutrophil extracellular traps was enhanced in the pre-eclampsia group compared to the control group (21). Pre-eclampsia and eclampsia also seem to be highly associated with the APL syndrome (22).

The present study showed that rheumatologists and obstetricians have attributed the highest risk of miscarriage and foetal malformation to the APL syndrome and SLE, respectively; these findings were coherent with the literature, which suggests that women with APL syndrome are at high risk for recurrent spontaneous miscarriage (23) and that the rate of birth defects is increased in children born to mothers with SLE (19), compared to the general population.

We have also reported that, according to rheumatologists and obstetricians, SpA presented the lowest risk on all pregnancy outcomes. This finding has

previously been reported and confirmed in the literature, as it is currently established that no adverse pregnancy outcome is expected in patients with SpA (24).

Concerning the modulation of RD course during pregnancy, participating rheumatologists and obstetricians reported that remission during pregnancy is most likely to happen in RA patients, in agreement with the medical experience (25, 26). On the other hand, SLE, APL syndrome and vasculitis are believed to flare-up during pregnancy, as reported in this study and validated by recent studies (6, 27). However, opinions about SLE flares during pregnancy are more controversial; indeed, while studies suggested increased pregnancy-associated SLE flare-ups (28, 29), others were unable to identify any association (30, 31). RA was frequently associated with post-partum flare-ups, according to rheumatologists and obstetricians participating in this study. Post-partum flare of RA is well described and indeed exacerbated by breastfeeding (32, 33). Obstetricians also considered SLE likely to flare up in the post-partum period. However, although SLE could progress upon exposure of mice to oestrogen and prolactin, little evidence supports SLE progression due to those hormones in humans (3). Moreover, studies in humans suggest that breastfeeding correlates with a low risk of SLE, further diminishing with increasing number of breastfed infants and duration of breastfeeding (34).

The present investigation emphasised the negative impact of several anti-rheumatic drugs on fertility, pregnancy and breastfeeding, as viewed by practitioners in Lebanon. The majority of rheumatologists and obstetricians are aware of the harmful effect of cyclophosphamide on fertility but only a small percentage of them know that NSAIDs and sulphasalazine could have harmful effect on fertility while other RD medications (such as methotrexate, leflunomide, mycophenolate mofetil, hydroxychloroquine and biologics) were considered harmless on fertility in accordance with guidelines. Rheumatologists and obstetricians are aware that the worst drugs in terms of pregnancy and breastfeeding safety are methotrexate, cyclophosphamide, leflunomide and mycophenolate mofetil, in contrast with glucocorticosteroids that were described as compatible with pregnancy and breastfeeding, confirming previous reports from the region (35). However, many rheumatologists and a higher proportion of obstetricians are not aware about the compatibility of cyclosporine, azathioprine, sulphasalazine and hydroxychloroquine with pregnancy and breastfeeding, despite the fact that azathioprine and hydroxyxhloroquine were found to be the most studied traditional disease-modifying agents (36). In particular, a recent case-report study supported the safety of foetal exposure to hydroxychloroquine and showed that no histologic evidence of foetal cardiotoxicity was revealed after such exposure (37). In addition, around 30 to 60% of rheumatologists and obstetricians thought that NSAIDs and anti-TNF alpha are not compatible with pregnancy and breastfeeding, which is not accurate. In fact, recent guidelines stated that NSAIDs could be safe during the first and second trimester of pregnancy and during breastfeeding (8, 9). Also, recent guidelines bring additional safety data for the use of anti-TNF alpha in pregnancy and breastfeeding. Indeed, infliximab may be continued until 16 weeks of gestation and adalimumab may be continued until the end of the second trimester. Certolizumab is compatible during the whole pregnancy and has reduced placental transfer compared with other TNF-alpha inhibitors (8, 9). Etanercept may be continued until the end of the second trimester according to the BSR/BHPR guidelines (8) or even throughout pregnancy according to the EULAR recommendations (9). Golimumab is unlikely to be harmful in the first trimester. Also, limited transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab. Continuation of TNF-alpha inhibitors should therefore be considered compatible with breastfeeding (9).

Although obstetricians are well aware of disease flares during and after pregnancy, they seem more conservative in the use of anti-rheumatic drugs compared to rheumatologists. This was clearly shown for azathioprine, sulphasalazine and hydroxychloroquine, where the difference was statistically significant between both specialties.

Many observations were in compliance with the EULAR and the BSR/BHPR guidelines (8, 9), justifying the high scores achieved by participants, indicating that most of their answers matched international guidelines. However, some disagreement was expressed around the use of some medications, especially cyclosporine and anti-TNF-alpha agents; in fact, physicians still seem reticent to prescribe these medications, despite safety indications from the EULAR and the BSR/BHPR guidelines. This could be explained by the recent nature of these safety data and the relatively limited clinical experience of the participating physicians with these drugs during pregnancy.

Finally, although this study provides strong and interesting data coming from the real practice, potential limitations might arise and affect the strength of the data. One of these limitations might be the use of a "home-made" questionnaire. These questionnaires are not published and validated, but were rather designed and tailored for the requirements of this study. To circumvent this limitation, Cronbach's alpha coefficient test for internal consistency was performed, and the obtained score indicated the reliability of the questionnaires scoring system. Another limitation might arise from the fact that all physicians were asked to choose diseases and medications from set lists, which might be incomplete. This would lead to a lack of information about medications that are less prescribed and diseases that are rarer.

In conclusion, our data showed a relatively good concordance of the physicians' beliefs with the current literature and official recommendations. However, we identified misconceptions about the anti-rheumatic drugs safety in pregnancy and divergence between rheumatologists and obstetricians practicing in Lebanon. Therefore, elaborating unified local guidelines for the management of pregnancies in RD patients,

promoting collaboration between specialties and disseminating knowledge to physicians and to patients in the Middle East region would be important for enhanced clinical care.

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