

## Appendix VIII: Research on Therapies in Pregnant and Lactating Women

To ensure that pregnant and lactating women and their children benefit from safe and effective therapies, many different types of research are necessary, and research projects of all types must be designed and implemented with the needs of pregnant and lactating women specifically in mind. Pre-clinical, fundamental research discoveries in biology, disease, and behavior are essential so that scientists can understand the underlying basis of a condition and identify potential therapeutic targets. Cell or tissue samples, animal models, and/or computer simulations are critical precursors to the design and testing of new approaches to diagnosis, prevention, and treatment. For pharmaceutical interventions, pharmacokinetics and pharmacodynamics (PK/PD) research -- the study of how drugs move through the body and the relationship between drug concentration and the resulting effect -- are needed for developing safe and effective formulations and doses. Observational studies in humans -- often through case series or cohort studies -- shed light on the risk factors associated with a condition and describe prevention and treatment approaches used in the community. Epidemiological research can describe population trends in diseases or conditions and associated risk and resilience factors, giving scientists clues to improving human health. Randomized controlled clinical trials (RCTs) provide rigorous evidence that interventions are safe and effective for human use. Other types of research -- such as studies of adherence and surveys to uncover variation in clinical practice -- can help inform clinical decisions. Unfortunately, the pace of research progress across all types and methods has not been sufficient to ensure that pregnant and lactating women and their providers have enough scientific evidence for well-informed clinical decisions.

### Objectives, Scope, Methodology, and Limitations

This analysis of published scientific evidence on therapies in pregnant and lactating women is based on research articles published over the last ten years. The analysis focuses on research in 15 selected categories, relating to conditions for which pregnant and lactating women are known to use medicinal therapies. (See Figure 1). For purposes of the analysis, medicinal therapies were defined to include drugs and vaccines, as well as vitamins, minerals, herbal remedies, and other supplements. The objectives were to supplement the expertise of the Task Force members by:

- Quantifying the research literature involving medicinal therapies for pregnant and lactating women, by category, topic, and research type;
- Identifying substantial research gaps, by category, topic, and research type; and
- Determining funding sources for the research, with a focus on identifying gaps and potential opportunities for collaborations.

The analysis focuses on distinguishing and reporting the types of research, as opposed to judging the scientific merit or rigor of the design, implementation and conclusions of each published research project. The analysis provides information on the utilization of research approaches that can expand the scientific evidence base to inform clinical decisions about the use of therapies in pregnant and lactating women. "Original" research that systematically collects and reports new data, rather than describe individual cases or summarize previous findings, is most important to

#### Figure 1: Categories for Analysis (Selected Conditions)

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

expand the scientific evidence base. For this analysis, original research was defined to include basic/preclinical research; PK/PD; pop/DB; RCT; Case series and cohort studies; and other research. These types of research are described more fully in Figure 2.

Selection of the 15 categories was based on published reports<sup>1</sup>; the recommendations of Task Force members; and presentations by experts and comments provided to the Task Force. The categories selected include some known to be associated with pregnancy, such as preeclampsia and preterm birth, along with “pre-existing” conditions, such as cancer, that may occur in pregnant or lactating women but are not associated with pregnancy.

For each category, an information specialist, in consultation with the analytic team, developed a detailed PubMed search strategy to identify publications that focused on the research category, the population of pregnant and lactating women, and medicinal therapies (as defined above). The search was limited to articles published between January, 2006 and August, 2017. The search was not limited by language. To avoid substantial double counting, two categories – autoimmune disorders and endocrine disorders – were defined to exclude diabetes, although diabetes could have been considered in these categories also. Some articles were necessarily included in more than one category. For example, research on pregnant women with HIV and substance abuse disorders was included in both the infectious diseases and substance abuse categories. In the analyses that addressed the literature as a whole, each article was counted only once. In analyses by category, each article was counted within each applicable category. Slightly less than 8 percent of articles were included in more than one category. A total of 24,969 records were retrieved using these searches, and 13,632 unique publications were included in the final combined dataset.

Analysts screened each publication by considering its title and abstract and (where necessary) the full article, to eliminate false positives. The analysts classified the

## Figure 2: Research Types

- **Basic/fundamental:** pre-clinical research designed to improve understanding of a condition, identify targets, obtain toxicology data, design interventions, or conduct pre-clinical testing;
- **PK/PD:** pharmacokinetic and/or pharmacodynamic research on the time course of drug absorption, distribution, metabolism, excretion; and the relationship between drug concentration and effect;
- **Pop/DB:** case-control or epidemiological studies involving large scale or population-representative data;
- **RCT:** randomized controlled clinical trials, where human subjects are prospectively randomly assigned to one or more interventions to evaluate the interventions' safety and/or effectiveness.
- **Case series or cohort study:** a study that follows one or more groups of individuals and assesses condition status, outcome, and/or risk.
- **Case report:** detailed report of the symptoms, signs, diagnosis, treatment, and follow-up of an individual patient.
- **Review:** a summary of previously-published work.
- **Editorial/commentary:** a statement of opinion about a research study, a scientific body of work, or science or public policy.
- **Other:** original research content not described by any of the previous categories. Examples may include methodology papers, non-representative cross-sectional surveys, economic analyses, and others.

<sup>1</sup> Andrade SE, Gurwitz JH, Davis RL et al. Prescription drug use in pregnancy. *Am J Ob & Gyn.* 2004;191:398-407. <https://www.ncbi.nlm.nih.gov/pubmed/15343213>; Andrade se, Raebel MA, Morse AN et al. Use of prescription medications with a potential for fetal harm among pregnant women. *Pharmacoepidemiol Drug Saf* 2006;15:546-554. <https://www.ncbi.nlm.nih.gov/pubmed/16586470> ; Mazer-Amirshahi, M, Samiee-Zafarghandy SS, Gray G, van den Anker JN. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. *Am J Obstet Gynecol* 2014;211:690.e1-11. <https://www.ncbi.nlm.nih.gov/pubmed/24912093>.

remaining articles by type of research reported and coded whether the research was specifically focused on vitamins, dietary supplements, or herbal remedies. For articles reporting original research, the analysts also recorded all funding sources from the acknowledgement or funding section of the original article.<sup>2</sup> For non-industry support, the country of the funding organization was also recorded. Because industry support is typically provided through large multinational pharmaceutical companies, it was not feasible to track country of origin for industry support.

For each category, publications were analyzed by subtopics using Medical Subject Headings (MeSH<sup>®</sup>), the National Library of Medicine's controlled vocabulary thesaurus. MeSH<sup>®</sup> consists of sets of terms naming descriptors in a hierarchical structure, which facilitates detailed searches. Analysts also applied automated text-searching software to publication abstracts to verify and in some cases supplement the information obtained by analysis of the MeSH<sup>®</sup> terms. Subtopics of interest included specific conditions (e.g. sites of cancers) within a general category, or such topics as specific substances (e.g. alcohol, opioids or marijuana) within a general category (substance abuse). The original search terms were used initially in the text searching software, then supplemented by a "like" algorithm that matched publications based on shared terms. Articles with like terms were reviewed to set the algorithm threshold.

Several limitations affect this analysis. Practical considerations with regard to the volume of publications made it necessary to limit the analysis to published research of the last decade that focused on medicinal therapies for pregnant and lactating women within 15 selected categories. The analysis did not attempt to encompass published research on every medicinal therapy for every disorder that may occur in pregnant or lactating women. Finally, in less than one half of one percent of cases, neither an article nor its abstract were available, and the analysts jointly made judgments about its type, based on its title. In less than 10 other cases, automated translations were used when an article or abstract was available only in a language other than English.

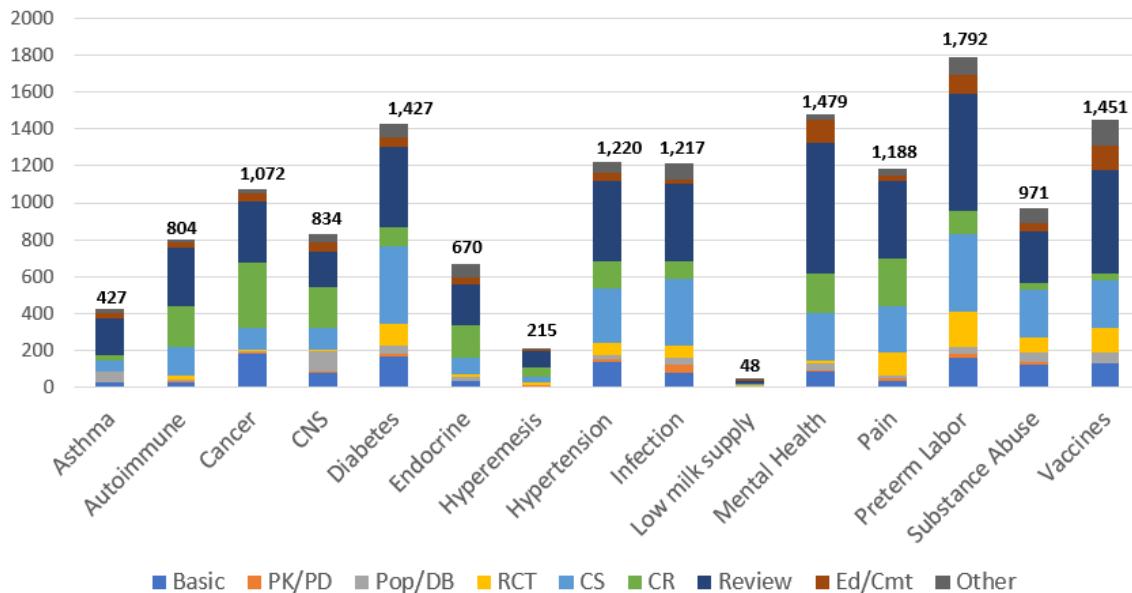
## Summary

The number of articles by category and type of research is shown in Figure 3. Over this period of slightly longer than a decade, preterm birth had the highest number of publications among the categories studied. Some categories that include pregnancy-specific conditions – such as diabetes, which includes gestational diabetes – had relatively high numbers of publications, but pregnancy-associated nausea and vomiting and low milk supply had relatively fewer. Some conditions that are pre-existing or not directly associated with pregnancy (like infection and vaccines) also had over 1,000 publications, while others (like asthma) had fewer.

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<sup>2</sup> The PubMed database does include some funding information, although not at the level of detail required for this analysis; therefore, review and coding by the analysts was required. Text retrieval and analysis software was used to assist with this task, but all information was reviewed and verified by the analysts.

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

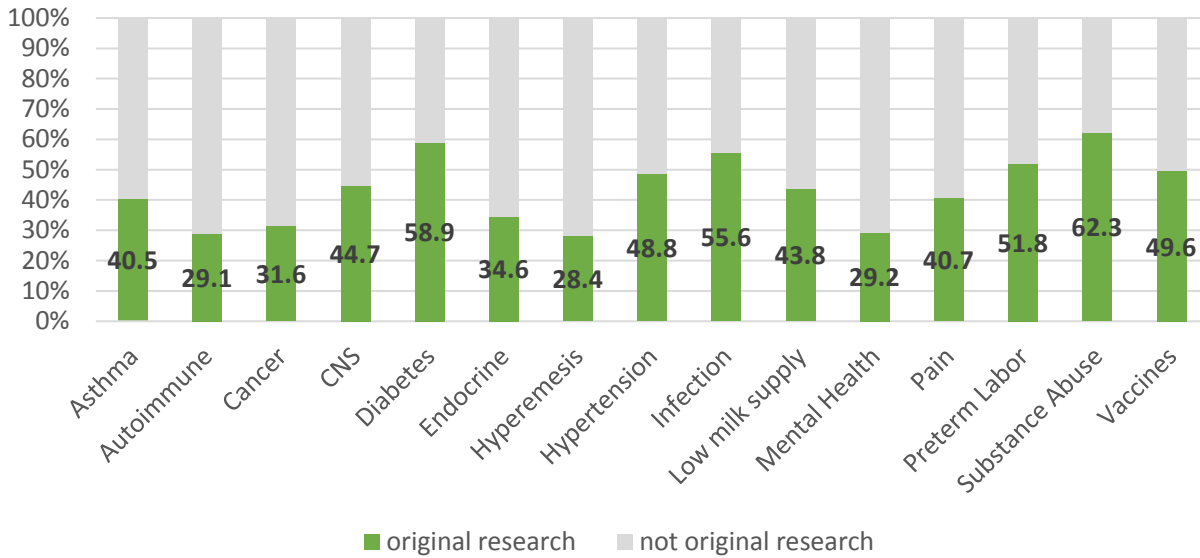


Notes: the Autoimmune and Endocrine categories exclude diabetes. A publication that reported research on multiple conditions and/or medications for the conditions (substance abuse and mental health, for example) may be included in more than one category if appropriate.

The distribution of publications by type of research varied across categories. As shown in Figure 3, RCTs represented a larger share of the research in the low milk supply, pain, preterm birth, and vaccine categories compared with other categories such as asthma; autoimmune disorders; cancer; CNS disorders; endocrine disorders; and mental health. Population-based and large database studies were most prominent in the CNS disorders category. Basic and preclinical research were a larger share of the research on cancer; diabetes; hypertension; and substance abuse compared with autoimmune disorders; low milk supply; and pain. PK/PD studies were rare for all categories, although slightly more common in infectious diseases compared with other categories.

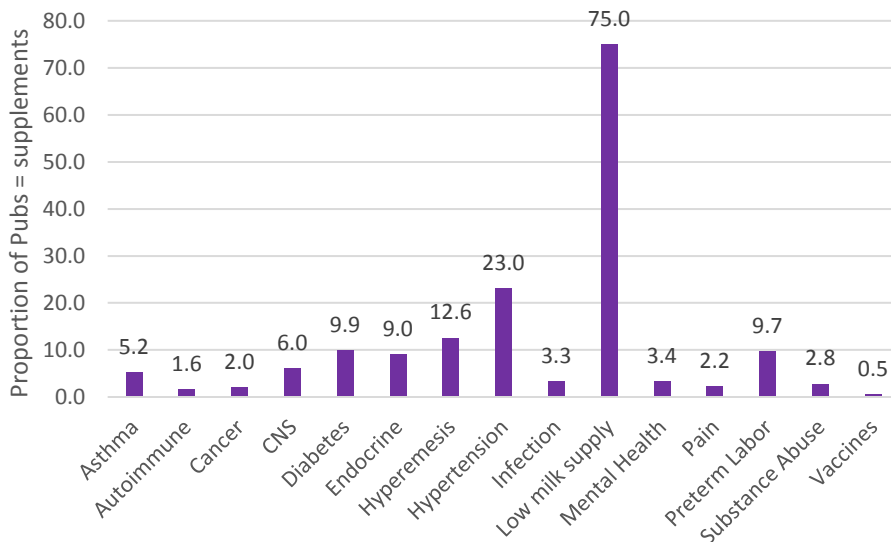
As noted, for purposes of the analysis, “original research” publications included articles basic, PK/PD, Pop/DB, RCT, case series (CS), and the “other research” category. (The “other” category included, for example, surveys of physicians about clinical practice related to treating a condition during pregnancy.) Figure 4 shows the percent of total publications that were original research, by category. For two-thirds of the categories, the majority of the publications were not original research. Only one category (substance abuse) had the proportion of original research exceeding 60 percent.

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



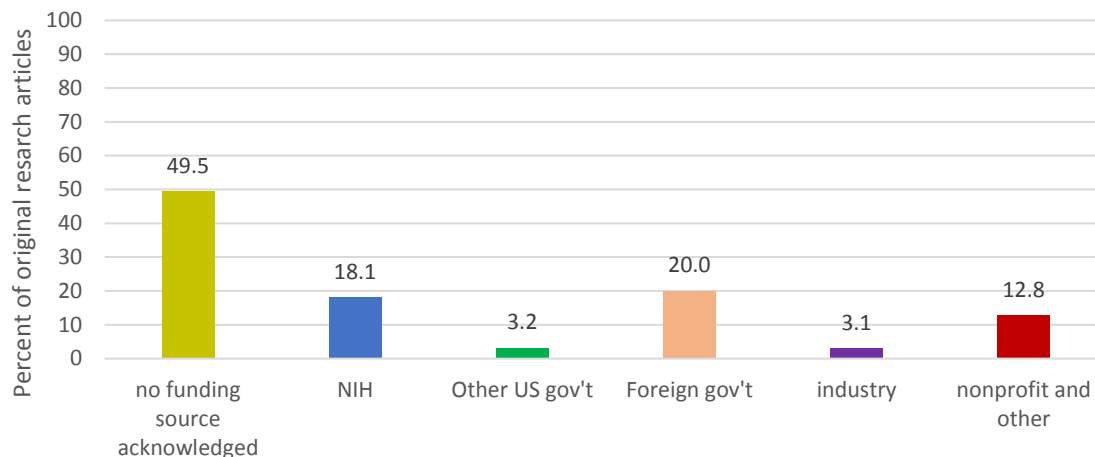
The proportion of research that focused on vitamins, minerals, herbal remedies, and/or other dietary supplements varied widely across categories, as shown in Figure 5. For autoimmune diseases, cancer, infection, mental health, pain, and substance abuse, these remedies accounted for less than 5 percent of publications on the topic. However, the proportion was much larger for low milk supply, hypertensive disorders, diabetes, and preterm birth. Most of these publications focused on vitamin and mineral supplements, and a substantial number were RCTs. However, because of variability in the composition and other characteristics of unregulated products, there are difficulties in interpreting study results for application to clinical practice.

*Figure 5: Percent of Publications Related to Therapies for Pregnant and Lactating Women That Focused on Supplements, by Category, January 2006—August 2017*



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. As is common in published research generally, many publications did not acknowledge a funding source. Industry and nonprofit organizations also support research in this area. Figure 6 shows the distribution of funding sources across all categories, 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 6: Funding Sources for Original Research Publications Related to Therapies for Pregnant and Lactating Women, January 2006—August 2017*



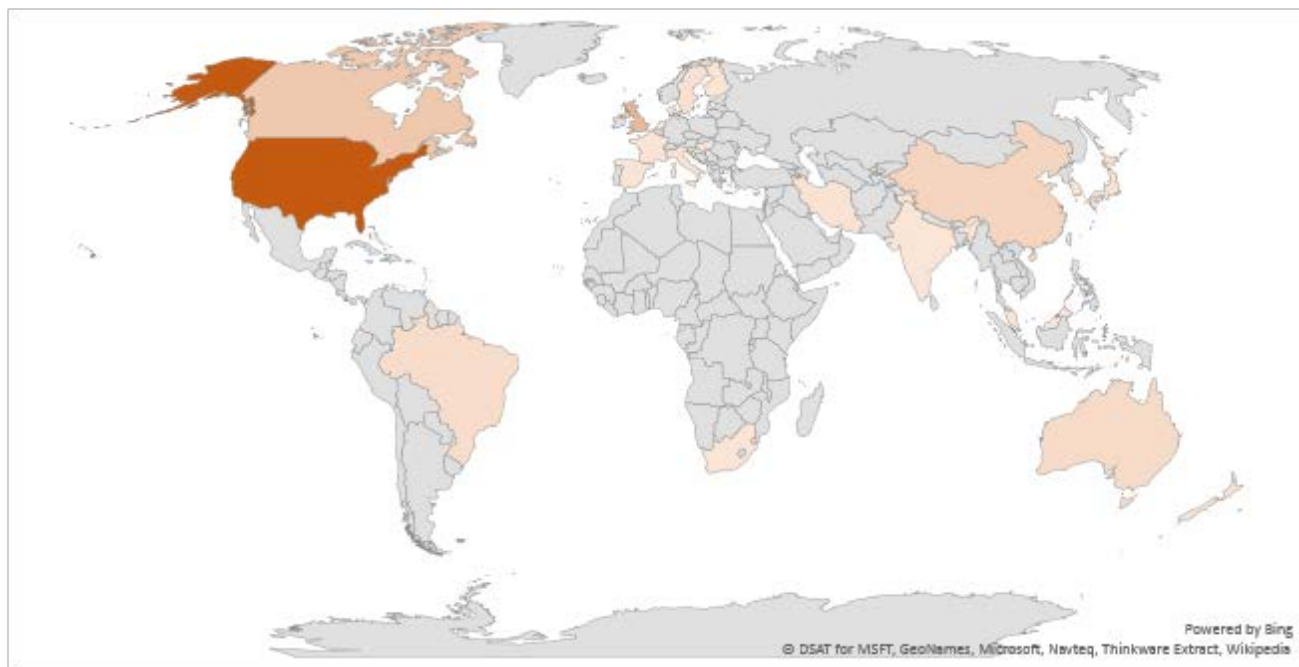
Note: a single article was counted in multiple groups if multiple types of funding sources are acknowledged. As a result, the sum of the percentages exceeds 100.

Funding sources varied considerably across the 15 selected categories and by 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 fewer research publications on substance abuse and relatively more on infectious diseases.

Across all research types, both U.S. and foreign government funding was more typically found in publications that reported results from basic/preclinical research and randomized controlled trials. Industry funding was disproportionately represented in the population/database category; in several European countries, industry funding helped to establish, maintain, and analyze data from population databases and registries. (See Appendix IX for more information about population databases and registries.)

The number of articles by country of origin for non-industry funding -- government, nonprofit, and other organizations -- is shown in Figure 7. Slightly less than half of the articles that credited government or nonprofit sources were supported by organizations in the United States. The remainder were supported by organizations in other countries. Organizations in the United Kingdom supported the second-largest number of publications in both the government and non-profit sections. Government agencies in Canada and China supported a relatively large number of publications, but the share of the nonprofit support from those countries was smaller than several European countries, including Sweden, Denmark, and Finland. Both government agencies and nonprofits in Australia supported this research.

*Figure 7: Country of Origin for Funding Sources for Original Research Publications Related to Therapies for Pregnant and Lactating Women, Excluding Industry Funding, January 2006—August 2017*



# Asthma

## Introduction

Asthma is a chronic (long-term) lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when you breathe), chest tightness, shortness of breath, and coughing. Asthma most often begins during childhood, but affects people of all ages. In the United States (U.S.), more than 25 million people are known to have asthma.<sup>3</sup> Asthma is one of the most common chronic conditions in pregnant women, and asthma (especially if it is poorly controlled) is associated with risks and adverse outcomes for both mother and baby, including preeclampsia, preterm birth, and low birth weight.<sup>4</sup>

## Scientific Literature

The analysis identified 427 articles, published between January 2006 and July 2017, that related to medicinal therapies for asthma in pregnant and lactating women. Figure 1 shows the distribution of publications by type of research..

*Figure 1: Publications on Medicinal Therapies for Asthma in Pregnant and Lactating Women, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Asthma	24	0	60	4	59	30	195	29	26

There were no publications on PK or PD of asthma-related drugs, and there were few RCTs related to asthma in pregnant women. Most of these studies were conducted in Australia. Two studies determined that pharmacist-led and nurse-led educational interventions can help pregnant women with asthma to control its symptoms.<sup>5</sup> Another study found that asthma episodes during pregnancy could be significantly reduced with a validated treatment algorithm, and follow-up data found that mothers who were randomized to the treatment algorithm had infants with fewer recurrent episodes of bronchiolitis, a lung condition.<sup>6</sup>

A substantial number of publications used population-level data or large databases to address research questions related to asthma in pregnancy. Population-level pregnancy registries have been established in a range of countries with national health systems, including Denmark, the United Kingdom, Australia, Norway, and Finland. For some but not all of these registries, data on symptoms could be linked with pharmaceutical records. Researchers analyzed these types of data to address several types of questions related to asthma and pregnancy. Studies across a range of countries described physician prescribing patterns for pregnant and/or lactating women with asthma. For example, a recent study in France found that compared to pre-pregnancy prescriptions for the same women, during the pregnancy physicians typically increased prescriptions for inhaled corticosteroids, and reduced prescriptions for Montelukast (a leukotriene receptor antagonist) and for fixed-combination therapies that combined inhaled corticosteroids with short-acting or long-acting beta-2 agonists.<sup>7</sup> A similar study in the Netherlands found that although use of most prescription medications for asthma

<sup>3</sup> <https://www.nhlbi.nih.gov/health/health-topics/topics/asthma/> .

<sup>4</sup> <http://emedicine.medscape.com/article/796274-overview> .

<sup>5</sup> [PMID 24522786](#); [PMID 24401041](#).

<sup>6</sup> [PMID 21907861](#); [PMID 24068472](#).

<sup>7</sup> [PMID 27657554](#).



continued through pregnancy, such use decreased significantly in the first few months of pregnancy, especially for long-acting bronchodilators.<sup>8</sup>

Most studies of potential effects of antenatal asthma medications on offspring focused on structural birth defects. Over a dozen population-based or registry-based studies assessed associations between fetal exposure to untreated asthma during pregnancy or asthma-related medications during pregnancy. Results of the studies have been mixed, although negative effects reported (if any) have been small. Using data from the Canada, the U.S. and the U.K. , several studies found no increased risk of congenital malformations associated either with asthma medications or with the underlying condition.<sup>9</sup> However, other studies found some increased risks for congenital anomalies among pregnant women with asthma and/or women taking asthma medications while pregnant. For example, a study using data from Sweden found a small increased risk of cardiac defects, cleft palate, and anal atresia associated with antenatal asthma medication.<sup>10</sup> An analysis of data in a New York state registry also found an increased risk for cardiac anomalies.<sup>11</sup>

Twenty-two publications concerned vitamins and other supplements in the treatment of asthma in pregnant or lactating women. . Of these, half were original research articles. Many of these articles focused on potential mechanisms of action, to assess how the active agents could affect inflammation and/or immune function in pregnant women with asthma.

Figure 2 shows the pregnancy and lactation publications by type, separately. Almost all the pregnancy- and lactation-related research focused on pregnancy only, and not lactation.

*Figure 2: Pregnancy and Lactation Publications on Medicinal Therapies for Asthma, Shown Separately, by Publication Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Asthma	21	0	60	4	58	29	184	29	26
<b>Lactation</b>									
Asthma	3	0	0	0	1	1	11	0	0

## Current Research Activities

NIH is supporting several projects related to asthma in pregnancy. For example, NICHD is funding a study to increase understanding of factors that predict poor asthma control during pregnancy. Researchers are assessing predictors of asthma control variability during pregnancy, including demographic, biologic, genetic and environmental factors, with particular interest in the role of maternal allergy. Women whose asthma is exacerbated during pregnancy may be at elevated risk from environmental exposures, such as poor air quality.

Figure 3 shows external funding sources acknowledged by original research articles published from 2006-2017 on medicinal therapies for asthma in pregnant and lactating women. About 40 percent (70 of 173) did not

<sup>8</sup> [PMID 23063582](#).

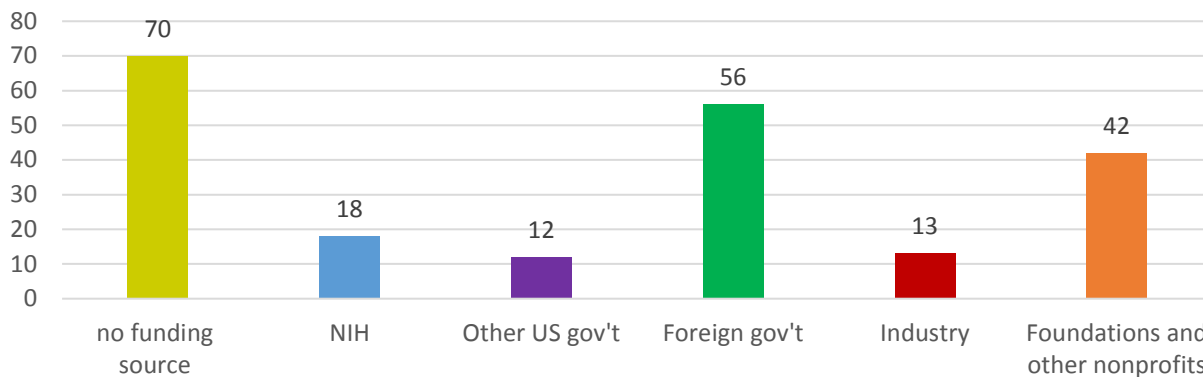
<sup>9</sup> For example, see [PMID 23450814](#), [PMID 17121872](#), and [PMID 22000568](#) (among others).

<sup>10</sup> [PMID 17279357](#).

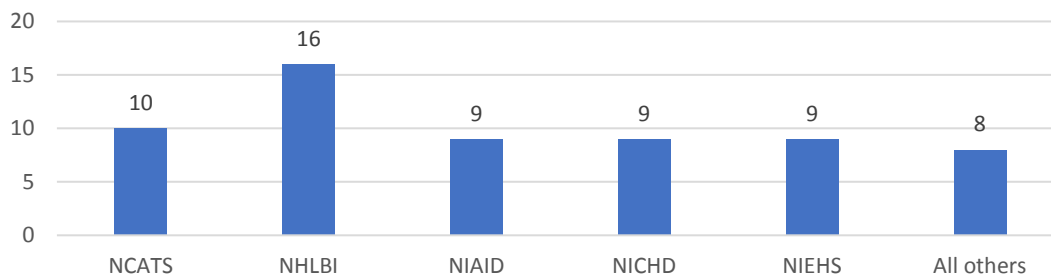
<sup>11</sup> [PMID 19067406](#).

acknowledge any external funding source. Government agencies from non-U.S. countries supported the largest share of funded research, followed by foundations and other nonprofit organizations. Among NIH ICs supporting in this research, NINDS, NICHD, and NHLBI supported the greatest number of publications.

*Figure 3: Original Research Publications (n=173) for Asthma in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: foreign government agencies included the Canadian Institutes of Health, the Medical Research Council of the UK, and similar health research agencies in 10 countries. A single publication may be reported in multiple categories if multiple funding sources were cited.



Note: Other NIH ICs included NCI, NIA, NIDA, NLM, and the NIH OD.

## Research Gaps

The existing research base on medications for asthma in pregnant and lactating women and severely limited. For pregnant women, for example, no PK/PD studies have been published on asthma medications in the past decade. Existing database research suggests that some asthma drugs may have teratogenic effects, but the results are mixed and when effects have been observed, these effects have been small. More information on potential teratogenic effects and subtle and/or long-term consequences of prenatal exposures is needed. In addition, research on exposures to these therapies through breast milk is needed.

# Autoimmune Disorders

## Introduction

Autoimmune disorders occur when the immune system mistakenly attacks healthy cells in the body. Women - particularly African-American, Hispanic-American, and Native-American women – are at higher risk than men for certain autoimmune diseases. There are more than 80 types of autoimmune diseases, and some have similar symptoms, which can make diagnosis a challenge.<sup>12</sup> Rheumatoid arthritis, antiphospholipid antibody syndrome, scleroderma, multiple sclerosis (MS), and systemic lupus erythematosus (SLE) are the autoimmune disorders most frequently reported in pregnant and lactating women.<sup>13</sup> Pregnancy may improve symptoms of certain autoimmune disorders, such as rheumatoid arthritis but for others, such as SLE, pregnancy may produce no change or worsen symptoms.<sup>14</sup>

## Scientific Literature

The analysis identified 804 articles published between January 2006 and July 2017 that related to medicinal therapies for autoimmune disorders in pregnant and lactating women. Of these, 13 publications (about 1.6 percent) related to research on vitamins, minerals or other supplements.. Figure 1 shows the literature by publication type.

*Figure 1: Publications on Medicinal Therapies for Autoimmune Disorders in Pregnant and Lactating Women, by Type of Research, 2006-2017*

	Basic	PK/ PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ comment	Other
<b>Autoimmune</b>	29	3	13	16	155	221	321	28	18

Of the articles, 234 (29 percent) reported on original research. The majority of articles were either case reports or reviews, although observational case series were also common. For example, a recent cohort study of SLE assessed the risk of renal flares (an increase in disease activity affecting the kidney) during pregnancy in women with a history this disorder. The researchers found that kidney involvement in SLE was uncommon during pregnancy, especially in women with no history of kidney disease.<sup>15</sup> Other researchers followed pregnant women with one of six different autoimmune disorders, who were treated with cyclosporin A, an immunosuppressant drug. The scientists found that the rate of adverse pregnancy outcomes for these women was similar to the rate in the general population, and they suggested that discontinuing the drug during pregnancy was not warranted for women who benefit from it.<sup>16</sup>

There were few reports of RCTs in pregnant and lactating women with autoimmune disorders. A pilot trial compared bromocriptine and prednisone with prednisone-only for pregnant women with SLE in the third trimester. The researchers found that treatment was well tolerated and fewer women in the bromocriptine

<sup>12</sup> <https://medlineplus.gov/autoimmunediseseases.html> .

<sup>13</sup> Although diabetes mellitus and some thyroid disorders are often considered autoimmune diseases, these conditions are covered elsewhere in this report.

<sup>14</sup> [PMID 18716941](#).

<sup>15</sup> [PMID 28400421](#).

<sup>16</sup> [PMID 27145741](#).

group experienced pregnancy complications such as premature rupture of the membranes or preterm birth.<sup>17</sup> A larger study, comparing bromocriptine to a control group, suggested that this medication also may help reduce the risk of postpartum SLE relapse.<sup>18</sup>

Of the autoimmune disorders addressed in the articles, the most frequent were rheumatoid arthritis, antiphospholipid antibody syndrome (AA syndrome), MS, and SLE. Other publications addressed autoimmune disorders generally or focused on medications, not a specific disorder. For the most common disorders in the literature, Figure 2 shows the distribution of publications by type of research..

*Figure 2: Publications on Medicinal Therapies for Autoimmune Disorders in Pregnant and Lactating Women, by Type of Research and Disorder, 2006-2017*

		Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Rev	Edit/Comment	Other
<b>Autoimmune</b>	AA syndrome	9	1	1	3	24	32	81	4	4
	SLE	2	1	2	3	42	28	52	4	4
	MS	5	0	2	3	30	21	42	9	3
	Rheum. Arthritis	3	0	5	2	55	21	55	3	3

Figure 3 shows the pregnancy and lactation publications, by disorder and type of research, separately. Lactation was very infrequently the subject of autoimmune-related research.

*Figure 3: Pregnancy and Lactation Publications on Medicinal Therapies for Autoimmune Disorders, Shown Separately, by Disorder and Research Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
AA syndrome	9	1	1	3	24	32	80	4	4
Lupus	2	1	2	2	41	26	48	4	4
MS	4	0	1	2	25	18	32	4	3
Rheum. Arthritis	3	0	5	2	55	19	39	3	3
<b>Lactation</b>									
AA syndrome	0	0	0	0	0	0	1	0	0
Lupus	0	0	0	1	1	2	4	0	0
MS	1	0	1	1	5	3	10	5	0
Rheum. Arthritis	0	0	0	0	0	2	16	0	0

<sup>17</sup> [PMID 17911444](#).

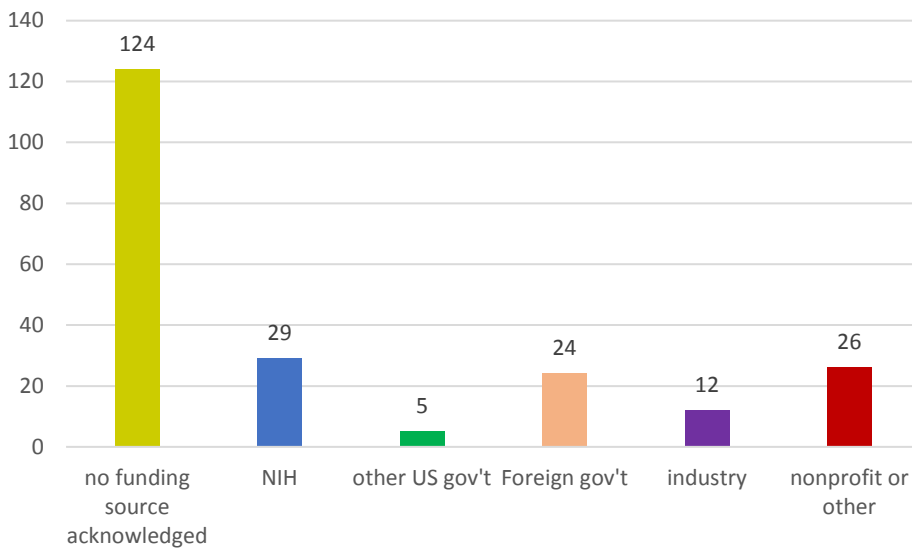
<sup>18</sup> [PMID 25973434](#).

## Current Research Activities

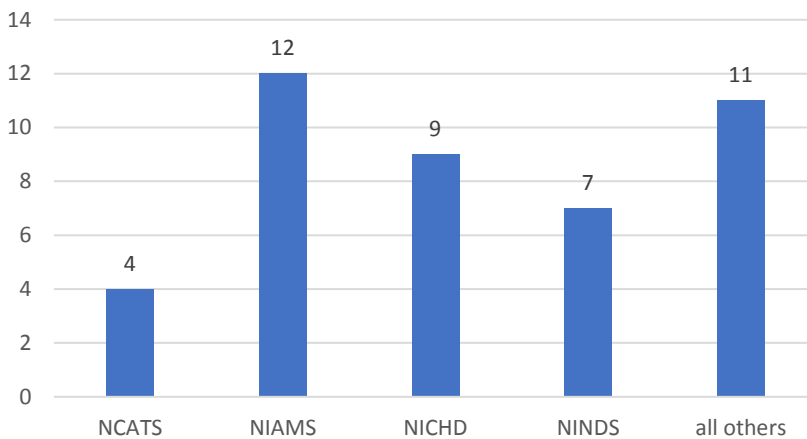
NIH supports few projects related to autoimmune disorders in pregnancy, and some are only indirectly related to medication. For example, researchers funded by NIAMS are analyzing gene expression to help understand the natural amelioration of RA during pregnancy; such mechanistic investigation of disease process can inform pharmaceutical research, however.<sup>19</sup>

Figure 3 shows external funding sources acknowledged by original research articles, published from 2006-2017, on autoimmune disorders in pregnant and lactating women. Of the 234 original research publications, slightly fewer than half (47 percent) acknowledged at least one external funding source.

*Figure 3: Original Research Publications (n=234) on Medicinal Therapies for Autoimmune Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited. Other U.S. government agencies included CDC, DoD, USDA, and AHRQ.



Note: Other NIH ICs included NCCIH, NCI, NHLBI, NIA, NIAAA, NIAID, NIDCR, NIEHS, NIGMS, and NIMH.

<sup>19</sup> [R01AR073111](#).

## Research Gaps

Research in autoimmune diseases during pregnancy is scattered and some conditions are especially understudied. Few studies are available, in either animals or humans, to describe the PK/PD of commonly-used medications for women with an autoimmune disease during pregnancy. Also limited is the number of RCTs, and of the few published, at least half were small pilot trials of fewer than 30 participants. Medicinal therapies in lactating women with autoimmune disorders appear to be especially understudied.

# Cancer

## Introduction

Cancer can occur during pregnancy or lactation, although it is relatively rare. Breast cancer is the most commonly- diagnosed type of malignancy during pregnancy. It affects about 1 in 3,000 women who are pregnant. Other cancers that affect younger populations, including cervical and lymphatic cancers, may also occur during pregnancy.<sup>20</sup>

## Scientific Literature

The analysis identified 1,072 articles, published between January 2006 and July 2017, that related to medicinal therapies for cancer in pregnant and lactating women. Of these, 21 publications (about 2 percent) related to vitamins, minerals and other supplements. Figure 1 shows the literature by publication type.

*Figure 1: Publications on Medicinal Therapies for Cancer in Pregnant and Lactating Women, by Research Type, 2006-2017*

	Basic	PK/ PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ comment	Other
<b>Cancer (all)</b>	181	10	5	4	118	357	333	46	18

The large majority of articles were either case reports or reviews; a more limited number of original research publications focused on disease mechanisms of cancer in pregnant women and on the potential impact of exposure to chemotherapy on fetal development. For example, one animal study showed that a cancer drug (ifosfamide) resulted in changes in placental size and structure and may negatively alter fetal brain, liver, and kidney tissues..<sup>21</sup> Another animal study showed that Gleevac therapy for cancer very early in pregnancy resulted in reduction of the mammary gland tumor without reducing the animal’s the ability to lactate.<sup>22</sup>

Few RCTs were reported. One publication, on outcomes for women who became pregnant during the course of a clinical trial for a breast cancer treatment, reported no congenital malformations in offspring exposed antenatally to the experimental treatment.<sup>23</sup>

In contrast to other conditions affecting pregnant women, there were few studies that used population-level data, registries, or large databases to address research questions related to cancer in pregnancy. Few studies reported on pharmacokinetic and/or pharmacodynamic effects of cancer drugs specifically when taken during pregnancy or lactation. One such study, however, analyzed pooled data on four anti-cancer drugs used in pregnant and non-pregnant women. The researchers found higher rates of renal clearance of the drugs among the pregnant women and suggested that higher dosing for two of the drugs may be needed to achieve therapeutic efficacy, although they cautioned that additional research is needed to confirm their results.<sup>24</sup>

<sup>20</sup> <http://www.cancer.net/navigating-cancer-care/dating-sex-and-reproduction/cancer-during-pregnancy> .

<sup>21</sup> [PMID 27124550](https://pubmed.ncbi.nlm.nih.gov/27124550/).

<sup>22</sup> [PMID 27550925](https://pubmed.ncbi.nlm.nih.gov/27550925/).

<sup>23</sup> [PMID 22367645](https://pubmed.ncbi.nlm.nih.gov/22367645/).

<sup>24</sup> [PMID 24713311](https://pubmed.ncbi.nlm.nih.gov/24713311/).

Figure 2 shows the distribution of publications by type of article.

*Figure 2: Publications on Medicinal Therapies for Cancer in Pregnant and Lactating Women, by Research Type and Cancer Site, 2006-2017*

		Basic	PK/ PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ Comment	Other
Cancer	Breast	29	0	0	2	26	69	62	14	7
	Lymphatic	7	1	1	0	11	64	27	6	2
	Gynecologic	10	0	1	0	26	88	23	10	4
	Lung	11	0	0	0	5	38	7	1	0

The most common type of cancer in this literature was breast cancer, followed by gynecologic, lymphatic, and lung cancers. Many other publications were either not focused on these types of cancer or did not focus on a specific type. Figure 3 shows the pregnancy related publications and lactation-related publications, by type, separately. Lactation was only infrequently the subject of cancer-related research.

*Figure 3: Pregnancy and Lactation Publications on Medicinal Therapies for Cancer, Shown Separately, by Cancer Type and Research Type, 2006-2017*

Condition	Basic	PK/PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ Comment	Other
<b>Pregnancy only</b>									
Breast	29	0	0	2	23	65	60	14	7
Lymphatic	7	1	1	0	10	62	26	6	2
Gynecologic	10	0	1	0	25	86	23	10	4
Lung	11	0	0	0	5	38	7	1	0
<b>Lactation</b>									
Breast	0	0	0	0	3	4	2	0	0
Lymphatic	0	0	0	0	1	2	1	0	0
Gynecologic	0	0	0	0	1	2	0	0	0
Lung	0	0	0	0	0	0	0	0	0

## Current Research Activities

NIH supports several projects related to cancer in pregnancy, including analyses of registry and/or population-based data. For example, NCI funds a large, population-based study of incidence, diagnostic characteristics, and mortality associated with cancers in pregnant and postpartum women. The scientists will use national Swedish medical datab to determine if pregnancy is associated with increases in the risk for certain cancers.<sup>25</sup> Several NCI-funded grants are focused on possible reasons why pregnancy may increase a woman's long-term cancer risk. For example, one project focuses on invasive placentation, an obstetric condition involving lack of control of the maternal/fetal interface that results in cellular invasion of placental tissue into the surrounding tissues.<sup>26</sup>

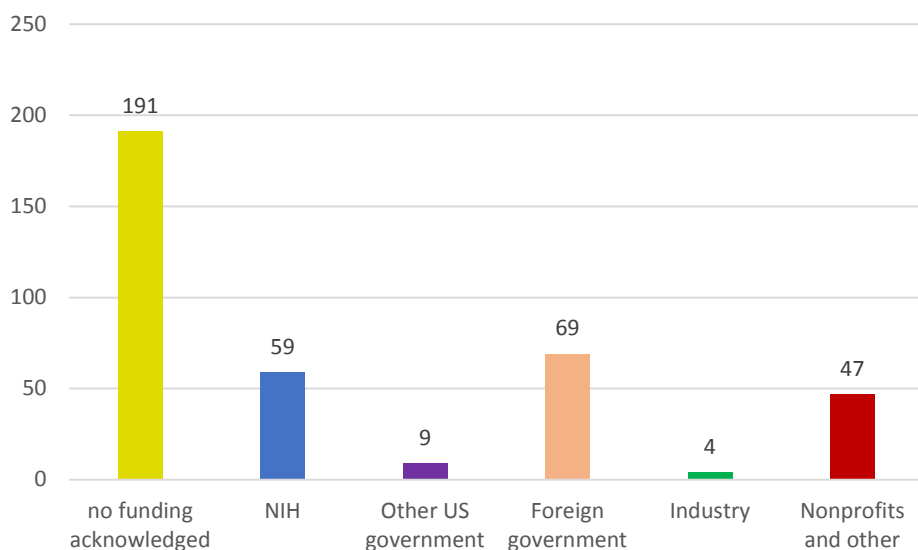
<sup>25</sup> [R21CA208793](#).

<sup>26</sup> [R21CA212429](#).

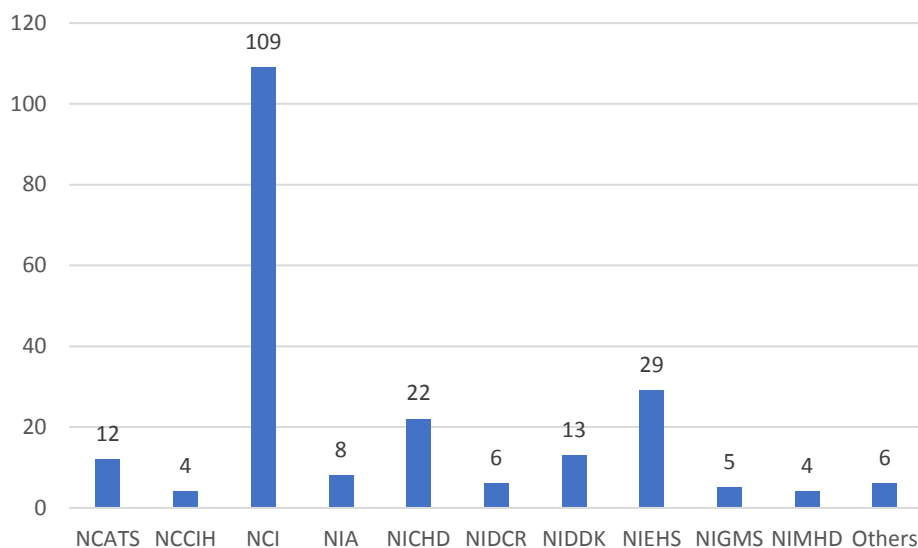


Figure 4 shows external funding sources acknowledged by original research articles, on medicinal therapies for cancer in pregnant and lactating women. Of the 357 original research publications, slightly over half (53 percent) acknowledged at least one funding source. Government agencies from non-U.S. countries supported the largest share of research, followed by the NIH. Among NIH ICs involved in this research, NCI supported the greatest number of research publications by a very wide margin. However, Of the 59 publications that acknowledged NIH funding, 42 (71 percent) acknowledged more than one NIH IC. Nonprofit organizations, including professional societies, foundations, and universities in the U.S. and elsewhere, also supported this research. Little industry support was acknowledged.

*Figure 4: Original Research Publications (n=357) on Medicinal Therapies for Cancer in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited. Other than NIH, U.S. government agencies included CDC, DoD, VA, NSF, USDA, and the Department of Energy.



Note: Other NIH ICs included NIMH, NIAAAA, and NHLBI.

## Research Gaps

Lactation in women with cancer is understudied. In pregnant women, very few PK/PD studies have been published on cancer medications in the past decade, even for the types of cancers that occur in pregnant women with some frequency. Only limited database/registry/population research has been conducted to investigate potential teratogenic or other adverse effects of anti-cancer medications during pregnancy.

# Central Nervous System Disorders

## Introduction

The central nervous system (CNS), consisting of the brain and spinal cord, coordinates and integrates most functions of the body. CNS conditions include epilepsy and other seizure disorders, migraine and other types of headaches, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and stroke. In the U.S., about 3.4 million people have epilepsy, including an estimated 400,000 children under 18 years of age.<sup>27</sup> According to some reports, anti-seizure medications are commonly used in pregnancy for control of epilepsy. (These drugs are also used for certain mental health conditions.<sup>28</sup>) Although the risk of stroke is considerably higher in older individuals, about one-third of individuals hospitalized for stroke are under the age of 65.<sup>29</sup> Headache disorders, including migraine, may improve during pregnancy. However, because headache disorders are very common, many pregnant women seek to continue treatment during their pregnancies.<sup>30</sup>

## Scientific Literature

The analysis identified 834 articles, published between January 2006 and July 2017, that related to CNS conditions in pregnant and lactating women. For all CNS conditions combined, about 38 percent of the publications reported original research. Fifty publications, 22 reporting on original research – addressed vitamin, mineral or other supplements in pregnant or lactating women with epilepsy. Most of those articles focused on whether folic acid and/or vitamin K could improve outcomes for pregnant women with epilepsy.

The CNS conditions most commonly addressed in the publications were epilepsy and other seizure disorders, stroke, and headache disorders. For these conditions, Figure 1 shows the distribution of publications by condition and type of research.

*Figure 1: Pregnancy- and Lactation-Related Publications on Medicinal Therapies for CNS Disorders, by Condition and Research Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Seizure disorders	9	8	52	2	44	2	19	25	13
Stroke	1	0	4	0	7	2	4	3	0
Headache/migraine	0	0	5	1	6	13	41	3	0

As shown in Figure 1, for each of these conditions in pregnant or lactating women, there were few publications reporting research on basic science or mechanism of disease, PK/PD, or RCTs. Half of the PK/PD studies in seizure disorders focused on the anti-convulsant drug lamotrigine, with three other drugs addressed in one or two articles each.<sup>31</sup> These studies reported that pregnant women cleared the anti-seizure drugs from their

<sup>27</sup> [PMID 28796763](#).

<sup>28</sup> [PMID 15343213](#).

<sup>29</sup> <https://www.cdc.gov/stroke/facts.htm> .

<sup>30</sup> [PMID 21442333](#).

<sup>31</sup> [PMID 18180176](#); [PMID 18201913](#); [PMID 27818298](#).

system relatively quickly and had lower concentrations of a drug in their system, compared with non-pregnant women. A study of multiple anti-seizure drugs found lower concentrations of the medications in the pregnant research participants, along with increased seizure activity, compared to their pre-pregnancy history.<sup>32</sup>

For seizure disorders generally, there was a substantial number of publications that analyzed population-level data or large databases. In addition to pregnancy and other registries in foreign countries, there are several large U.S. health-related sources of data, including administrative records and electronic health records. . These include the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), a collaborative effort between the FDA and researchers from Vanderbilt University, the HMO Research Network, and that of Kaiser Permanente Northern and Southern California as well as state Medicaid program data. Researchers have analyzed these types of data to address several types of questions related to CNS conditions and pregnancy, both for individual drugs and for the general class of anti-seizure drugs. These types of studies include:

1. Descriptions of physician prescribing patterns for pregnant and/or lactating women<sup>33</sup>;
2. Assessments of the effectiveness of these medications in controlling seizures in pregnant women<sup>34</sup>; and (in one study) the effect of untreated disease on seizure incidence in pregnant women with and without seizure disorders<sup>35</sup>; and
3. Analysis of potential effects of these medications on the offspring.

Most of the studies of potential effects on offspring of maternal anti-seizure medications focused on risk of structural birth defects. Studies of subtle or later-emerging outcomes for offspring were relatively rare. One such study, of data from an Australian pregnancy registry, assessed language ability at six to eight years of age among children exposed to anti-seizure medications during their mothers' pregnancy. The researchers found a negative correlation between medication exposure and language ability for valproate, one specific drug, but no relationship for other drugs in the same class.<sup>36</sup> Another study, of Danish registry data, assessed behavioral problems at four to five years of age in children exposed antenatally to maternal anti-seizure medications. Such children had higher scores in an assessment for behavioral problems than either children of mothers without epilepsy or those whose mothers had epilepsy but avoided medication while pregnant.<sup>37</sup>

Few clinical trials were published in this area. One study addressed infection-related seizures during pregnancy; another was a secondary analysis of limited relevance to seizure disorders; while a third focused on preventing infection in pregnant women with spinal cord injury.<sup>38</sup>

Although there were multiple review articles on headache and migraine in pregnant and lactating women, relatively little original research in this area was published..

Figure 2 shows the pregnancy and lactation publications, by disorder and type of research, separately. The very large majority of these publications report research on pregnancy, and not lactation. Some of the few lactation publications also involve pregnancy. For example, one PK/PD publication looked at the concentrations of the

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<sup>32</sup> [PMID 23911354](#).

<sup>33</sup> [PMID 19453723](#); [PMID 25653296](#); [PMID 23061694](#).

<sup>34</sup> [PMID 24995555](#).

<sup>35</sup> [PMID 25218112](#).

<sup>36</sup> [PMID 21339499](#).

<sup>37</sup> [PMID 24090777](#).

<sup>38</sup> [PMID 18986822](#).

drug levetiracetam, an anti-seizure medication, in both blood plasma of pregnant women and the breast milk of nursing mothers.<sup>39</sup>

*Figure 2: Pregnancy and Lactation Publications on Medicinal Therapies for CNS Disorders, Shown Separately, by Condition and Research Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Seizure disorders	6	7	50	1	35	1	8	18	7
Stroke	1	0	4	0	7	2	4	3	0
Headache/migraine	0	0	5	1	6	13	36	3	0
<b>Lactation</b>									
Seizure disorders	0	1	1	1	3	0	2	3	2
Stroke	0	0	0	0	0	0	0	0	0
Headache/migraine	0	0	0	0	0	0	5	0	0

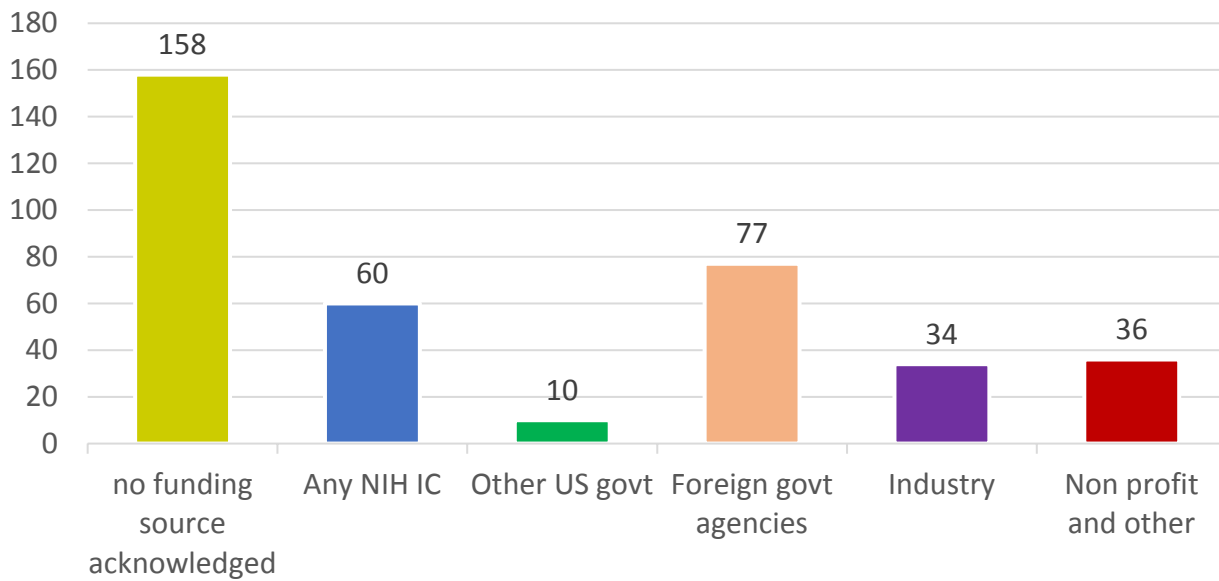
### Current Research Activities

NIH supports several projects related to medicinal therapies for CNS in pregnancy. For example, NINDS funds a group of scientists whose long-term goals are to (1) define changes in the brain and cerebral circulation during pregnancy that promote seizure in circumstances other than preeclampsia; and (2) describe how preeclampsia can predispose the brain to seizure, leading to eclampsia ([R01NS045940](#)). In some states, CDC’s Pregnancy Risk Assessment Monitoring System gathers information about the use of anti-seizure drugs in pregnant women. The North American Antiepileptic Drug Registry (<http://www.aedpregnancyregistry.org/>) (affiliated with Harvard Medical School), is a voluntary registry of women exposed to anti-seizure drugs during pregnancy.

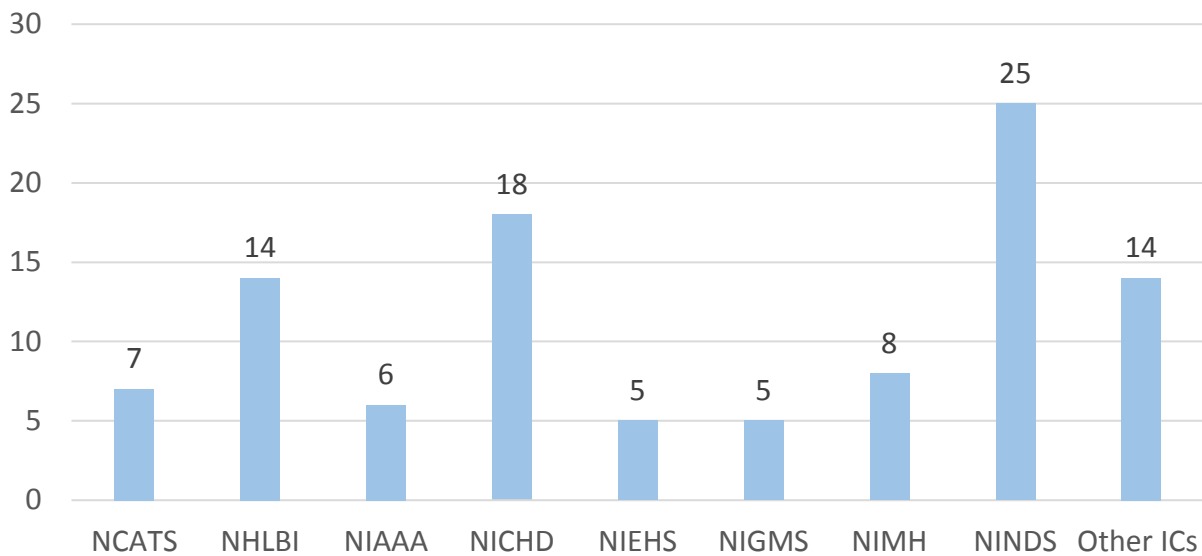
Figure 3 shows external funding sources acknowledged by original research articles published from 2006-2017 on CNS conditions in pregnant and lactating women. Over 45 percent of the publications did not acknowledge any external funding source. Government agencies of foreign countries supported the largest share of funded research, followed by the NIH. Among NIH ICs funding this research, NINDS, NICHD, and NHLBI supported research resulting in the greatest number of publications.

<sup>39</sup> [PMID 17381438](#).

*Figure 3: Original Research Publications on Medicinal Therapies for CNS Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Note: Foreign government agencies included the Canadian Institutes of Health Research, the U.K. Medical Research Council and similar health research agencies in 14 other countries.



Note: Other NIH ICs included NIDA, FIC, NCI, NIA, NIAID, NIAMS, NIDCR, NIDDK, and the NIH OD.

## Research Gaps

Research on medicinal therapies for CNS disorders in pregnant and lactating women is very limited. Results of PK/PD studies show that pregnant women clear anti-seizure drugs quickly, indicating the need for dosing studies. More information on potential teratogenic effects of medications for CNS disorders is certainly needed, especially studies that address subtle and/or long-term consequences. Clinical trials and/or rigorous comparative effectiveness studies on effectiveness of drugs in controlling seizures in pregnancy have not been conducted to inform prescribing decisions.

# Diabetes

## Introduction

Poor control of diabetes during pregnancy increases the chances both r birth defects and other health problems for a child and pregnancy complications with immediate and/or lasting impact on a woman’s health. Some women have either type 1 or type 2 diabetes before pregnancy, while others may develop gestational diabetes mellitus (GDM) during pregnancy. Each type of diabetes during pregnancy is a serious concern. After the baby is born, however, many diabetic women prefer to breastfeed, and available evidence suggests that breastfeeding may help the mother’s glycemic control and may help reduce the risk of diabetes later in life for the newborn. Scientific information to assess the impact of diabetes treatment during lactation on the infant is limited.<sup>40</sup>

## Scientific Literature

The analysis identified 1,427 articles, published between January 2006 and July 2017, that related to medicinal therapies for some form of diabetes in pregnant or lactating women. Of these, 141 publications (10 percent) concerned vitamin, mineral or other supplements. Figure 1 shows the distribution of publications by type of research.

*Figure 1: Publications on Medicinal Therapies for Diabetes in Pregnant and Lactating Women, by Research Type, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/ Comment	Other
Diabetes	164	21	44	114	423	101	437	49	74

Nearly three-fifths (59 percent) of the publications on medications for diabetes in pregnant and lactating women reported on original research. As shown in Figure 1, basic science studies, RCTs , and case series or cohort studies were common. The basic science studies typically used animal models to investigate the mechanisms of GDM and/or potential therapies for it. One mechanistic study in a mouse model of GDM found that resveratrol, a plant-based compound reported to exhibit beneficial effects in treating type-2 diabetes, relieved GDM in the mice by enhancing activation of the factor known as AMP-activated protein kinase.<sup>41</sup> Another study isolated a polysaccharide containing the element selenium from lotus leaf and found that this substance had positive effects in a rat model of GDM.<sup>42</sup>

A large number of case series and cohort studies investigated outcomes of women with diabetes during pregnancy and their babies. Most of these studies focused on GDM rather than pre-existing type 1 or type 2 diabetes. One cohort study in China found no differences in the rates of macrosomia (significantly larger than average size of newborn), neonatal hypoglycemia, or cesarean delivery for women who were treated for mild GDM, compared pregnant women with untreated GDM and pregnant women without the disorder.<sup>43</sup> Researchers at an Israeli treatment center followed pregnant women with GDM who were initially treated with glyburide (an oral diabetes medicine), then switched to insulin if they failed to achieve glycemic goals. The

<sup>40</sup> <https://www.cdc.gov/pregnancy/diabetes.html> ; PMID 21348815.

<sup>41</sup> PMID 26542478.

<sup>42</sup> PMID 27580896.

<sup>43</sup> PMID 25068946.



researchers reported that about three-quarters of the women achieved glycemic control with glyburide, and about half of the remaining women achieved the glycemic control goals with insulin.<sup>44</sup>

U.S. RCTs and those elsewhere assessed differing treatments for diabetes in pregnancy. Researchers in Brazil reported that treatment of GDM with metformin or glyburide (two oral diabetes medications) was equivalent for both women and newborns.<sup>45</sup> In Pakistan, an open-label, randomized trial found that metformin, or metformin with insulin if needed to maintain glycemic control, was effective for treating type 2 diabetes in pregnancy.<sup>46</sup> In a larger trial, researchers in the U.S. found that one-third of women with recent GDM experienced delays in lactation and that insulin treatment, maternal obesity, and suboptimal in-hospital breastfeeding were risk factors for such delay.<sup>47</sup>

Of the 141 articles reporting research on vitamin, mineral or other supplements, 93 (66 percent) were original research articles and 37 (26 percent) were clinical trials. Nearly all the trials focused on GDM. . Researchers tested a number of different vitamins and supplements, including vitamins D and E, omega 3, capsaicin, magnesium, selenium, probiotics, , zinc, and iron (among others).<sup>48</sup>

Figure 2 shows the pregnancy and lactation publications by research type, separately. As with many other conditions, most publications focused on pregnancy, not lactation. Of the lactation publications, a subset focused on the composition of breast milk and how its various components differed between women with and without GDM.

*Figure 2: Pregnancy and Lactation Publications on Medicinal Therapies for Diabetes, Shown Separately, by Research Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Diabetes	148	19	41	105	404	92	403	43	63
<b>Lactation</b>									
Diabetes	16	2	3	9	19	9	34	6	11

<sup>44</sup> [PMID 21067291](#).

<sup>45</sup> [PMID 20542272](#).

<sup>46</sup> [PMID 25874236](#).

<sup>47</sup> [PMID 24196401](#).

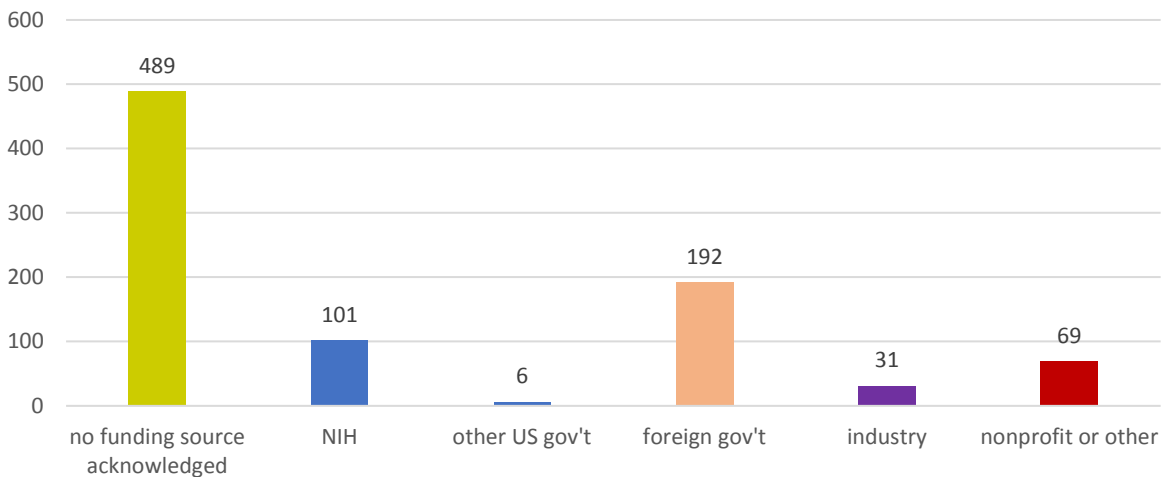
<sup>48</sup> [PMID 25771490](#); [PMID 25747955](#); [PMID 25790761](#); [PMID 26016859](#); [PMID 26250486](#); [PMID 28367765](#); [PMID 26465829](#); and others.

## Current Research Activities

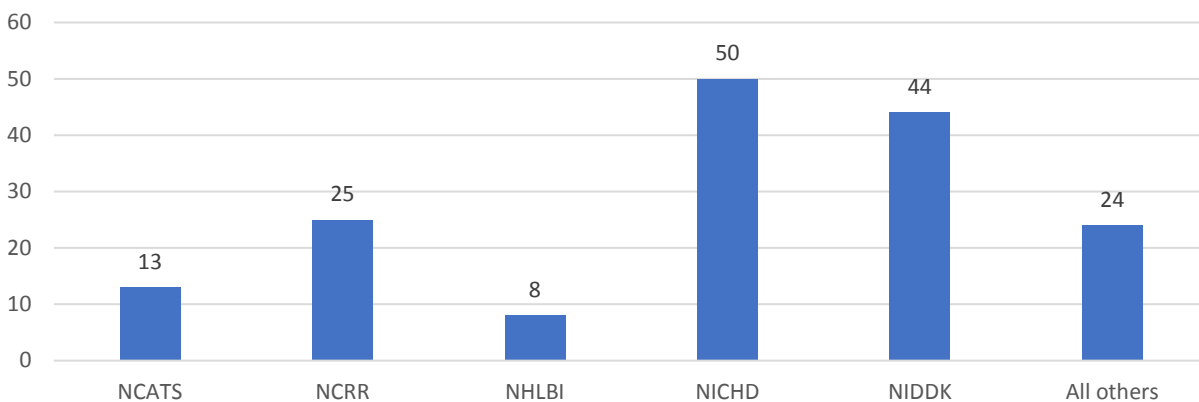
Gestational diabetes mellitus is an important area of research focus for several institutes at NIH, especially NICHD and NIDDK. Currently-funded NIH projects include several on screening approaches for GDM,<sup>49</sup> an NIEHS-funded study of BPA (bisphenol A, a chemical compound) exposure and risk of GDM,<sup>50</sup> and a study of follow-up care for women with GDM.<sup>51</sup>

Figure 3 shows external funding sources acknowledged by original research articles published from 2006-2017 on medicinal therapies for diabetes in pregnant and lactating women. Of the 840 original research publications, 489 (58 percent) did not acknowledge any external funding source. Nearly twice as many publications were associated with research supported by foreign governments, compared with NIH; nonprofit and industry funding were less common. NICHD, NIDDK, and NCATS were most frequently represented among the NIH funders.

*Figure 3: Original Research Publications (n=840) on Medicinal Therapies for Diabetes in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.



<sup>49</sup> [R01HD079647](#); [R01HD074794](#).

<sup>50</sup> [R01ES019196](#).

<sup>51</sup> [R01DK107528](#).

## Research Gaps

Most of the literature on diabetes in pregnancy addresses GDM, not pre-existing type 1 or type 2 diabetes. Type 1 diabetes, especially, is not well represented. Information about the impact of diabetes and diabetes treatment on lactation is needed.

# Endocrine Disorders

## Introduction

Endocrine disorders involve dysfunction in one or more of the body’s endocrine glands, which may produce either too much or too little of hormones needed for basic bodily functions. Among the endocrine disorders affecting pregnant women, thyroid problems are the most common, occurring in 1 to 2 percent of pregnant women. (Diabetes and hypertensive disorders that may be associated with endocrine system dysfunction are addressed separately in this analysis.). It can be challenging to diagnose an emerging endocrine disorder during pregnancy, because symptoms of pregnancy and symptoms of some common endocrine disorders are similar, and endocrine function is naturally altered during pregnancy.<sup>52</sup>

## Scientific Literature

The analysis identified 670 articles, published between January 2006 and July, 2017, that related to medicinal therapies for endocrine disorders in pregnant and lactating women. Figure 1 shows the distribution of publications by type of research.

*Figure 1: Publications on Medicinal Therapies for Endocrine Disorders in Pregnant and Lactating Women, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Endocrine	36	2	21	9	89	179	220	39	75

As shown in Figure 1 the majority of articles were case reports and reviews; 232 publications (35 percent) were original research. Among all types of research, thyroid disorders were the most common endocrine conditions addressed. Basic science research used animal models to explore the impact of thyroid treatments on fetal development, especially brain development.<sup>53</sup> Case series and cohort studies followed women who were treated for endocrine disorders during pregnancy and recorded a variety of outcomes, including congenital malformations, low birth weight, and preterm birth.<sup>54</sup> A clinical trial funded by the NICHD found that treatment of subclinical thyroid disease, beginning between eight and 20 weeks of gestation, did not result in significantly better cognitive outcomes in children through five years of age, compared with no treatment.<sup>55</sup>

Sixty of the publications (9 percent) addressed vitamins or other supplements for pregnant women with endocrine disorders. The very large majority of this research focused on iodine and/or selenium supplements to prevent or treat thyroid disorders in pregnancy. Of articles on supplements, 35 were original research articles, of which four were RCTs. Two trials found that selenium supplementation could improve maternal thyroid function.<sup>56</sup> Another study found that in Morocco, where iodine deficiency is common, lactating women who received iodine supplements soon after delivery could provide adequate iodine to their infants through

<sup>52</sup> [PMID 23681868](#).

<sup>53</sup> [PMID 22192600](#); [PMID 24712473](#); [PMID 22024639](#).

<sup>54</sup> [PMID 22547422](#); [PMID 27112035](#); [PMID 23811188](#).

<sup>55</sup> [PMID 28249134](#).

<sup>56</sup> [PMID 25524327](#); [PMID 17284630](#).

breastmilk for at least six months. Direct supplementation to the infants was less effective in improving infant iodine status.<sup>57</sup>

Figure 2 shows the pregnancy-related publications and lactation-related publications, by research type, shown separately. Almost all of the pregnancy- and lactation-related research focused on pregnancy, not lactation.

*Figure 2: Pregnancy and Lactation Publications on Medicinal Therapies for Endocrine Disorders, Shown Separately, by Publication Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Endocrine	34	2	21	8	86	174	212	39	71
<b>Lactation</b>									
Endocrine	2	0	0	1	3	5	8	0	4

### Current Research Activities

NIH is funding several projects on endocrine disorders in pregnant women. For example, an NICHD-supported research contract is designed to assess whether the level of iodine deficiency in U.S. pregnant women is severe enough to cause congenital hypothyroidism. The researchers will compare iodine concentrations in blood samples of newborns with the congenital disorder to samples from unaffected newborns.<sup>58</sup> An NIEHS-funded study is investigating the association between early-life environmental exposures to phthalate, triclosan, and BPA and maternal/child thyroid hormone concentrations, to determine if thyroid hormones (prenatal and postnatal) mediate the associations between chemical exposures and neurobehavioral outcomes.<sup>59</sup>

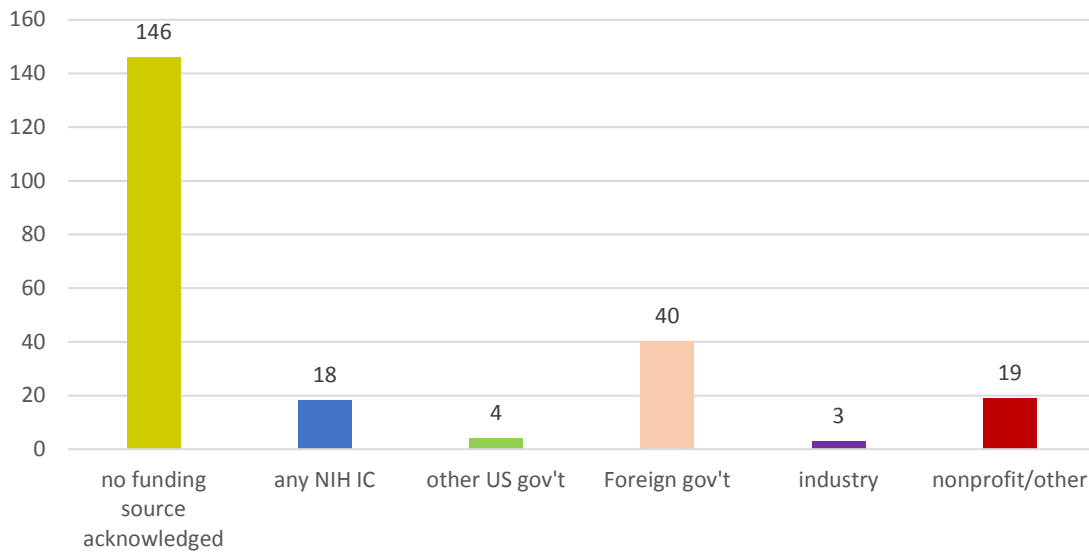
Figure 3 shows external funding sources acknowledged by original research articles on medicinal therapies for endocrine disorders in pregnant and lactating women. Nearly two-thirds (63 percent) did not acknowledge any external funding source. Foreign governments (Japan, China, Europe) supported 17 percent of the publications. About 8 percent of articles were supported by nonprofit organizations; very few reflected industry funding.

<sup>57</sup> [PMID 24622750](#).

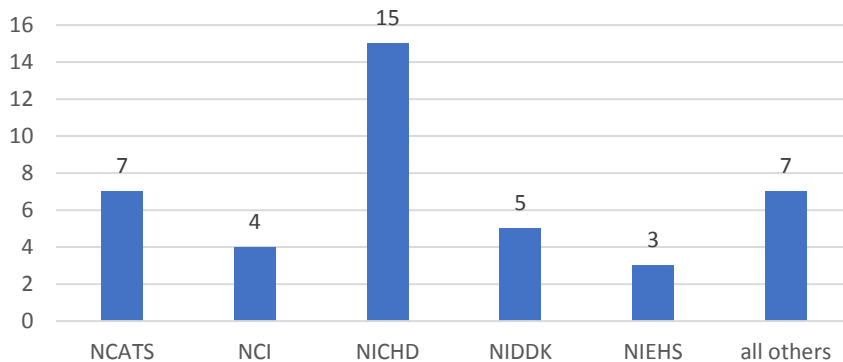
<sup>58</sup> [NICHD contract](#).

<sup>59</sup> [R01ES024381](#).

Figure 3: Original Research Publications (n=232) for Medicinal Therapies for Endocrine Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.



Note: Other NIH ICs included NIA, NIDCR, NIGMS, and NINDS. A single publication may be reported in multiple categories if more than one IC was acknowledged.

## Research Gaps

A limited evidence base is available to physicians to diagnose and treat pregnant women with pre-existing or emerging endocrine disorders. Few recent research studies have assessed the underlying disease mechanism, PK/PD of iodine supplementation, replacement hormone treatment, or other therapies. Few RCTs of endocrine disorder treatment options for pregnant women were published in the past decade. Even less information is available on endocrine disorder therapies for n lactating women and their breastfeeding infants.

# Hyperemesis Gravidarum and Other Nausea and Vomiting of Pregnancy

## Introduction

Nausea and vomiting in pregnancy is typically called “morning sickness,” but can occur at any time. The symptoms usually start before nine weeks of pregnancy and, for most women, resolve by the second trimester (14 weeks of pregnancy), but can last longer, even throughout the pregnancy. The most severe form of pregnancy-associated nausea and vomiting is hyperemesis gravidarum, which occurs in up to 3 percent of pregnancies. . Nausea and vomiting are considered hyperemesis if a woman has lost at least 5 percent of her pre-pregnancy weight and/or has other problems, related to dehydration. Women with hyperemesis need therapy to stop the vomiting and restore body fluids, so as to prevent harm to mother and fetus.<sup>60</sup>

## Scientific Literature

The analysis identified 264 articles, published between January 2006 and July 2017, that related to medicinal therapies for nausea and vomiting in pregnant women. Figure 1 shows the distribution of publications by type of research.

*Figure 1: Publications on Medicinal Therapies for Nausea and Vomiting in Pregnant Women, by Research Type, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Nausea and vomiting	5	6	4	22	30	62	106	17	12

Although the largest number of publications were reviews and case reports, there were multiple RCTs of therapies for nausea and vomiting in pregnancy. Several of these related to doxylamine-pyridoxine, a combination drug approved by the FDA for treatment of refractory nausea and vomiting in pregnancy.<sup>61 62</sup> There were five RCTs of herbal or other "natural" therapies for nausea and vomiting in pregnancy; four such studies focused on ginger and one focused on lemon essential oil.<sup>63</sup> Almost all of the 17 editorials and commentaries published on the topic called for more research on nausea and vomiting in pregnancy, and nearly half of these called for additional research on herbal, supplemental, or "natural" remedies.

Of publications on nausea and vomiting in pregnancy, 78 (30 percent) addressed non-drug medicinal therapies. Of these, 33 (42 percent) were original research articles. The majority of these articles reported pregnant women's use of these therapies. A survey of Texas midwives, for example, found that 90 percent had recommended at least one herbal or other complementary medicine product to their patients and nausea and

<sup>60</sup> <https://www.acog.org/Patients/FAQs/Morning-Sickness-Nausea-and-Vomiting-of-Pregnancy> .

<sup>61</sup> [PMID 25884778](#); [PMID 20843504](#); [PMID 27881103](#).

<sup>62</sup> A product with this same formulation of ingredients was available in the U.S. where it had been approved in the 1950s. During the 1970's, the drug was widely used, but it was voluntarily withdrawn from the market in 1983 amid litigation. Subsequent clinical and epidemiological research supported its safety profile and when the same formulation was submitted to the FDA, it was again approved for use. See [PMID 24645939](#).

<sup>63</sup> [PMID 22545357](#); [PMID 17957907](#); [PMID 19250006](#); [PMID 18272271](#); [PMID 24829772](#).

vomiting of pregnancy was one of the most common indications associated with such products.<sup>64</sup> One publication addressed the composition of alternative remedies, which are generally unregulated. Researchers examined the composition and product labeling of ten ginger preparations from different manufacturers, and found wide variation in concentrations of the active ingredient (gingerol) and suggested serving sizes of ginger root powder.<sup>65</sup>

Figure 2 shows the pregnancy-related publications and lactation-related publications, by type, separately. Because nausea and vomiting of pregnancy is a pregnancy-specific condition, it was unsurprising that nearly all of the pregnancy and lactation research in this area addressed pregnancy, not lactation. All of the lactation publications were review articles.

*Figure 2: Pregnancy and Lactation Publications on Medicinal Therapies for Nausea and Vomiting of Pregnancy, Shown Separately, by Condition and Publication Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Nausea and vomiting	5	6	4	22	30	62	101	17	12
<b>Lactation</b>									
Nausea and vomiting	0	0	0	0	0	0	5	0	0

### Current Research Activities

NIH is supporting a RCT to compare the efficacy and tolerability of two anti-nausea drugs -- gabapentin and ondansetron -- for treatment of hyperemesis gravidarum ([R01HD076313](#)).

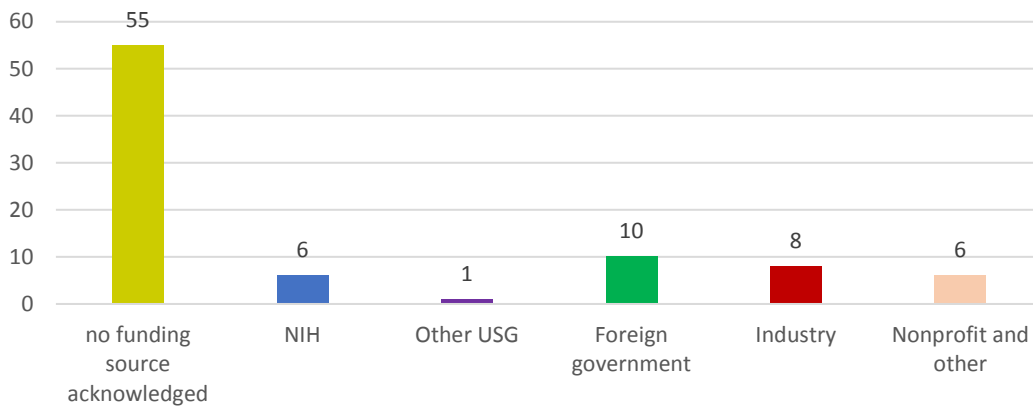
Figure 3 shows funding sources acknowledged by original research articles on medicinal therapies for nausea and vomiting in pregnancy. Of 84 such publications, 55 (65 percent) did not acknowledge an external funding source. Two NIH ICs – NICHD and NCATS – jointly funded research in this area, as acknowledged by two publications. Three additional articles were funded by NICHD and one additional article was funded by NCATS. Government agencies of foreign countries supported the largest share of funded research, followed by industry and foundations and other nonprofit organizations.

<sup>64</sup> [PMID 17826710](#).

<sup>65</sup> [PMID 16738161](#).



Figure 3: Original Research Publications (n=84) on Medicinal Therapies for Nausea and Vomiting in Pregnant Women, by External Funding Source, 2006-2017



Notes: Eight countries were represented in the foreign government category, with only one country (Canada) supporting more than one published research project. NICHD and NCATS were the only NIH ICs that were acknowledged.

### Research Gaps

Limited research is available on medicinal therapies for nausea and vomiting in pregnancy. Although supplement products may be widely used for these purposes, few studies have been reported on their composition, safety or efficacy.

# Hypertensive Disorders

## Introduction

High blood pressure (hypertension), whether chronic or associated with pregnancy, health risks for both the pregnant woman and fetus, with with adverse effects that may persist well after delivery. Hypertension is associated with an increased risk for pregnancy complications including preeclampsia (abrupt spike in blood pressure with signs of damage to another organ system, typically renal or liver), placental abruption (separation of the placenta from the wall of the uterus), GDM, and preterm birth. Unchecked preeclampsia can progress to eclampsia, seizures and coma, and death.<sup>66</sup> Between 3 percent and 4 percent of pregnant women in the U.S. develop preeclampsia.<sup>67</sup> CDC has reported that the overall rate of hypertensive disorders in pregnancy has increased substantially over past 20 years.<sup>68</sup>

## Scientific Literature

The analysis identified 1,027 articles, published between January 2006 and July 2017, that related to medicinal therapies for hypertensive disorders in pregnant and lactating women. Of these publications, 595 (58 percent) reported on original research.

*Figure 1: Pregnancy and Lactation Publications on Medicinal Therapies for Hypertensive Disorders, by Research Type, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Hypertension	141	11	20	71	295	147	432	46	57

Over the past decade scientists have investigated the biological mechanisms of pregnancy-associated hypertensive disorders, identified possible targets and pathways for treatment, and identified and assessed potentially therapeutic compounds in animal models of hypertension in pregnancy. One group of researchers used a mouse model of pregnancy-associated hypertension to determine that hydralazine (an anti-hypertensive drug) increased the levels of tele-methylhistamine (a metabolite of histamine) in the blood during pregnancy. The finding suggested a potential mechanism of action for the drug.<sup>69</sup> Another group found that preeclamptic mice treated with injections of vascular endothelial growth factor did not have growth-restricted offspring, compared to mice with untreated preeclampsia.<sup>70</sup>

A large proportion of research on disease and treatment outcomes of hypertensive disorders during pregnancy was case series and cohort studies. A case-control study in the U.S. and Canada found that both treated and untreated hypertensive disorders in pregnancy were associated with specific birth defects.<sup>71</sup> A cohort study

<sup>66</sup> <https://www.nichd.nih.gov/health/topics/preeclampsia/Pages/default.aspx>.

<sup>67</sup> [PMID 24201165](#).

<sup>68</sup> <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-complications-data.htm>.

<sup>69</sup> [PMID 28069864](#).

<sup>70</sup> [PMID 27996960](#).

<sup>71</sup> [PMID 25395267](#).

using VA maternity benefit data found that women veterans had a higher risk of developing hypertensive disorders during pregnancy compared with other women who delivered in the U.S.<sup>72</sup>

Almost a quarter (236 articles or 23 percent) of the literature on hypertensive disorders in pregnancy addressed vitamin or other supplement products. Of 71 RCTs of medicinal therapies for these disorders, more than 40 percent focused on vitamin or mineral supplements, including vitamin D, folic acid, selenium, and fish oil. An analysis of data from one clinical trial in a racially/ethnically diverse sample found that supplementation with vitamins C and E did not reduce pregnant women’s risk of preeclampsia, regardless of genetic phenotype.<sup>73</sup> The results were generally consistent with other findings, although a few studies reported reductions in preeclampsia risk associated with use of various supplements.

Figure 2 shows the pregnancy and lactation publications on medicinal therapies for hypertension, separately. Because preeclampsia is a common, pregnancy-specific condition, it was unsurprising that nearly all the pregnancy and lactation research for hypertensive disorders addressed pregnancy, not lactation.

*Figure 2: Pregnancy and Lactation Publications on Medicinal Therapies for Hypertensive Disorders, Shown Separately, by Publication Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Hypertension	136	10	20	66	288	137	421	44	52
<b>Lactation</b>									
Hypertension	5	1	0	5	7	10	11	2	5

### Current Research Activities

NIH supports an extensive portfolio of research on hypertensive disorders in pregnancy, with grants funded by NICHD, NHLBI, NINDS, NIGMS, NIDDK, and other ICs. Several research groups are assessing the role of genetic factors in preeclampsia.<sup>74</sup> Others are assessing long-term effects of hypertensive disorders in pregnancy and evaluating therapies.<sup>75</sup>

Figure 3 shows external funding sources acknowledged by original research articles on medicinal therapies for hypertensive disorders in pregnant and lactating women. Of the 595 original research publications, 348 (58 percent) did not acknowledge any external funding source. National government agencies and nonprofit organizations in the U.S. and elsewhere were the primary funders, with little reported research funded by industry. Among NIH ICs, NICHD and NHLBI supported research reported in the largest number of publications, but multiple IC sponsorship was common.

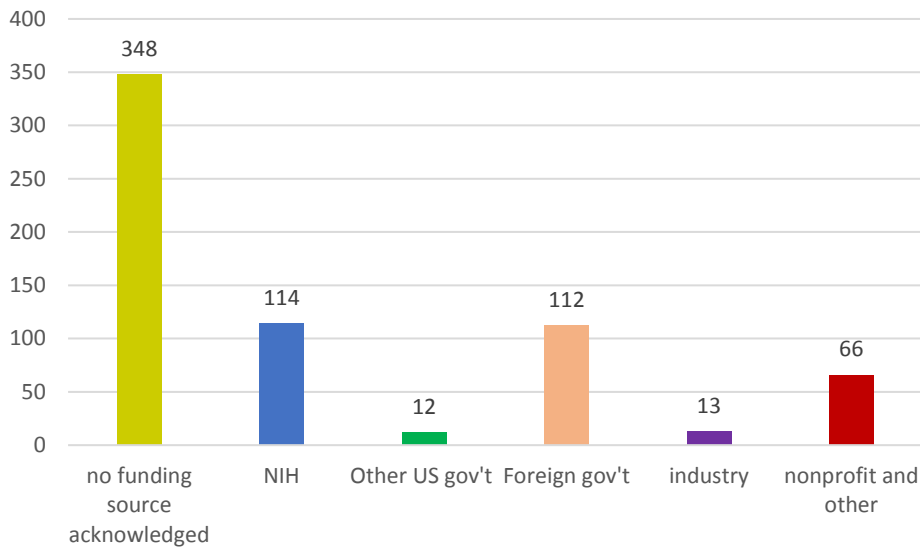
<sup>72</sup> [PMID 25090022](#).

<sup>73</sup> [PMID 23573260](#).

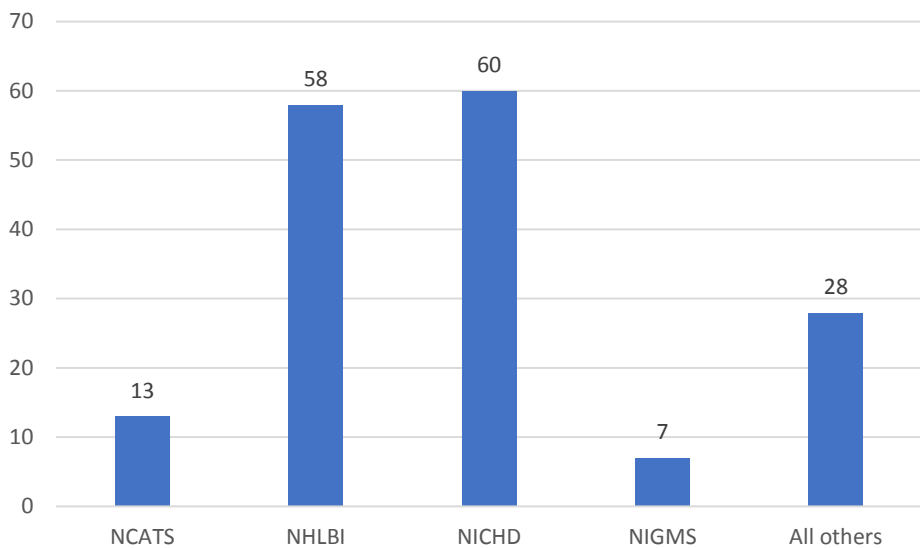
<sup>74</sup> [R37HD0762853](#); [P20GM109035](#); [R01HD084628](#).

<sup>75</sup> [K08DK101560](#); [R01HL121527](#); [F32HL129677](#); [U54HD047891](#).

*Figure 3: Original Research Publications (n=595) on Medicinal Therapies for Hypertensive Disorders in Pregnancy and Lactation, by External Funding Source, 2006-2017*



Notes: A single publication will be reported in multiple categories if more than one type of funding source was acknowledged.



Notes: Many articles with NIH funding credited multiple ICs. A single publication will be counted in multiple categories when more than one IC is credited.

## Research Gaps

Although the research community has continued to address hypertensive disorders in pregnancy, the search for more effective prevention therapies continues. Researchers have conducted studies of the effect of vitamins and other supplements on preeclampsia, with mixed results, and few studies have been available to describe the PK/PD of these substances when taken during pregnancy. The effect of hypertension medications on lactation and breast milk remains a substantial gap.

# Infectious Diseases

## Introduction

Infections during pregnancy are common; one report of infection rates in a large registry “control” group indicated that nearly two-thirds (63 percent) of 4,967 women experienced at least one infection (respiratory, sexually-transmitted, “fever,” urinary tract, others) during pregnancy.<sup>76</sup> Infectious diseases in pregnant women commonly cause substantial maternal and neonatal morbidity and mortality, especially in low- and middle-income countries. Several maternal mechanical and pathophysiological changes and immune system adaptations that occur during pregnancy may elevate the severity of infection during pregnancy.<sup>77</sup> Infections including Zika, hepatitis B virus (HBV) tuberculosis (TB), toxoplasmosis, cytomegalovirus, malaria, group B streptococcus (GBS), and influenza are known risks for both the pregnant woman and fetus. Apart from the well-documented risk of HIV transmission via breast milk, few data appear to be available on the prevalence or effects of infection among lactating women.

## Scientific Literature

The analysis identified 1,227 articles, published between January 2006 and July 2017, that related to medicinal therapies for infectious diseases in pregnant and lactating women. Figure 1 shows the literature by type of research. (Vaccines are addressed separately in this analysis.)

*Figure 1: Publications on Medicinal Therapies for Infectious Diseases in Pregnant and Lactating Women, by Research Type, 2006-2017*

	Basic	PK/ PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ comment	Other
<b>Infection (all)</b>	78	44	40	62	363	97	420	23	100

A majority of the publications (687, or 56 percent) reported original research. Although case series and cohort studies were the most common type of research, there were 62 RCTs. Many articles focused on maternal-child transmission of infection, both for HIV and other conditions. For example, a case-control study of maternal to child transmission of hepatitis b virus (HBV) in China found that family history of HBV infection, intrahepatic cholestasis (a liver disorder in pregnant women), and premature rupture of membranes were risk factors for perinatal transmission of HBV. HBV immunoglobulin injections for HBV-positive pregnant women and systemic treatment prevented the infection in newborns.<sup>78</sup> Scientists also used cohort studies to investigate risks both of infection and its treatment, for the pregnant woman and fetus. For example, researchers found elevated biomarkers for oxidative stress in Nigerian women with malaria, whether or not they were treated for the infection.<sup>79</sup> Another RCT compared two treatment regimens for malaria in pregnant women.<sup>80</sup>

<sup>76</sup> [PMID 19086018.](#)

<sup>77</sup> [PMID 25207782.](#)

<sup>78</sup> [PMID 21987612.](#)

<sup>79</sup> [PMID 21495615.](#)

<sup>80</sup> [PMID 27326859.](#)

Forty-one (about 3 percent) of the publications focused on vitamin or other supplements. About half of the publications were original research, and 7 were RCTs, focused on vitamins or other supplements, including “natural” products. For example, researchers in Finland assessed the impact of black currant seed oil on immune function and the composition of breast milk.<sup>81</sup> Publications related to various supplements were more likely to focus on urinary tract infections or mastitis, compared with publications related to drugs.

Many studies in the literature focused on medications used for a variety of infections, or focused on infection symptoms (such as fever). Because so many different specific infections occur in pregnant women, there were relatively fewer studies for individual infections. However, TB, UTI and , parasitological infections were addressed even less frequently. Figure 2 shows the distribution of publications by specific infection and type of article.

*Figure 2: Publications on Medicinal Therapies for Infections in Pregnant and Lactating Women, by Infection and Type of Research, 2006-2017*

		Infections				Case series	Case Reports	Reviews	Edit/Comment	Other
		Basic	PK/PD	Pop/DB	RCT					
	CMV	3	0	4	2	7	9	21	0	6
	Group B strep	4	0	3	2	19	5	18	2	8
	Hepatitis B	6	1	2	2	42	6	21	1	5
	HIV/AIDS	16	7	3	14	44	6	54	2	14
	Influenza	13	2	15	2	80	26	86	15	33
	Malaria	4	12	1	5	21	6	30	2	3
	Parasites	6	1	2	0	8	10	22	0	3
	Pertussis	6	1	2	0	8	4	8	0	2
	Rubella	2	0	3	0	22	0	4	0	1
	Tetanus	0	0	0	0	6	4	4	0	2
	TB	0	0	0	0	3	2	2	0	0
	UTI	1	0	0	2	3	0	0	0	1
	Zika	6	0	0	0	0	2	13	9	2

As with other conditions, most published research on medicinal therapies for infectious diseases in pregnant and lactating women focused on pregnancy, not lactation. Figure 3 shows pregnancy-related and lactation-related publications, by type and infection, separately.

<sup>81</sup> [PMID 23980846](https://pubmed.ncbi.nlm.nih.gov/23980846/).

Figure 3: Pregnancy and Lactation Publications on Medicinal Therapies for Infectious Diseases, Shown Separately, by Infection and Type of Research, 2006-2017

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
CMV	3	0	4	2	7	9	21	0	5
Group B strep	4	0	2	1	17	1	10	1	6
Hepatitis B	4	1	2	2	40	6	13	0	3
HIV/AIDS	16	7	3	11	38	6	48	2	11
Influenza	12	2	15	2	78	26	84	14	32
Malaria	4	12	1	5	21	6	29	2	3
Parasites	6	1	2	0	8	10	21	0	3
Pertussis	6	1	2	0	8	4	7	0	1
Rubella	2	0	2	0	22	0	4	0	1
Tetanus	0	0	0	0	6	4	2	0	2
TB	0	0	0	0	3	2	2	0	0
UTI	1	0	0	1	1	0	0	0	1
Zika	0	0	0	0	0	0	0	2	0
<b>Lactation</b>									
CMV	0	0	0	0	0	0	0	0	1
Group B strep	0	0	1	1	2	4	8	1	2
Hepatitis B	2	0	0	0	2	0	8	0	0
HIV/AIDS	0	0	0	3	6	0	6	0	3
Influenza	1	0	0	0	2	0	2	1	1
Malaria	0	0	0	0	0	0	1	0	0
Parasites	0	0	0	0	0	0	1	0	0
Pertussis	0	0	0	0	0	0	1	0	1
Rubella	0	0	1	0	0	0	0	0	0
Tetanus	0	0	0	0	0	0	2	0	0
TB	0	0	0	0	0	0	0	0	0
UTI	0	0	0	1	2	0	0	0	0
Zika	0	0	0	0	0	0	0	0	0

### Current Research Activities

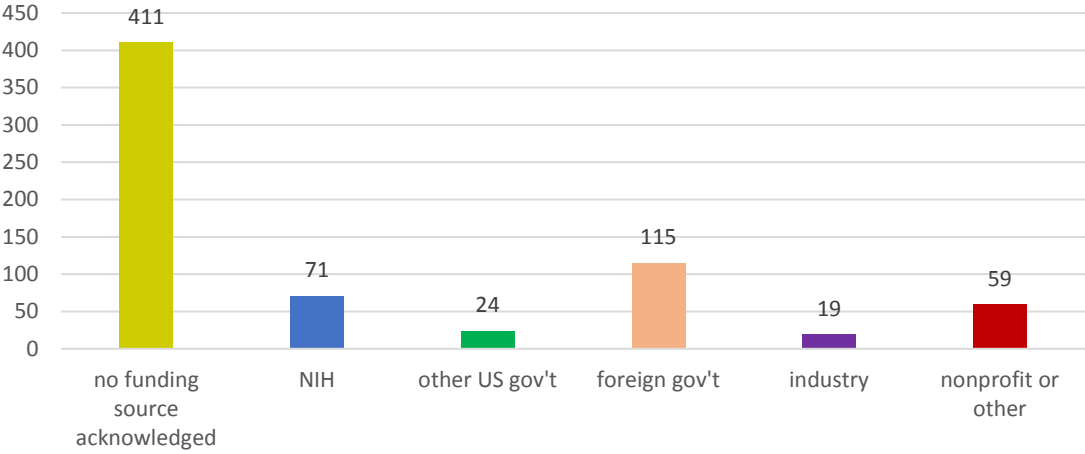
. NIH-supported projects are addressing a variety of infections in pregnancy, including HIV/AIDS, malaria, hepatitis C virus, and listeria.<sup>82</sup>

Some of the research focuses on how the placenta can defend the fetus against infection

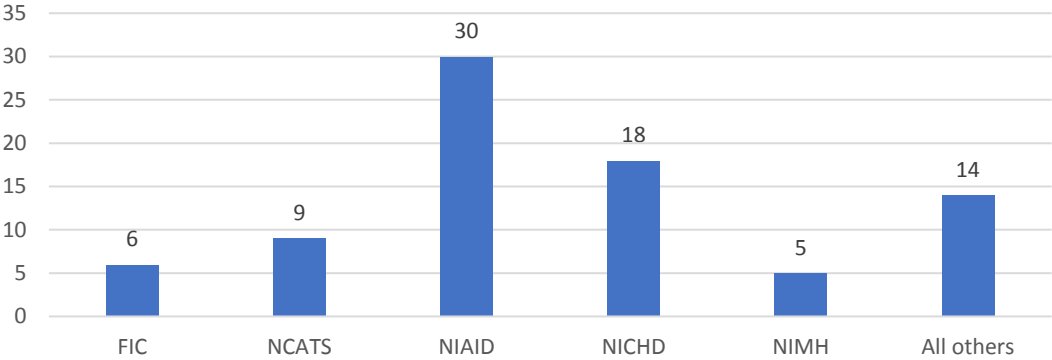
<sup>82</sup> [R01HD080485](#); [R01HD086124](#); [R01HD075549](#); [R21HD090635](#).

Figure 3 shows funding sources acknowledged by original research articles on medicinal therapies for infectious diseases in pregnant and lactating women. A total of 411 publications, or 60 percent of the total, did not acknowledge any external funding source. Foreign governments and NIH accounted for nearly 200 publications. Of the NIH ICs, NIAID and NICHD accounted for the most publications.

*Figure 3: Original Research Publications (n=689) on Medicinal Therapies for Infections in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.



Note: A single publication may be reported in multiple categories if multiple funding sources were cited.

**Research Gaps**

There is very limited scientific information for pregnant and lactating women and their providers on how and whether to treat infectious diseases during pregnancy and lactation. . Some common infections worldwide, such as tuberculosis, are clearly understudied in pregnant and lactating women. Few original research publications assessed the impact of untreated infection. The effect of infection and its treatment on breast milk and lactation is still largely unknown.



# Low Milk Supply

## Introduction

Breastfeeding is strongly recommended to promote infant health. However, many women perceive that their milk supply is too low, and there may be a clinical reason that milk production or release is inadequate. Insufficient milk supply is one of the most commonly cited reasons for early cessation or decreased exclusivity in women who have initiated breastfeeding.<sup>83</sup> However, it is often unclear whether milk production is actually insufficient, or there is a problem with the breastfeeding process, such as insufficient stimulation.

## Scientific Literature

The analysis identified 48 articles, published between January 2006 and July 2017, that related to medicinal therapies for low breast milk supply. Figure 1 shows the distribution of publications by type of research.

*Figure 1: Publications on Medicinal Therapies for Low Milk Supply in Lactating Women, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Low milk supply	1	0	0	8	8	3	18	6	4

Of the different types of research reported, eight were RCTs of various medications. Three trials, all conducted overseas, focused on the drug domperidone. Opinion is mixed on domperidone’s use in lactation because of reported risk of cardiac arrhythmias in trials of the drug for gastrointestinal disorders. It is not approved for use in the U.S. any purpose, including lactation. The FDA issued a domperidone import alert in 2004 and updated it in 2012, and also issued a public safety warning against the drug’s use for lactation. The most recent of the clinical trial studies of domperidone found that mothers in the intervention group experienced an increase in milk supply, but that actual gain in milk supply was modest.<sup>84</sup> A previous study had found larger reported gains in milk supply as well as no changes to the composition of breast milk.<sup>85</sup> In a small crossover trial, researchers found that milk supply increased for two-thirds of the women in the domperidone group.<sup>86</sup> None of the studies assessed longer-term effects or addressed possible cardiac concerns.

Two other RCTs provided data showing that recombinant human prolactin increased milk volume and induced changes in milk composition similar to those that occur during normal lactogenesis (breast milk production).<sup>87</sup> The remaining four trials were concerned with herbal therapies or alternative Chinese medicine.<sup>88</sup>

## Current Research Activities

<sup>83</sup> [PMID 19094151](#).

<sup>84</sup> [PMID 28107101](#).

<sup>85</sup> [PMID 20008425](#).

<sup>86</sup> [PMID 18507654](#).

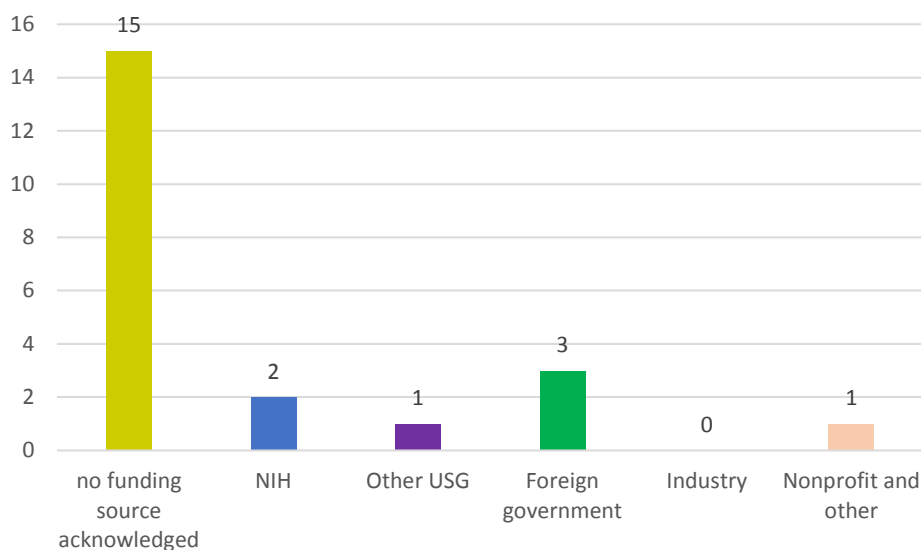
<sup>87</sup> [PMID 20718766](#); [PMID 21262884](#).

<sup>88</sup> [PMID 18652318](#); [PMID 26430522](#); [PMID 28569619](#).

The majority of NIH's portfolio in lactation research is related to the composition and protective effects of human breast milk, maternal and infant microbiome, immunity, and related areas. However, NIH also funds several grants related to promoting breastfeeding, and this research may directly or indirectly address perceived low milk supply. For example, researchers supported by NINR are testing a mobile, semi-automated text message-based intervention, designed for mothers without prior breastfeeding experience, to prevent or mitigate inaccurate perceptions of low or insufficient milk supply.<sup>89</sup>

Figure 2 shows external funding sources acknowledged by original research articles, published 2006-2017, on insufficient milk supply. Of the 20 original research publications, 75 percent (15 articles) did not acknowledge an external funding source. Canadian and Chinese government agencies funded two and three studies, respectively. Two NIH ICs – NIDDK and NCATS – funded research on low milk supply, resulting in one publication each.

*Figure 2: Original Research Publications (n=20) on Medicinal Therapies for Low Milk Supply, by External Funding Source, 2006-2017*



Notes: if multiple sources are acknowledged, a single publication may be classified in more than one category.

## Research Gaps

Limited research is available on insufficient breast milk supply. Although various supplement products may be widely used to promote lactation, very few studies have been conducted on the effectiveness of these remedies and their safety remains largely unaddressed.

<sup>89</sup> [R00NR015106](#).

# Mental Health

## Introduction

Many women experience mental health disorders during pregnancy and the postpartum period, with onset either preceding pregnancy or emerging during pregnancy or subsequently. For example, as many as one in nine women experience depression during pregnancy. Pre-pregnancy mental illness, including bipolar disorder, schizophrenia, or other conditions, may flare up during pregnancy.<sup>90</sup> Women who rely on medication to treat these conditions face a dilemma when they become pregnant. There is little data to establish whether the medications for the disorders are safe during pregnancy, yet untreated mental illness may also pose risks for both the woman and the developing fetus<sup>91</sup>.

## Scientific Literature

The analysis identified 1,479 articles, published between January 2006 and July 2017, that related to medicinal therapies for mental health disorders in pregnant and lactating women. Figure 1 shows the literature by type of research.

*Figure 1: Publications on Medicinal Therapies for Mental Health in Pregnant and Lactating Women, by Research Type, 2006-2017*

	Basic	PK/ PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ comment	Other
<b>Mental health</b>	87	10	34	15	257	216	709	122	29

There were many reviews, editorials, comments, and case reports discussing the safety of antidepressant and antipsychotic medications during pregnancy. A significant number of basic science studies were conducted, using animal models to assess how prenatal exposure to antidepressants (particularly selective serotonin reuptake inhibitors, SSRIs) may affect the offspring.<sup>92</sup> Researchers have investigated potential effects on neurodevelopment and cardiovascular development, among other systems. However, there is much more limited evidence of effects in human subjects.

A number of studies have leveraged large-scale population databases to identify relationships between prenatal exposure to medications and outcomes in the offspring. These cohort and population studies have shown mixed results. Several studies of Swedish and Norwegian data found no increased risk to the offspring from exposure to SSRIs.<sup>93</sup> However, other studies have found adverse outcomes. A study of data from other countries found an increased risk of pulmonary hypertension in the offspring for children who were prenatally exposed to SSRIs<sup>94</sup>

<sup>90</sup> <https://www.cdc.gov/features/maternal-depression/index.html> ; <http://www.nhs.uk/Conditions/pregnancy-and-baby/pages/mental-health-problems-pregnant.aspx> .

<sup>91</sup> [PMID 28237726](https://pubmed.ncbi.nlm.nih.gov/28237726/).

<sup>92</sup> [PMID 18700684](https://pubmed.ncbi.nlm.nih.gov/18700684/); [PMID 18716672](https://pubmed.ncbi.nlm.nih.gov/18716672/); [PMID 18996131](https://pubmed.ncbi.nlm.nih.gov/18996131/); [PMID 19384594](https://pubmed.ncbi.nlm.nih.gov/19384594/).

<sup>93</sup> [PMID 17216624](https://pubmed.ncbi.nlm.nih.gov/17216624/); [PMID 22367660](https://pubmed.ncbi.nlm.nih.gov/22367660/).

<sup>94</sup> [PMID 22240235](https://pubmed.ncbi.nlm.nih.gov/22240235/).

and a Canadian study suggested a possible increased risk of low birth weight associated with these antidepressants.<sup>95</sup>

Of the 1,479 publications, 53 (about 4 percent) related to vitamin or other supplements. Although a small proportion of the overall total, these publications were disproportionately represented in RCTs. For example, one small trial suggested that supplements with omega 3 fatty acids may have some benefits in treatment antenatal depression.<sup>96</sup>

Many of the human studies in this literature focus on specific medications rather than specific disorders.<sup>97</sup> Of the research that focused on disorders, the most common was major depression. For the most common mental health disorders in the literature, Figure 2 shows the distribution of publications by type of research.

*Figure 2: Publications on Medicinal Therapies for Mental Health in Pregnant and Lactating Women, by Disorder and Type of Research, 2006-2017*

		Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Mental Health</b>	Anxiety	17	0	3	2	31	33	82	7	3
	Bipolar	1	1	1	0	15	21	67	10	0
	Depression	23	5	22	8	164	44	423	64	20
	Schizophrenia	11	0	1	0	6	38	43	1	0

Figure 3 shows pregnancy and lactation publications, by research type, separately. Lactation was only infrequently the subject of this research.

*Figure 3: Pregnancy and Lactation Publications on Medicinal Therapies for Mental Health Disorders, Shown Separately, by Disorder and Type of Research, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Anxiety	16	0	3	2	30	32	75	7	3
Bipolar	1	1	1	0	15	16	52	9	0
Depression	21	4	21	8	154	34	358	57	18
Schizophrenia	9	0	1	0	6	30	39	1	0
<b>Lactation</b>									
Anxiety	1	0	0	0	1	1	7	0	0
Bipolar	0	1	0	0	0	5	15	1	0
Depression	2	1	1	0	10	10	65	7	2
Schizophrenia	0	0	0	0	0	8	4	0	0

<sup>95</sup> [PMID 16894066](#).

<sup>96</sup> [PMID 18370571](#).

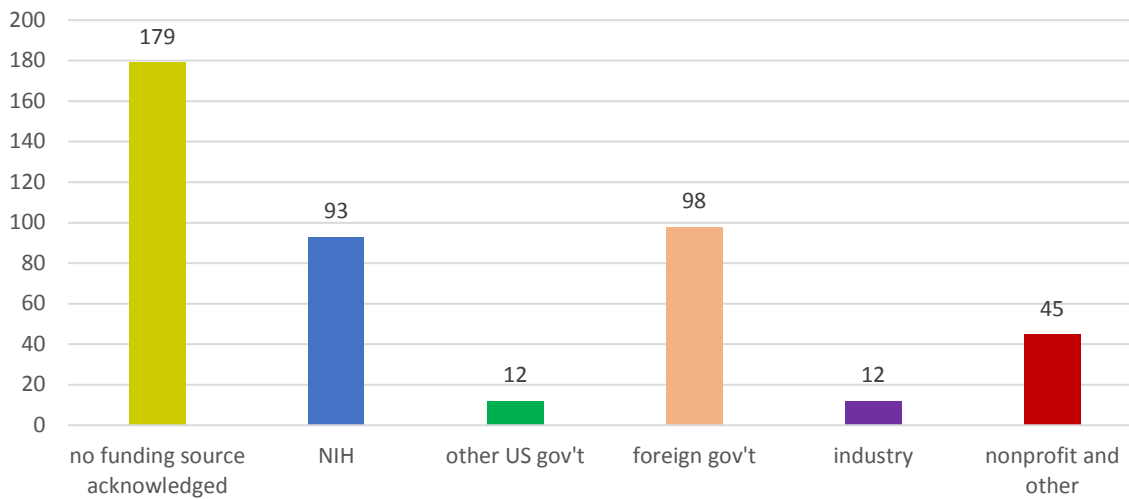
<sup>97</sup> For example, SSRIs, in addition to treating major depression are used by themselves or in conjunction with other medications for substance use disorders, psychosis, schizophrenia, certain neurological disorders, smoking cessation, and other indications. .

## Current Research Activities

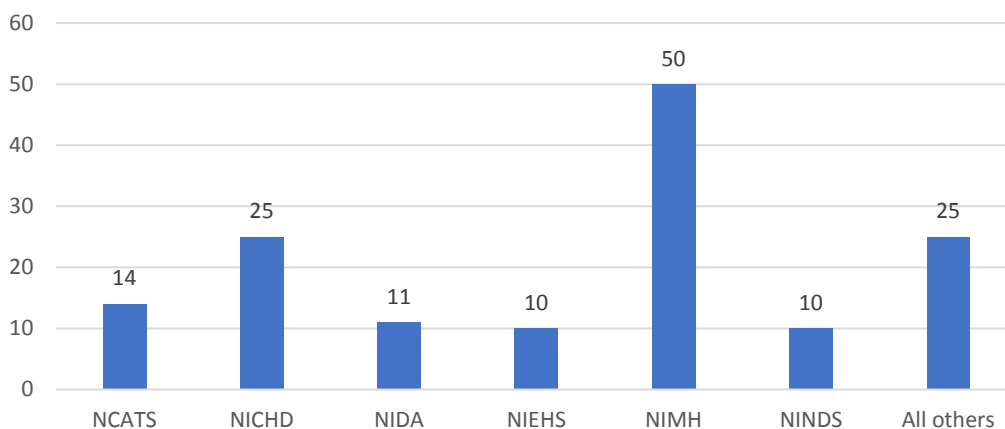
NIH supports research on mental health disorders in pregnant and lactating women that focuses largely on perinatal and postpartum depression. Several projects relate to sleep disorders and therapies designed to address circadian rhythms and sleep patterns to improve symptoms in pregnant and postpartum women with depression.<sup>98</sup>

Figure 3 shows external funding sources acknowledged by original research articles published from 2006-2017 on research on medicinal therapies for mental health disorders in pregnant and lactating women. Of the 432 original research publications, 253 (59 percent) acknowledged at least one external funding source.

*Figure 3: Original Research Publications (n=432) on Medicinal Therapies for Mental Health Disorders in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.



Note: Other NIH ICs included NCI, NHLBI, NIA, NIAAA, NIAID, NIDDK, NIGMS, NIH OD, NLM, and NINR.

<sup>99</sup> [PMID 26527601](https://pubmed.ncbi.nlm.nih.gov/26527601/).

## Research Gaps

Research on medicinal therapies for mental health disorders in pregnant and lactating women remains limited. Few studies on PK/PD of commonly-used medications have been published in the past decade, and few RCTS have been reported. Mental health disorders other than depression, and drugs other than antidepressants, remain especially understudied.

# Pain

## Introduction

Pregnant women often experience both acute and chronic pain, including that associated with childbirth, pregnancy-associated back pain, pre-existing chronic conditions or short-term injuries. (See CNS disorders for migraine and other headache disorders.) Pain left untreated during pregnancy can have negative effects on both mother and offspring, but pain-relieving medications may also have negative consequences, including blood thinning that can initiate or worsen pregnancy complications, maternal dependence and/or neonatal opioid withdrawal syndrome (NOWS).<sup>99</sup>

## Scientific Literature

Analysis identified 1,188 articles, published between January 2006 and July 2017, that related to medicinal therapies for pain relief in pregnant and lactating women. Figure 1 shows the distribution of publications by type of research.

*Figure 1: Publications on Medicinal Therapies for Pain in Pregnant and Lactating Women, by Research Type, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Pain	32	14	20	123	252	257	419	28	43

A total of 484 articles represented original research (41 percent of the total). Case series or cohort studies and RCTs were relatively common. The large majority of publications focused on pain during labor and delivery and the impact of anesthesia on women and their offspring. A U.K. trial compared the epidural anesthesia with a single local anesthetic (ropivacaine) to a combination of the local anesthetic ropivacaine and an opioidergic analgesic, sufentanil. The results showed that the single local anesthetic produced comparable pain relief at different stages of labor, with fewer side effects and lower cost.<sup>100</sup> In Australian clinical trial to compared two analgesic drugs, fentanyl and pethidine, for labor pain. Fentanyl resulted in greater patient satisfaction, less sedation, shorter labor, fewer nursery admissions, and fewer difficulties in establishing breastfeeding.<sup>101</sup> Twenty-six publications addressed vitamins and other supplements for pregnant women with pain. Of these, 40 were original research articles.

Figure 2 shows the pregnancy lactation-related publications, by type of research, separately. Almost all the pregnancy and lactation research addressed pregnancy, not lactation.

<sup>99</sup> [PMID 26527601](#).

<sup>100</sup> [PMID 26512604](#).

<sup>101</sup> [PMID 25558983](#).

*Figure 2: Pregnancy and Lactation Publications on Medicinal Therapies for Pain, Shown Separately, by Condition and Research Type, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Pain	31	12	20	120	242	251	404	26	41
<b>Lactation</b>									
Pain	1	2	0	3	10	6	15	2	2

### Current Research Activities

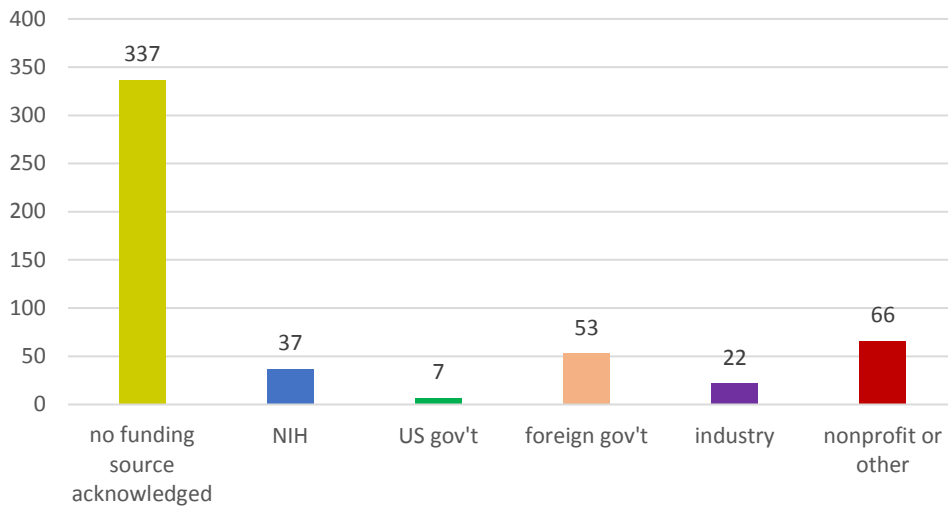
Current NIH-funded studies include an effort to develop cognitive behavioral therapy approaches to help reduce chronic pain and opioid use in pregnant women, and a RCT to optimize management of the second stage of labor.<sup>102</sup>

Figure 3 shows external funding sources acknowledged by original research articles published from 2006-2017 on pain in pregnant and lactating women. A total of 337 articles (69 percent) did not acknowledge any external funding source. Foundations and other nonprofit organizations supported the highest number of publications, followed by foreign governments and the NIH. Among NIH ICs funding this research, NCATS, NICHD, and NIDA supported the greatest number of publications.

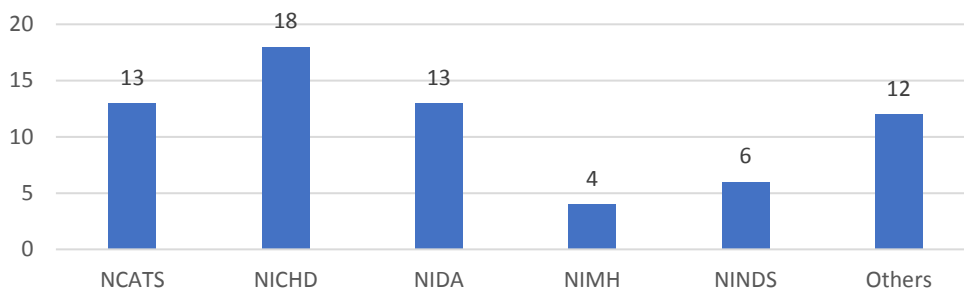
<sup>102</sup> [K23DA039318](#); [U01HD077384](#).



Figure 3: Original Research Publications (n=484) on Medicinal Therapies for Pain in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.



Note: Other NIH ICs included NIDDK, NIEHS, NIA, NIGMS, and the NIH OD.

## Research Gaps

Although there have been a substantial number of publications over the last decade about pain and pregnancy, most of these have focused on childbirth pain specifically. However, many pregnant women have chronic pain from pre-existing conditions, as well as pregnancy-associated back, pelvic, and other pain. Few studies have been conducted to describe the effect of pain medications on lactation. Moreover, although many pregnant women try various supplement products to alleviate pain-related conditions, few studies have assessed the efficacy or safety of these therapies.

# Preterm Birth

## Introduction

Preterm birth, before fetal maturation is complete, poses risks of acute or long-lasting health and/or developmental problems for a child, even if birth is just a few weeks short of full-term pregnancy. The brain, lungs, and liver, for example, need the final weeks of pregnancy to develop fully. In 2013, about one third (36%) of infant deaths in the U.S. were due to preterm-related causes and preterm newborns are at risk for breathing problems, feeding difficulties, cerebral palsy, developmental delay, and/or impaired vision or hearing.<sup>103</sup> The adverse effects of preterm births may take an emotional toll on families and impose financial burdens. Although U.S. rates of preterm birth have declined over the last decade, nearly 10 percent of U.S. infants still arrive too early.<sup>104</sup> Preterm birth is a global public health problem and is especially prevalent in low-income countries, where preterm infants face even greater risks because of very limited access to advanced medical care.

## Scientific Literature

The analysis identified 1,792 articles, published between January 2006 and July 2017, related to medicinal therapies for preterm birth. Figure 1 shows the distribution of publications by type of research.

*Figure 1: Publications on Medicinal Therapies for Preterm Birth, by Research Type, 2006-2017*

	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
Preterm birth	159	22	40	193	419	121	633	109	96

The largest number of preterm birth publications were reviews but more than half (929, or 52 percent) were original research, including RCTs, basic science or mechanistic studies, and case series or cohort studies, conducted in the U.S. and elsewhere. Nearly 10 percent (173) of the articles reported studies on various supplements to prevent preterm birth. Of these, 55 percent (95) were research articles. Compared with articles on drug therapies, a slightly higher percent of articles on non-drug therapies reported on RCTs (14 percent compared with 10 percent overall). Very few articles on non-drug therapies concerned basic research or PK/PD.

Figure 2 shows the pregnancy lactation-related publications, by type, separately. Because preterm birth is a pregnancy-specific condition, it was unsurprising that nearly all of the pregnancy- and lactation-related research for preterm birth involves pregnancy only, and not lactation.

<sup>103</sup> <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm> .

<sup>104</sup> <https://www.cdc.gov/mmwr/volumes/65/wr/mm6543a1.htm> .

*Figure 2: Pregnancy and Lactation on Medicinal Therapies for Preterm Birth, Shown Separately, by Type of Research, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Preterm birth	158	22	40	193	416	121	623	109	96
<b>Lactation</b>									
Preterm birth	1	0	0	0	3	0	10	0	0

### Current Research Activities

NIH is supporting an extensive portfolio of research on preterm birth, focused on therapies to prevent early delivery. For example, NICHD and the NIH OD currently support an assessment of whether DHA supplementation (an essential omega 3 fatty acid) in early pregnancy can reduce the risk of preterm birth.<sup>105</sup> Another NICHD-funded study is examining the PK and optimal dosing of betamethasone, a corticosteroid often used in pregnant women at high risk of preterm birth, to improve fetal lung development.<sup>106</sup> Studies funded by NIMHD and NINR are exploring possible mechanisms (e.g. microbiome, epigenetic) underlying racial and ethnic disparities in preterm birth.<sup>107</sup> Basic understanding of mechanisms underlying disorders is an essential preliminary step in developing effective therapies.

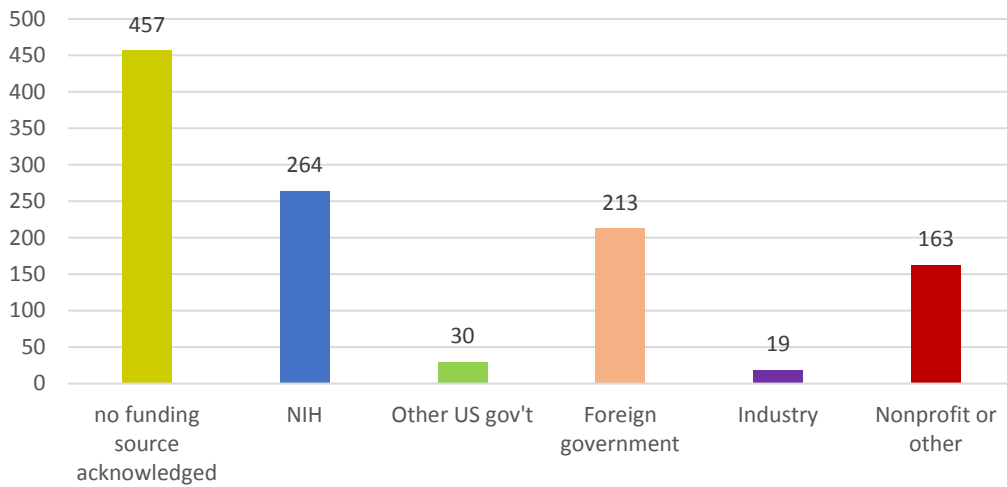
Figure 3 shows external funding sources acknowledged by original research articles, published from 2006-2017, on medicinal therapies for preterm birth. Of the 929 original research publications, 49 percent (457 articles) did not acknowledge an external funding source. National government agencies and nonprofit organizations in the U.S. and elsewhere supported the research. Little industry support was reported, but several reported studies were funded by European and multinational companies that manufacture prenatal vitamins and dietary supplements. Among NIH ICs, NICHD supported by far the largest number of research projects reported in the articles. Still, 22 NIH ICs plus the NIH Office of the Director were acknowledged in this literature, with multiple acknowledging more than one NIH IC.

<sup>105</sup> [R01HD083292](#).

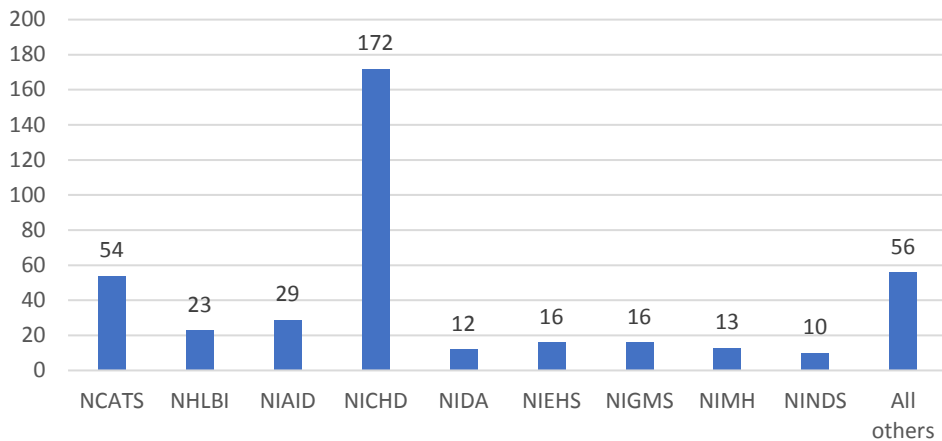
<sup>106</sup> [R01HD088014](#).

<sup>107</sup> [R01MD009064](#); [R01MD011504](#); and [R01NR014800](#).

*Figure 3: Original Research Publications (n=929) on Medicinal Therapies for Preterm Birth, by External Funding Source, 2006-2017*



Notes: A single publication will be reported in multiple categories if more than one type of funding source was acknowledged.



Notes: Many articles with NIH funding credited multiple ICs. A single publication will be counted in multiple categories when more than one IC is credited. Other ICs include FIC, NCCIH, NCI, NIA, NIAAA, NIAMS, NIBIB, NIDCD, NIDCR, NIDDK, NIH OD, NIMHD, NINR, and NLM.

## Research Gaps

Although the research literature on preterm birth is relatively large compared with other conditions in this analysis, there is still limited scientific understanding of the mechanisms underlying preterm birth, and the search for more effective preventive therapies continues. Researchers have conducted studies of the effect of vitamins and other supplements on preterm birth, with mixed results, and few studies have been available to describe the safety and efficacy, or PK/PD of the substances when taken during pregnancy.

## Substance Abuse

### Introduction

The use of alcohol, tobacco, or illicit drugs during pregnancy or lactation is a significant public health concern in the U.S. In the 2013 National Survey on Drug Use and Health, 5.4 percent of women reported using illicit drugs during pregnancy (including cocaine, methamphetamine, marijuana, and other substances). About 3 percent reported binge or heavy alcohol consumption and 9.4 percent reported using alcohol. More than 15 percent of pregnant women reported using tobacco.<sup>108</sup> The opioid epidemic has spread among pregnant women, and a large and increasing number of infants have been adversely affected. From 2009 to 2012, the incidence of neonatal opioid withdrawal syndrome (NOWS) increased nationally from 3.4 to 5.8 per 1,000 hospital births, or 21,732 newborns.

### Scientific Literature

The analysis identified 949 articles, published between January 2006 and July 2017, that related to medicinal therapies for substance abuse in pregnant and lactating women. Of these, about 3 percent (27 articles) related to vitamins or other supplements. The latter group of articles primarily reported case series studies examining how prenatal use of vitamin or other supplements may affect outcomes for children with prenatal exposure to alcohol and/or tobacco. For the literature as a whole, Figure 1 shows the number of publications by type of research.

*Figure 1: Publications on Substance Abuse in Pregnant and Lactating Women, by Type, 2006-2017*

	Basic	PK/ PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ comment	Other
<b>Substance abuse (all)</b>	125	13	48	82	257	44	274	48	80

Many studies focused on the mechanisms of how fetal development is affected by prenatal exposure to alcohol, tobacco, or illicit drugs, and how medication-assisted maternal treatment for addiction may affect these outcomes. For example, a recent study found that certain placental changes were more likely in pregnancies of women on medication-assisted treatment for opioid use.<sup>109</sup> Studies in animal models have assessed how alcohol, tobacco, and opioids affect neurological, respiratory, and other fetal systems.<sup>110</sup>

A large number of clinical trials have evaluated nicotine-replacement therapies for tobacco addiction, or medication-based treatment for opioid dependence, in pregnant women. For nicotine replacement therapy, the trials suggested only limited benefit. For example, one study in the U.K. found that adding a nicotine replacement patch to behavioral support for women who smoked during pregnancy was ineffective, largely because of poor adherence.<sup>111</sup> A longer-term study, also conducted in the U.K. also found that nicotine patches had no enduring, significant effect on smoking in pregnancy; however, at 2 years old, children born to women

<sup>108</sup> <https://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf>

<sup>109</sup> [PMID 28024988](#).

<sup>110</sup> [PMID 23174390](#); [PMID 20043989](#); [PMID 18852877](#).

<sup>111</sup> [PMID 22375972](#).

who used the patches were more likely not to have impaired development.<sup>112</sup> A study of nicotine gum found that although the gum did not increase maternal smoking quit rates, children of women in the intervention arm had increased birth weight and gestational age.<sup>113</sup> Clinical trials of medication-assisted therapies for opioid dependence in pregnant women have demonstrated that these treatments can be effective. For example, a recent study showed that antenatal buprenorphine exposure results in superior neurobehavioral scores and less severe withdrawal for the children than does antenatal methadone exposure.<sup>114</sup>

Alcohol, tobacco and opioids were the substances of abuse most commonly addressed in this literature. Methamphetamines drew relatively little attention from researchers. A substantial number of the clinical trials addressed use of multiple substances, with tobacco frequently addressed with othersubstances. Figure 2 shows the distribution of publications by substance and type of research.

*Figure 2: Publications on Medicinal Therapies for Substance Abuse in Pregnant and Lactating Women, by Type of Research and Substance, 2006-2017*

		Research Type				Case series	Research Type			Other
		Basic	PK/PD	Pop/DB	RCT		Case Reports	Reviews	Edit/Comment	
<b>Subst. Abuse</b>	Alcohol	3	1	1	31	10	4	18	2	5
	Cocaine	0	1	0	6	7	2	7	1	1
	Meth/amph	3	1	0	10	4	1	3	0	1
	Opioids	6	10	26	24	102	17	90	23	22
	Tobacco	3	17	28	24	34	7	65	15	26

Figure 3 shows the pregnancy and lactation publications, by type, separately. Lactation was studied less frequently. Several articles on various supplements focused on lactation, but clinical trials of medication-assisted substance abuse therapies focused only on pregnancy.

<sup>112</sup> [PMID 25158081](#).

<sup>113</sup> [PMID 18827129](#).

<sup>114</sup> [PMID 23106928](#).

*Figure 3: Pregnancy and Lactation Publications on Medicinal Therapies for Substance Abuse, Shown Separately, by Substance and Type of Research, 2006-2017*

Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Edit/Comment	Other
<b>Pregnancy only</b>									
Alcohol	6	1	1	31	9	4	17	2	5
Cocaine	0	1	0	6	7	2	7	1	1
Meth/amph	3	1	0	10	4	1	3	0	1
Opioids	4	9	25	24	94	13	78	22	18
Tobacco	2	17	27	24	33	7	64	15	23
<b>Lactation</b>									
Alcohol	3	0	0	0	1	0	1	0	0
Cocaine	0	0	0	0	0	0	0	0	0
Meth/amph	0	0	0	0	0	0	0	0	0
Opioids	3	1	1	0	8	4	12	1	4
Tobacco	1	0	1	0	1	0	1	0	3

### Current Research Activities

NIH supports a portfolio of research related to substance use among pregnant and lactating women. For example, researchers supported by NICHD are working to develop a drug therapy that could prevent fetal opioid dependence, so as to reduce or mitigate NOWS.<sup>115</sup> Scientists funded by NIDA are conducting a unique long-term study of adults exposed in utero to cocaine. They hope to understand how individuals with prenatal cocaine exposure may differ from the unexposed with respect to their substance use, psychiatric disorders, and risky sexual behaviors in early adulthood.<sup>116</sup> NIDCR-funded researchers are working to characterize the effect of in-utero and lactation nicotine exposure on craniofacial development.<sup>117</sup>

Figure 3 shows external funding sources acknowledged by original research articles published from 2006-2017 on medicinal therapies for substance abuse in pregnant and lactating women. Of the 605 original research publications, 275 (45 percent) acknowledged at least one external funding source. NIH funded more than twice as many publications as foreign government agencies. Among the NIH ICs, NIDA supported the most publications, followed by NCATS, NICHD, and NIAAA.<sup>118</sup> A small number of publications reported research supported by other Federal agencies, including CDC, AHRQ, HRSA and USDA. Government agencies in a variety of countries supported this research, with Australia, the UK, and Canada supporting the largest portfolios. Industry funding was acknowledged in few publications.

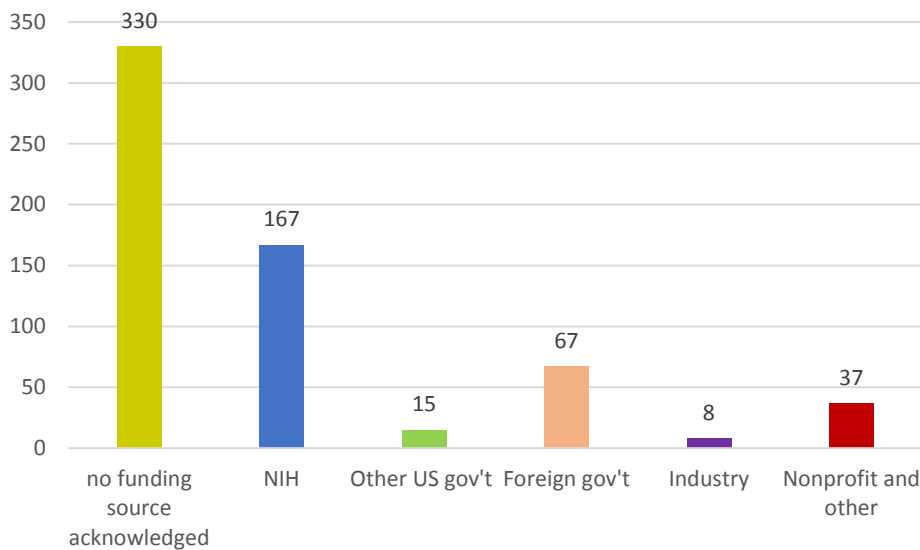
<sup>115</sup> [R21HD092011](#).

<sup>116</sup> [R01DA008916](#).

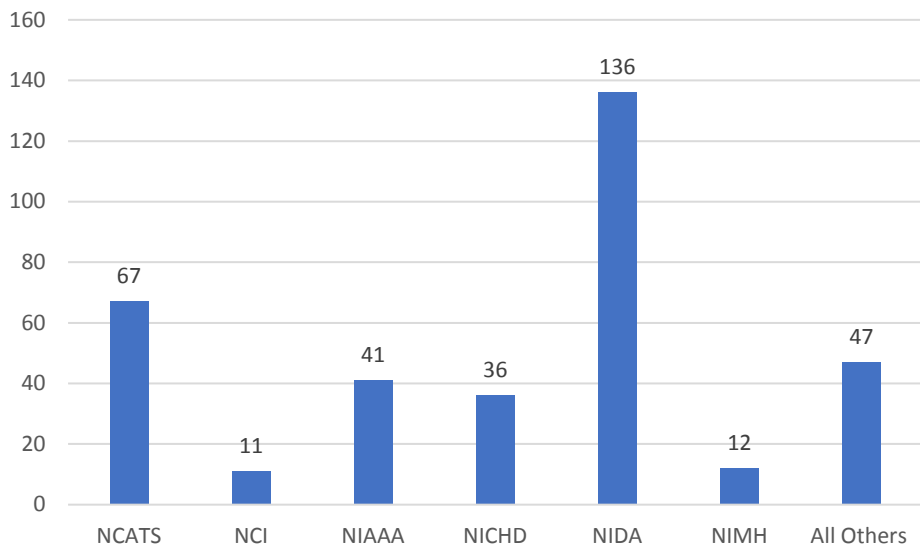
<sup>117</sup> [R03DE026192](#).

<sup>118</sup> Publications that acknowledged funding from NCRR were included in the NCATS total.

*Figure 3: Original Research Publications (n=275) on Medicinal Therapies for Substance Abuse in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited. Other US government agencies included AHRQ, CDC, FDA, HRSA, USDA, and VA.



Note: Publications may be counted in more than one column if multiple NIH ICs were acknowledged.

## Research Gaps

Few studies have addressed how substance abuse, and medicinal therapies for it, affect lactation and breast milk. Similarly, basic mechanistic studies of substance use in pregnancy, which could contribute to better understanding of possible therapies, are limited. Relatively few studies of any type were available to inform understanding of possible therapeutic approaches in pregnant women using several commonly-abused illicit drugs, including amphetamines, amphetamine and cocaine.



# Vaccines

## Introduction

Vaccination for pregnant and lactating woman is a public health priority because infectious disease is not uncommon during pregnancy and poses potentially serious risks for both a woman and the developing fetus or breastfed infant. In some instances, maternal vaccination can extend protection to her child. Certain vaccines (tetanus, diphtheria and pertussis (Tdap), seasonal influenza) are now recommended by the CDC for pregnant women generally as well as seasonal influenza vaccination for women pregnant during influenza season. Other vaccines (such as hepatitis A or hepatitis B) may also be recommended for women at high risk of these infections during pregnancy.<sup>119</sup>

## Scientific Literature

The analysis identified 1,451 articles, published between January 2006 and July 2017, that related to vaccination in pregnant and lactating women. Of these articles, 50 percent (719) were original research publications. Figure 1 shows the literature by publication type.

*Figure 1: Publications on Vaccines in Pregnant and Lactating Women, by Research Type, 2006-2017*

	Basic	PK/ PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ comment	Other
<b>Vaccines</b>	128	2	58	131	262	39	552	134	138

More than 100 RCTs were reported that addressed maternal immunization. The trials occurred in multiple foreign countries, including (for example) Australia, Nepal, Nigeria, Pakistan, South Africa and Vietnam. The most common outcome variables in the trials were infant immune response to antenatal exposure to maternal vaccination, though maternal immune response and pregnancy outcomes were also assessed in a number of trials. For example, a clinical trial of influenza vaccine for pregnant women and infants in Bangladesh showed benefits to both mothers and infants.<sup>120</sup> A trial of an investigational GBS vaccine in Canada and Belgium showed that maternal immunization during pregnancy was effective in creating antibodies in infants.<sup>121</sup> Clinical trials of behavioral interventions that addressed vaccine decision-making were also published during this period. Researchers tested video, text messaging, tailored education, and other interventions in several populations to see if they improved vaccine uptake. Although some of the interventions increased uptake, vaccination rates tended to remain suboptimal. In several studies, the suboptimal rates were attributed to the lack of a recommendation for vaccination from pregnant women's primary care providers.<sup>122</sup>

Multiple vaccines were addressed in this literature, with following addressed most frequently: cholera, CMV, diphtheria, GBS, hepatitis B, HPV, influenza, malaria, pertussis, rubella, and tetanus. Because so many different vaccines were studied, the number of publications on vaccines in general is far greater than the available evidence on any one specific vaccine might suggest.

<sup>119</sup> <https://www.cdc.gov/vaccines/pregnancy/pregnant-women/index.html> .

<sup>120</sup> [PMID 18799552](#); [PMID 22353593](#).

<sup>121</sup> [PMID 26942345](#).

<sup>122</sup> [PMID 28216190](#); [PMID 28062124](#); [PMID 27667330](#); [PMID 26775454](#) (for example).

Figure 2 shows the pregnancy lactation publications on vaccine research, by type of research, separately. Lactation was infrequently the subject of vaccine research.

*Figure 2: Pregnancy and Lactation Publications for Vaccines, Shown Separately, by Research Type, 2006-2017*

	Basic	PK/PD	Pop/ DB	RCT	Case series	Case Reports	Reviews	Edit/ Comment	Other
<b>Pregnancy only</b>									
Vaccines	126	2	58	129	259	39	547	129	133
<b>Lactation</b>									
Vaccines	2	0	0	2	3	1	12	5	5

### Current Research Activities

NIH supports a number of projects on vaccination in pregnancy. NIAID-supported researchers have been studying the mechanisms by which maternal immunity is transmitted through the placenta and/or breast milk to prevent shigellosis in young infants.<sup>123</sup> Researchers funded by NINR are examining the roles of obesity and stress in determining the immune response of pregnant women to seasonal influenza vaccine, and the transfer of protective maternal antibodies to the fetus<sup>124</sup>

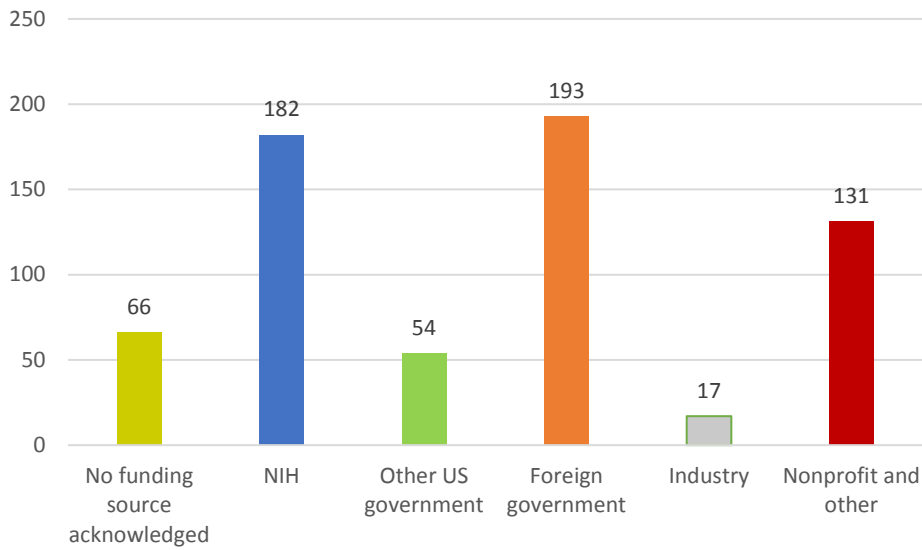
Figure 3 shows external funding sources acknowledged by original research articles published from 2006-2017 on vaccines in pregnant and lactating women. Of the 719 original research publications, 653 (90 percent) acknowledged at least one external funding source – a much higher percentage than was the case for other categories of research on medicinal therapies for pregnant and lactating women. As was the case for cancer research, a large number of foreign countries dedicated funding for this area of science. Nonprofit and other organizations also supported such research.

The largest proportion of NIH support for this research was from NIAID, but the NICHD and NCATS also supported a substantial number of projects. Of non-NIH federally supported research in this area, 76 percent of the articles acknowledged CDC funding.

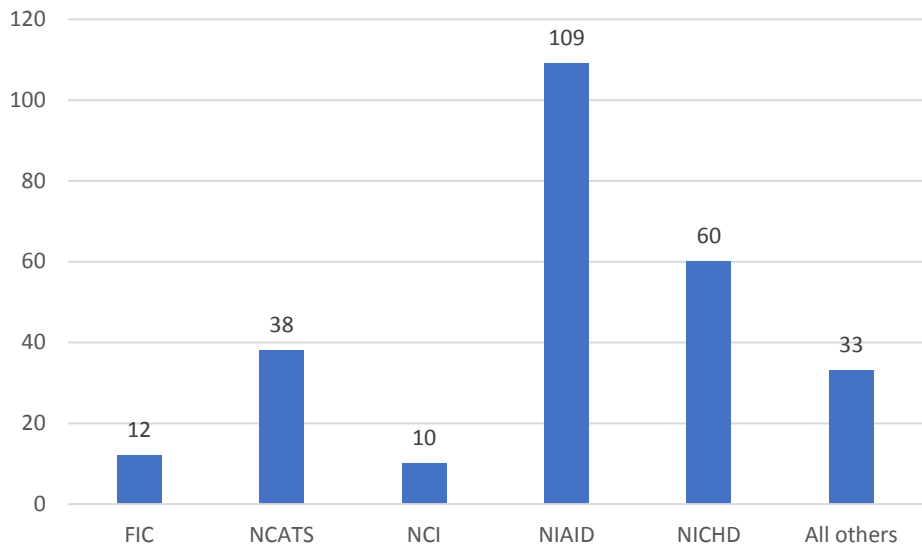
<sup>123</sup> [R01AI117734](#).

<sup>124</sup> [R01NR013661](#).

*Figure 3: Original Research Publications (n=719) for Vaccines in Pregnant and/or Lactating Women, by External Funding Source, 2006-2017*



Notes: A single publication may be reported in multiple categories if multiple funding sources were cited.



Note: Other NIH ICs included NIMH, NIAAA, and NHLBI.

## Research Gaps

Although a large number of original research studies have been conducted on vaccines, primarily in pregnant rather than lactating women, there are few clinical studies of many individual vaccines. Very few studies address vaccination of lactating women.