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Clinical Data for Informed Medication Use in Pregnancy: Strengths, Limitations, Gaps, and a Need to Continue Moving Forward

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Abstract

The objective of this paper is to explore the strengths, weaknesses, gaps, and needs in research on medication use in pregnancy, where opportunities have been bypassed to develop standards and collaborations for collecting data to better understand how medications can impact clinical outcomes in pregnant women and developing fetuses. The availability of existing data and the methods of its capture are reviewed, including registries, claims and health record databases, and meta-analyses. The paper focuses on why these efforts have not fundamentally provided benefit-risk information and clinical treatment algorithms for medication use in pregnant women. Methodological issues, such as lack of standardization and central data collection, are discussed. Common barriers are examined, including a lack of awareness and education, cultural hurdles, collaboration deficiency, and an insufficient development of new data collection methods.

Keywords

pregnancy, pregnant, medicine, medication, drug, data

Introduction

Many scientific initiatives have been undertaken to fill the important knowledge gaps associated with medication use in pregnant women. Because randomized controlled clinical trials, the gold standard for establishing the safety and efficacy of medications, generally exclude pregnant women, most medications are not indicated for use during pregnancy. At the same time, the vast majority of women require medication therapy during their pregnancy.[1,2] Thus, there is a significant unmet need for data to guide decision making for medication use during pregnancy.[3]

This paper explores why so many scientific initiatives in the area of medication use in pregnancy have failed to bring about a major improvement in health care for pregnant women as measured by regulatory-endorsed medicine use or provider-endorsed treatment algorithms, despite research efforts that have provided valuable information.[4–7] Surveys, blogs, and experience in specialized referral centers all show that pregnant women continue to lack easy access to clear and consistent information.[8,9] For pregnant patients with concomitant medical or dental health concerns, there is still a sense that fear, ignorance, inconsistency, and avoidance largely remain as the standard experience for both health care providers and women throughout pregnancy.[3] The Internet and social media sites provide conflicting, confusing, and often incorrect information to women seeking answers.[10,11]

Research efforts to date include clinical registries, claims or health record database studies, meta-analyses, case studies, and literature reviews. Despite multiple research efforts, progress

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has been slow. This paper discusses strengths and limitations common to these research efforts that limit the development of benefit-risk information on appropriate medication use in pregnancy. It is important to understand common limitations that may inhibit the development of data-driven, decision-making treatment algorithms. Beyond methodological issues, we explore common barriers in communication, collaboration, and culture, and associated medical information gaps. This article is intended to stimulate discussion about addressing identified issues and information gaps.

This is the second in a 3-part series on the topic of medication use during pregnancy. The first paper identifies the overall problem and the urgent need for better data to guide clinical decision making during pregnancy.[3] The current paper assesses the strength of existing data-collection efforts and explores underlying reasons for our current failure to enable data-driven decision making. The third paper is a detailed exploration of issues that must be addressed in order to effect change in cultural, educational, and research paradigms for informed medication use in pregnancy.[12]

Existing Data—Strengths and Limitations

Table 1 summarizes the methodological strengths and limitations of current research on medicine use in pregnancy.

Table 1. Summary of strengths and limitations of current research methodology.[a]

Study Type	Strengths	Limitations
Registry	Prospective enrollment, evaluation of spontaneous abortions and stillbirths	Lack of control groups and confounder control, time to enroll sufficient patients, loss to follow-up, selection bias
Case control	Study of specific birth defects, confounder control, low-cost and high-motivation data collection	Delay in data collection, limited data, data accuracy, selection bias
Health care and claims database	Large sample size, standardized data, ethnically and geographically diverse population	Data gaps and accuracy, less information for low-prevalence disease, data confirmation, missing non–live birth outcomes
Meta-analysis	Early signal prediction	Confounding factors, detection bias

[a]Strengths and limitations are variable across studies based upon multiple factors specific to each study. Not all strengths and limitations are listed. Common limitations across current methods include retrospective and observational nature.

Registries

Pregnancy registries are often established by pharmaceutical companies to meet postmarketing regulatory requirements. The US Food and Drug Administration (FDA) website features a list of 74 active pregnancy registries.[13] Prospective enrollment is a methodological strength of registries, as retrospective methods can bias results toward adverse outcomes.[14] Registries have the potential to provide important information, but this potential is limited by the absence of data collection standardization and data integration. For example, there are 4 registries for the antiepileptic levetiracetam, collectively reporting on over 1100 pregnancies, but information on specific patterns of congenital malformations is lacking.[15–17] Combined data could have a better potential to show, or rule out, drug-related specific patterns of malformation.

Other general limitations of registries include limited sample sizes, potential selection bias resulting in a nonrepresentative population, inability to control for various confounders/covariates, length of time to enroll patients, lack of internal controls, loss to follow-up, a general observational nature, inability to confirm causality, difficulty detecting minor malformations, bias against the null hypothesis, and/or bias associated with poor recall, noninclusion of elective abortion data, and retrospective ascertainment of maternal lifestyle.[18–20] Enrollment can be a significant hurdle. For example, GlaxoSmithKline had 4 pregnancy registries running between approximately 1989 and 2008, none of which was able to meet enrollment milestones during the first 10 years of the medications being marketed.[21] At best, it takes many years to accrue sufficient numbers of cases in registries, during which time pregnant women and their health care providers (HCPs) struggle with risk-benefit evaluation. Resulting limitations in statistical powering of registries challenge the ability to identify risk. These types of issues, along with bias against the null hypothesis and citation bias, often lead to signals of teratogenicity, only to be found later to be false.[18] Despite these potential limitations, some registry efforts, including population-based surveillance registries, have produced valuable data in various disease states including epilepsy, migraine, depression, antiretroviral, and herpes.[21]

The Medical Birth Register in Denmark contains data on all births by women residing in Denmark and includes information for the newborn and the parents by personal identification number.[22] The unique identifiers allow linkage to the National Prescription Registry, a registry of all prescriptions filled in Denmark, and the National Patient Registry, which contains data on inpatient and outpatient health care services.[23,24] A study of the major congenital malformation and fetal death associated with metoclopramide use for nausea during pregnancy illustrates the benefits of these registries.[4] This register-based cohort study examined 28,486 exposure cases

from a cohort of 1,222,503 pregnancy cases and found no increased risk of major malformations or fetal death (spontaneous abortions or stillbirth) associated with metoclopramide use. This study may help inform decision making when treatment with metoclopramide is considered during pregnancy.

Case-Control Studies

Ongoing case-control database studies allow for examination of birth outcomes associated with pharmaceutical use. Examples include the US Centers for Disease Prevention and Control (CDC) National Birth Defects Prevention Study (NBDPS), which collects data from mothers by telephone interview, the Hungarian Case Control Surveillance of Congenital Abnormalities Study, and Estudio Colaborativo Latino Americano de Malformaciones Congenital. NBDPS studies have investigated fetal risks associated with the use of asthma and antiherpetic medications during pregnancy.[25,26] The Slone Epidemiology Unit Birth Defects Study assessed folic acid antagonist use in cases with birth malformation outcomes compared to matched controls.[27] Another program using case-control studies is the Metropolitan Atlanta Congenital Defects Program (MACDP) in Georgia, which leverages state-mandated reporting of birth defects to collect data through several mechanisms. While not focused on medication research, MACDP evaluation of stillbirths provides an example of the potential for such programs.[28] Case-control studies enable study of specific birth defects with minimal heterogeneity in case groups across a large number of patients and allow control of a variety of potential confounders. Conversely, limitations of this method include the issues that data are often collected long after delivery, sparse data may compromise analyses, accuracy of exposure data can be a concern, and matching controls with malformations may result in selection bias.

Vaccines and Medication in Pregnancy Safety Surveillance (VAMPSS) is a collaboration of the American Academy of Allergy, Asthma & Immunology (AAAAI), the North American Organization of Teratogen Information Specialists (OTIS), and the Slone Epidemiology Center. VAMPSS is specifically designed to facilitate the study of the risk of exposure to vaccines, prescription medications, and over-the-counter (OTC) medications during pregnancy. Researchers have looked at the risks and safety of selected vaccines (including influenza vaccines) and the medications used to prevent or treat influenza.[5] VAMPSS uses a 2-pronged research approach, conducting hospital-based, case-control database analyses along with prospective registry-based cohort surveillance. This system combines the prospective ability of a registry to examine major and minor congenital anomalies, spontaneous abortions, and stillbirths with the volume of patients that can be examined in a retrospective medical database, allowing for evaluation of specific birth defects.

The Motherisk Program of the Division of Clinical Pharmacology and Toxicology at the Hospital for Sick Children in Toronto has published over 900 prospective observational studies with control groups on dysmorphology and on neurobehavioral follow-up after exposure to drugs and chemicals. These data are based on approximately 200 daily cases seen by the program for clinical counseling. This approach has been successful, as the program was the first to report on the fetal safety of drugs such as fluoxetine, newer selective serotonin reuptake inhibitors, and gabapentin. Many of the studies are collaborative efforts with other teratology information services. The program also conducts systematic reviews and meta-analyses, and was the first to show the teratogenicity of corticosteroids and the safety of azathioprine.[29]

Teratology information services collect and analyze pregnancy outcomes data from women who are exposed to drugs and chemicals during pregnancy. These services have access to large numbers of pregnant women through their call centers, allowing for prospective follow-up of pregnancies using structured questionnaire or phone interviews.[30] Controls are defined as pregnancies in which pregnant women were exposed to agents known to be nonteratogenic. One advantage these groups offer over other methods of data collection is their ability to use existing communication infrastructures to collect information from motivated participants. A study by Schaefer and colleagues[6] using information collected by organizations participating in the European Network of Teratology Information Services (ENTIS) on exposure to vitamin K antagonists during pregnancy demonstrates the utility of such data. Use of vitamin K antagonists during pregnancy has been shown to increase the risk of structural defects and other adverse pregnancy outcomes, yet little was previously known about the relative risk of birth defects in relationship to trimester of medication exposure. The study found that the risk of coumarin-induced embryopathy is very small, particularly when exposure occurs no later than 8 weeks after the first day of the last menstrual period.[6] Thus, elective termination of a wanted pregnancy may not be warranted if coumarin exposure took place in early pregnancy. Teratology information services can be effective in providing data to inform therapeutic decision making during pregnancy, although the effectiveness of these services may be limited by chronic underfunding.[30]

Health Care and Claims Database Studies

Analysis of data from health care payer databases can facilitate the examination of pregnancy cases. As an example, the General Practice Research Database (GPRD) in the UK is a primary-care medical records database with over 3 million

active patients that includes mother-infant linkage and birth outcome data for investigating teratogenicity.[21] While potentially valuable for data related to highly prevalent diseases treated in a primary care setting (eg, depression), the database is less informative for diseases of lower prevalence and those managed in specialty care settings (eg, epilepsy). While the utility of retrospective claims and electronic medical record (EMR) database studies is limited due to difficulties in confirming data accuracy (eg, mother-baby linkage, drug exposure, timing of exposure, and birth outcomes) and to the retrospective nature of the data, heath care record databases can provide useful information. A variety of ongoing practice-based research projects have elements that could be modeled for pregnancy research. Pediatric Research in Office Settings (PROS), associated with the American Academy of Pediatrics, allows HCPs across the US to engage in EMR research while gaining operational, funding, and patient-education support, and other engagement incentives through centralized efforts of the association and its network of partners.[31] The PROS network has approximately 1700 pediatric practitioners from 700 practices across 50 states. Direct engagement with HCPs can aid in standardization of data collection. The Slone Center Office-based Research (SCOR) Network of Boston University is a similar example.[32] Looking at data on more than 84,000 patients, SCOR researchers assessed the risks of ibuprofen use in children,[33] showing the potential of such efforts.

The Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) is a multisite collaborative research program developed to enable the conduct of studies of medication use and outcomes in pregnancy.[34] Collaborators include the FDA, HMO Research Network (HMORN), Kaiser Permanente Northern and Southern California, and Vanderbilt University. This effort shows the potential of collaborative efforts, with over 1,200,000 children linked to over 900,000 mothers. Strengths include standardized data files across sites and the ability to examine data across a large ethnically and geographically diverse population. Limitations of the retrospective claims database research include inconsistent capture of inpatient medication use, data inaccuracy, need for chart confirmation of some diagnostic codes, and failure to capture pregnancy outcomes other than live births, including spontaneous and induced abortions.

Meta-analyses

Systematic reviews and meta-analyses of observational studies in clinical teratology have been published with increasing frequency in the past 2 decades. In an attempt to assess the validity of the conclusions of these analyses by comparing them to more recent large-cohort studies, a recent study identified all relevant meta-analyses of observational studies published in peer-reviewed journals.[35] Meta-analyses with outcome measures of risk of congenital malformation and/or long-term neurodevelopment of children after first trimester in utero exposure to a therapeutic drug were eligible for consideration. Next, large registries published at a later date on the same drug and the same endpoint were identified. Nine different meta-analyses published through December 31, 2012, were successfully matched to a large registry study. Seven meta-analyses showed no teratological effects, and 2 showed either morphological or developmental adverse effects. In all 9 instances, the meta-analyses accurately predicted the results of the later large-cohort studies.[35] The ability of meta-analyses of earlier, smaller cohort studies to generate an accurate overall teratogenic signal of risk or lack of risk may offer earlier opportunities to affect clinical practice.

Informative examples are available when extensive research exists, as observed in examination of antidepressant exposure during pregnancy.[7] But even when meta-analysis data suggest a potential safety issue, such as an increased risk of cardiovascular malformation associated with paroxetine, potential confounding factors such as detection bias raise concerns about conclusions and associated treatment decisions.[36] Convenience sampling (ie, recruitment without consecutive or random sampling strategies), nonstandard event definitions, and lack of distinction between statistical and clinical significance can be issues.[7] Thus, while the synthesis of small-cohort studies into a systematic review and meta-analysis can yield important early signals on the safety and risk of medicine use in pregnancy, benefit-risk conclusions should be made with caution and with data from research addressing methodological concerns.

Data—Needs, Gaps, and Barriers

Table 2 presents identified data collection gaps on medication use in pregnancy.

Randomized Controlled Clinical Trials

Typically, randomized controlled drug studies, the gold standard of research, exclude pregnant women due to fear of teratogenicity. The ethical and legal issues regarding research in pregnancy are complex, and to identify the relative safety of a drug during pregnancy can require trials with thousands of pregnant women, rendering such research impractical. However, there may be reasonable exceptions. Controlled studies are needed when a drug is specifically indicated for use in pregnancy, for example, treatments for the symptoms or complications of pregnancy itself. In addition, research subjects sometimes become pregnant while participating in clinical trials. Such participants often have uniquely well-documented medical histories as part of their screening and inclusion in a

Table 2. Summary of data needs, gaps, and barriers.

Need	Gap	Barrier
Randomized controlled clinical trial	Gold standard of research excludes pregnant women for safety concerns even when potential exception justified	Ethical and legal concerns, lack of regulatory guidance, large sample size to detect birth defect
Standards	Lack of standards for endpoints, assessments, time points, duration of follow-up, well-documented case; this inhibits data integration	Lack of cross-stakeholder collaboration, lack of regulatory guidance
Collaboration and data integration	Leadership to build coalition for issue resolution, new data-capture tools	Lack of cross-stakeholder engagement, competitive interests, data quality, lack of patient incentives

study. Today, these participants are simply forced off the trial, which may, arguably, conflict with appropriate and ethical medical care. Drug safety research during pregnancy for patients with human immunodeficiency virus (HIV) may be a template for the study of pharmaceuticals for other disease states.[37] Several articles provide considerations for navigation of the ethical and legal concerns, giving insight into appropriateness and inappropriateness of research in pregnancy and relating arguments to societal understanding of the benefit-risk equation.[20,38–41] Discussion of controlled trial research methodologies is relevant, as such data are typically required to meet regulatory requirements for inclusion in labeling.

Standards

An important hurdle to pregnancy research is the lack of standards for data collection and assessment methods that will enable reliable conclusions across studies. Standards are lacking for endpoints, assessments, time points, and duration of follow-up, including the definition of a well-documented case of pregnancy and pregnancy outcome. More basic knowledge is needed on how pregnancy, which alters the physiology of most organ systems,[42] affects a drug's disposition, but there are no standards for making such assessments. This lack of standardization inhibits the integration of data across studies and limits the ability to power data analyses statistically to make treatment-based decisions with confidence.

The Clinical Trials Transformation Initiative (CTTI) is working on a Pregnancy Testing in Clinical Trials project with the objective of developing evidence-based recommendations for clinical research in pregnancy that improve protection of research participants and reduce the risk of unintended fetal exposure.[43] The goal is to incorporate a rational process to assess pregnancy risk, exposure risk, and benefits of pregnancy testing within a specific study population so that researchers and regulators can develop testing protocols that maximize patient safety, minimize patient burden, and increase trial efficiency. The intention is to create universal study-design tools for the development of evidence-based protocols for pregnancy research.

In the US, the Best Pharmaceuticals for Children Act (BPCA)[44] and the Pediatric Research Equity Act (PREA)[45] provide incentives and requirements, respectively, for pediatric research. In the EU, Regulation (EC) No 1901/2006 mandates and incentivizes pediatric research via paediatric investigation plans (PIPs).[46] While not to the level observed for pediatrics, regulators have issued guidance related to pregnancy research. A 1997 hearing on the current category requirements for pregnancy labeling and subsequent work with focus groups and the FDA Reproductive Health Drugs Advisory Committee culminated in the FDA's issuance of proposed new regulations for pregnancy and lactation labeling in 2008.[47] The proposed regulations would require benefit-risk assessment and clinical advice for pregnancy, along with supporting data. However, it is concerning that more than a decade after their inception, these regulations have not been implemented. Further, unlike previous regulations that have significantly improved the availability of data to guide pediatric drug-use decisions, the proposed regulations lack directives or incentives regarding human data collection. Pregnant patients are defined as a special patient population in the European Medicines Agency (EMA) guidance for postauthorization data,[48] risk management,[49] and risk minimization.[50] There seems to be a low expectation for human data collection geared toward clinical decision making within the pregnancy component of these guidance, which focus more on pregnancy prevention and on registries. Adding only preclinical research requirements may not add useful evidence, as risk in animals does not always accurately predict risk in humans.[29]

Collaboration and Data Integration

In general, there is a lack of collaboration across stakeholders regarding pregnancy research data collection and analysis. Moreover, regulatory requirements, particularly for human data, are limited. Without transformation, it is unlikely that decision-making data will find its way into labeling, labeling supplements, or other medication guidance for patients and providers. To aid in moving pregnancy research forward, leadership is needed in raising issues, facilitating discussion, pushing for improvements, and starting the collaboration process.

One collaboration effort focused on the safety of medication use in pregnancy is EUROmediCAT. This partnership is comprised of several academic centers and governmental registries, with financial support provided by the EU under the 7th Framework Program.[51] Its aim is to build a European central database and associated software system for reproductive safety postmarketing evaluation for antiepileptics, insulin analogues, antiasthmatics, and antidepressants by combining an existing network of congenital anomaly registers in Europe with existing health care databases that will cover over 3.7 million births from 1995 to 2010. CHICOS, another 7th Framework Program tasked with describing potential mother-child cohorts and registries in Europe, has teamed up with EUROmediCAT. This group's first report demonstrates the collaborative potential of the project and the need for standardization of data collected, such as stage of pregnancy recruitment, medication dose and timing, and stillbirth or abortion case data collection, as well as data transfer format, data coding and collection, confirmation processes, and follow-up duration.[52]

Another effort is the OpenMedNet database, which is integrating data from insurers, providers, pharmacies, regional registries, and directly from patients in an attempt to comprehensively track exposure, outcomes, and health over time with a community-based model across health service organizations.[53] This collaborative model relies heavily on patient and provider engagement.

The concern for this area of research is growing. The American College of Obstetricians and Gynecologists (ACOG) is seeking a congressional resolution to call for more research information for pregnant women. The Agency for Healthcare Research and Quality (AHRQ), within the US Department of Health and Human Services (HHS), has a mission to improve the quality, safety, efficiency, and effectiveness of health care (including pregnancy) through research of health care interventions and policy making. The International Society for Pharmacoepidemiology (ISPE) has a Medications in Pregnancy Special Interest Group. The DIA convened special stakeholder forums in Europe and the US in 2013 to define and address the issue. The Society for Women's Health Research (SWHR), formed in 1990 to advocate for the inclusion of women in clinical trials,[54] has spearheaded efforts that led to a mandate for women to be included in clinical trials, and is now collaborating to raise awareness of the medication and pregnancy issue. CDC's Treating for Two Initiative, the EMA PROTECT Project, and other programs with objectives around collecting medication use data in pregnant women have expertise to share. Collaboration among these and other stakeholders on standards, data sharing, and efforts to increase education, awareness, and collaboration would be beneficial in transforming this area of research.

Table 3. Summary of communication needs, gaps, and barriers.

Need	Gap	Barrier
Awareness	Communication of existing data to patients in reliable manner	Lacking patient-friendly format and access, litigation fear, lack of credible source
Benefit-risk assessment	Benefit-risk assessments to guide treatment decision making	Culture of risk rather than benefit-risk paradigms, lack of topic knowledge
Address publication bias	Reporting outcomes with no adverse event	Inclination to only publish more alarming outcomes, lack of context or holistic reporting
Address litigation concerns	Decision-helping information made available to patients	Fear of litigation, lack of regulatory and professional guidance
Patient/health care provider (HCP) data contribution	Data provided by HCPs and patients for research	Fear of litigation and misperception, lack of education, regulatory hurdles

Communicating Data—Needs, Gaps, and Barriers

Table 3 presents identified communication gaps in the exchange of medical information for pregnant women.

Education and Awareness

Existing data on medicine use in pregnancy must be readily accessible in order to facilitate decision making. Recent studies indicate that such data are not always delivered to clinicians or patients, and when they are, there is often uncertainty about interpretation.[30] There is a critical need to collate the available information and make it easily accessible to health care providers and their patients.

Existing teratology information services that strive to stimulate and facilitate the exchange of information and advance skills in pregnancy risk assessment counseling include ENTIS and OTIS. These services process thousands of counseling requests from health care providers and their pregnant patients per year and can be an excellent provider of information on medication use in pregnancy.[30]

In a study of obstetrician-gynecologists' knowledge and access to information about risks of medication use during pregnancy, 42% of the study participants selected lack of sufficient information as the greatest barrier to counseling pregnant women about medication use, emphasizing the need for better information and access.[55] Further, there is insufficient information on the risks of medication use during pregnancy for the vast majority of medications,[8] with teratogenic risk in

pregnancy estimated to be undetermined for over 90% of medications approved in the US between 1980 and 2000.[56] Among the 54 most commonly used medications during pregnancy, only 3 had "good to excellent" data available to assess teratogenic risk in humans based upon Teratology Information System expert Advisory Board review.[57] Moreover, patients need better access to accurate and reliable information for health decisions surrounding pregnancy. About half of all pregnant patients seek information over the Internet, but there they often find conflicting and inaccurate information.[9]

Culture—Benefit-Risk Assessment

A key limitation in the prevailing approach to treatment and research in pregnancy is the focus on risk without equal focus on benefit. Much of the data on medicine use in pregnancy is anecdotal, which compounds this particular issue. Indeed, the issuance of warnings by regulators, industry, and researchers against the use of medicines in pregnancy and lactation is not because harmful effects are known, but because these effects are unknown.

Current surveillance systems focus on detection of abnormal or unwanted events but typically do not capture the overall benefit-risk outcomes associated with medication use during pregnancy. This is important because the risk and potential harm of not treating a patient may outweigh the risk and harm of treating.[58,59] Discontinuation of medication for a pregnant woman exchanges the fetal or neonatal risks of medication exposure for the risks of untreated maternal illness. There are a growing number of clinical examples where nontreatment can have untoward, unintended consequences. For example, maternal psychiatric illness, if inadequately treated, may result in poor compliance with prenatal care, inadequate nutrition, exposure to additional medication, increased alcohol and tobacco use, deficits in mother-infant bonding, and family disruption.[60] Further, the impact of not providing treatment can include such poor outcomes as increased preterm delivery, low birth weight, slowed neonatal development, and higher rates of neonatal hospital admissions. Not treating with medications in pregnancy carries risk for other diseases such as HIV infection, asthma, and rheumatoid conditions.[37,61,62] Not treating pregnant patients for hypertension[63] or epilepsy[21] often presents a greater risk to both mother and child.

A study examining medication use for pregnant patients with breast cancer provides further evidence of the importance of benefit-risk–based treatment algorithms for pregnant patients.[66] Approximately 1 in 1000 women are diagnosed with cancer during pregnancy, and breast cancer occurs in approximately 1 in every 3000 pregnancies.[64,65] Historically, antimitotic agents have been withheld from pregnant women. However, this prospective observational study showed that women who were treated for their cancer while pregnant, and their babies, had better survival and long-term outcomes than those who aborted or those who delayed cancer treatment until an early caesarian section was performed.[66]

Culture—Publication Bias

Cultural issues may influence the preoccupation with the risks of medicating during pregnancy. A natural publication bias toward studies describing a fetal safety issue may result in a distorted view of arguably safe medicines and termination of pregnancy or failure to treat serious medical conditions.[67] When pregnancy goes well, even when using medicine off-label, the outcome may not be published. However, if an adverse outcome is observed, there is a greater propensity for the case to be submitted and accepted for publication. Moreover, literature describing a safety issue is 70% more likely to be cited than negative papers.[67] Compounding this issue is the tendency for medical research to be typically communicated through medical publications, possibly preventing important insights from reaching the public forum. This is particularly likely if the translation from the medical article to the public is left to chance, as the media frequently focus reports on alarming news from single studies or case reports.[68] While case reports contribute to medical knowledge, they are less important when informing the treatment decision to medicate or not during pregnancy. Health literacy is an important determinant of public health in general,[69] as well as for pregnancy outcomes.[70]

Culture—Litigation

Concern over potential medical malpractice litigation has been shown to influence treatment recommendations made by physicians,[71] and it may be a factor in physicians' recommendations regarding treatment in pregnant patients. For example, 50% of women with immunological disease noted that their health care provider never discussed fertility, family planning, or pregnancy in relationship to their treatment management plan.[72] Increased availability of data, evidence-based guidelines covering treatment during pregnancy, and information in product labeling will help overcome this barrier to treatment.

Culture—Patient and Health Care Provider Data Contribution

Patients and health care providers do not volunteer in sufficient numbers to provide data under current industry and government research paradigms, likely driven in part by litigation fears and lack of education on the topic.[73] There are many hurdles for the public to become more engaged in clinical research.[74] While pregnant patients may be reluctant to

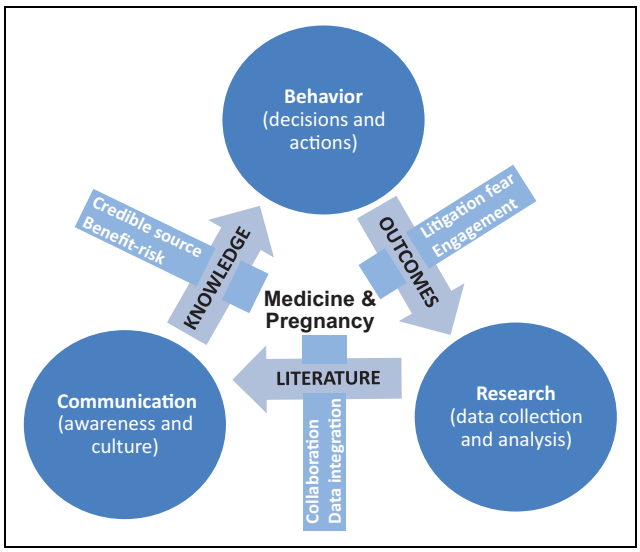

Figure 1. Medicine and pregnancy: research, communication, behavior, and barriers.

discontinue medications that have stabilized their respective diseases, they do not want to be perceived as putting their baby at risk or being held legally negligent for participating in a treatment.

The importance of patient reported outcomes to complement medical data is increasingly recognized and addressed via initiatives such as the Patient Centered Outcomes Research Institute (PCORI). While some studies have included patient reports of well-being, this is an area in pregnancy-related research where gaps remain.

Only a small minority of physicians participate in clinical trials,[73] and institutional review boards (IRBs) may be inclined to reject studies including pregnant women in the absence of a clear regulatory framework.

Discussion

Research on questions about medication use in pregnancy has been undertaken and reported in the literature. However, limitations with pregnancy research methodology and communication contribute to unmet needs for information, physician-to-patient interactions that are not meeting patient needs (eg, lack of well-informed choices),[3] and clinical treatment that is not always aligned with current knowledge (Figure 1). This lack of clear and helpful medical information to guide medication use during pregnancy is an important global public health concern.

This paper has examined strengths and weaknesses associated with the most frequent types of research in the area of medicines and pregnancy. Moving forward, there is an important need for consensus on standards of measurement, assessment, outcome reporting, and general protocol methods. Harmonization is crucial to enable integration of data across research efforts that will enable capture of major and minor malformations and adverse events, spontaneous abortions and stillbirths, as well as more subtle effects on growth and development. Harmonization and collaborative data integration is also critical for enhancing our understanding of disease outcomes in pregnant women.

Communication and cultural barriers must be overcome in order to better apply insights in data-driven literature to decision making and care for the pregnant. In the current culture of concern and absence of awareness, existing data are often incomplete, inconclusive, fragmented, not well dispersed, and sometimes contradictory or ignored.

Fragmentation of efforts is perhaps the single most important barrier to advancing medical and public knowledge about this issue. Cross-stakeholder engagement (Figure 1) among drug companies, regulatory bodies, clinical research groups, health care providers, and patients can enable effective data integration, foster new data collection methods, enhance communication, and improve patient education.[12]

Conclusions

Factors leading to a lack of data-supported decision making on medication use in pregnancy include restricted research approaches, limitations of current research methodologies, lack of data and research standards, fragmentation of existing data, inconsistent application of findings to clinical practice, and poor patient communication. Risk-based approaches that do not consider benefit of treatment and litigation concerns are cultural factors that also impede provision of proper medical guidance. A paradigm change is needed to move medicine in pregnancy research and communication forward.

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