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SPECIAL ARTICLE

Proceedings From the American College of Rheumatology Reproductive Health Summit: The Management of Fertility, Pregnancy, and Lactation in Women With Autoimmune and Systemic Inflammatory Diseases

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Introduction

Most autoimmune and systemic inflammatory diseases are more common in women than in men, including women of child-bearing age. Therefore, for many of our patients, family planning is an important clinical issue. The management of pregnancy in autoimmune diseases is complex, benefitting optimally from a multidisciplinary approach that takes into consideration: prepregnancy counseling; treatments received prior to, during, and after pregnancy; early recognition of both obstetric complications and medical complications relating to the underlying disease; prenatal fetal development; and postnatal management of the

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patient and infant. The ideal would be for patients to be followed by clinicians with specialized expertise in early recognition and treatment of complications of pregnancy, to allow appropriate risk assessment/stratification of the patient and provision of a tailored plan for antenatal and postnatal management of such high-risk pregnancies. This approach is not achievable for most patients, so there is a need to improve pregnancy-related knowledge among health care providers (HCPs) and patients without access to such resources. Furthermore, there is a need to address the considerable existing evidence gaps on drug data and guidelines for the management and treatment of pregnant women with autoimmune and systemic inflammatory disorders.

Following a previous 2012 American College of Rheumatology (ACR) Drug Safety Summit, wherein unmet needs for drug safety were discussed and prioritized, on January 10–11, 2014, the ACR hosted a Reproductive Health Summit on the management of fertility, pregnancy, and lactation in women with autoimmune diseases. The summit brought together clinical specialists in rheumatology, gastroenterology, dermatology, obstetrics and gynecology, maternal–fetal medicine (MFM), and neonatal medicine; researchers focused on pregnancy and neonatal medicine; patient advocacy groups; and representatives from the National Institutes of Health (NIH) and regulatory agencies (i.e., the Food and Drug Administration [FDA]). The purpose of the meeting was to review the available data pertaining to state-of-the-art management of therapeutic interventions before, during, and after pregnancy among women with autoimmune diseases; to understand the regulatory considerations concerning pregnancy and lactation; and to help define future research needs in this area. The following article is a synthesis of the presentations, discussions, and outputs of the meeting.

Current challenges and unmet needs in fertility, pregnancy, and lactation

Clinical trial data in pregnant and breastfeeding women are rare. In the interest of protecting the fetus, pregnant women have generally been excluded from participation in clinical studies, and women who become pregnant while in a trial are immediately stopped from continuing the medication intervention. Women who are forced to discontinue clinical trial medications may in fact be responding to the drugs, with a subsequent flare in their underlying disease compounding the ethical and clinical dilemmas of discontinuing the trial medication. Prelicensing and premarketing data on drug safety in pregnancy are usually limited to data from animal toxicity studies (fertility, reproductive, and developmental toxicity), where the relevance of the findings to human pregnancy is not always clear. Additionally, inadvertent exposures in women who become pregnant while in clinical trials provide anecdotal experience. Postmarketing data are also limited, coming from pregnancies incurred during drug development, pregnancy registries, spontaneous adverse event reporting, and reports in the literature. These data may be subject to reporting bias.

In practice, pregnant and lactating women are frequently exposed to medications. Only about half of all pregnancies are planned (1) and, as a result, many women are already taking medications when they become pregnant. More than 6 million pregnancies occur in the US annually, with 90% of women taking at least one medication and an estimated 50% taking 3 or 4 medications during pregnancy (2–4). Furthermore, many women need medications for pregnancy-induced conditions (morning sickness), chronic conditions (rheumatoid arthritis [RA], depression, asthma) that predate the pregnancy, and intercurrent conditions (allergies, infections).

The exclusion of pregnant and breastfeeding women from clinical trials of experimental drugs results in large gaps in our knowledge on the use of medications in these populations. Knowledge on drug metabolism and transfer as well as the drug safety profiles during pregnancy and lactation is lacking. Pharmacokinetic (PK) studies in nonpregnant women may not accurately predict exposure in pregnant women, making appropriate dosing difficult. Treatment choices to manage women during pregnancy are based on the physician's clinical experience and knowledge of medications that may or may not be compatible with the biologic challenges of a pregnancy. This knowledge is limited to existing data or information sources on those medications and is sometimes based only on the FDA pregnancy category (A, B, C, D, X) for the drug.

Perception, or misperception, of teratogenic risk may lead to anxiety over birth defects and to women not taking medications during pregnancy or while breastfeeding. Even when exposed to nonteratogenic drugs, women have assigned themselves a 25% teratogenic risk, when the actual estimated risk for major malformation is $<5\%$ (5,6). Perception of teratogenic risk may contribute to lessened interest by pharmaceutical companies in developing drugs for pregnant or lactating women and to unnecessary pregnancy terminations (7,8). Importantly, all anomalies are not caused by drug exposure; various studies describe a background rate of congenital anomalies that ranges between 1% and 5% (7,9,10).

While the need for more data is urgent, better communication of existing data needs to happen now. This will lead to informed risk/benefit decisions on medicine use in healthy pregnant women as well as women with chronic disorders that require long-term treatment.

New FDA proposed updates to pregnancy and lactation labeling. The exclusion of pregnant women from clinical trials means that, often, when new drugs are approved there are no data on pregnancy other than animal toxicology data. Under current regulations, the FDA includes available information on pregnancy, labor and delivery, and nursing mothers in product labeling and assigns a pregnancy category of A, B, C, D, or X (Table 1) based on available data and risk/benefit considerations. Under the FDA Amendments Act of 2007, the FDA was given new authority to require postmarketing studies to evaluate serious risks related to use of a drug. Therefore, the FDA can now require companies to conduct studies to obtain data in pregnant and lactating women, such as pregnancy registries and lactation studies, to clarify safety issues. However, companies often encounter difficulties enrolling

Table 1. Current Food and Drug Administration pregnancy categories (107)

A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not been done during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (e.g., safer drugs or other forms of therapy are available).

pregnant women. There is, therefore, often a delay in fulfilling postmarketing commitments and requirements for pregnancy registries and in filing final study reports by requested deadlines.

The FDA has issued a proposed new Pregnancy and Lactation Labeling Rule (PLLR) to help address current problems with pregnancy and lactation labeling and to improve information that is used to make prescribing decisions. Existing pregnancy categories of risk (Table 1) are often incorrectly assumed to represent an increasing level of risk, when in fact they are descriptive of the type of data and the level of uncertainty for a specific drug. Categories are not well understood and the reproductive risk within a category is unclear. Therefore, prescribing decisions in practice may be misguided, leading to unnecessary switching or discontinuation of drugs in women contemplating pregnancy or pregnant women, or unnecessary termination of the pregnancy.

The key proposed changes in the PLLR include a change to the format and content of pregnancy and lactation labeling, merging the current "Pregnancy" and "Labor and Delivery" subsections and renaming the "Nursing mothers" subsection "Lactation" (Table 2). The biggest change will be elimination of the pregnancy letter categories, to be replaced by narrative descriptions of the available data with a summary statement up front, a clinical considerations section, and the supporting data. The PLLR is yet to be finalized and published. The FDA has encouraged sponsors to voluntarily update the pregnancy and lactation sections of labeling to incorporate the new format prior to publication of the final rule. In the interim, the pregnancy letter category will remain, even if the new format is used, until the final rule is published. Ultimately, the existing pregnancy categories will be removed from all drug labeling.

Potential challenges exist with implementation of this transition. These include educating prescribers on the new format and absence of prior pregnancy letter categories and minimizing inconsistencies of labeling within drug classes and between innovator and generics. While many agree the pregnancy risk categories may be simplistic and denote a rank safety that may not be true, there was concern by some conference discussants that the replacement of this identifiable and simplistic classification with a much longer narrative of a particular drug's maternal–fetal safety and developmental and lactation research may obscure and confuse clinicians who prefer better information to more information. Given the perceptions of risk associated with drug safety in pregnancy, a default position by some physicians is to "do no harm" and either not to prescribe or to recommend stopping treatments. Therefore, it is critical to communicate the risk/benefit of treatment as clearly as possible and to facilitate cross-disciplinary communication between specialties to help physicians and patients make informed choices. More data, particularly human data in pregnant and lactating women, are needed to inform FDA product labeling.

Table 2. Proposed Pregnancy and Lactation Labeling Rule (PLLR) format, Section 8*

- Section 8: use in specific populations
  - 8.1 Pregnancy
    - Pregnancy registry information (if available)
    - Risk summary
      - Risk statement based upon human, animal, pharmacology data
      - Background risk information in general population, disease population (if available)
    - Clinical considerations (if applicable)
      - Disease-associated maternal and/or embryo–fetal risk
      - Dose adjustments during pregnancy, postpartum
      - Maternal adverse reactions
      - Fetal/neonatal adverse reactions
      - Labor and delivery
    - Data human and animal
  - 8.2 Lactation
    - Risk summary
    - Presence of drug in human milk
      - Effects of drug on the breastfed child
      - Effects of drug on milk production
      - Risk and benefit statement
    - Clinical considerations (if applicable)
      - Minimizing exposure
      - Monitoring for adverse reactions
    - Data (if available)

* Key point: no pregnancy letter category.

Table 3. Code of Federal Regulations on Protection of Human Subjects: 45 CFR46 Subpart B—46.204 Research involving pregnant women or fetuses (11)*

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

(c) Any risk is the least possible for achieving the objectives of the research.

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions.

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

(g) For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of the Protections for Children Involved as Subjects (Subpart D).

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy.

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

* Available from: http://www.hhs.gov/ohrp/archive/humansubjects/guidance/45cfr46.html#46.204.

Changing research attitudes and initiatives in pregnancy and lactation

Despite the known and quite extensive major physiologic changes that occur during pregnancy, we use the same drugs at the same doses, tested and validated in men and nonpregnant women, to treat pregnant women. In order to change research and clinical practice for the better, major ethical, legal, and scientific considerations need to be addressed about where to place pregnant women in the process of drug development. Do we wait until the drugs are licensed, or should pregnant women be part of the process from the outset? Improving research opportunities in pregnancy and lactation requires advocacy and major legislative effort as well as novel approaches to scientific study.

Legal and ethical considerations for inclusion of pregnant women in research. The Code of Federal Regulations on Protection of Human Subjects (45 CFR46 Subpart B) (11) creates a high burden for inclusion of pregnant women in clinical studies, requiring that pregnant women or fetuses may be involved in research only if all of 10 very specific conditions are met (Table 3). There is a mandate that clinical research in pregnancy can be conducted only "if there is direct benefit to the fetus or mother," and prohibiting research that is of more than minimal risk to the fetus. This directive does not allow for assessment of the potential importance of adequate disease control on fetal outcome. To change this mandate, advocacy is needed to build awareness through strategic communication and education of both providers and patients, and should involve multiple stakeholders, including institutional review boards, legal departments, regulators, researchers, and payers, as well as clinicians and patients themselves.

Approaches to pregnancy research: pregnancy registries. Pregnancy registries are a useful approach to collecting data on drug use in pregnancy, particularly on new medications, in situations where there might be a predicted low number of exposures in pregnancy or where there is an absence of any human epidemiologic data. Registries are typically prospectively designed to examine the incidence of adverse outcomes in a group of women exposed to a specific medication. For example, the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry, discussed in more detail below, was initiated to examine the effect medications have on pregnancy in patients affected with the autoimmune disorder, inflammatory bowel disease (IBD). Registries may collect data on a broad range of outcomes, particularly adverse outcomes associated with perinatal drug exposure, including pregnancy loss, malformations, growth abnormalities, and functional deficits. To evaluate whether adverse outcomes occur more frequently in women with a specific medication exposure, registries are generally designed to compare adverse outcome rates to population data. Some pregnancy registries, however, include comparator groups: both patients with the same underlying autoimmune disease but no exposure to the medication under study and healthy comparison women without autoimmune disease. Registries with such internal comparator groups enable investigators to control for confounders.

Organization of Teratology Information Specialists (OTIS) and "MotherToBaby" services. "MotherToBaby" services were originally established in 1979 in the US and Canada in response to a public need for mothers and families to obtain advice and information relating to drug exposures during pregnancy. The OTIS Collaborative Research Center was established in 1998 at the University of California San Diego, with the leflunomide pregnancy registry. The OTIS Research Center recruits women throughout the US and Canada and has ongoing or planned federally funded and pharmaceutical-sponsored registries for the following drugs: leflunomide; abatacept; etanercept; adalimumab; tocilizumab; certolizumab; tofacitinib; ustekinumab; teriflunomide; apremilast; influenza, meningitis and tetanus, diphtheria, and pertussis vaccines; and antiviral and asthma medications, including long-acting beta agonists for asthma. In all cases, data are collected from enrolled patients before pregnancy outcomes are known, and a broad range of maternal and fetal outcomes are collected, including in many studies the examination of the infants by specialized dysmorphologists.

There are several challenges in interpretation of data collected from pregnancy registries, including the possibility of selection bias. Since enrollment is voluntary, subjects may have a tendency toward less racial diversity (e.g., more white patients) and higher socioeconomic status and education, which may be related to pregnancy outcomes and, therefore, may influence the ability to extrapolate observations to the general population.

Limitations of registries and potential alternative sources of information. The value in any pregnancy registry relies on the robustness of the design and the original questions asked. In 2002, the FDA outlined general considerations for the creation of pregnancy registries (12), including 1) identifying and establishing a diverse and experienced group of key stakeholders, 2) asking the right clinical questions (on drug exposure, fetal malformations, adverse outcomes, partner exposures, maternal health including pregnancy-related outcomes, the impact of pregnancy on disease activity and of disease on patients' willingness and ability to conceive), and 3) ensuring that correct eligibility criteria, comparison groups (external and/or internal), source of data, timing of data capture, and statistical power are present.

There are several challenges in conducting pregnancy registries, even among those with comprehensive data collection and internal comparator groups, that can potentially influence interpretation of findings. These include difficulty in obtaining precise and valid measures of the level of maternal disease activity, differentiating disease-related versus pregnancy-related symptoms, and understanding the influence or possible effect modification of comorbid illnesses. Recruitment challenges may lead to differential timing of enrollment. For example, women exposed to a drug may enroll earlier in their pregnancy than women in comparison groups, and differential risks based on timing of enrollment must be accounted for. In addition, women who enroll later in their pregnancy are not informative relative to risks for early pregnancy events such as spontaneous abortion or elective termination. A lack of diversity in the enrolled sample poses challenges in generalizability if risks or safety for a specific drug exposure in pregnancy differ by factors such as maternal education or race. There may also be recall bias on the part of the mother (13) in those pregnancy registries that are not truly prospective, i.e., for pregnancies that are enrolled when adverse pregnancy outcomes are already known. Finally, sample sizes that are attainable in pregnancy registries may limit power. This may be unavoidable if use of the drug in pregnancy is low. However, the British Society for Rheumatology Biologics Register (BSRBR), arguably one of the largest registries of biologic agents in the world, has recruited very small numbers of pregnant woman exposed to biologic agents. Among 16,000 patients in more than 10 years, they have reported on 88 live births of a total of 130 pregnancies in patients who received a tumor necrosis factor (TNF) inhibitor before or during pregnancy (14). Among 38,337 RA and psoriatic arthritis patients in the Consortium of Rheumatology Researchers of North America (CORRONA) registry, only 251 pregnancies were identified over a similar timeframe (15). Although this limited information is useful, registries that only enroll very small numbers of exposed pregnancies may require a substantial amount of resource and investment to have statistical power that is limited to ruling out only very high risks.

With such limitations in mind, it is important to explore other opportunities to supplement data on drug exposures in pregnancy. An analysis of pregnancy drug exposures in a large US health claims database demonstrated that it is possible to identify similar numbers of pregnant patients to the BSRBR without the investment required to set up a registry (16). Complementary approaches that could be considered are partnering with, or nesting a pregnancy-focused study within, an existing disease registry (BSRBR, CORRONA) or data system (health plans, FDA Mini-Sentinel [17], ACR Rheumatology Informatics System for Effectiveness [RISE] Registry [18]). Structured data or natural language processing of parsed text notes could be used to trigger referral to a pregnancy registry such as OTIS (a process of semiautomated recruitment), with the registry then conducting prospective, longitudinal followup on maternal/fetal drug exposures. It may also be possible to utilize novel channels to recruit eligible women for pregnancy studies through patient groups such as the Arthritis Foundation and social media sites. Finally, alternative and more rapid approaches to obtaining patient consent might be considered in certain cases (19).

Novel approaches to pregnancy research: the NIH/National Institute of Child Health and Human Development (NICHD) Obstetric–Fetal Pharmacology Research Unit (OPRU) Network. In recent years, the Eunice Kennedy Shriver NICHD at the NIH has made a major commitment to promoting research in pediatrics and pregnancy. The Obstetric and Pediatric Pharmacology and Therapeutics Branch at the NICHD promotes basic, translational, and clinical research on various medications in children and pregnant women, primarily to help ensure their efficacy and safety in preventing, treating, and managing various diseases. The OPRU Network, which has been funded

by the NICHD since 2004, supports preclinical and clinical research, designed and conducted in parallel, to answer specific questions relating to gaps in fundamental knowledge about physiologic and pharmacologic mechanisms in pregnancy and to translate discoveries into better medical practice. The OPRU's successful approach to the study of medication use in pregnancy could be of benefit to promoting research in autoimmune disorders.

Understanding placental physiology and drug transport. The placenta, a tissue of fetal origin, acts as the interface between maternal and fetal circulation and is responsible for a multitude of functions to ensure healthy growth of the fetus. Understanding how drugs are transported across and metabolized by the placenta is critical to understanding the potential risk of any agent to an unborn baby. Currently, it is accepted that compounds with molecular weight <900 kd can be transferred across the placenta to the fetal circulation (monoclonal antibodies are ~150 kd). The question is, to what extent? Compounds can cross the placenta through simple passive diffusion, facilitated diffusion, or active transport by uptake and efflux transporters, and can cross unchanged or are partially consumed or metabolized with biotransformation by placental enzymes into different products; others are not transported at all. These placenta-related features may also change or evolve during the different trimesters of pregnancy. Drug placental transfer is heavily dependent on gestational age and the development of the placenta through different trimesters; therefore, timing of drug exposure is important when considering relative risk to the fetus. There are also significant variations between placental and adult hepatic drug metabolic enzymes and metabolism, and between rodent and human placental physiology and pharmacology. Therefore, extrapolation of PK data from men or nonpregnant women, from adult hepatic pharmacology, or from animal studies is often not applicable. The only way to truly understand the metabolism and transfer of drugs across the placenta is to study them, individually, in placental models (in vitro and in vivo) that are applicable to human beings (20–22).

Autoimmune disease and pregnancy: challenges and unmet needs

Burden of autoimmune disease and pregnancy. Autoimmune and systemic inflammatory disorders are common among women of child-bearing age, with variation among different conditions. Women are 2–3 times more likely to develop RA than men and 10 times more likely to develop systemic lupus erythematosus (SLE). The onset of autoimmune disorders tends to overlap with patients' peak reproductive years, particularly in SLE and IBD. Therefore, family planning and provision of prepregnancy counseling and appropriate management and treatment for patients is an important, and often unmet, need. In SLE, the issue of pregnancy and drug metabolism must be carefully examined because peak disease onset varies by race, thereby making these issues more relevant for certain population subsets over others (23). In RA, peak disease onset is at age 30–55 years, so pregnancy is perhaps less of an issue for some women than for those with SLE or IBD, where onset occurs earlier. However, it is important to consider both patients with juvenile forms of arthritis where onset occurs in childhood or adolescence, coinciding with the onset of their fertility, and other forms of arthritis such as spondyloarthritis and psoriatic arthritis.

Alterations in pathophysiology as a result of pregnancy are disease specific and may affect disease activity and severity. Irrespective of treatment, the risk of complications in pregnancy (maternal and fetal), labor, and delivery is increased in certain conditions compared with the general population (24). Therefore, it is important to separate the risk of active disease to a healthy pregnancy versus the risk of medications.

Historically, RA has been associated with improvement in disease activity during pregnancy, which may be related to immunomodulation to protect the fetus, resulting in improved maternal self-tolerance (25–28). However, RA is also associated with reduced fertility (29–31) and poor pregnancy outcomes, including increased rates of preterm birth and low birth weight (32,33). Importantly, improvements in RA disease activity during pregnancy may be far less pronounced than in the past due to secular trends in lower RA disease severity and the availability of more effective treatments that are implemented earlier in the disease course. Women who stop TNF inhibitors during pregnancy may have more disease activity in pregnancy (34). Regardless of modest improvements that may occur during pregnancy, RA flares are common postpartum (32).

Pregnancy morbidity is a well-recognized and often severe complication in SLE patients, and in the distant past, women were regularly advised against pregnancy or to consider termination. SLE is associated with increased adverse pregnancy outcomes, including maternal mortality; a reduced rate of live births; increased risk for thrombosis, infection, thrombocytopenia, and transfusion; Cesarean sections; preterm labor and preeclampsia; antenatal hospitalization; and other medical conditions such as diabetes mellitus, hypertension, and thrombophilia (30,35–37). However, rates of adverse pregnancy outcomes have improved considerably over the last few decades (37), perhaps due to changes in treatment options, such as the use of hydroxychloroquine (38), and guidance for optimizing lupus pregnancies.

In IBD, even with inactive or mild disease, there tends to be higher rates of complications in pregnancy, labor, and delivery compared with the general population (39), and preterm birth is clearly associated with active disease (40). Premature delivery is one of the biggest predictors of poor postpartum outcomes that can extend from infancy into childhood, adolescence, and young adulthood (41–46). For many gastroenterologists, remission or low disease activity is considered the best possibility for a healthy pregnancy and, therefore, IBD medications are commonly continued during pregnancy.

Treatment-specific experience from an IBD cohort. The PIANO registry is a large national prospective cohort of IBD patients initiated to determine whether medication exposure during pregnancy affects pregnancy complica-

tion rates and to assess fetal and early childhood outcomes. Data are collected at intake, during each trimester, at delivery, and every 4 months for the first year of the child's life to assess maternal IBD history and disease activity, medication exposure, pregnancy and postpartum complications, and infant developmental milestones at 1 year. Offspring of drug-exposed women are compared with offspring of unexposed women with IBD during the same period. Patients are classified into 4 groups based on drug exposure between conception and delivery: unexposed (which includes steroids, aspirin, and antibiotics), those receiving azathioprine/6-mercaptopurine, those receiving biologic agents (infliximab, adalimumab, certolizumab, and natalizumab), and those receiving combination azathioprine/biologic agents (47). As of November 2013, 1,289 women have been enrolled with 1,085 pregnancies completed; these include 356 unexposed patients, 230 receiving azathioprine/6-mercaptopurine, 392 receiving biologic agents, and 107 receiving combination azathioprine and biologic agents. More patients with Crohn's disease than with ulcerative colitis (UC) have been enrolled, and there is a significantly higher rate of disease activity among UC patients compared with Crohn's disease patients. Compared with national averages, rates of Cesarean section (mostly elective) are high (43%), whereas neonatal intensive care unit (NICU) rates and general anomalies are similar. By drug exposure, adjusted for disease activity, there has been no observed increase in birth defects or other complications for azathioprine or biologic agents alone versus unexposed patients. With combination therapy, there is a statistical increase in preterm birth, possibly because these patients have higher baseline disease activity. By disease state, there has been no observed increase in complications for Crohn's disease patients, whereas UC patients receiving combination therapy have increased rates of preterm birth and low birth weight and increased NICU stays, indicating that they may have more pregnancy-related problems. Based on drug exposure, no differences have been observed in congenital malformations, height and weight of infants when adjusted for maternal age and disease activity, developmental milestones, or infection rates in babies. In contrast, although an analysis of steroid use showed no increase in infections at 4 and 12 months or in congenital anomalies, there was a 2.8-fold increase in gestational diabetes mellitus, low birth weight, and preterm birth in steroid-exposed babies compared to non–steroid-exposed babies of mothers with IBD (48).

How should we manage active autoimmune disease in pregnancy and lactation? Discussion and consensus opinion from the Reproductive Health Summit

Management of drug therapy. Uncontrolled disease activity and disease flares during pregnancy and in the postpartum period may represent the greatest risks to the outcome for both mother and fetus. The opinion among both MFM and inflammatory disease specialists at the meeting was that an unhealthy mother leads to an unhealthy pregnancy and consequently to poor pregnancy outcomes, including spontaneous abortion, prematurity, low birth weight, and longer-term issues that can extend into infancy, childhood, and adolescence. However, based on the available data, many questions remain on how to risk stratify existing treatments for use during pregnancy, and how to best manage autoimmune disease patients before, during, and after pregnancy. Moreover, it is unclear how best to improve and optimize communication of these issues to practitioners and patients.

Medication risk: guidance for use of individual medications. *High-risk medications.* Medications that are considered to be teratogenic or high risk, such as cyclophosphamide (49,50), mycophenolate mofetil (MMF) (51,52), methotrexate (MTX) (53), and leflunomide (54), should be switched several months prior to conception and avoided during pregnancy. Women of reproductive age should be given counseling on contraceptive and prepregnancy planning when taking these medications. Recently published data indicate that prepregnancy exposure to MTX (as opposed to exposure during the first trimester) does not increase the risk for fetal malformations and a washout period may not be necessary (55). There is, however, an increased risk of miscarriage and congenital anomaly with exposure to MTX during the first trimester (55). For leflunomide, medication either needs to be washed out with cholestyramine (per product label) or discontinued 2 years prior to conception. Compared with the general population, data from the OTIS leflunomide registry show no increase in adverse pregnancy outcomes among women exposed to leflunomide in early pregnancy who underwent cholestyramine washout (54).

Low- to moderate-risk medications. Given the existing data, hydroxychloroquine and sulfasalazine were considered to be compatible with pregnancy (38,56,57). In SLE, hydroxychloroquine could be continued throughout pregnancy. It is important to note that these medications are considered to be of low to moderate risk only when referring to congenital and neonatal disorders. Long-term effects on children born to mothers who were treated with these medications during pregnancy have not been well studied. Immunosuppressants such as azathioprine, 6-mercaptopurine, cyclosporine, and tacrolimus were generally considered to be relatively low risk during pregnancy, although some data suggest that they may increase the risk of small for gestational age infants and preterm premature rupture of membranes (PPROM) (58,59). Recent data also suggest that azathioprine exposure in utero potentially leads to developmental delays, although further research is still needed (60). It is difficult to determine whether it is the medications or disease activity that is causing these complications.

Use of high-dose nonsteroidal antiinflammatory drugs (NSAIDs) potentially impacts fertility (impaired ovulation and implantation), and their use should be carefully considered on a case-by-case basis in women with fertility issues. There are conflicting data on whether these medications increase the risk of spontaneous abortion, suggesting that they should be used sparingly during the first 2 trimesters. In addition, they should be discontinued after 30 weeks gestational age, due to the potential risk of premature closure of the ductus arteriosus (56).

While glucocorticoid use during the first trimester may increase the risk of oral cleft formation, this is not the case later in pregnancy (61). Clinicians should also be aware of the increased risk of gestational diabetes mellitus, hypertension, PPROM, and small for gestational age infants in pregnancies where the mother is taking glucocorticoids (62,63). Although prednisone is often the treatment of choice for management of disease activity during pregnancy for many physicians, it may be associated with higher rates of adverse pregnancy outcomes than other agents. Approximately 10% of nonfluorinated corticosteroids, such as prednisone, cross the placental barrier and reach the fetus. Therefore, if the goal is to treat the mother, the nonfluorinated form is the better option. However, if the goal is to treat the fetus, the fluorinated form is not well metabolized by the placenta, allowing for more of the drug to reach the fetus. The fluorinated corticosteroids have increased placental transfer; approximately 33% of betamethasone and 50% of dexamethasone have been detected in fetal circulation (56,64). Adverse side effects to both the mother and the fetus can result if glucocorticoids are given at concentrations >10 mg/day over a prolonged period of time. For the mother, some of the most common side effects include diabetes mellitus, hypertension, osteopenia, and increased risk of infection, whereas for the fetus, low birth weight and prematurity are most often reported. The risk for infection is also dose dependent and increases greatly when glucocorticoids are given at high dosages (≥15 mg/day) and in combination with biologic agents (64). Therefore, improved information on the safety of other disease-modifying antirheumatic drugs and immunosuppressive agents is critical for decision making.

Based on the current literature and available evidence, TNF inhibitors are considered to be compatible with pregnancy, since they do not appear to cross the placenta during the first trimester, when the risk for congenital malformation is highest (65). In women with very active disease, experts in inflammatory arthritis and MFM advise these medications to be continued during pregnancy. If they are maintained or initiated during pregnancy, it has been suggested that consideration be given to stopping most TNF inhibitors at approximately 30–32 weeks gestational age to circumvent the increased passage of these drugs across the placenta and potential immunosuppression of the newborn (66).

During pregnancy, neonatal Fc receptors (FcRn) bind the Fc portion of whole antibodies and transport them across the placenta; therefore, IgG levels in fetal circulation are positively correlated with gestational age, and highly efficient transfer in the third trimester leads to elevated IgG levels in the newborn compared with maternal levels (67,68). FcRn are not expressed in significant amounts by the placenta in the first trimester, i.e., when embryogenesis is taking place. Therefore, it is likely that there is a relatively low risk of malformations with monoclonal antibody drugs. Many TNF inhibitors (infliximab, adalimumab, golimumab, and etanercept) possess a functional Fc portion, and drug levels of infliximab and adalimumab have been shown to be elevated in cord blood at delivery compared with maternal plasma levels (66). Another TNF inhibitor, certolizumab, is a PEGylated Fab fragment that is not actively transferred across the placenta, and cord blood levels are significantly lower than maternal levels (66). The impact of this placental transfer of most TNF inhibitors on the fetus is unknown. There is, however, a potentially increased risk of infections in the newborn due to drug exposure during the third trimester. This concern is based on individual cases, such as the baby exposed to infliximab throughout pregnancy who died at 4.5 months of age of disseminated bacillus Calmette-Guérin (BCG) following BCG vaccination at 3 months (69). Therefore, the use of live vaccines (e.g., BCG, rotavirus) should be postponed in the immediate postpartum period (delay to after 5 months) in infants exposed in utero to TNF inhibitors, to allow time for passive maternal antibodies to clear. In the PIANO registry, however, among patients exposed to a biologic agent (n = 422) compared with patients not exposed (n = 617) in the third trimester, there was no increase in the rates of preterm birth, disease activity in the third trimester or to 4 months postpartum, or infections in the infant to 1 year of age. This was controlled for maternal age, preterm birth, and certolizumab use (70).

Unknown risk. Currently, there are insufficient data on biologic agents with other mechanisms of action (e.g., abatacept, tocilizumab, anakinra, rituximab, ustekinumab, and belimumab) and novel small molecule agents (e.g., JAK inhibitors or apremilast) to make risk assessments.

General management approaches and inadvertent medication exposure during pregnancy. Although beyond the scope of this study, a general treatment approach for each condition needs to be considered. Even after prepregnancy counseling, it is important to consider that inadvertent medication exposures will likely occur; therefore, rheumatologists and other specialties need contingency plans to handle them. Assessing the true potential risk of such exposure, including the particular drug and the timing of exposure (prepregnancy, early versus later trimesters), is important, as is discussing the risk fully with the patient. High-technology in utero screening to look for malformations could be helpful in informing patients about potential teratogenicity after drug exposure in individual cases, but may not identify all anomalies. Likewise, further research is needed to investigate the effect of drugs such as statins, antihypertensives, and diabetes mellitus medications that are used to treat common comorbidities in autoimmune patients.

Fertility and contraception. For patients with active disease, the importance of contraception should be discussed and emphasized with patients, including pediatric patients. This is particularly important for, but not confined to, those who are taking drugs not considered safe in pregnancy. Most oral and nonoral methods of contraception are considered low risk and appropriate to use in patients with autoimmune disease, with some caveats. Estrogen-containing contraceptives are probably associated with an increased risk of blood clotting and should be avoided in some SLE and all antiphospholipid syndrome patients. Progesterone injections, when used long term, may have an increased risk of osteoporosis. While there may be some risk of related sexually transmitted or pelvic

inflammatory diseases associated with intrauterine devices, they are generally considered an effective and low-risk contraceptive option among autoimmune disease/immunosuppressed patient populations, having been studied in some lupus populations and in human immunodeficiency virus patients without a significant safety signal (71,72).

Prepregnancy counseling, education, and planning should be available for patients of child-bearing potential. Patients who are planning a family and are currently taking treatment considered potentially toxic to the fetus should stop, or be counseled to consider stopping, and switch to safer agents. For RA, there is some evidence to suggest that patients have lower fertility than the general population, and investigations into potential infertility could be recommended earlier in these patients (31). There are potential risks to fertility associated with cyclophosphamide, in particular, and potentially with the use of high-dose NSAIDs. These issues should be considered in patients of child-bearing age. In both cases, patients should be advised of the potential risk and treated accordingly. There are limited data on in vitro fertilization and male infertility in patients with autoimmune diseases. For in vitro fertilization, there may be an increased risk of venous thromboembolism and disease flares in certain conditions such as SLE, and there may be a need to monitor these patients more frequently.

Lactation in autoimmune disease. In most cases, drug transfer to breast milk is thought to occur via diffusion rather than active secretion. Certain drug characteristics determine how they will be transferred into breast milk, including the degree of plasma protein binding, degree of ionization, lipid solubility, molecular weight, and drug kinetics. Highly protein-bound drugs are unlikely to cross to any significant degree, whereas nonionized drugs and more lipophilic and lower molecular weight agents are more likely to be transferred.

Currently, although not strictly evidence based, it is generally considered that safe milk to plasma drug concentration ratios have a value of ≤10% of the therapeutic dose for infants (or adult dose standardized by weight if infant therapeutic doses are not known). There are, however, many factors that may determine drug levels in both the breast milk and infant circulation. Premature and newborn infants (<2 months) have a greater risk of developing a high plasma drug concentration than older infants due to the immature hepatic and renal systems. Most of the breast milk is produced in a very short period prior to nursing, which makes a difference to infant drug exposure. Gastrointestinal absorption may vary; even though a drug is transferred to breast milk, this does not necessarily mean that it will be transferred to the baby's circulation, and protein-based agents such as biologic agents may be broken down by infant digestion. Only by testing drug levels can we determine how much drug is transferred to breast milk and baby. It is also important to consider that drug concentrations are not the only measure of risk. Monitoring for potential clinical effects on the baby is critical to determining the impact of breastfeeding while taking medication.

In terms of breastfeeding drug risk, agents used to treat autoimmune and systemic inflammatory disorders can be approximately categorized into 3 risk categories. The first category includes low-risk drugs that are generally considered safe to use during pregnancy, and include NSAIDs, prednisone, hydroxychloroquine, sulfasalazine, heparin, and intravenous immunoglobulin (68,73–83). High-risk drugs, i.e., those contraindicated during pregnancy, are also contraindicated during lactation, and include MTX, leflunomide, MMF, warfarin, and cyclophosphamide (84–87). For the remainder, including azathioprine (88–90), cyclosporine (91–94), tacrolimus (94–97), rituximab, abatacept, tocilizumab, belimumab, and tofacitinib, there are insufficient data and a need for further research. For TNF inhibitors, limited data suggest that very small quantities are transferred to term infants (98–105).

The benefits of breastfeeding to both infant and mother are well studied and publicized, and those benefits need to be balanced against the potential impact of medications used for the treatment of autoimmune diseases. Ultimately, breastfeeding while receiving therapy comes down to individual choice; patients should be provided with the information they need to weigh the benefit of maternal disease control versus the benefits of breastfeeding.

Communication and public education. When faced with issues of fertility and pregnancy, we need better communication between patients and physicians treating autoimmune disease and between physicians of different specialties. We can improve communication on the relative risks of drug safety versus the significant risks of uncontrolled disease during pregnancy and lactation in order to address the apparent disconnect between perceived risk (by patients and physicians) and the actual risk from drug exposure and active disease during pregnancy.

Increased collaboration between rheumatologists and other specialties (dermatology, gastroenterology) and between rheumatologists and obstetricians, MFM specialists, and family physicians, who are managing these patients specifically during pregnancy, would help address the current lack of communication between specialty providers. By bringing together experts in all of these fields, the Reproductive Health Summit is a first step toward improving that communication. However, there are many other resources that are currently underused, and there is both the opportunity and the need for rheumatology and the ACR to drive this agenda forward.

Existing resources. There are substantial existing pregnancy healthcare resources that could be promoted, of which patients and HCPs are often unaware. These include Motherisk, MotherToBaby (OTIS), "IBD & She" from the Crohn's & Colitis Foundation, the "Treating for Two" Safer Medication Use in Pregnancy Initiative at the Centers for Disease Control and Prevention (106), and the NIH's DailyMed. A useful database for information on drug safety in lactation is the LactMed.nlm.nih.gov website, maintained by the National Library of Medicine. Addition-

ally, there are many disease-specific patient organizations and publications where there is potential to co-develop risk communication tools for patients and promote information on pregnancy in autoimmune disease (e.g., Arthritis Foundation, Crohn's & Colitis Foundation of America, National Psoriasis Foundation).

Digital and social media represent a vast and varied means of communication with patients and providers that has increased in popularity in recent years. There are a number of online resources and medical apps that might help transmit relevant information to patients.

Other potential resources/actions. Repackaging the expertise and resources shared by the speakers from the Reproductive Health Summit to make them available to a wider audience could be an effective means of raising the profile of pregnancy issues in autoimmune disease to a variety of audiences. Methods of wider dissemination could include a turnkey program to be made available to all societies in related specialties, short instructional videos hosted on the websites of major societies and patient organizations, educational series and continuing medical education symposia at national and regional conferences, and preconference courses at major meetings, such as the ACR/ARHP Annual Meeting and the American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting. There may be value in creating primers for obstetricians, family physicians, and MFMs on the specific needs of patients with autoimmune and systemic inflammatory diseases, or to codevelop practice guidelines and educational bulletins in conjunction with other societies. Finally, there could be opportunities to partner with major organizations, such as the NIH and patient foundations, that may have resources and the will to raise awareness.

Discussion

Currently, there are significant unmet needs in the management of pregnancy and lactation in women with autoimmune and systemic inflammatory diseases, including a paucity of data on drug efficacy and safety and poor communication between physician specialties and between physician and patient. The desire for healthy pregnancies among our patients is a very real and pressing issue that needs to be addressed. Provision of improved prepregnancy, antenatal, and postnatal counseling for patients on issues relating to treatment and pregnancy; improvement in education and information sources for patients and physicians; new approaches to study in pregnant and lactating women; and a better understanding of existing and generation of new data on drug pharmacology and safety will all serve to improve patient management. Maximizing the use of existing information sources and developing risk communication tools for patients and physicians to promote education on pregnancy in autoimmune disorders are eminently achievable goals. Ultimately, new comprehensive systematic reviews of the existing literature and the provision of treatment guidelines for managing issues of fertility, pregnancy, and lactation in autoimmune and systemic inflammatory disorders should be considered.

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