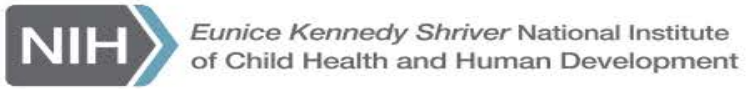
Task Force on Research Specific to Pregnant and Lactating Women

Summary and Discussion of Work Products from Meeting 1



Background

SEC. 2041. TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN.

ESTABLISHMENT.—Not later than 90 days after the date of enactment of this Act, the Secretary of Health and Human Services (referred to in this section as the "Secretary") shall establish a task force, in accordance with the Federal Advisory Committee Act…

(2) DUTIES.—The Task Force shall provide advice and guidance to the Secretary regarding Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities.

Important Deadlines

- September 2018 – Send report to HHS Secretary and Congress
- December 2018 – Secretary required to act on Task Force recommendations

- March 2019 – Task Force will sunset after two years unless extended

Report to Include

(1) A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies;

(2) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research;

(3) Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women;

Report to Include (continued)

(4) Identification of Federal activities, including:

(a) The state of research on pregnancy and lactation;

(b) Recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;

(c) Dissemination of research findings and information relevant to pregnant women and lactating women to provides and the public; and

(d) Existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities; and

(5) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women.

Strategy for Report

TF 3	(1) A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies;
TF 2	(2) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research;
TF 3	(3) Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women;
TF 1	(4) Identification of Federal activities, including: (a) The state of research on pregnancy and lactation; (b) Recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women; (c) Dissemination of research findings and information relevant to pregnant women and lactating women to provides and the public; and (d) Existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities; and
TF 4	(5) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women.

Task Force Report
Draft of Federal Activities Section

(4) Identification of Federal Activities, Including:

(a) The state of research on pregnancy and lactation;

(b) Recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;

(c) Dissemination of research findings and information relevant to pregnant women and lactating women to provides and the public;

(d) Existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities;

Report – Draft Sections

- Current state of research
- Federal activities
- Appendices
  - Research on Therapies in Pregnant and Lactating Women
  - Federal Activities Related to Pregnancy and Lactation
  - Pregnancy Registries

Current Research

Current Research on Therapies for Pregnant and Lactating Women

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

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

Literature Analysis: Objectives, Scope, Methodology, and Limitations

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

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

Figure 1: Categories for Analysis (Selected Conditions)

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

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

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

- Literature Analysis
- Results
- Key Research Gaps
- Funding Sources

Federal Activities

Federal Activities Related to Pregnancy and Lactation

An array of federal agencies support research, health care and clinical practice, communications, and collaborative efforts that are directly applicable to the HHS Task Force on Pregnant and Lactating women. Figure 1 lists federal agencies included in this report. Federal activities were identified by Task Force agencies, supplemented by systematic searches of agency databases, websites, and publications.

Figure 1: Federal Agencies
- Agency for Healthcare Research and Quality (AHRQ)
- Centers for Disease Control and Prevention (CDC)
- Department of Agriculture (USDA)
- Department of Defense (DoD)
- Department of Veterans' Affairs (VA)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA)
- Health Resources and Services Administration (HRSA)
- National Institutes of Health (NIH)
- National Vaccine Program Office (NVPO)
- Office of the Assistant Secretary for Health (OASH)
- Substance Abuse and Mental Health Services Administration (SAMHSA)

Research Activities

Each of the featured federal agencies offer unique contributions to research related to pregnancy and lactation. Agencies with a strong foundation in toxicology, maternal and fetal medicine, teratology, and epidemiology often collaborate to assess how prenatal exposures can affect risks to the offspring. Biomedical research agencies have taken a lead role in studying the safety and effectiveness of interventions for pregnant and lactating women and their children. Health care services agencies, along with their medical research counterparts, support efforts to measure the utilization, quality, and impact of health care services and interventions.

Prenatal Exposures

Identifying the impact of prenatal exposures is a shared research interest of several federal agencies. The National Toxicology Program (NTP) is an interagency program, involving NIH, EPA and others, that provides scientific information about hazardous substances in the environment and serves as a central resource for activities, programs, and policies that advocate for health and disease prevention. For example, one NTP-supported study examined the developmental effects and pregnancy outcomes associated with cancer chemotherapy use in pregnant women. At the FDA, researchers are evaluating prenatal exposure to hand-held metal detectors and MRIs. Through its epidemiological research, CDC addresses the impact of occupational and environmental exposures that affect the health of pregnant women and their offspring. Figure 2 lists examples of studies of prenatal exposure in military personnel and veterans.

Figure 2: Prenatal Exposure and the Military

Military personnel and veterans may be exposed to stresses and toxins not typically found in civilian life. Examples of DoD and VA studies include:
- the effect of maternal PTSD on preterm birth (VA);
- environmental exposures for women who served in the Gulf War (DoD); and
- procedures for counseling female veterans about the teratogenic risks of prescription medications.

CDC and NIH support a range of structured cohort and case-control studies to help assess whether prenatal exposures – including prenatal exposure to medications – are related to specific structural birth defects. For example, the National Birth Defects Prevention Study (NBDPS) and the Birth Defects Study To Evaluate Pregnancy ExposureS (BD-STEPS) have provided insight into antibiotic and asthma medications

10/30/2017 1

- Research Activities
  - Prenatal Exposures
  - Safety and Efficacy of Medicinal Therapies in Pregnant and Lactating Women
  - Utilization and Quality of Care for Pregnant and Lactating Women
  - Health Care and Clinical Practice
- Communications
- Trans-Federal Collaborative Efforts

Summary Document

Appendices

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 anddescribe 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.

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

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

10/30/2017 1

Appendix VIII: Research on Therapies in Pregnant and Lactating Women

- Literature review: overall therapies
- Funding sources
- Specific conditions:
  - Literature
  - Current research activities
  - Research gaps

Categories for Analysis (Selected Conditions)

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

Appendices

Appendix VII: Federal Activities Related to Pregnancy and Lactation, by Agency

Introduction

An array of federal agencies support research, health care and clinical practice, communications, and collaborative efforts that are directly applicable to the HHS Task Force on Pregnant and Lactating women. Federal activities for 12 key agencies were identified by Task Force agencies, supplemented by systematic searches of agency databases, websites, and publications. These agencies include:

1. Agency for Healthcare Research and Quality (AHRQ)
2. Centers for Disease Control and Prevention (CDC)
3. Department of Agriculture (USDA)
4. Department of Defense (DoD)
5. Department of Veterans' Affairs (VA)
6. Environmental Protection Agency (EPA)
7. Food and Drug Administration (FDA)
8. Health Resources and Services Administration (HRSA)
9. National Institutes of Health (NIH)
10. National Vaccine Program Office (NVPO)
11. Office of the Assistant Secretary for Health (OASH)
12. Substance Abuse and Mental Health Services Administration (SAMHSA)

Agency Activities: Agency for Healthcare Research and Quality (AHRQ)

Research

A key part of AHRQ's mission is to invest in research to improve safety and quality of health care (https://www.ahrq.gov/research/ahrq-research.html). AHRQ supports extramural and intramural research related to pregnant and lactating women, often using large population-based and claims data. AHRQ also provides research resources, including health services databases, that can be used to develop evidence about utilization and effectiveness of treatments and quality of care.

AHRQ supports some studies specifically related to the safety and effectiveness of medications and therapies in pregnant and lactating women. These studies address a variety of conditions that are common in pregnant women. Some examples include:

- Researchers supported by AHRQ are combining previously collected data on the management of lupus during pregnancy to yield new information about optimal medication therapies to control lupus and improve pregnancy outcomes. In addition, researchers will be obtaining information from community rheumatologists to identify better ways to integrate expert recommendations for lupus management into medical practice.
- AHRQ supports multiple projects on the safety and effectiveness of antidepressants in pregnancy. One of these projects is using a large population-based Medicaid claims database to conduct a comparative effectiveness study, incorporating both maternal and fetal outcomes. A two-stage cohort study, using a large claims database, is designed to assess whether treatment of depression during pregnancy reduces the risk of postpartum depression.

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Appendix VII: Federal Activities Related to Pregnancy and Lactation, by Agency

- Agency for Healthcare Research and Quality (AHRQ)
- Centers for Disease Control and Prevention (CDC)
- Department of Agriculture (USDA)
- Department of Defense (DoD)
- Department of Veterans' Affairs (VA)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA)
- Health Resources and Services Administration (HRSA)
- National Institutes of Health (NIH)
- National Vaccine Program Office (NVPO)
- Office of the Assistant Secretary for Health (OASH)
- Substance Abuse and Mental Health Services Administration (SAMHSA)

Appendices

Appendix XII: Pregnancy Registries

Pregnancy exposure registries have been developed to collect health information on exposure to medical products (such as drugs and vaccines) during pregnancy. These databases can be helpful resources for researchers and regulatory agencies. Pregnancy registries were identified based on several sources: a listing provided by the FDA's Office of Women's Health[1], publications obtained through literature analysis, and web searches. A list of the pregnancy registries and large databases is provided below.

Summary

A total of 45 distinct registries were identified. As shown in Figure 1, about two-thirds were sponsored by industry and about one-quarter by nonprofit organizations. Although government organizations may be involved in providing expertise and in encouraging the establishment of registries, government organizations are typically not the sponsor or manager of registries. Several registries did not list a primary sponsor or responsible organization.

Figure 1: Pregnancy Registries, by Type of Sponsoring Organization

Registries may focus on a condition, medication, or both. As shown in Figure 2, most registries determine eligibility based on either medication or condition or both, but some restrict eligibility to only those women taking a specific medication.

Figure 2: Pregnancy Registries by Eligibility Criteria

[1] https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm

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Appendix XII: Pregnancy Registries

- Summary
  - 45 registries: 2/3 industry, ¼ non-profit
  - Majority by condition or medication
  - 46% Europe, 40% USA/Canada
  - Enrollment varies, most at 101-500
- Table of Registries
  - Name
  - Medicine(s)
  - Medical condition(s)
  - Organization/sponsor
  - Enrollment
  - Date established
  - website

Feedback & Input

- Format
- Corrections / additions / suggestions?
- Anything missing?

Work in progress – finalized document ~September 2018

Summary Recommendations from Federal Activities Discussion

Striking Statistics

- 4M pregnant, 3M breastfeed (80%) and 30% are breastfeeding at a year
- >90% of women are prescribed medications in the first year
- 500K woman annually have difficulty making milk

State of Research on Pregnancy and Lactation

- Literature
  - Limited basic science, population database, PK/PD, clinical trials of medications and vaccines in pregnancy
  - Extremely limited literature in lactating women
- Complexity of pregnancy
  - Fetus and placenta change over gestation, timing of exposure
  - Physiologic changes of pregnancy
  - Impact of external factors: obesity, environment
- Lactation
  - Benefits of breastfeeding vs medications in woman
  - Limited assays for assessment of medications in breastmilk
  - Pharmacogenomics: baby & mom
- Limited pipeline even compared to rare diseases

(D) Identification of Federal Activities, Including-
(ii) recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;

- Clinical trial networks needed, build on existing successful networks
- Explore opportunistic studies, modeling/simulation designs
- Need incentives to engage industry, agencies; facilitate collaboration
- Facilitate registries to provide needed data
    - Data collaboration/warehouse publicly accessible for baseline information, generate safety signals, study design
    - Drug centric registry design is limiting – disease focused registry provides more information
    - Registries are not owned by FDA, sponsor
    - Not uniform in design, quality, or reporting
- Encourage new product development, women should not be the post-market evaluation

(D) Identification of Federal Activities, Including-
(iii) dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public;

- Incorporate new models of dissemination
  - Collaborate with online sites
- Millennials, Gen X Gen Y are digital savvy and comfortable sharing things online, tap into this resource to engage in research
- Health literacy needs to be considered, multilingual communication, include rural and minority communities
- Provide access to evidence based treatment information
- Database online for federal information on medication safety for pregnancy and lactation
- Provide information on “what research means” for pregnant and lactating women

Feedback & Input

- Format
- Corrections / additions / suggestions?
- Anything missing?

Work in progress – finalized document ~September 2018

Discussion