Rheumatologists' knowledge of contraception, teratogens, and pregnancy risks

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Abstract

Introduction: Rheumatologists are essential partners in planning and managing pregnancies in women with lupus. Whether they know the essentials of contraceptive and medical treatment in pregnancy, however, is unknown.

Method: Anonymous in-lecture surveys were completed by 270 rheumatologists to assess knowledge of contraceptive effectiveness, emergency contraception, medication teratogenicity, and lupus pregnancy risk assessment.

Results: Rheumatologists knew the high effectiveness of the intrauterine device, but over-estimated the effectiveness of injectable medroxyprogesterone and condoms. Almost all identified methotrexate as a teratogen, but only 69% identified cyclophosphamide and 37% mycophenolate. Most rheumatologists knew that lupus activity in pregnancy is the main predictor of pregnancy outcomes, but underestimated the risks of hypertension and race.

Conclusion: To improve lupus pregnancy planning and management, rheumatologists would benefit from improved knowledge about contraceptive effectiveness, teratogens, and the risks from non-lupus factors for pregnancy complications.

Keywords

Rheumatology, high-risk pregnancy, contraception, medical education

Introduction

Systemic lupus erythematosus (lupus) is a complicated, multi-system autoimmune disease that primarily affects women. Lupus typically starts during a woman's reproductive years, making decisions about contraception and pregnancy integral components of lupus care. Unplanned pregnancies in women with lupus are complicated by higher rates of pregnancy loss, preterm birth, and lupus flares.¹ Up to half of women with lupus are taking rheumatic teratogens, which includes methotrexate, mycophenolate, and cyclophosphamide. These medications cause pregnancy loss in 40% of exposed pregnancies and a major birth defect in 10–25% of live offspring.^{2,3} Pregnancies conceived during periods of lupus flare put the pregnancy at risk for loss and preterm delivery, the offspring at risk for life-long sequelae of prematurity, and the mother at risk for permanent organ and joint damage.⁴ Planned pregnancies, however, can be remarkably uncomplicated for the majority of women with lupus, with only modest increases in preterm birth and no increase in birth defects compared to the general population.⁵

Despite the importance of avoiding unplanned pregnancy, the use of effective contraception among women with rheumatic disease, especially lupus, is inadequate. A recent study revealed that women with lupus and rheumatoid arthritis had the lowest rate of prescribed contraception (20–22%) compared to the general population (41%) and other populations of women with chronic illness (asthma 36%, diabetes 34%).⁶ Within the Duke Rheumatology Clinic in 2014, only 32% of women of reproductive age on a teratogenic medication were

using highly effective contraceptive.⁷ While prescribing contraceptives is outside most rheumatologists' scope of practice, guiding women to safe, effective contraceptives must be part of disease management. Quality indicators in lupus management and the European League Against Rheumatism guidelines include recommendations to discuss contraception with women with lupus.⁸

If planned pregnancies are clearly preferable, why do so many lupus pregnancies occur without notice? We hypothesized that, in general, rheumatologists have insufficient knowledge to be able to guide patient decision-making. We sought to determine the attitudes of rheumatologists towards pregnant lupus patients and their

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knowledge about contraception, medications in pregnancy, and high risk lupus pregnancies by seeking anonymous answers to questions during didactic talks.

Methods

The Duke University Institutional Review Board (IRB) declared this study as exempt from review. Before any questions were shown, a slide informed potential responders that participation was optional and anonymous, and answering the poll questions implied their consent to have responses analyzed and reported in aggregate.

Attendees at lectures about contraception and pregnancy management in women with lupus were invited to anonymously answer questions embedded into the presentation (given by MEBC) using PollEverywhere software (Supplemental Table 1). Poll responses were displayed in real-time and correct answers discussed to further the educational value of the presentation. All lecture attendees could answer questions, not just clinicians. The only demographic information collected was the respondents' job position (fellow, nurse, nurse practitioner or physician assistant, attending, industry, or other), and respondents who self-reported as 'industry' were removed from the analysis as they were assumed to not be in active clinical practice. Not all questions were posed in every lecture. Individual attendees could choose which questions to answer.

Data analysis

Simple statistics were used to interpret the polling data. Qualitative results were coded by theme by two reviewers, with discrepancies decided by consensus. Poll results from all lectures were aggregated for analysis. A sensitivity analysis was performed removing university-based lectures, but as results remained similar, results are presented for all nine lectures.

Results

At least 270 individual participants contributed to this study by answering at least one question in one of the nine sessions. This lecture was presented at rheumatology meetings in 2016 and 2017 including: Virginia Rheumatology Society, South Carolina Rheumatology Society, North Carolina Rheumatology Association, American College of Rheumatology Scientific Meeting in Washington, DC, and annual Association of Women in Rheumatology. Additional presentations were given to university-based rheumatologists at the following institutions: Emory University, Stanford University, the University of Alabama, Birmingham, and to a group of rheumatology fellows from Duke University, the University of North Carolina at Chapel Hill, Wake Forest University, the Medical University of South Carolina, and Boston University. Among participants in four lectures for whom

the question was asked, 69% of respondents were attending-level rheumatologists, 22% fellows, 4% NP/PA's, and 6% other.

The first question requested clinicians provide their reaction to having a pregnant lupus patient present to clinic. We received 135 responses that varied from "Oh Dear!" to "Yay!". When coded into thematic groups, 51% responded with nervousness, 19% with alarm, and 15% with excitement.

Contraceptive knowledge

In multiple choice questions, most rheumatologists (94%) could correctly identify the high five-year effectiveness of the levonorgestrel intrauterine device (IUD) (Mirena® IUD) (Table 1). Most rheumatologists knew that condoms were not very effective contraception. However, only 20% correctly estimated a pregnancy rate of 60–63% over five years and 68% chose a lower risk. Most rheumatologists over-estimated the effectiveness of Depo-Provera®, with 72% answering that no more than 5% of women would be pregnant after five years of use. Only 9% of rheumatologists correctly estimated a pregnancy rate of 27% over five years.^{9,10}

Emergency contraception

Only 40% of respondents answered all three emergency contraception questions correctly. Many (29%) respondents thought emergency contraception (such as Plan B®) pills contained estrogen. A third of respondents incorrectly answered that emergency contraception could cause an abortion, and 25% incorrectly answered that a woman would need to show ID to pick up emergency contraception.

Long-acting reversible contraception

The majority (89%) of rheumatologists correctly knew there are no contraindications to the hormonal IUD for women with lupus or antiphospholipid syndrome.⁸ Several answered, however, that the IUD might be rejected due to a woman's autoimmune disease or that the hormones in the IUD may increase the thrombotic risk, both concerns that have proved unfounded.

Rheumatic teratogens

Participants were asked to identify the three teratogens (methotrexate, cyclophosphamide, mycophenolate) out of a list of nine rheumatic medications (prednisone, methotrexate, cyclophosphamide, leflunomide, cyclosporine, hydroxychloroquine, azathioprine, mycophenolate, and adalimumab). Methotrexate was correctly selected by 88% of respondents, cyclophosphamide by 69%, and mycophenolate by 37%. Leflunomide was incorrectly selected by 60%, cyclosporine by 22%, and azathioprine by 5%. Leflunomide has been shown in a prospective, observational studies to not increase the risk for

Table 1. Efficacy of commonly used contraceptives.

	IUD N = 266 (%)	Depo-Provera® N = 280 (%)	Condoms N = 277 (%)
Typical use reported effectiveness over 1 year ^{9,10}	<1	6	18
Typical use reported effectiveness over 5 years ^{9,10}	1	27	63
Rheumatologists who estimated 5-year pregnancy rate correctly	83	9	20
Rheumatologists who under-estimated 5-year pregnancy rate	0	88	68

Note: Rows 1 and 2 include reported efficacy of each contraceptive. Rows 3 and 4 display survey results for the rheumatologists' responses to the question "What is the likelihood that a woman will get pregnant over 5 years if she uses *this method* for birth control?".

pregnancy loss, minor or major birth defects in humans.^{11,12} Cyclosporine has been used extensively during pregnancy in women with solid organ transplants without evidence of teratogenicity. Rheumatology respondents correctly did not select prednisone, hydroxychloroquine, or adalimumab as teratogens.

Rheumatologists at two sessions were asked to order four medications (methotrexate, leflunomide, cyclophosphamide, and mycophenolate) from most to least teratogenic. Almost one-third (29%) incorrectly identified methotrexate and leflunomide as more teratogenic than cyclophosphamide and mycophenolate.

Assessment of pregnancy risk in lupus

Two-thirds of participating rheumatologists accurately estimated the risk of major pregnancy complication for cases of women with lupus at very low and very high risk, but had more difficulty estimating moderate risk (Table 2). When risk came from non-lupus related factors, including antihypertensive medication (despite being normotensive early in pregnancy) and African-American race,⁵ 88% of participants underestimated the risk of complications in inactive lupus. Respondents' confidence in their ability to manage pregnancy decreased with increasingly complicated pregnancies, with 58% reporting they felt very confident managing a low-risk lupus pregnancy compared to 36% when managing a moderate-risk lupus pregnancy.

Discussion

While rheumatologists are often the main healthcare provider for young women with lupus, these informal assessments demonstrated that many lack up-to-date knowledge on the efficacy of contraceptives, rheumatic medications that cause birth defects, and how to assess pregnancy risk outside of lupus activity. Half of all rheumatologists reported being nervous about seeing a pregnant woman with lupus and another 19% were alarmed. Despite this, when faced with a woman with mild lupus, most felt fairly confident in their ability to manage the situation. In some areas, rheumatologists demonstrated fairly uniform high levels of knowledge including the high effectiveness and safety of the IUD, teratogenicity of methotrexate, low pregnancy risk posed by low-activity lupus, and the high pregnancy risk of active lupus nephritis. We conclude that the majority of

rheumatologists can provide this needed information accurately to their patients.

One key way to improve overall lupus pregnancy outcomes is to prevent pregnancy in women with active disease or taking teratogenic medications by using highly effective contraception. In this survey, rheumatologists over-estimated the effectiveness of both injectable medroxyprogesterone and condoms. Lacking accurate knowledge about the most effective long-acting reversible contraceptives, rheumatologists may not be able to guide their patients towards the best methods to avoid ill-timed pregnancies.

We were pleased that no rheumatologists identified hydroxychloroquine or prednisone as teratogens and only a few identified azathioprine as a teratogen. This finding suggests comfort with these medications in pregnancies, which experts consider the mainstays of lupus medical management in pregnancy.⁸

It appears, unfortunately, that rheumatologists do not know that an estimated 40% of pregnancies with mycophenolate exposure result in a miscarriage and an estimated 25% of exposed live births will have a major birth defect.² In our surveys, only 37% of rheumatologists identified mycophenolate as a teratogen and many did not rank it as a high-risk teratogen, even though the United States Food and Drug Administration required a Risk Evaluation and Mitigation Strategy program to alert "doctors, nurses, pharmacists and patients about the risks of taking mycophenolate during pregnancy".¹³ If rheumatologists are not relaying this information to women when prescribing this medication, it is likely that women will not take the necessary steps to avoid teratogen-exposed conceptions. Additionally, in these surveys, rheumatologists identified methotrexate as the most teratogenic, while data suggests an under 10% risk of birth defects – a fact that surprised many in the audience. Thus, targeted education for rheumatology providers about the teratogenic risk of commonly prescribed anti-rheumatic drugs appears needed.

Participating rheumatologists clearly knew that the degree of lupus activity is a major predictor of poor pregnancy outcomes, including pregnancy loss and preterm birth. A key finding in the PROMISSE Study, the multicenter prospective study of pregnancies in women with lupus, was the role that non-lupus related factors play in pregnancy outcomes.⁵ In PROMISSE, independent of lupus activity, taking antihypertensive medications and non-Caucasian race both significantly increased the risk for adverse pregnancy outcomes.

Table 2. Pregnancy risk assessment for women with lupus.

	Patient 1: Low-risk lupus pregnancy	Patient 2: Moderate-risk lupus pregnancy	Patient 3: High-risk lupus pregnancy
Risk factors	<ul style="list-style-type: none"> • No lupus activity • No history of nephritis • No prednisone • No hypertension • Caucasian • On hydroxychloroquine 	<ul style="list-style-type: none"> • Anti-hypertensive medication • Normal blood pressure • African-American • Low lupus activity • No nephritis • On hydroxychloroquine 	<ul style="list-style-type: none"> • Active lupus nephritis • On prednisone
Risk of major pregnancy complications	Risk is <10% ^a	Risk is 57% ^a	Risk is >80% ^b
Rheumatologists who correctly estimated risk	65% (n=155)	11% (n=166)	67% (n=170)
Very confident managing this patient in pregnancy	58% (n=98)	36% (n=99)	Not asked ^c

Note: Rheumatologists were asked to estimate the risk of major pregnancy complications – such as pregnancy loss and preterm birth – for each hypothetical patient. Before learning the correct answer to the risk assessment, they were asked how confident they felt managing each patient. Rows 1 and 2 list known risk factors and the known risk of major pregnancy complications. Rows 3 and 4 list survey results from this study.

^aBased on pregnancies in the PROMISSE Study.

^bBased on pregnancies in the Hopkins Lupus Cohort.

^cNot asked as there is not a clear approach to managing active nephritis in pregnancy, and we expect that no rheumatologist would be confident managing this patient.

The main limitation of this project was the uncontrolled environment in which surveys were conducted. As responses were anonymous, we have minimal demographic information about respondents. Additionally, participants were not required to respond to all questions, and may have been more likely to answer questions when they felt confident in the answers, though anonymity may have mitigated this effect. Strengths of this project include the involvement of community practicing rheumatologists, a group that is difficult to query for knowledge. Although this study was primarily conducted in the southeast United States, participating physicians spanned practice settings, improving the generalizability of these findings.

Along with maternal–fetal medicine and obstetric medicine physicians, rheumatologists are essential partners to improve pregnancy outcomes among women with lupus. As planned lupus pregnancies have the best chance for success, rheumatologists should have the knowledge essential to guide women's pregnancy planning to coincide with a period of lupus quiescence, on safe medications. This survey shows that rheumatologists have some of this knowledge, but remain nervous about managing these patients and have clear deficits in understanding, including the failure rates of user-dependent contraceptives and the relative risks of teratogens to developing fetuses. While the expectations for general rheumatologists to counsel or initiate specific contraceptive regimens may vary, they should be able to identify when contraception is required, to know the safety of different contraceptive options in women with lupus, and be able to appropriately refer their patients. Future work should focus on improving rheumatologists' ability to give accurate and up-to-date guidance to their young, female patients with lupus.

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Ethical approval

This study was approved by Duke Medicine IRB (Pro00070302). Participation in the surveys provided implicit consent for participation.

Guarantor

MEBC.

Contributorship

All authors contributed to the design and conduct of the study; data collection and management; interpretation of the data; and preparation, review, or approval of the manuscript.

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