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The safety of asthma medications during pregnancy and lactation: Clinical management and research priorities

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Abstract

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Asthma is one of the most common underlying diseases in women of reproductive age that can lead to potentially serious medical problems during pregnancy and lactation. A group of key stakeholders across multiple relevant disciplines was invited to take part in an effort to prioritize, strategize, and mobilize action steps to fill important gaps in knowledge regarding asthma medication safety in pregnancy and lactation. The stakeholders identified substantial gaps in the literature on the safety of asthma medications used during pregnancy and lactation and prioritized strategies to fill those gaps. Short-term action steps included linking data from existing complementary study designs (US and international claims data, single drug pregnancy registries, case-control studies, and coordinated systematic data systems). Long-term action steps included creating an asthma disease registry, incorporating the disease registry into electronic health record systems, and coordinating care across disciplines. The stakeholders also prioritized establishing new infrastructures/collaborations to perform research in pregnant and lactating women and to include patient perspectives throughout the process. To address the evidence gaps, and aid in populating product labels with data that inform clinical decision making, the consortium developed a plan to systematically obtain necessary data in the most efficient and timely manner.

Keywords

Asthma medication; lactation; pregnancy

Asthma affects 3% to 10% of women of reproductive age in the United States and is one of the most common underlying health conditions that can complicate pregnancy and lactation.[1] In addition, there are substantial inequities in the burden of asthma in pregnancy by race and ethnic group.[2] Asthma is associated with increased risk of maternal morbidity and perinatal complications including spontaneous abortion, gestational diabetes, hypertensive disorders of pregnancy, preterm delivery, fetal growth restriction, antepartum and postpartum bleeding, and congenital anomalies.[3–5] The mechanisms underlying these are likely multifactorial, but an important element appears to be asthma control. Unfortunately, asthma medication nonadherence is common in pregnancy and has implications for disease activity.[6–10] Many women report that concerns about medication safety are reasons for discontinuing appropriate therapies.[11] The maternal need for medication is also frequently cited as a reason for early termination of breast-feeding, based on lack of data confirming safety for the infant.[12]

In 2015, the US Food and Drug Administration (FDA) introduced the Pregnancy and Lactation Labeling Rule, a new system that removed the pregnancy letter ratings (A, B, C, D, X) from all prescribing information for drugs approved after June 30, 2001, replacing the letters with a narrative summary of animal and human gestational safety data and clinical considerations. The intent is to provide the prescriber and patient with important safety and risk information about the use of a prescription product during pregnancy and lactation. More than 1500 drug labelings have been converted to the Pregnancy and Lactation Labeling Rule format since 2015. However, there has been a growing awareness that many prescription products lack good quality clinical pregnancy and lactation safety information, including most asthma medications. The revised prescribing information highlights a critical

need for high-quality human safety data to inform the use of asthma medications during pregnancy and lactation.

WORKSHOP STRUCTURE AND OBJECTIVES

In November 2019, the National Heart, Lung, and Blood Institute and the Office of Research on Women's Health in the Office of the Director, of the National Institutes of Health, and the US Food and Drug Administration Office of Women's Health hosted a workshop titled "The Safety of Asthma Medications during Pregnancy and Lactation: Research Priorities and Methodology." A group of key stakeholders across multiple relevant disciplines was invited to take part in an effort to prioritize, strategize, and mobilize action steps on gaps in knowledge regarding asthma medication safety in pregnancy and lactation. Stakeholder representatives included academic researchers, obstetric/maternal-fetal medicine specialists, regulatory and other federal agencies, the pharmaceutical industry, clinicians, patient advocacy groups, and patients. The conference was developed in response to recommendations of the Department of Health and Human Service's Task Force on Research Specific to Pregnant Women and Lactating Women pursuant to the 21st Century Cures Act. The workshop proceedings are summarized in this article.

WORKSHOP PROCEEDINGS

Substantial gaps in the literature on the safety of asthma medications used during pregnancy and lactation were identified and strategies prioritized to fill those gaps. Recommended short-term actions include linking data from existing complementary study designs (US and international claims data, single drug pregnancy registries, case-control studies, and coordinated systematic data systems). Proposed long-term actions include creating an asthma disease registry, incorporating the disease registry into electronic health record systems, and coordinating care across disciplines. The stakeholders also prioritized establishing new infrastructures and collaborations to increase research in pregnant and lactating women and to include patient perspectives throughout the process.

Existing safety data and gaps

Recommended pharmacologic management of asthma during pregnancy follows a stepwise approach (Table I), based on the determination of asthma control. Medication is typically stepped up for uncontrolled asthma, after issues such as avoidance of environmental triggers, inhaler technique, and medication adherence are optimized. The available safety data for asthma medications in pregnancy are generally reassuring for several older and commonly used asthma medications, such as inhaled corticosteroids and short-acting beta agonists (Table II).

However, many older and most newer medications, such as asthma biologics, have limited epidemiologic studies on human pregnancy available. Despite lack of such data, current recommendations are to continue biologics during pregnancy, especially if a woman has shown a significant response to treatment before pregnancy.[47] In addition, to minimize known maternal and fetal risks for poorly controlled asthma in pregnancy, providers may

consider starting a biologic in a pregnant woman with severe asthma at risk for asthma exacerbations or need for oral corticosteroids.

Breast-feeding provides numerous health benefits for the mother and infant and is the recommended primary source of nutrition throughout the first 6 months of life and to be continued throughout the first year of life with complementary foods. However, it is estimated that 50% of postpartum women require the use of 1 or more prescription medication, including those to treat asthma.[48] Multiple factors should be considered when determining drug compatibility with breast-feeding including chemical properties, dose/exposure/toxicity relationship, chronicity of exposure, health status and developmental stage of the infant, pharmacogenomics, and health status of the mother. Resources used to inform compatible medication use in the mother while breast-feeding include *LactMed, Breastfeeding Handbook for Physicians, Hale and Rowe's Medication and Mother's Milk, Briggs and Freeman's Drugs in Pregnancy and Lactation*, and the FDA-approved labeling. However, the utility of these resources to inform medication safety during lactation for any indication, including asthma, is limited by the lack of informative data. As shown in Table II with data drawn from *LactMed*, for most asthma medications used during lactation, there are no published human data.[49]

Study methodologies and sources of data

Existing pregnancy registries.—Single drug registries are designed to capture data on exposed pregnancies and outcomes for new or existing medications, and have been a commonly used method for detection of early pregnancy safety signals for several decades. The typical design of a pregnancy registry is a convenience sample of pregnant women who have had exposure to the medication of interest and who provide informed consent to participate in the registry. Follow-up data collection is carried out to determine rates of major congenital malformations overall, and to capture information on preterm delivery, infant birth size, and pregnancy losses. Some registries use an external comparator group, and others are compared with an internal unexposed group. Advantages of pregnancy registries are that they can be initiated as soon as a new drug is marketed, can provide early signal detection for any unusual pattern of birth defects or other adverse pregnancy outcomes, and can capture data on a range of adverse outcomes. In addition, pregnancy registries are uniquely well positioned to capture information on lactation and the use of medications continued into the postpartum period. In many registries, the mother herself reports on medications, because medications recorded in medical records may not always reflect actual usage.[50] In addition, the mother is the best source of information on relevant covariates such as folic acid supplementation, and tobacco and alcohol use. Limitations of pregnancy registries include that they rely on a volunteer sample, which may introduce selection bias, require informed consent, may not be representative of all pregnant women exposed to the drug, and are typically limited by small samples sizes. As a result, pregnancy registries are usually underpowered to examine risks for specific birth defects unless the magnitude of the risk is very large, and registries may take more than 10 years to accrue even modest sample sizes (Table III).

Databases.—In the postmarketing setting, population-based automated health care databases, including national registries (eg, Nordic registers), administrative claims databases (eg, Medicaid), and electronic health record databases (eg, Clinical Practice Research Datalink), are standard sources of information for drug safety studies.[51–55] They provide prospectively collected data for large populations, and the clinical care represented in these databases reflects the real world.[56] Although the cost and time of working with health care data sets can be high, this approach is usually less costly than collection of data directly from women and providers for a specific study (Table III).

Some automated health care databases have substantial limitations, for example, incomplete information on birth weight, gestational age, maternal smoking, or use of nonprescription drugs.[57,58] When the specific drug of interest is used by a small fraction of pregnant women, as new medications often are, even these large cohorts are constrained in their number of exposed subjects. Multisite collaborations such as the Medication Exposure in Pregnancy Risk Evaluation Program,[59] now part of the Sentinel network,[55] or the International Pregnancy Safety Study[60] consortium can offer larger sample sizes. For asthma in particular, one limitation of databases is the underrecording of mild asthma because patients with no clinical encounters or prescriptions for asthma will not be identified as subjects with asthma. However, claims-based asthma definitions validated by chart review have had high specificity and a positive predictive value of around 95%.[59,61] Although ascertainment of outcomes from coded claims can also lead to misclassification (eg, ruleout diagnosis codes may generate false positives), the most common pregnancy outcomes of interest are also typically identified through validated algorithms with moderate or higher positive predictive value.[62,63] For example, Andrade et al[59] reported a positive predictive value of 71% for congenital heart defects and 87% for preterm birth. Most concerning is that drug utilization is based on filled prescriptions, which does not guarantee that the medication was actually taken, therefore potentially overestimating and misclassifying exposure. Moreover, treatments used may be missed if prescriptions were filled before the exposure window (eg, an old prescription still being used). The observed irregular prescription dispensing patterns in database studies support the difficulties of assessing asthma treatment use based on pharmacy claims.[61,64]

Case-control studies.—Population-based case-control studies can make a unique contribution to understanding the safety or risk of asthma medication use in pregnancy by providing an efficient study design to detect increases in specific serious birth defects. Since 1998, the US Centers for Disease Control and Prevention has funded and coordinated 2 major case-control studies of birth defects: the National Birth Defects Prevention Study, which was succeeded by the Birth Defects Study to Evaluate Pregnancy Exposures.[65–67] Because individual types of birth defects are relatively rare, this study design is most effective when implemented in multiple sites and for multiple years. These case-control studies are built on a foundation of population-based birth defects surveillance, meaning that they represent all residents of a defined geographic region. They include major birth defects of unknown etiology, with a goal of identifying modifiable risk factors, and have also been extended to include all stillbirths in some sites. These case-control studies use maternal interviews to assess exposures including dates of exposure relative to pregnancy timing and

include an assessment of use of asthma medications. A major strength of this approach is that it relies on maternal report of actual exposure and does not rely on prescribing or dispensing records, and the maternal interview collects important data on additional factors such as maternal smoking, substance use, travel history, and illnesses (Table III). Limitations of case-control studies include that participants selected from a pool of eligible cases and controls must volunteer to enroll, require informed consent, may not be representative of all pregnant women exposed to the drug, are challenged by control selection and recall biases, which can misclassify exposure status, and assess a limited number of outcomes. Moreover, they are usually underpowered to examine risks for infrequently used drugs unless the magnitude of the risk is very large.

Surveillance systems.—The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) was initiated in 2009 to be a national systematic postmarketing surveillance system combining multiple study designs. The goals were to (1) identify as early as possible the circumstances in which a drug or immunization causes harm and (2) to provide reassuring data for those drugs and immunizations (likely the majority) that are safe during pregnancy. The VAMPSS is coordinated by the American Academy of Allergy, Asthma, and Immunology and includes 3 research arms and an independent Advisory Committee.[68–71]

The 3 complementary VAMPSS research arms represent examples of each of the approaches described above. One arm is a prospective cohort single drug registry design conducted under the MotherToBaby Pregnancy Studies program at the University of California San Diego. This arm provides information on multiple outcomes, including spontaneous abortion, preterm delivery, pre- and postnatal growth deficiency, and birth defects overall. The second is a database arm using Medicaid and commercial claims databases. Outcomes assessed in this arm include preterm delivery, prenatal growth deficiency, and specific congenital malformation groups. The Pregnancy Research Team at Harvard University conducts this study component. The third research arm is the Birth Defects Study, a case-control birth defects surveillance design conducted by the Slone Epidemiology Center at Boston University, which assesses specific congenital malformations and exposure prevalence. Although the Birth Defects Study does not have information regarding drugs marketed after November 2015, the VAMPSS will be collaborating with the 2 Centers for Disease Control and Prevention case-control surveillance studies, which are described above, and all 3 arms have a focus on the safety of asthma medications in pregnancy. This approach takes advantages of the strengths of each design, and one design’s strengths compensates at least to some degree for another design’s limitations (Table III).

Regulatory perspective

Since the implementation of Pregnancy and Lactation Labeling Rule, FDA has sought and received input on improving the communication of information under the rule. This lack of clinical safety information is due in part to the long-standing, standard practice of excluding pregnant and lactating women from clinical trials. Systematic exclusion of pregnant and lactating women from trials due to concern for fetal safety has prevented the earlier collection of needed safety information.[72,73] FDA has been working to increase the

appropriate enrollment of pregnant patients in clinical trials, and published a draft guidance in 2018 titled “Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials.”[74]

FDA has relied primarily on collection of human safety data on a prescription product’s use during pregnancy after the drug has been approved. After the medication is marketed, case reports help to generate hypotheses about a potential increased risk for malformations or other adverse pregnancy outcomes. However, these reports are generally inadequate by themselves to support labeling or pregnancy risk information for prescribers because they do not allow for estimation of the incidence of the finding, and they tend to be biased toward reporting of adverse outcomes. Under the Food and Drug Administration Amendments Act (2007), FDA may require companies to conduct postapproval studies, such as pregnancy safety studies.[56] In 2019, the FDA published the Postapproval Pregnancy Safety Studies Guidance, which discusses 3 approaches to postmarketing data collection in pregnant women: pharmacovigilance, pregnancy registries, and studies using electronic health care data, each of which can provide important information for product labeling.[75] In each of these approaches, there are asthma-specific challenges in producing data appropriate for the labeling. These include attention to appropriate measurement of asthma severity and symptom control in women who are treated with the medication as well as valid comparator groups.

In addition to these FDA guidances related to pregnancy, in 2019, FDA published a guidance titled “Clinical Lactation Studies: Considerations for Study Design.” This guidance provides new recommendations related to the conduct and analysis of clinical lactation studies.[76] These efforts are part of FDA’s overall efforts in addressing the need for data collection in pregnant and lactating women.

Pharmaceutical company perspective

When developing a new medicine, pharmaceutical companies, in conjunction with regulators, use nonhuman data (eg, animal and reproductive toxicology studies) to evaluate any potential reproductive effects of a medication. These studies may not predict human outcomes and may be challenging for a clinician to use to inform patient care. The first human exposure data in pregnancy may come from clinical trials for a new medication. However, pregnant women have been typically excluded from trials, and trials are usually not designed to study pregnancy outcomes. Therefore, the numbers of exposed pregnancies are small, and important relevant confounding information is not always collected.

After marketing, the pharmaceutical company conducts pharmacovigilance, which includes spontaneous reporting and can include monitoring for exposure counts from health care databases to determine the prevalence of the new medication’s use among pregnant women. These data can inform the feasibility of conducting postmarketing safety studies, when deemed necessary, using 1 or more of the various approaches described above. If postmarketing studies are conducted, they need to be well designed to achieve adequate sample size, evaluate a range of adverse outcomes including nonlive births, incorporate systematic and validated collection of exposure and outcomes, include an appropriate comparison group, be representative of a generalizable population, and not be limited by

self-referral bias or losses to follow-up. Such studies, especially those for asthma medications, should also have the ability to assess confounding by indication, disease severity, dose and duration, and other factors and comorbidities that could be related to the outcomes. These strategies were supported by the stakeholders. Well-conducted and well-designed postmarketing studies can provide robust effect estimates of an association between medication and adverse pregnancy outcomes, which may be informative for the pharmaceutical company's pregnancy labeling.

Addressing evidence gaps

Among the challenges of single drug pregnancy registries described above are the difficulties in raising and maintaining awareness among clinicians and patients about the existence of a registry for a specific medication. In the case of asthma, several distinct registries, even if they meet sample size goals, are inefficient and unlikely to be individually adequate to provide definitive evidence of risk or safety. A multiproduct, disease-based approach can help overcome this limitation.

An example of a successful multiproduct registry is the Antiretroviral Pregnancy Registry (APR). The APR is a voluntary, international, prospective exposure-registration cohort study designed to assist clinicians and patients in weighing potential risks and benefits of HIV treatment during pregnancy. Its objectives are to provide any early warning signals of major teratogenicity, to estimate prevalence of major birth defects and compare to prevalence in the general population, and to supplement preclinical, clinical, and epidemiological study data. The APR was established in 1989 and has been used to address FDA postmarketing commitments or requirements for the 28 sponsoring manufacturers. Currently, the APR monitors prenatal exposures to 164 drugs used for HIV treatment and prevention. The APR has outcomes of more than 20,000 prospective enrollments from 70 countries (78% are from the United States).

The APR uses multiple levels of analysis: overall, for each drug class, and at the individual drug level. Comparisons are made internally based on timing of exposure and externally to 2 background reference groups. The APR uses a Scientific Advisory Committee that reviews the data and forms an independent consensus statement.[77]

Despite their complexity, multiproduct, disease-based registries such as the APR have distinct advantages, as shown in Fig 1, including efficiency, interpretation, and enhanced/facilitated recruitment. Also shown in Figure 1 are some challenges. In addition, as with any study sample, those pregnancies included in a disease-based registry may not represent the entire range of exposed women. As a recent example, a signal of concern for a antiretroviral drug, dolutegravir, was identified in a Botswana sample but the same signal was not evident in the APR.[79] However, the return on investment for evaluating safety of multiple products used for the same or similar indications compares favorably to other alternative approaches and would be amenable to a disease state such as asthma in pregnancy and lactation.

Research networks

The Maternal Fetal Medicine Unit (MFMU) network was established in 1986 and has been continuously funded by the *Eunice Kennedy Shriver* National Institute of Child Health and

Development to facilitate well-designed clinical trials in maternal fetal medicine and obstetrics. Over the years, the MFMU network has completed more than 50 studies (more than 30 randomized trials) that have provided an evidence base for obstetric practice. These have included studies specific to maternal conditions such as asthma, diabetes, and thyroid disorders; preterm birth studies aimed at improving outcome, prediction, and prevention; labor management, including assessment of adjuncts to fetal heart rate monitoring and assessment of vaginal birth after cesarean; and studies of fetal growth, stuck twins, and delivery timing.

The strengths of using a network such as the MFMU for clinical research include the use of a common protocol, an independent data center, availability of large populations (>120,000 deliveries/y), long-term follow-up, nimbleness to address pressing issues (such as H1N1), and cost-effectiveness by leveraging the infrastructure to support numerous trials simultaneously. The MFMU network has been an important resource for the study of the safety of asthma medications in pregnancy. For example, 1 MFMU study provided safety information for short-acting beta agonists, inhaled corticosteroids, and theophylline in a cohort of 2123 pregnant asthmatic women.[15]

Similar to the MFMU, the *Eunice Kennedy Shriver* National Institute of Child Health and Development's Pediatric Trials Network is sponsored by *Eunice Kennedy Shriver* National Institute of Child Health and Development and represents an alliance of clinical research sites cooperating in the design and conduct of pediatric clinical trials. The Pediatric Trials Network has recently applied its methodology to study drug exposure in lactating women and their breast-fed infants. The objective of the Commonly Used Drugs During Lactation and Infant Exposure (clinicaltrials.gov NCT03511118) trial is to characterize the pharmacokinetics of understudied, off-patent drugs administered to lactating women receiving these medications per standard of care as prescribed by their treating caregiver. To understand drug transfer into breast milk and subsequent infant exposure, biological samples are collected from lactating women (blood and expressed breast milk) and infants (blood). Ideally, all 3 matrices are provided for each mother-infant pair at multiple time points. However, to be enrolled in the study, a mother-infant pair only needs to provide 1 breast milk and 1 infant plasma sample. Convenience sampling techniques are used by collecting biological samples during routine lab draws at clinic visits and hospitalization whenever possible. During the first year, this trial enrolled more than 500 mother-infant pairs on 10 commonly used medications. As drug cohorts fill, new medications of interest will be added to the trial. The data collected through this initiative will provide valuable pharmacokinetics, dosing, and safety information that will be appropriate to include in the product labels to inform clinicians and patients.

Incorporating data into clinical guidelines

Clinical practice guidelines are critical to establishing evidence-based standards to inform decision making by patients, caregivers, clinicians, payers, policymakers, and other stakeholders. There is a scarcity of information in clinical practice guidelines for the management of asthma in individuals who are pregnant or lactating. To be useful and trustworthy, the development of guidelines should follow best practices and be developed in

concert with relevant professional groups such as The American College of Obstetricians and Gynecologists, the American College of Physicians, and the American Thoracic Society. In 2011, the National Academy of Medicine (previously known as the Institute of Medicine) published a seminal report about 8 standards that today are considered the bedrock of "trustworthy guidelines"[80]: (1) establishing transparency in the methods; (2) managing conflicts of interest; (3) composition of guideline development groups; (4) systematic reviews to synthesize the evidence; (5) rating the strength of recommendations; (6) articulating the recommendations; (7) external review of draft guidelines; and (8) updating the guidelines as new evidence is identified.

The American Thoracic Society adheres to these standards in the development of its official guidelines, and starting in 2005, has been using the "Grading of Recommendations, Assessment, Development and Evaluations" (GRADE) framework for developing and presenting evidence summaries and transforming the evidence to clinical recommendations.[81] GRADE recognizes the importance of all the available evidence, including the trade-offs inherent to relying on randomized clinical trials. GRADE encourages the integration of evidence from randomized clinical trials, observational study designs about treatment effects, and expert opinion. GRADE also takes into account patient values and preferences; balance between benefits and harms; burden of treatments on patients, providers, and society due to resource requirements; and feasibility, acceptability, and impact on equity. Recommendations using the GRADE framework are worded as "strong" in cases in which there is certainty that desirable effects of intervention substantially outweigh undesirable effects and that virtually all well-informed patients would want the intervention, or "weak" when there is uncertainty, and when most well-informed patients would want the intervention, but a substantial minority of patients may not. The standardization of wording to support clinical decision making will facilitate communication between decision makers. In addition, the GRADE approach to formulating recommendations highlights the importance of shared decision making, irrespective of the quality of evidence to support a course of action. Unfortunately, there are no GRADE-based guidelines available for the management of asthma and pregnancy, but it is hoped that such guidelines could be developed in the future on the basis of more robust data using methods described in this report.

Patient engagement

Diverse patient involvement is essential at every stage of research on the safety of asthma medications during pregnancy and lactation. Partnering with patient advocacy and other community groups at every step can engage potential study participants and ensure that the study design elements are responsive to patient concerns and are adequately representative of the population. A systematic review of strategies for disseminating recommendations or guidelines to patients found that diverse patient participation in the entire process is one of the most important keys to success.[82] However, support and training for researchers and patients alike is necessary for that patient involvement to be successful.[82,83] Diverse patient involvement in developing participant materials that use best practices in health literacy can help ensure successful patient engagement in research studies. The inclusion of trained and diverse patient advisors can increase participant's comfort level with the research process as

well as increase knowledge of their health condition. Participants in the PCORI-funded *Training Patients with Asthma to Understand and Participate in Patient Centered Outcomes Research* demonstrated a 10% increase in correct research-related knowledge and a 16% average increase in correct general asthma information.[84] Patients may also benefit from peer support. The *2019 Perceptions and Insights* study by the Center for Information and Study on Clinical Research Participation found that 75% of survey respondents (n = 12,451) overall indicated interest in discussing research participation with their peers in an online patient community.[85]

CONCLUSIONS

Asthma is one of the most common underlying medical conditions complicating pregnancy and lactation. As a result of this conference, a multistakeholder consortium on asthma medications in pregnancy and lactation has been developed. To address the evidence gaps and aid in populating product labeling with data that inform clinical decision making, the consortium has developed a plan to systematically obtain necessary data in the most efficient and timely manner. Existing data on the effects of asthma and asthma medications on pregnancy and the infant can be used to formulate current management guidelines. Therefore, the consortium recommends the development of multisociety guidelines with the support of the US federal government for the evaluation and management of asthma during pregnancy and lactation that adheres to the “trustworthy” standards developed by the National Academy of Medicine. Guidelines that use National Academy of Medicine standards would not only offer recommendations for patients, caregivers, and health care providers at the point of care but also systematically highlight specific evidence gaps that merit further research.

However, even with the development of management guidelines, many knowledge gaps remain regarding the safety of asthma medications during pregnancy and lactation, particularly for newer medications. A number of perspectives must be considered relative to obtaining and disseminating the needed information, including those of patients, clinicians, pharmaceutical companies, and regulators. Various study methodologies exist to study the safety of medications during pregnancy, each with strengths and weaknesses. An asthma disease-based registry approach along with the coordinated use of additional complementary methodologies would seem to be the most productive way forward. Ultimately, the collaboration of all these stakeholders using traditional and novel approaches to collection of safety data may help patients with asthma who need treatment during pregnancy and lactation.

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Abbreviations used

APR	Antiretroviral Pregnancy Registry
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
MFMU	Maternal Fetal Medicine Unit
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

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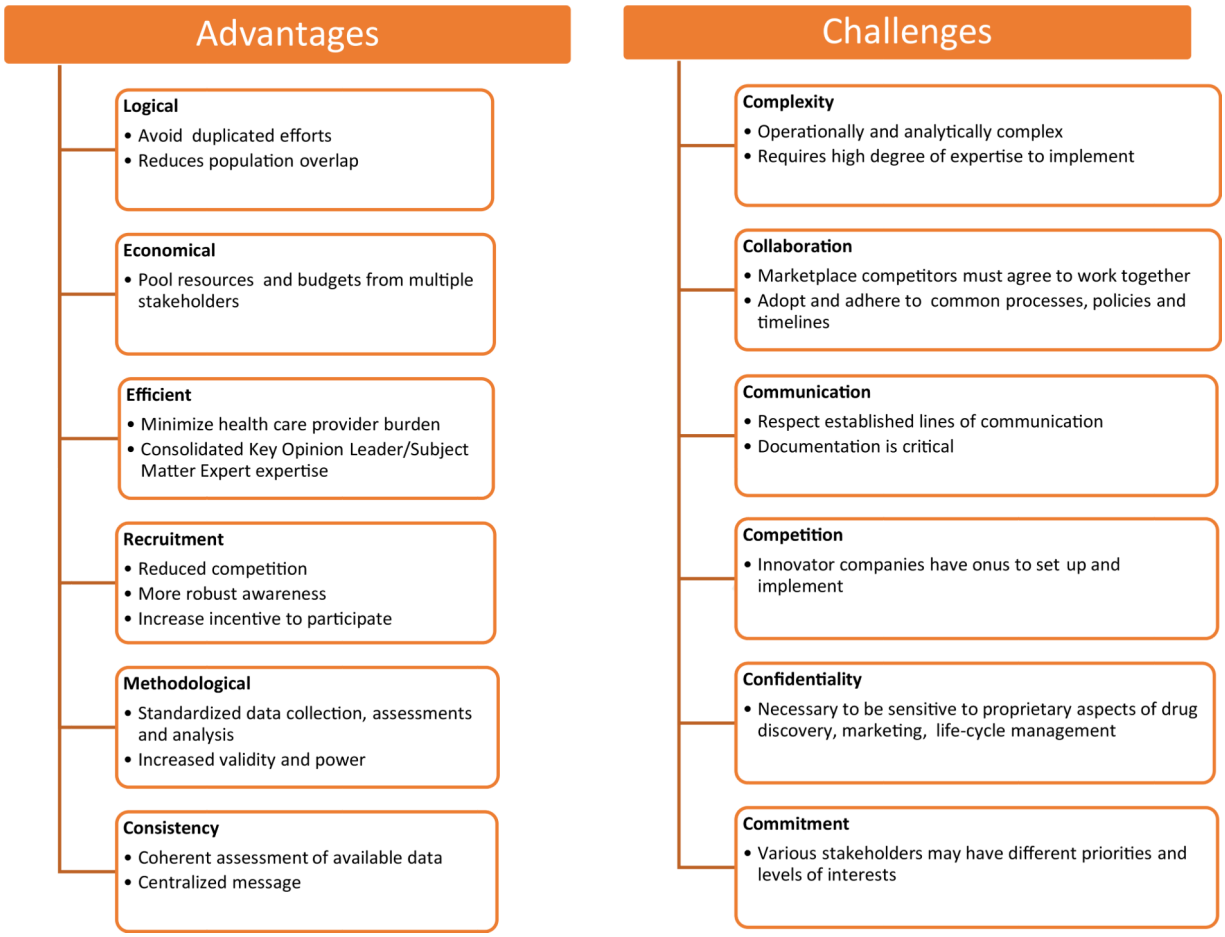

FIG 1.

Advantages and challenges of conducting multiproduct, disease-based registries.[78]

TABLE I.

Steps in asthma therapy during pregnancy

Step	Preferred controller medication	Alternative controller medication
1	None	—
2	Low-dose ICS	LTRA, theophylline, or cromolyn
3	Medium-dose ICS or low-dose ICS plus LABA	Low-dose ICS plus LTRA or theophylline
4	Medium-dose ICS plus LABA	Medium-dose ICS plus either LTRA or theophylline
5	High-dose ICS plus LABA	Medium-dose ICS plus LABA plus tiotropium; consider adding omalizumab for patients with allergy or adding other asthma biologics (anti–IL-5, anti–IL-5Rα, anti–IL-4Rα) for appropriate candidates
6	High-dose ICS plus LABA plus oral prednisone	Consider adding omalizumab for patients with allergy or adding other asthma biologics (anti–IL-5, anti–IL-5Rα, anti–IL-4Rα) for appropriate candidates

ICS, Inhaled corticosteroid; *LABA,* long-acting β-agonist; *LTRA,* leukotriene receptor antagonist.

There are no randomized clinical trials of asthma biologics that intentionally included pregnant women.

Data modified from Schatz and Dombrowski.[13]

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TABLE II.

Human pregnancy summary safety data for selected asthma medications

Medication	Major birth defects	Other birth outcomes	Evidence gaps and recommendations	Lactation
Short-acting beta agonists (any, primarily albuterol)	No increase in major birth defects over expected among 1090 albuterol-exposed pregnancies in a claims database.[14] No increase in major birth defects in 1753 albuterol-exposed pregnancies compared with other asthmatic pregnancies.[15] Modest increased risk in isolated cleft lip or cleft palate (odds ratios from 1.65 to 1.79) in albuterol-exposed pregnancies in case-control study of 2711 cases of oral clefts and 6482 controls.[16] Several additional studies have suggested modest increased risks (odds ratios, <3) for specific birth defects such as any cardiac or gastroschisis, esophageal atresia, or omphalocele[17–19]	No increase in preterm delivery, low birth weight, or small-for-gestational-age infants in 1828 pregnancies exposed to short-acting beta agonists compared with other asthmatic pregnancies[15]	First patented in 1972, albuterol is one of the most commonly used asthma medications. Despite this, there is still a lack of evidence regarding its safety when used during pregnancy. There have been reports of associations with specific congenital defects. These observations may be a result of uncontrolled confounding by indication	No published data. Poor bioavailability and low serum levels expected to produce low levels in milk
Any inhaled corticosteroid (ICS) including beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone	No increased risk for major birth defects in 396 exposed compared with the general population.[20] A meta-analysis of studies of inhaled steroids did not find increased risk of major birth defects overall[21]	No increased risks for preterm delivery, low birth weight, or pregnancy-induced hypertension in 396 exposed or in metaanalysis.[22,23] Higher doses of ICSs may be associated with an increased risk of low birth weight, preterm delivery, and small-for- gestational-age infants[21]	Budesonide and fluticasone may be preferred if starting ICS during pregnancy. Other ICSs may be continued in patients who were well controlled by these agents before pregnancy, especially if it is thought that changing formulations may jeopardize asthma control. Adverse outcomes associated with higher doses of ICSs need further study because confounding by severity may explain this association	
Budesonide	No increased risk for major birth defects overall or oral clefts among 2014 exposed in population-based Scandinavian register[24]	No increased risks for preterm birth, reduced birth weight or length, or stillbirths in 2968 exposed in population-based Scandinavian register[25]		Small amounts excreted in 8 women with asthma using inhaled budesonide[26]
Fluticasone	No increased risk of major congenital malformations overall in a cohort study of 1602 mother-infant pairs exposed to fluticasone compared with 3678 exposed to other ICSs, stratified by severity[27]	No increased risk of low birth weight, preterm birth, or small-for-gestational-age infants in retrospective database study of infants of 3190 mothers exposed to fluticasone compared with 608 mothers exposed to budesonide[28]		No published data. Poor bioavailability and low serum levels expected to produce low levels in milk
Long-acting beta agonists (LABAs)	No evidence of increased risk in major birth defects in 65 salmeterol-exposed pregnancies.[29] In an analysis of a database, increased risks for major cardiac and major l to produce low levels in milk pairs expo- trimester exposure in 165 pregnancies. [30] However, in a later study from the same database, 841 pregnancies exposed to LABAs with low- or medium-dose ICSs showed no increased risk of major birth defects overall compared with	No difference in low birth weight, preterm birth, or small-for-gestational-age infants was noted in infants of mothers exposed to salmeterol vs formoterol in a retrospective database study[28]	Limited observational data are available regarding the safety of LABA use during pregnancy. The benefits of the use of LABA appear to outweigh the risks as long as they are used concurrently with ICSs	Salmeterol: No published data. Poor bioavailability and low serum levels expected to produce low levels in milk

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Medication	Major birth defects	Other birth outcomes	Evidence gaps and recommendations	Lactation
	pregnancies exposed to medium- to high-dose ICSs alone[31]			
Montelukast/ leukotriene receptor antagonist (LTRA)	No increased risk of major birth defects overall in 74 and 180 exposed pregnancies.[32,33] No increased risk in major birth defects overall or specific birth defects in 1164 exposed pregnancies in claims study.[34] No increased risk in major birth defects in 1827 exposed pregnancies in Danish register study[35]	No increased risk for reduced birth weight or shortened gestational age in 180 exposed when compared with other asthmatic patients.[32] No increased risk for preterm delivery, low birth weight, or preeclampsia in 1827 exposed compared with other treated asthmatic [35] patients	Data on the use of LTRA during human pregnancy are limited	Very low levels in breast milk of 7 women given 10 mg dose—0.68% of weight-adjusted maternal dose[36]
Systemic corticosteroids	Meta-analysis of cohort studies showed no overall increased risk of major birth defects in pooled 535 exposed pregnancies; meta-analysis of 4 case-control studies showed an increased risk of ~3-fold for oral clefts.[37] However, most recent and largest case-control study from US National Birth Defects Prevention Study showed no increased risk for oral clefts with first-trimester systemic steroid use for any indication in 2372 cases and 5922 controls[38]	Preterm delivery, low birth weight or reduced birth weight, preeclampsia, and gestational diabetes have all been reported to occur more frequently in women treated with systemic steroids in pregnancy; however, studies that attempted to control for underlying maternal disease and disease activity typically find the associated risks for these outcomes reduced or eliminated[39]	Adverse outcomes seen may be a result of severe asthma or the medication itself. These outcomes would be outweighed by the potential risks of a severe asthma exacerbation, which include maternal or fetal mortality. Oral corticosteroids are recommended when indicated for the management of severe asthma during pregnancy	Prednisone: Amounts very low in breast milk; no adverse effects noted in breast-fed infants.[40,41] High doses may cause temporary loss of milk supply[42,43]
Tiotropium			No published human data	No published data. Poor bioavailability and low serum levels expected to produce low levels in milk
Biologics			Continue biologics in patients who are responding to them before pregnancy. Consider starting biologics during pregnancy in women who (1) are candidates for the therapy, and (2) who have severe asthma and are at risk of asthma exacerbations or oral corticosteroid use. Data are needed	
Omalizumab/anti-IgE	No increased risk compared with general population for major birth defects overall in 169 exposed pregnancies enrolled in a registry.[44] Also when compared with a disease-matched unexposed cohort[45]	The rates of prematurity (<37 wk' gestation) and small for gestational age were not unlike those seen in other studies of severe pregnant asthmatic patients	Continue omalizumab in patients who are responding to it before pregnancy. Consider starting omalizumab during pregnancy in patients who (1) are candidates for this therapy and (2) have severe asthma and are at risk of asthma exacerbations or oral corticosteroid use. Consider omalizumab over other biologics in women who are candidates for more than 1 biologic due to some available human data. More data are needed	No published data. Large protein is likely destroyed in infant gastrointestinal tract
Mepolizumab/anti–IL-5			No published human data/Pregnancy registry through mothertobaby.org	No published data. Large protein is likely destroyed in infant gastrointestinal tract
Reslizumab/anti–IL-5			No published human data	No published data. Large protein is likely destroyed in infant gastrointestinal tract

Medication	Major birth defects	Other birth outcomes	Evidence gaps and recommendations	Lactation
Benralizumab/anti–IL-5 receptor			No published human data/Pregnancy registry through mothertobaby.org ongoing	No published data. Large protein is likely destroyed in infant gastrointestinal tract
Dupilmuab/anti–IL-4 receptor			No published human data/Pregnancy registry through mothertobaby.org ongoing	No published data. Large protein is likely destroyed in infant gastrointestinal tract

Adapted from Namazy et al.[46]

TABLE III.

Complementary strengths and weaknesses of the 3 study arms of VAMPSS

Characteristic	Strengths	Potential weaknesses
Study design		
Cohort	• Prospective • Multiple outcomes	• Limited statistical power for specific birth defects • More costly
Case-control	• Multiple exposures • Statistical power for specific birth defects • Less costly	• Retrospective • Limited statistical power for infrequent exposures
Database	• Prospective • Population-based • Multiple exposures • Multiple outcomes • Statistical power for groups of defects possible • May be least costly	
Medication exposure capture		
Cohort	• Data captured on medication as actually taken • Data captured on OTC medications (including vitamins) • Data captured on borrowed medication	
Case-control	• Data captured on medication as actually taken • Data captured on OTC medications (including vitamins) • Data captured on borrowed medication	• Retrospective exposure information
Database		• Medication prescribed may not be taken • Timing of exposure estimated when gestational age is not captured
Bias and confounding		
Cohort	• Outcomes confirmed by interview and medical records • Data available on confounders, eg, alcohol, tobacco, and folic acid use	• Potential volunteer bias
Case-control	• Outcomes confirmed by interview and medical records • Data available on confounders, eg, alcohol, tobacco, and folic acid use	• Potential volunteer bias • Potential recall bias • Potential biased control selection
Database	• No selection bias • Diagnoses in pregnancy losses rarely captured	• Data not available for some key confounders, eg body mass index

OTC, Over-the-counter.