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Implications of Changes in FDA Prescribing Information Regarding the Safety and Use of Asthma Biologics during Pregnancy

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Many lung diseases occur in women of child-bearing age and treating these conditions requires knowledge of the safety of the treatments during pregnancy as well as understanding the risks of the disease itself for the mother and the infant. An important source of this information has been the U.S. Food and Drug Administration (FDA)-approved Prescribing Information. The long-standing FDA lettered pregnancy labeling (Categories A, B, C, D, F) often provided inadequate information to apply benefit-risk considerations to gestational management decisions, especially for newer medications. The FDA revised the format of the pregnancy information provided in the Prescribing Information by instituting the Pregnancy and Lactation Labeling Rule (PLLR) on June 1, 2015. Clinicians managing pulmonary disease in pregnant women must know how to access this safety information, how to interpret it, and how to use it to determine optimal therapy for their pregnant patients.

This Perspective provides a description of the new FDA Prescribing Information format for medication safety during pregnancy and then discusses asthma, the most common pulmonary condition in pregnant women, as a use case. Specifically, we review the effects of uncontrolled or severe asthma during pregnancy, summarize the information in the Prescribing Information for currently available asthma biologics, and discuss the types of studies that provide safety information for medications during pregnancy.

The Effects of Asthma on Adverse Outcomes during Pregnancy

Studies have shown that uncontrolled or severe asthma, as assessed by symptoms, lung function, or exacerbations, is associated with an increased risk of adverse perinatal outcomes,

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especially prematurity and reduced fetal growth, compared to asthma that is better controlled or less severe (1-9). In addition, one study has linked first trimester asthma exacerbations with an increased risk of congenital malformations (10). The data in these reports do not differentiate the effects of uncontrolled asthma due to undertreatment from the effects of severe asthma that is uncontrolled despite appropriate asthma guideline-recommended care (11)

An important potential mechanism for perinatal risks is hypoxia and other blood gas abnormalities associated with uncontrolled asthma. Other possible explanations include unmeasured confounders and common pathogenetic factors linked to asthma severity. In addition, medications used to treat more severe asthma could themselves contribute to the adverse perinatal outcomes. Although results of several studies are reassuring regarding the use of inhaled corticosteroids (ICS) (12-16) and long-acting beta agonists (LABA) (15, 17-19), use of oral corticosteroids during pregnancy has been associated with increases risks of preeclampsia (20), preterm birth (1,21,22), lower birth weight (22), and oral clefts (23-25). However, results of studies to date may be confounded by the effects of uncontrolled asthma ("disease effect"), rather than reflecting the effects of the medications per se ("drug effect").

FDA Prescribing Information during Pregnancy until 2015 and after 2015

An important source of information regarding the safety of medications during pregnancy is the FDA-approved Prescribing Information. Since 1979, all prescription drugs in the U.S. were labelled with letter categories to summarize their safety during pregnancy (Table 1).

The two major problems with this system were that 1) the categorization often relied only on animal studies, and 2) even if there were existing human data, it was often not considered.

In 2015, the FDA introduced a new system referred to as the "Pregnancy and Lactation Labeling Rule" that is removing the letter ratings from all Prescribing Information. For any prescription drug marketed after June 30, 2001, the old letter categories will be replaced with structured narrative summaries in accordance with a specified timetable for phasing these in. The new label format is intended to provide more complete, balanced and clinically relevant information (Table 2).

Prescribing Information for Asthma Biologics during Pregnancy

Patients with severe asthma may require FDA-approved biologics directed at inhibiting IgE-mediated (omalizumab [approved in 2003]) or IL-5-mediated (mepolizumab [2015], reslizumab [2016], benralizumab [2017]) mechanisms of asthma pathogenesis. However, randomized clinical trials that formed the basis of FDA approvals of these medications commonly excluded pregnant women. Thus, the applicability of data regarding the safety and efficacy of these biologics when used in pregnant women is unknown.

The Risk Summary of the Prescribing Information for all of the asthma biologics includes the following statement*: "The data with [name of biologic] use in pregnant women are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as [name of biologic], are transported across the placenta in a linear fashion as pregnancy progresses;*

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therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy. In animal reproduction studies, no evidence of fetal harm was observed in [specific species and dose]." The Clinical Considerations section of the Prescribing Information for all of the biologics includes the following statement: "*In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.*"

Missing from the Prescribing Information are results of any human pregnancy safety studies. In the case of omalizumab, the one published study (26) is not included. In that study, investigators used data from a registry of 169 pregnancies to describe outcomes, including 156 live births (of 160 infants, 4 twin pairs), one fetal death, 11 spontaneous abortions, and one elective termination. The rates of major congenital anomalies (4.4%), small for gestational age (10.9%) and low birth weight infants (3.2%) were similar to general population figures, and the somewhat elevated rate of prematurity (14.5%) was consistent with findings from other studies of pregnant women with moderate to severe asthma. In the case of mepolizumab, reslizumab, and benralizumab, there are no published human data.

To adequately consider benefits and risks of the use of asthma biologics during pregnancy, human safety data are critically important. The pregnancy section of the Prescribing Information for mepolizumab does indicate that there is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to mepolizumab during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves

by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma. This contact information refers the patients to the cohort arm of VAMPSS described in detail below.

As noted above, the new Prescribing Information also has a section specifically regarding lactation. For asthma biologics, the lactation Risk Summary states the following: "*There is no information regarding the presence of [name of biologic] in human or animal milk, and the effects of [name of biologic] on milk production are not known. However, [name of biologic] is a humanized monoclonal antibody, and immunoglobulin G (IgG) is present in human milk in small quantities. If [name of biologic] is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to [name of biologic] are unknown. The development and health benefits of breastfeeding should be consi8dered along with the mother's clinical need for [name of biologic]and any potential adverse effects on the breast-fed child from [name of biologic] or from the underlying maternal condition.*" Since there are no available human data regarding the safety of asthma biologics during lactation, the only risks that can be put into the benefit/risk "equation" currently are the risks of the uncontrolled asthma (under-treated or severe asthma).

Human Studies Regarding the Safety of Medications during Pregnancy

Randomized Controlled Trials

The previous discussion highlights the need for higher quality evidence human data regarding the safety of asthma medications during pregnancy that adequately accounts for the potential adverse effects of uncontrolled asthma. A randomized controlled trial would be ideal to cleanly

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disentangle the effects of asthma from those of medications on adverse perinatal outcomes. However, randomized clinical trials of routinely-used medications (e.g., prednisone or inhaled corticosteroids) are not likely to be feasible during pregnancy. Institutional review boards are unlikely to approve studies designed to withhold medications that are commonly used in clinical practice and for which there are no medication or non-medication alternatives (27). Pregnant women may also be unlikely to participate in such studies that require withholding "standard-of-care" treatments, although some investigators have found that the majority of pregnant women would be interested in a randomized clinical trial if it could benefit their pregnancy or improve the baby's health (28). Randomized clinical trials of new medications in pregnant or lactating women have not typically been performed until there was efficacy or safety data in other patient populations first.

The FDA could require additional studies in pregnant or lactating women to support an indication in pregnant or lactating women. In April 2018, the FDA issued a draft guidance entitled "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry" (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm603873.pdf). This draft guidance outlines specific circumstances under which pregnant women should be considered for inclusion in clinical trials. However, there are at least three difficulties with randomized clinical trials in pregnant women. First, it would require randomly assigning a pregnant woman to the medication being studied in comparison to a placebo or an alternate medication. The placebo is not an option since an alternative medication would be needed to control the asthma (i.e., an active comparator trial would be required). In selected circumstances, an equally effective comparator (or at least

considered equally effective on the basis of data available at the time of the trial) may be available, such as the randomized clinical trial comparing theophylline to beclomethasone (29). However, comparisons between medications from a different class ignores the potential for heterogeneity of treatment effects based on asthma severity and phenotypes. Also, active comparator trials using a different medication from a similar class may be difficult to interpret if there is a class effect for fetal harm. Second, there is increasing concern that randomized clinical trials may have limited external validity (generalizability) to populations traditionally under-represented in clinical trials, including minorities and other vulnerable populations (30-32). Third, randomized clinical trials need to be adequately powered to provide interpretable results for specific adverse effects. Birth defects, which are among the most important adverse effects, are rare, with an estimated prevalence of 2-4% of the general population. Even the most well-known teratogens do not generally increase the overall incidence of birth defects but instead the risk of individual specific birth defects. Oral clefts, among the most common birth defects, only occur in approximately 1 out of 1,000 pregnancies (33). Thus, active comparator randomized controlled trials would have to be very large to be sufficiently powered for such key outcomes.

Observational Studies

Observational studies offer an additional source of evidence regarding the safety of medications used during pregnancy. Observational studies are those that rely on patients being treated or not treated with specific medications and comparing the incidence of adverse events between two or more groups based on medication exposure. Because observational studies

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leverage data from treatments that are occurring in "real-world" contexts, observational studies generally offer greater external validity to clinical practice than randomized clinical trials. However, observational studies are generally more prone to bias and confounding (i.e., threats to internal validity) compared to randomized clinical trials, which could limit the interpretability of study results suggesting no difference or a difference in harm between the comparator populations. Several publications, including a recent review of observational study designs to inform healthcare decisions (34), offer various strategies to limit the risk of confounding and bias in observational studies. Strategies to limit threats to internal validity include use of restriction, matching, stratification, or multivariable adjustment to address the possibility of confounding. Avoiding immortal person-time in the analyses can reduce the risk of selection biases.

When appropriately designed, a range of observational study designs can help address evidence gaps in evaluating the safety of medications during pregnancy or lactation (Table 3). Each design has distinct advantages and disadvantages (Table 3). The most comprehensive approach would be to use all of these methods to study the safety of a specific medication during pregnancy, while also attempting to control for the underlying severity and control of the asthma itself.

Vaccines and Medication in Pregnancy Surveillance System (VAMPSS)

VAMPSS is coordinated by the American Academy of Allergy Asthma and Immunology (AAAAI) and has three research arms and an independent Advisory Committee (Figure 1). Funding has

been provided by government agencies (e.g. Biomedical Advanced Research and Development Authority and the Agency for Healthcare Research and Quality) and individual pharmaceutical companies to employ a range of observational study designs. The prospective cohort study, conducted by the MotherToBaby research center at the University of California, San Diego, recruits primarily through the MotherToBaby network, a North American-wide network of university or hospital-based services in existence since 1979 which provide risk counseling to 80-100,000 pregnant women and health care providers per year. However, direct to provider recruitment is also conducted through professional organizations and direct to patient recruitment through social media. Major outcomes include spontaneous abortion, preterm delivery, pre and postnatal growth deficiency, and birth defects overall.

The case-control study, conducted by the Slone Epidemiology Center at Boston University, provides birth defects surveillance (specific congenital malformations) and exposure prevalence for drugs available before November 30, 2015. This study identifies infants with specific major malformations and infants without malformations at a network of birth hospitals and tertiary hospitals and via state-based surveillance programs. Although this arm is not currently enrolling new patients and thus cannot capture exposure to asthma biologics, it can evaluate the relationship between birth defects and asthma itself as well as other asthma medications, on which any risks due to asthma biologics will be superimposed.

The database retrospective cohort study, using Medicaid and commercial databases, is conducted by the Pregnancy Research Group at Harvard University. This study captures a wide range of study outcomes including preterm delivery, prenatal growth deficiency, and specific congenital malformation groups. The Medicaid database captures approximately 2.8 million

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pregnancies, while the Marketscan commercial database captures 604,420 pregnancies. The research group has developed algorithms for outcomes with high positive predictive values compared to manual review of hospital records.

The final component of VAMPSS is the independent Advisory Committee, which reviews study protocols, data output, and manuscripts to be submitted for publication. The committee consists of government (CDC, NICHD) and professional organization (AAP, ATS, ACOG, SMFM) representatives as well as a consumer representative and an independent biostatistician (Table 42).

Conclusion (Table 5)

Managing pulmonary diseases during pregnancy is a challenge regarding both control of the disease and optimizing fetal outcomes. The new pregnancy section of the FDA Prescribing Information is intended to help clinicians make management decisions in pregnant patients. VAMPSS was developed to provide safety information on the wide range of vaccines and medications taken by pregnant women, including asthma biologics.

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Table 1. Previous FDA Prescribing Information Pregnancy Categories

Category	Definition	Asthma Examples
A	Animal studies and "adequate and well-controlled studies in pregnant women" revealed no adverse effects	None
B	Animal studies revealed no adverse effects, but human studies have not been performed	Cromolyn, montelukast
B	Animal studies revealed adverse effects, but adequate human data were reassuring	Budesonide
C	Human studies not performed, and animal studies were either not reassuring or not performed	Most asthma medications
D	Human data suggest adverse effects, but benefits of use may outweigh risk.	None
X	Human data suggest adverse effects, but benefits of use do not outweigh risk	None

Table 2. New FDA Pregnancy and Lactation Labeling Rule (PLLR) Prescribing Information Format

Section 8.1. Pregnancy (includes labor and delivery)

Pregnancy registry if applicable

Risk Summary: The known risks in the context of the background risk

Clinical Considerations: The medical/disease factors that should be considered such as the impact on pregnancy outcome of under-treatment or no treatment of active disease

Data: The data that support the risk summary

Section 8.2. Lactation

Risk Summary: The known risks

Clinical Considerations: Minimizing exposure or monitoring for adverse reactions

Data: the data that support the risk summary

Section 8.3. Males and Females of Reproductive Potential

Pregnancy testing

Contraception

Infertility

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Table 3. Advantages and disadvantages of various study designs for the evaluation of the safety of medications during pregnancy

Design	Advantages	Disadvantages
Prospective cohort	Minimizes recall bias Captures actual exposure (patient report) Captures potential confounders by direct patient contact Can evaluate multiple outcomes Outcomes can be validated by record review	Often does not include a concurrent non-exposed control group Not population-based (participation bias) Lacks power for specific birth defects Possible bias due to loss to follow-up
Case-control	Outcome typically based on medical record Has power for specific birth defects Captures actual exposure (patient report) Captures potential confounders by direct patient contact Can evaluate multiple exposures Can be population-based	Susceptible to recall bias Susceptible to selection bias Limited outcomes (typically birth defects and pre-term birth)
Database retrospective cohort	Large sample size Captures multiple outcomes, including specific birth defects Population-based	Captures dispensations, not actual exposure (potential for misclassification bias) Outcomes based on encounter or billing coding Some confounders not captured

Table 4. Current Members of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) *Advisory Committee*

Organization	**Name of representative**
Centers for Disease Control (CDC)	Margaret Honein, PhD, MPH (Chair)
American Academy of Pediatrics	Robert A. Saul, MD
American Congress of Obstetricians and Gynecologists (ACOG)	Alison Bryant Mantha, MD
American Thoracic Society (ATS)	Jerry A. Krishnan, MD, PhD
Biostatistician	M. Alan Brookhart, PhD
Consumer Representative	Elizabeth Conradson Cleary, JD, MA
National Institute of Child Health and Human Development (NICHD)	James L. Mills, MD, MS

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Table 5. Summary of Key Points from this Article

**In 2015, the FDA introduced the Pregnancy and Lactation Labeling Rule, a new system that removed the pregnancy letter ratings from all Prescribing Information and is replacing them with a narrative summary of animal and human gestational safety data and clinical considerations. **The revised Prescribing Information highlights a critical need for high quality human safety data to inform the use of asthma therapies, including biologics, during pregnancy.

**Randomized controlled trials are not likely to address the evidence gaps due to ethical, feasibility, and statistical power considerations.

**Several types of observational study designs exist, each with particular strengths and weaknesses

**The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) combines three complementary observational study designs (prospective cohort, case-control, and database retrospective cohort) to identify risks and safety of vaccines and medications used during pregnancy

**Clinicians can refer pregnant women who have severe asthma (with or without exposure to asthma biologics) to VAMPSS by having them call 1-877-311-8972 or visiting www.mothertobaby.org/asthma

Figure Legend:

Figure 1. The structure of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

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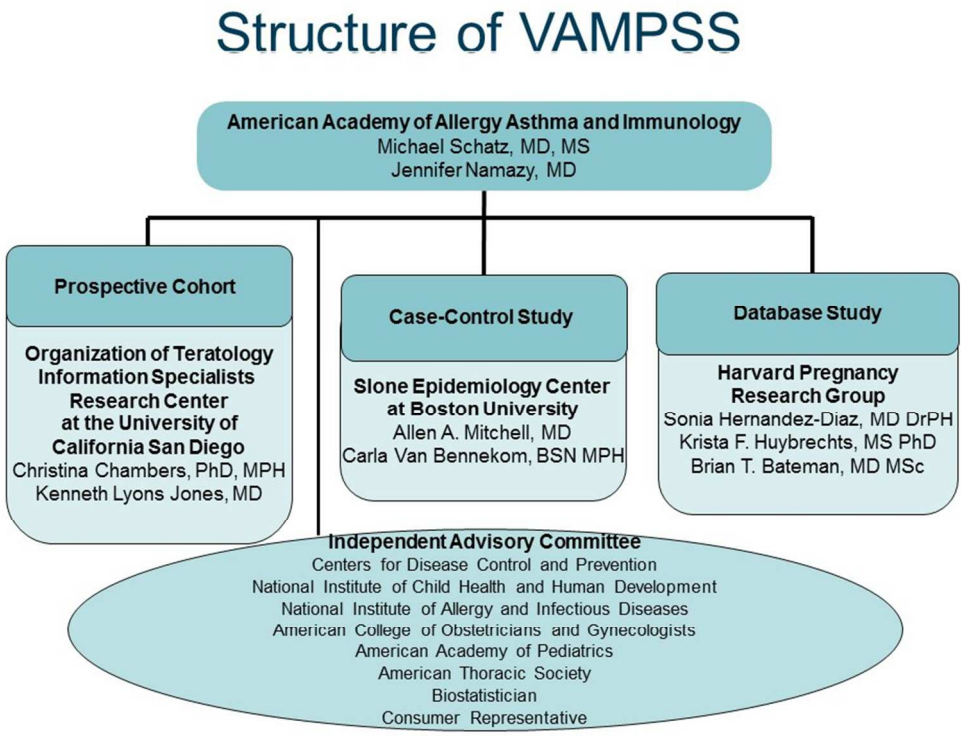

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