

Current Research on Therapies for Pregnant and Lactating Women

Randomized controlled clinical trials of pharmaceuticals and other medicinal therapies for pregnant and lactating women are critical for informed clinical decisions, yet relatively few of these rigorous studies have been available. Moreover, ethical and scientifically rigorous clinical trials cannot be optimally designed without a base of strong pre-clinical knowledge – and the number of these studies has also been limited. Scientists have not yet determined how underlying disease mechanisms, along with metabolic and other important factors, affect medication efficacy, safety and dosing in pregnant and lactating women. Pharmacokinetics and pharmacodynamics research – describing how drugs move through the body and the relationship between drug concentration and the resulting effect – is essential to developing safe and effective doses and formulations. Observational studies in humans, typically case series or cohort studies, can also contribute knowledge on the risk factors associated with a condition, and to describe prevention or treatment approaches used in a community. Other types of research, including studies of adherence to treatment regimes or clinical practice variation – can also inform clinical decision making. Research progress is, as yet, insufficient to ensure that pregnant and lactating women and their providers have the full range of information they need.

The Task Force finds that research on therapies for pregnant and lactating women is in urgent need of attention from researchers, federal agencies, and public and private partners. The findings detailed below reflect the scientific and programmatic expertise of the Task Force members, and additional input by scientific experts, comments from the public, and a quantitative overview of the research literature over the past decade.

Literature Analysis: Objectives, Scope, Methodology, and Limitations

The research literature on medicinal therapies for pregnant and lactating women was identified for the past ten years, for 15 individual disorders and categories of disorders that are most commonly medicated in these women. The objective was to supplement the scientific and programmatic expertise of the Task Force members by:

- Quantifying the research literature on medicinal therapies (pharmaceutical, dietary supplement, and herbal/alternative) for pregnant and lactating women, by condition, topic, and type of research;
- Identifying key research gaps, by condition, topic, and type of research; and
- Determining funding sources for the research.

The analysis did not attempt to assess the rigor or quality of research in each published report, in part because of the very large volume of publications. The analysis focused on characterizing and quantifying the *types* of research conducted for each disorder or category of disorders, because of the essential role of each type of research in informing clinical practice for pregnant and lactating women.

Figure 1: Categories for Analysis (Selected Conditions)

- Asthma
- Autoimmune diseases (excluding diabetes)
- Cancer
- Central nervous system disorders
- Diabetes (all types)
- Endocrine disorders (excluding diabetes)
- Hypertensive disorders
- Infectious diseases
- Low milk supply
- Mental health
- Nausea and vomiting
- Pain
- Preterm birth
- Substance abuse

For each of the 15 categories (see Figure 1), a librarian/information specialist developed a detailed PubMed search strategy to identify publications that focused on pharmaceutical, dietary supplement, and/or

herbal/alternative therapies specifically in pregnant and lactating women. The articles retrieved were published between January, 2006 and August, 2017. The search was not limited by language.¹

For each item, the title and abstract (and, where necessary, the entire article) were reviewed to identify and eliminate false positive cases, to classify the research by type, and to verify which publications related to dietary supplements, vitamins, and herbal remedies. The research type classifications are listed in Figure 2. For original research only – that is, articles that are not reviews, case reports, or editorial/commentaries – funding data were extracted from the acknowledgement or funding section of the article and recorded by type of funding source. For non-industry support, the country of the funding organization was also recorded.²

Within each condition, publications were analyzed by subtopics using Medical Subject Headings (MeSH®), the National Library of Medicine's controlled vocabulary thesaurus.³ Automated text-searching software was then applied to publication titles and abstracts to verify and in some cases supplement the information obtained by analysis of the MeSH® terms. Subtopics of interest included specific conditions within some of the broader categories. For example, publications related to specific substances including alcohol, opioids, and others were identified within the substance abuse category. Individual diseases and disorders were identified within broad categories, like infectious diseases and mental health. For all categories, publications related to lactation were also identified using this method.

Limitations of the analysis included restricting the searches to publications in the PubMed® database for the past decade. In the few cases where neither an article nor its abstract were available, article classification was based on title only. For a small number of articles or abstracts available only in languages other than English, automated translations were used. Finally, although efforts were made to include as many pertinent search terms as possible, some relevant items may have been inadvertently missed.

Results

Figure 3 shows the number of articles by condition or category and type of research. For the January 2006-August 2017 period, the highest number of publications addressed preterm birth. Some categories that include pregnancy-specific conditions, such as diabetes, which included gestational diabetes, had higher numbers of publications. However, pregnancy-associated nausea and vomiting and low milk supply had fewer.

Figure 2: Research Types

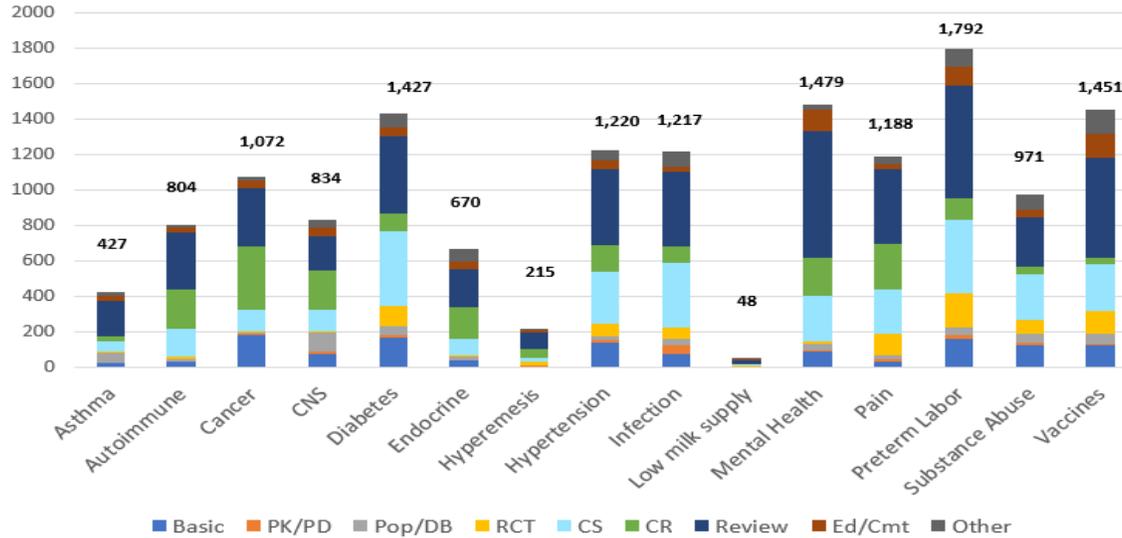
- **Basic/pre-clinical**
- **PK/PD**
- **Pop/DB:** studies involving large scale or population-representative data;
- **RCT:** randomized controlled clinical trials
- **Case series or cohort study**
- **Case report**
- **Review**
- **Editorial/commentary**
- **Other:** original research content not described by any of the previous categories

¹ Categories were defined to make them generally distinguishable from each other – for example, the autoimmune disorders and endocrine categories were defined to exclude diabetes. However, some articles were appropriately included in more than one category. For example, research on pregnant women who underwent simultaneous treatment for both HIV and substance abuse would have been included in both the infectious diseases and substance abuse categories.

² The majority of industry funding involved large, multinational pharmaceutical companies, so country of origin was not recorded for industry funding.

³ MeSH® consists of sets of terms naming descriptors in a hierarchical structure, to facilitate detailed searching and analysis.

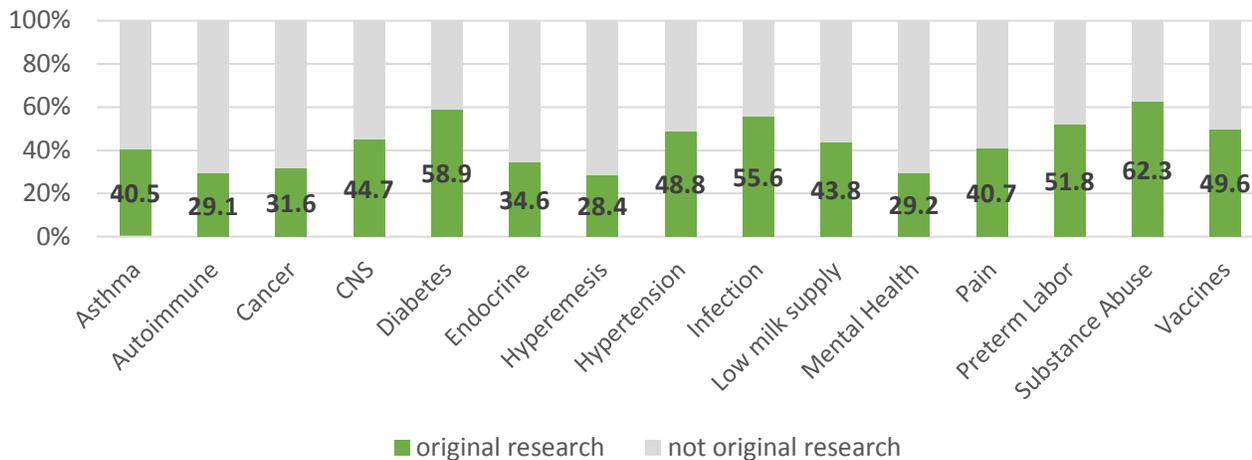
Figure 3: Number of Publications Related to Therapies for Pregnant and Lactating Women, by Condition and Type, January 2006—August 2017



Notes: the Autoimmune and Endocrine categories exclude diabetes, which is reported separately. A publication may be reported in more than one category if appropriate.

The distribution of research by type varied across categories. Randomized clinical trials were more numerous in the diabetes, pain, preterm birth, and vaccine categories. Population-based and large database (Pop/DB) studies were most prominent in the CNS disorders category. Pharmacokinetic and pharmacodynamic (PK/PD) studies were rare across all categories. "Original research" publications were defined to encompass studies that produced new systematic data, as opposed to describing individual cases or summarizing or commenting on a topic or specific publication. Thus, original research included the basic, PK/PD, Pop/DB, randomized controlled clinical trials (RCT), Case series and cohort studies (CS), and "Other Research" categories. Figure 4 shows the percent of publications that were original research, by category. In only one category (substance abuse) did the proportion of original research exceed 60 percent.

Figure 4: Percent of Original Research Publications Related to Therapies for Pregnant and Lactating Women, by Condition, January 2006—August 2017



Availability of research on non-pharmaceutical (vitamin, dietary supplement, and herbal/alternative) medications varied across disorder categories. For autoimmune diseases, cancer, infection, mental health, pain,

and substance abuse, these types of therapies accounted for less than 5 percent of publications.. However, the proportion was much higher for hypertensive disorders (23 percent), diabetes (9.9 percent), preterm birth (9.7 percent), and low milk supply (75 percent). Most of these publications focused on vitamin and mineral supplements, and a substantial number were controlled trials. However, because the amount of active ingredients in non-pharmaceutical medications may vary widely,, it may not be clear how studies on these therapies can best be interpreted and applied in clinical practice.

Key Research Gaps

The Task Force identified key research gaps that are imperative to address to improve health care for pregnant and lactating women (see Figure 5). A substantial number of both common and relatively rare, often serious conditions are largely unaddressed in the research literature. For example, among the nearly 1,500 articles for infectious diseases as a group, there were less than two dozen publications relating to pregnant and lactating women on several common and dangerous infectious diseases, such as hepatitis C and tuberculosis. The Task Force is also concerned about the paucity of information available on treating tuberculosis in pregnant women. Research on medications for mental health disorders has largely focused on depression, with relatively few original research publications on bipolar disorder or schizophrenia. Three or fewer clinical trials specific to pregnancy were available to inform clinical decisions on systemic lupus erythmatosis (SLE), multiple sclerosis, or rheumatoid arthritis. The Task Force is very concerned about the impact of the opioid epidemic on pregnant and lactating women. It is also concerning, however, that only 21 total publications addressed therapies for cocaine, amphetamine or methamphetamine abuse in pregnancy. Pain research specific to pregnancy has focused on labor pain, and little scientific information is available about therapies to treat chronic pain during pregnancy. (For more detailed information on publications within each category, see Appendix VIII.)

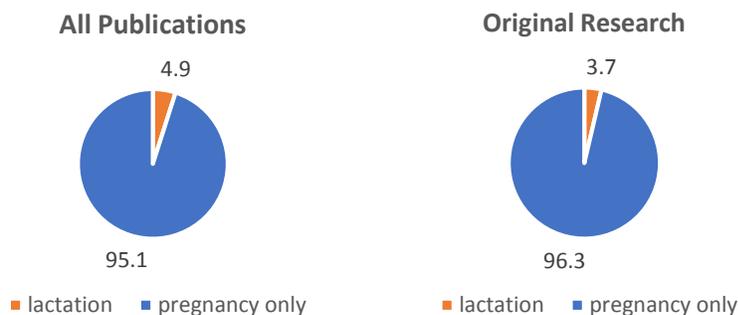
Several key research gaps emerged that cut across diseases and conditions. Lactation research was sparse across all conditions. Figure 6 shows that of all the publications across the 15 disorders and categories, 4.9 percent related to lactation. Because lactation publications were more likely to be reviews and editorials or commentaries, lactation publications accounted for only 3.7 percent of the original research articles. Studies of how drugs and supplements affect breast milk and, in turn, the newborn are challenging to perform, but urgently needed.



Figure 5: Key Research Gaps

1. **Specific Disorders within Categories** –
e.g. TB in Infectious Diseases
2. **Lactation**
3. **Understanding placental transport**
4. **PK/PD research**
5. **Later-emerging effects of prenatal medication exposure**
6. **Effects of untreated disease**
7. **New drugs for pregnancy-specific conditions**

Figure 6: Lactation Research as a Percent of Publications, January 2006-August 2017



Another important priority for the Task Force is research related to placental transport of drugs. Understanding how substances are transported to the fetus through the placenta is crucial for being able to ensure that the fetus is exposed to potentially beneficial agents, and also to ensure that the fetus is not exposed to harmful substances. For all of the 15 conditions reviewed, only 28 publications were directly related to placental transport of medicinal therapies – either in general, or for specific individual medications. The basic science of manipulating transport across the placenta is a potentially fruitful area of research that has not been sufficiently addressed. More sensitive assays are especially needed. Efforts like the Human Placenta Project have highlighted the need to understand how the placenta functions, and thus may facilitate this type of research.

The Task Force emphasized that PK/PD research specifically with regard to pregnancy and lactation women is very urgently needed. Across the 15 research conditions/categories, PK/PD research accounted for 1.3 percent of the total publications. Only in one category -- infectious diseases -- were more than 22 total PK/PD studies published during the 2006-2017 decade. Yet without well-conducted PK/PD studies, it is often inappropriate to conduct a clinical trial in pregnant or lactating women because there is not sufficient evidence to create a testable formulation and dose. For example, when events following the September 11, 2001 terrorist attacks raised concerns about weaponized anthrax, the FDA conducted a PK study of amoxicillin as a therapy for pregnant women exposed to the bacillus. The study found that because the antibiotic was metabolized so quickly in pregnant women, it was virtually impossible to administer enough for it to be therapeutically to be effective.⁴

Although safety, particularly for the fetus, is a dominant concern that often results in undertreatment of pregnant women, the Task Force is also concerned that few studies are available to describe later-emerging effects of prenatal medication exposure for mother or child. Some cohort or case-control studies have been conducted in countries with population-based pregnancy registries, but the majority of these focused on congenital birth defects or other outcomes that can be detected soon after birth. Less than 1 percent of all publications addressed subtle or late-emerging effects of prenatal exposure.

The Task Force is equally concerned that very few research articles address effects of untreated disease on the mother or fetus. Understanding these effects is essential to help women and their clinicians balance the risks and benefits of treatment. For example, a case control study in the United States and Canada found that both treated and untreated hypertensive disorders in pregnancy were associated with birth defects.⁵

Finally, there has been very little new drug development for pregnancy-specific conditions in recent years. Research on therapies for pregnant and lactating women typically involve drugs that have been used for similar

⁴ [PMID 24041894](#); [PMID 17329990](#).

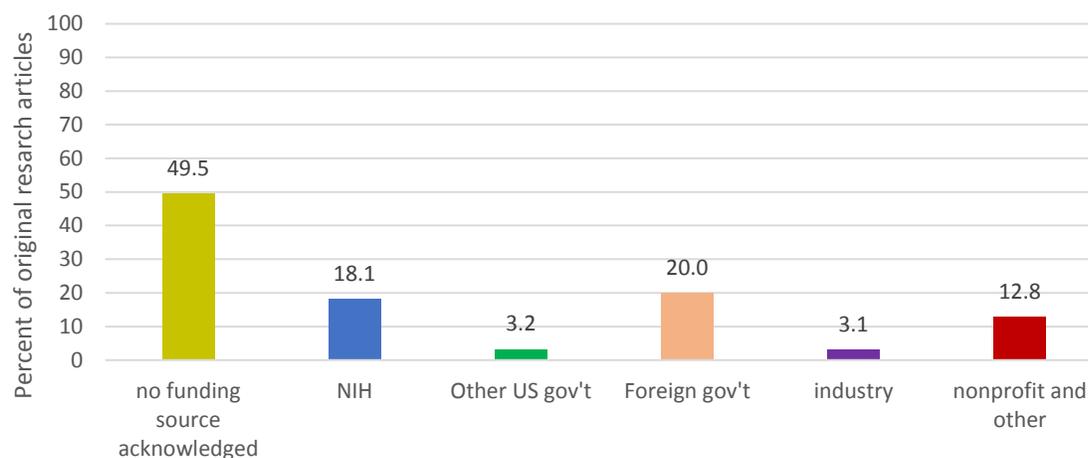
⁵ [PMID 25395267](#).

conditions in non-pregnant women. For example, clinical trials have tested whether medications commonly used to treat type 2 diabetes are effective in treating gestational diabetes in pregnant women.⁶ However, although researchers are investigating the mechanisms of gestational diabetes through animal models, it is not yet clear how similar are the exact disease mechanisms for type 2 diabetes and gestational diabetes.⁷

Funding Sources for Research on Therapies for Pregnant and Lactating Women

Many research studies on therapies for pregnant and/or lactating women are funded by national government agencies in the United States and around the world. For many publications, no external source of funding is acknowledged. Industry and nonprofit organizations also support research in this area. Figure 7 shows the distribution of funding sources across all conditions, for original research publications only. About half of all publications did not acknowledge any funding source. Eighteen percent of original research publications acknowledged at least one NIH IC, and 20 percent acknowledged funding from a government agency outside the United States. Industry support was acknowledged in 3 percent of publications.

Figure 7: Funding Sources for Original Research Publications Related to Medicinal Therapies for Pregnant and Lactating Women, January 2006—August 2017



Note: a single article was counted in multiple categories if multiple types of funding sources are acknowledged. As a result, the sum of the percentages exceeds 100.

Funding sources varied considerably across conditions and types of research. Vaccine research had the fewest publications with no acknowledged external funding. The proportion of articles supported by NIH funding was highest for preterm birth and substance abuse. Although foreign governments were typically acknowledged at a rate similar to NIH, foreign governments supported relatively less research on substance abuse and more on infectious diseases. (For more information on funding source by category and type of research, see Appendix VIII.)

Across all disease categories, both U.S. and foreign government funding was more typically found in the basic research and randomized controlled trial types. Industry funding was disproportionately represented in the population/database category; in several European countries, industry funding helped to establish, maintain,

⁶ [PMID 20542272](#).

⁷ [PMID 26542478](#).

and analyze data from population databases and registries. (See Appendix IX for more information about population databases and registries.)