Perceptions of Pregnancy and Lactation from the Pregnancy and Lactation Autoimmune Network (PLAN) Registry

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Abstract

Objective: The Pregnancy and Lactation Autoimmune Network (PLAN) registry was established to evaluate the concerns of women with autoimmune or inflammatory rheumatic diseases (AIRD) pertaining to pregnancy and lactation.

Methods: The registry was started as a survey of AIRD patients at a single rheumatology specialty center in November 2016 and included questions regarding fertility, pregnancy, miscarriages, and lactation before and after diagnosis.

Results: The study included 154 subjects from the PLAN registry. More than half (52%) of respondents indicated that their diagnosis negatively changed their views on pregnancy and nearly a third (30%) decided not to have children after AIRD diagnosis. Most (66%) women were concerned that medication use during the childbearing process would affect the baby. One-third (34%) indicated their views on breastfeeding negatively changed as a result of their disease diagnosis. The rates and duration of breastfeeding did not differ significantly for babies born before or after the mothers' diagnosis (P=0.50, P=0.21, respectively). Eighteen women in our study forewent breastfeeding or stopped breastfeeding earlier than planned to start a medication (including etanercept, adalimumab, hydroxychloroquine, and certolizumab) they believed to be contraindicated during lactation. The PLAN registry included nineteen women who breastfed twenty-one babies while being exposed to a DMARD or biologic. None of these 19 women reported a delay in their children's developmental milestones or higher infection rates.

Conclusion: This study highlights an unmet need in patients with AIRDs of childbearing potential for data and education regarding pregnancy and lactation.

INTRODUCTION

Many women with autoimmune or inflammatory rheumatic diseases (AIRD) are of child bearing potential. After diagnosis, some will defer or avoid pregnancy, fearing adverse outcomes for their offspring or themselves. Others forge ahead with stable, active, or worsening disease and forego medications during pregnancy and lactation due to safety concerns. Fewer are those who continue anti-rheumatic therapies during pregnancy and lactation.

Uncertainties surrounding the childbearing process stem from insufficient guidance and education, a lack of counseling, and statistics showing that nearly 50% of all pregnancies are unplanned. Physician knowledge gaps make them unable to guide their patients on the childbearing process, as many assume this is the responsibility of the obstetrician.

While some AIRDs go into remission during pregnancy, the frequency is often overstated.[1,2] For those patients with active inflammatory disease, the benefits of disease control during pregnancy favors optimal pregnancy outcomes.[3,4,5] Despite evidence that disease modifying anti-rheumatic drugs (DMARDS) or biologics may improve pregnancy outcomes when clinically indicated, many patients and physicians are reluctant to employ them during pregnancy or lactation.

The benefits of breastfeeding for both a mother and her infant are well established.[6,7,8,9] However, for women with rheumatic diseases who require DMARDS or biologics, the decision to breastfeed is a difficult one. While some patients may flare during pregnancy, most will exhibit active disease in the post-partum period necessitating medical intervention.[1] Limited data exist regarding the effect of lactation on disease

activity and the impact of disease activity on the ability to breastfeed. Frequently, these women feel conflicted, forced to choose between optimal treatment of their disease or breastfeeding their newborn. Even though there are published guidelines regarding the safety of synthetic and biologic DMARDS during lactation, long-term outcome data are lacking.[10]

The Pregnancy and Lactation Autoimmune Network (PLAN) Registry was established in November 2016 to collect data on women of childbearing potential who have AIRDs. The goal of this study was to: 1. evaluate the perceptions of women with rheumatic diseases toward pregnancy and lactation, 2. assess patients' recollections of the effect of breastfeeding on disease activity (and vice versa), and 3. examine the impact of DMARDs and biologics on pregnancy and lactation in the registry population.

METHODS

This is a single center retrospective cohort study of 154 women with AIRDs. To explore the pregnancy and lactation concerns of these women, a survey was developed and approved by the IRB (approval number 016-242) in November 2016. Inclusion criteria for the PLAN registry consisted of women aged 18-50 with a confirmed AIRD who were eligible and willing to participate in the survey. The AIRDs included in this study were systemic lupus erythematous (SLE), rheumatoid arthritis (RA), immune mediated inflammatory myositis (IIM), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), Sjogrens syndrome (SS) and ankylosing spondylitis (AS). All diagnoses were confirmed by a rheumatologist after at least two separate visits and have documented ICD-10 codes. Patients were recruited from a single rheumatology center in

Dallas that sees commercially insured individuals. Patients were identified via electronic medical record searches and 154 women were subsequently recruited either by telephone calls or during their scheduled clinic appointments. Written consent was obtained from all participants.

Data regarding the patients' attitudes and concerns toward the childbearing process along with pregnancy and lactation outcomes were gathered from the paper surveys, telephone interviews and chart review. The survey entailed two complementary questionnaires. The first was applicable to all women in the study and captured information regarding views on pregnancy and lactation, regardless of whether the recipient had ever been pregnant. The second survey was intended only for those who had previously had a successful pregnancy or were currently pregnant. Not all 154 subjects who filled out the final survey responded to every survey question, as some patients were uncomfortable or declined to answer specific questions.

The survey was modified in three stages. Initially an open-ended questionnaire was created, focusing on women's greatest concerns regarding the childbearing process. This questionnaire was given to thirty-five women with AIRDs. Based on the responses of these women, a revised survey was created utilizing multiple-choice questions to ensure the survey data was quantifiable. A draft of the survey was reviewed with five patients to identify questions that were confusing or could be misinterpreted. The final survey can be found in appendix 1.

Data collection for this paper occurred from November 2016 to May 2017. Neither patient care nor drug therapy was affected by participation or non-participation in this study. Continuous variables are reported as median [quartile 1, quartile 3].

Categorical variables are reported as frequencies and percentages. Variable relations were assessed via the Wilcoxon Rank Sum test, Chi-Square test, and Fisher's Exact test, as appropriate.

RESULTS

PART I: Survey of beliefs, advice, and visits

There were 154 subjects included in the analysis. Patient demographic and diagnostic information are provided in Table 1. More than half (52%) of respondents indicated that their disease diagnosis negatively changed their views on pregnancy. As depicted in Figure 1, pregnancy views after diagnosis differed significantly across the diagnoses AS, RA, JIA, and SLE, P=0.04. About one-third (30%) of respondents said their diagnosis changed their minds about having children altogether, a sentiment that also differed significantly by diagnosis as shown in figure 1 (P = 0.01). Of the 54 respondents who already had children prior to diagnosis, over three-quarters (80%) said their diagnosis changed their mind about having more children. When discussing concerns regarding maternal and fetal health during pregnancy, data from 121 subjects show that most woman (73%) are more concerned about the baby's health than their own health during pregnancy. One out of six women consulted with a fertility specialist for pregnancy assistance. Four women chose to adopt children, and two chose to have children via a surrogate; however, 16% of respondents considered a surrogate. Approximately one-third (34%) of respondents indicated that their views on breastfeeding negatively changed as a result of their disease diagnosis. Changes in breastfeeding opinions did not differ significantly between diagnoses.

The top three concerns from respondents included: 1. medication use during pregnancy or lactation affecting their offspring 2. concerns regarding their own health once pregnant, and 3. concerns regarding the ability to care for their child after delivery due to worsening of their disease during lactation. AIRDs respondents' top concerns regarding pregnancy and lactation are depicted in Figure 2.

Of the 117 subjects who said they received pregnancy advice prior to conception, their sources were as follows: rheumatologist (71%), obstetrician/gynecologist (ob-gyn) (63%), friends/family (24%), primary doctor (13%), and other patients (4%). These results are biased, as many of the patients included in our study see a rheumatologist with a special interest in women's health. Many patients also listed sources that may not be qualified to give advice, such as other patients, friends/family and the Internet. Over one-fifth (23%) of subjects said they were advised or warned not to get pregnant at some point by at least one of the above listed sources; this advice differed across diagnoses (AS: 12%, RA: 14%, SLE: 38%, P = 0.03). Of note, from respondents who became pregnant after disease diagnosis, the median number of ob-gyn, rheumatology, and primary care physician visits during pregnancy was 12, 1, and 1, respectively.

PART II: Pregnancy and post-pregnancy outcomes

Pregnancy: A total of 151 pregnancies, 88 of which occurred after disease diagnosis, were reported from 90 respondents. Seven of the respondents were pregnant at the time of the study. Eight women had children both before and after disease diagnosis. The median gestational periods did not differ between pregnancies that occurred before or after disease diagnosis (38 [36, 40] v. 38 [37, 39] weeks, respectively; P=0.93). Similarly, the median birth weights did not differ (6.7 v. 7.1 pounds, respectively;

P=0.22). Pregnancy complications also did not differ significantly between pregnancies occurring before and after disease diagnosis (9% v. 12%; P=0.45).

Lactation: Most (82%) infants were breastfed. Of children who were breastfed, about half (49%) were breastfed for less than six months and the other half (51%) were breastfed for greater than six months. The rates of breastfeeding did not differ significantly for babies born before or after the mothers' diagnosis (before: 87%, after: 82%; P=0.50). Similarly, breastfeeding duration did not differ by diagnosis status. Six women breastfed both before and after disease diagnosis. Five of these women reported breastfeeding for the same duration after diagnosis as before diagnosis.

For those women who breastfed their babies after disease diagnosis, medical therapy had to be changed due to worsened disease activity in 35% of patients. Lactation affected the mother's disease state positively in 22%, negatively in 44%, or not at all in 35%, based on patients' subjective reports.

The mothers of the 26 infants who were not breastfed cited several reasons for not breastfeeding. The three most common reasons were: a) they were taking medication they believed to be contraindicated (33%), b) they had poor milk production (33%), and c) their babies were unable to latch (19%). The reasons provided for not breastfeeding did not differ significantly between mothers who breastfed before and after disease diagnosis.

Some respondents stopped breastfeeding sooner than they originally planned. Six women with active disease (10%) stopped breastfeeding due to a disease flare, and 14 (12%) respondents with active disease explained that they stopped breastfeeding because they needed to start a medication for their AIRD that was thought to be contraindicated.

Other common reasons women stopped breastfeeding included: not enough milk (35%), fatigue or loss of patience (11%), and transitioning their child to table food (18%). Half (35/70) of respondents indicated that the information regarding the use of DMARDs and lactation was inadequate. Respondents received most of their breastfeeding information and education from their obstetrician followed by from nurses, family, friends, and books. Only 12% received breastfeeding information from their rheumatologist.

Offspring outcomes: Based on patient recall, developmental milestones were met in > 95% of babies for crawling, walking, and speech. Developmental milestone outcomes did not differ significantly before or after maternal AIRD diagnosis. The majority (98%) of babies had appropriate growth. One baby did not meet his/her crawling milestone and was born prior to the mother's AIRD diagnosis; the mother did not use DMARDs during pregnancy or while breastfeeding. Two of the six babies who did not meet the speech milestone were born to mothers who reportedly took no DMARDs during pregnancy or breastfeeding (both babies were born after diagnosis). Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and prednisone were the only medications reported as being used during pregnancy or breastfeeding for the mothers of babies who did not meet the speech milestone. Medication use for those who were diagnosed by the time of conception is illustrated in Table 2.

DISCUSSION

In our study of 154 women with AIRDs, nearly half negatively changed their views on pregnancy and a third negatively changed their views on lactation after receiving their disease diagnosis. Half of those with SLE opted not to have children at all

after receiving their diagnosis. The most common voiced concern was the potential adverse effects a DMARD or biologic may have on the respondent's or her baby's health, despite the availability of published literature citing the safe use of specific synthetic DMARDS and biologics, including hydroxychloroquine, azathioprine, sulfasalazine, and TNFα-inhibitors.[10,11,12,13]

The prudent use of some of these medications during pregnancy has allowed for better maternal disease control resulting in improved neonatal outcomes. [14] Despite the concerns of many regarding the safety of drug therapy during pregnancy, there has been a plethora of research showing that maternal health has primacy over other factors in determining pregnancy outcomes. Moreover, highly active inflammatory states and unstable autoimmune disease have repeatedly been associated with adverse pregnancy outcomes.[1,15]

The concerns of medication side effects during pregnancy and lactation are not unique to women with rheumatic diseases. It is known that pregnant women, regardless of diagnosis, often perceive or misconstrue medications as dangerous for their offspring despite contrary information provided by healthcare professionals.[16] Koren et al found that women generally overestimate the risks of teratogenicity associated with medications not known to be teratogens. Their study found that after counseling and education women better estimated rates of teratogenicity and were less likely to terminate their pregnancy.[17] By identifying medication use as the most concerning aspect of pregnancy for our patients, this study highlights the need for tactful patient education and communication regarding the safety profiles DMARDs and biologics during pregnancy.

Some women may have false perceptions of the true risks of pregnancy and lactation with regard to their disease. It is unfortunate that almost half of the women surveyed were concerned about directly passing their disease to their child, both during pregnancy and during lactation via breast milk. Having an open discussion with their physician may have helped to ease such worries. Women from the PLAN registry had visits with their rheumatologist equally as often as their obstetrician prior to conception, however once pregnant these women relied primarily on their obstetrician for care. Furthermore, even in the postpartum period only a small minority of the women in the PLAN registry received advice regarding lactation with regards to their AIRD from their rheumatologist. Perhaps, most women and rheumatologists believe the obstetrician is capable of managing both the pregnancy and the rheumatic disease or maybe physicians of other specialties do not feel comfortable seeing a pregnant woman. These data highlight the need for rheumatologists and other specialists to be more involved in their patients' care during preconception counseling, pregnancy, peripartum, and lactation periods. Patients concerns will be alleviated with additional education; in addition, pregnancy and lactation outcomes may improve.

A multidisciplinary approach to patient education is ideal. Many women in our study received their information regarding breastfeeding from non-physician sources, including the lactation counselors, nurses, and the internet. Eighteen women in our study forewent breastfeeding or stopped breastfeeding prematurely in order to start a medication (including etanercept, adalimumab, hydroxychloroquine, and certolizumab) they believed to be contraindicated during lactation. However, published guidelines indicate that the prescribed medications are compatible with lactation.[10] This study

highlights the need for accessible educational resources regarding DMARD and biologic use during pregnancy and lactation, not only for patients, but also for physicians and other healthcare providers.

Our data indicate that breastfeeding on selected DMARDs or biologics (listed in Table 2) may be safe. We evaluated nineteen women who breastfed twenty-two babies while taking a DMARD or biologic and none of these women reported a delay in their children's developmental milestones. More data are needed, including close review of pediatric records, to further assess the long-term outcomes of infants exposed to these medications during the breastfeeding period.

More studies are necessary to fully evaluate the relationship between AIRD activity and lactation. The breastfeeding rates among the respondents of our study were the same as the rates of breastfeeding rates in Texas according the 2016 CDC breastfeeding report card. Furthermore, our data showed no difference in the rates or duration of breastfeeding between women before and after their AIRD diagnosis. There are currently limited, but conflicting data regarding the relationship between AIRDs and lactation. With regards to Crohn's diseases, there is evidence that lactation may be protective against relapse in postpartum women.[18] However, in inflammatory arthritis, published data indicate that a post partum flare may be induced by breastfeeding.[19] It is unclear if milk production is low with higher disease activity, and equally unknown is if lactation affects disease activity. Additional research is needed to fully delineate this issue.

LIMITATIONS

These results are from a small single center experience and may not be generalizable. Further, as in any self-reported survey study, the results may be biased due to missing data as well as limited memory recall by the subjects and/or the sensitive nature of the material being studied.

CONCLUSION

There is an unmet need for data and resources about fertility, pregnancy, and lactation outcomes in patients with AIRDs who are of childbearing potential. This study and the PLAN registry highlight the pregnancy and lactation concerns of women with AIRDs and identify areas where communication and education for patients can improve.

DISCLOSURES

Dr. Cush is a consultant/advisor and researcher for UCB pharmaceutical company. Dr. Cush is a co-author on a published UCB data regarding certolizumab and pregnancy outcomes.

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Figure Legends:

Table 1. Characteristics of patients surveyed for the study. “Other” consists of patients with immune mediated inflammatory myositis, vasculitis, systemic sclerosis, and undifferentiated connective tissue disease.

Figure 1. The solid and dotted bars highlight those women who had more concerns about pregnancy and/or lactation after disease diagnosis. These women may have still had children. The striped bar represents those women who decided to forgo pregnancy altogether due to their disease diagnosis.

Figure 2. More than 65% of women were concerned about medication use during pregnancy adversely affecting their fetus. This was the most common concern among our respondents.

Table 2. Medication use among with AIRDs before, during and after pregnancy.

Table 1. Patient characteristics (n = 154)

Variable	Frequency (%)
Median Age (years)	38
Diagnosis	
Ankylosing Spondylitis	7.8%
Juvenile Idiopathic Arthritis	4.6%
Systemic Lupus	23.4%
Psoriatic Arthritis	10.4%
Rheumatoid Arthritis	37.7%
Other	16.2%

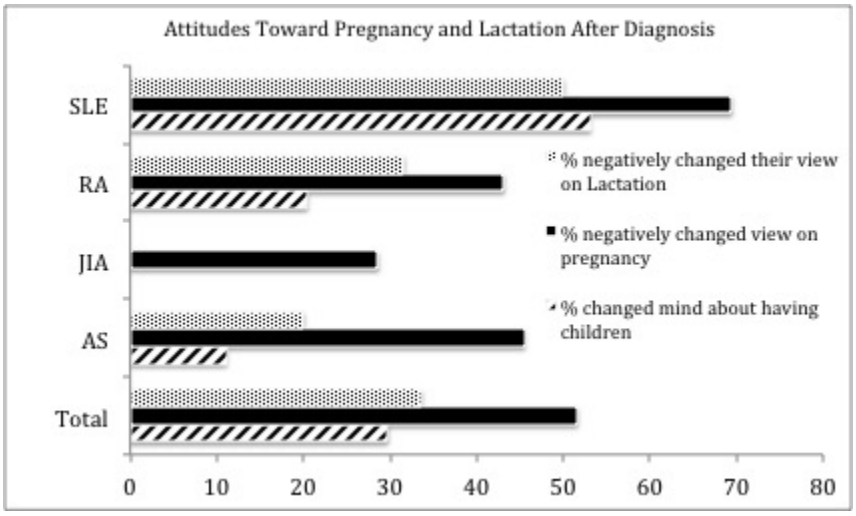

Figure 1.

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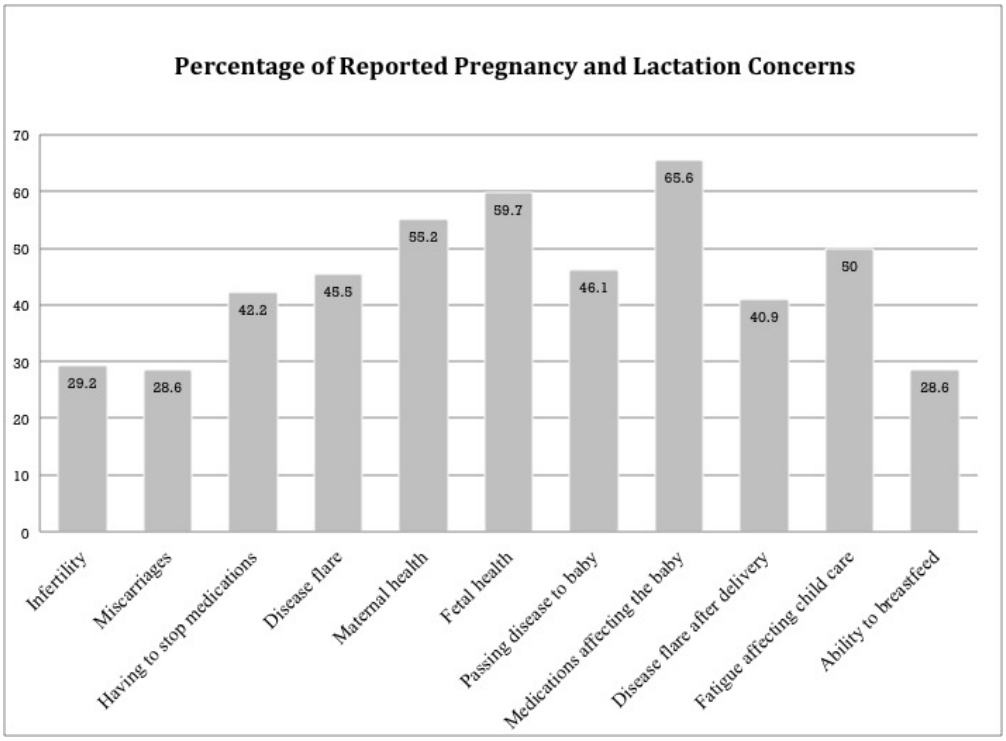

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Table 2. Medication Use During the Childbearing Process

Medication	Before Pregnancy (n=88)	During Pregnancy (n=88)	Breastfeeding (n=60)
Hydroxychlorquine	21 (23.9%)	14 (15.9%)	9 (15.0%)
Azathioprine	0 (0.0%)	2 (2.3%)	1 (1.7%)
Mycophenolate mofetil	1 (1.1%)	0 (0.0%)	0 (0.0%)
Sulfasalazine	4 (4.5%)	2 (2.3%)	1 (1.7%)
Methotrexate	12 (13.6%)	0 (0.0%)	0 (0.0%)
Leflunomide	2 (2.3%)	0 (0.0%)	0 (0.0%)
Cyclosporine	2 (2.3%)	0 (0.0%)	0 (0.0%)
Prednisone	18 (20.5%)	14 (15.9%)	8 (13.3%)
NSAIDS	27 (30.7%)	13 (14.8%)	10 (16.7%)
Etanercept	15 (17.0%)	5 (5.7%)	7 (11.7%)
Infliximab	3 (3.4%)	0 (0.0%)	0 (0.0%)
Adalimumab	9 (10.2%)	3 (3.4%)	2 (3.3%)
Certolizumab	4 (4.5%)	4 (4.5%)	3 (5.0%)
Golimumab	2 (2.3%)	0 (0.0%)	0 (0.0%)
Rituximab	1 (1.1%)	1 (0.0%)	1 (0.0%)
Narcotics	4 (4.5%)	2 (2.3%)	0 (0.0%)
Acetaminophen	24 (27.3%)	29 (33.0%)	20 (33.3%)