

March 30, 2018

Lisa Kaeser, JD

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National Institutes of Health
Bethesda, MD 20892

Dear Lisa Kaeser,

The Endocrine Society appreciates the opportunity to comment on gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. The Society's membership of over 18,000 includes experts in all research and clinical aspects of hormone health, including women's health and reproductive health. In our comments, we identify specific gaps in knowledge that would benefit from additional research, as well as general recommendations to improve inclusion of pregnant and lactating women in research.

Research Gaps and Opportunities

We acknowledge that clinical research involving women in general remains an urgent need, and pregnant and lactating women are an understudied population that stands to benefit greatly from improved access to clinical research. As an overarching point, we encourage the Task Force to consider opportunities to study and reduce health disparities that may manifest in pregnant women and lactating women, including pregnancy-associated health disparities covered in the Endocrine Society's Scientific Statement on Health Disparities in Endocrine Disorders¹. The specific research areas identified below include some endocrine-related topics where better knowledge would advance the health and well-being of pregnant woman and children:

- Diseases and conditions that affect younger women who may become pregnant, such as thyroid disorders, prolactinomas or other pituitary tumors, congenital adrenal hyperplasia, polycystic ovarian syndrome, and diabetes (including gestational diabetes). In many cases, such as thyroid disorders, we may have some knowledge about the effect of the condition and available treatments on pregnancy outcomes, but very little information about effects on lactation.
- Proper nutrition during pregnancy and nursing, including the effects of poor nutrition in disadvantaged populations, or undernutrition in the context of eating disorders. Supplement use should be examined to identify opportunities for better standardization; iodine content for example, while critically important, is not regulated in prenatal vitamins, making it difficult for pregnant and

¹ Golden SH., et al. Health Disparities in Endocrine Disorders: Biological, Clinical, and Nonclinical Factors – An Endocrine Society Scientific Statement. *The Journal of Clinical Endocrinology & Metabolism*, Volume 97, Issue 9, 1 September 2012, Pages E1579–E1639, <https://doi.org/10.1210/jc.2012-2043>



lactating women to know if they are receiving the Institute of Medicine (IOM) and World Health Organization (WHO) recommended amounts, which are higher than for the nonpregnant woman.

- The effects of obesity on pregnancy and lactation, including better information on optimal weight gain during pregnancy and optimal programs for weight loss.
- The impact of exercise on pregnancy.
- Pregnancy-associated breast cancer, including identification of the mechanisms underlying the disease and how to treat it effectively and safely for both the fetus and the mother.
- The mechanistic basis of protection from breast cancer later in life that is provided by pregnancy and lactation in young women.
- Developmental and epigenetic effects of chemicals, such as endocrine-disrupting chemicals (EDCs) for the pregnant woman, her fetus, and the germ cells of the fetus which could affect future progeny.
- The effects of androgens during pregnancy and on breastfeeding. This includes cases where androgens are endogenously produced, as in polycystic ovarian syndrome or congenital adrenal hyperplasia, or exogenously administered, as when used/abused by athletes or bodybuilders.
- The effects of hypertension during pregnancy.
- Osteoporosis during pregnancy.
- Primary ovarian insufficiency.
- Postpartum depression, including the role of hormones.
- Peri-partum cardiomyopathy and association with prolactin.

These research areas are not a comprehensive list of topics that require greater investigation. We encourage the Task Force to examine institute-specific strategic plans and priorities to identify other areas of need for pregnant and lactating women.

General Recommendations to Improve Inclusion

The Endocrine Society appreciates that the developing fetus and infant present challenging ethical considerations for the inclusion of pregnant and lactating women in research. Caution is advisable, given that developmental effects due to interventions and other environmental exposures might only manifest later in life and can last for an entire lifetime. We urge the Task Force to consider the following recommendations as they seek to promote safe and effective inclusive research practices for women and their children.

To build an evidence base for future clinical research, it would be extremely helpful to better understand situations where pregnant and lactating women are already taking drugs for common conditions, including the endocrine diseases and disorders listed above. Knowledge from these studies can be compared with animal research exploring effects at different developmental stages to evaluate drug safety at different trimesters and gather mechanistic information on commonly used drugs. After confirming safety in these cases, more advanced interventional trials may be considered for other drugs.



Research studies should carefully consider trimester-specific enrollment, accounting for the physiologic changes, particularly hemodynamic, in the mother from trimester to trimester, and then processes such as organogenesis in the developing fetus, which would be much more vulnerable during the first trimester. Also, studies should be carefully constructed so that they are able to distinguish effects on the fetus from effects on the mother. For drug trials involving lactating women, it should be required to measure the amount of the drug or metabolites that are present in breast milk. This is critical information to help determine the extent of exposure to the infant.

We support the proposal to remove the categorization of pregnant women as a “vulnerable population” from the revised Federal Policy for the Protection of Human Subjects (Common Rule). We recommend instead that pregnant and lactating women be defined as “scientifically complex populations” consistent with the 2015 American College of Obstetricians and Gynecologists Committee Opinion on Ethical Considerations for Including Women as Research Participants². Achieving both maternal and paternal consent for trials during pregnancy is not only challenging, but would be impossible for some family structures and is inconsistent with existing laws for parental consent involving children. Pregnant and lactating women can protect their interests and deliver informed consent for research studies, and it is not clear why maternal consent would be sufficient for a child, but insufficient for the developing fetus. In many cases, such as observational studies, maternal consent is clearly adequate. We urge the Task Force to explore this issue with patient advocates and other stakeholders and identify specific cases or situations where further community feedback is needed.

In conclusion, we thank the NIH for establishing the Task Force on Research Specific to Pregnant and Lactating Women and investing in workshops to further explore how inclusion of pregnant and lactating women may be improved in the future. We applaud NICHD for their leadership role in the activities of the Task Force and look forward to the publication of the Task Force Report. Thank you for considering the Endocrine Society’s comments, if we can be of further assistance, please contact Joseph Laakso, PhD, Director of Science Policy, at jlaakso@endocrine.org.

Sincerely,

Susan Mandel, MD, MPH
President
Endocrine Society

² Ethical considerations for including women as research participants. Committee Opinion No. 646. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;126:e100–7.