

March 20, 2015

Alan Guttmacher, MD
Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Guttmacher,

The Endocrine Society appreciates the opportunity to provide comments on the Request for Information NOT-HD-15-001 on Fertility Status and Overall Health. We consider fertility status to be a critical readout of overall health, and look forward to an impactful workshop on fertility status and overall health in Fiscal Year 2016. In our comments, we identify critical gaps in the field that would benefit from additional investment of resources; epidemiological evidence that could inform downstream research efforts; and several barriers that inhibit progress in this important area. 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 many experts on reproductive health and the close relationship between fertility and quality of life.

Critical gaps in the current state-of-the-science

We identify two overarching considerations that we feel strongly should be taken forward in the course of the workshop. First, fertility status and the menstrual cycle are an output of reproductive and endocrine system health. Research gaps and solutions need to include efforts to understand how the overall health of hormonal systems impact fertility. Second, reproduction and fertility exhibit tremendous species to species variation, and our members report that animal models of reproduction and fertility status are particularly challenging to translate to human biology and disease. To move the field forward, researchers require monovular animal models, such as bovine, in addition to poliovular animal models, such as the mouse. We acknowledge and appreciate that basic science has an important role to play, but we suggest that NICHD and CDC use the workshop to identify priority areas, such as the human ovary, where clinical research is absolutely needed. Finally, the associations between infertility and early ovarian aging, future risk of cancer, metabolic and cardiovascular disease, and overall mortality need to be better understood.

It is important to stress that infertility is associated with poor quality of life measurements in both males and females. Infertility is associated with metabolic syndrome, cardiovascular disease, endocrine diseases, psychiatric and emotional problems, and other disorders¹². The Endocrine

¹ Eisenberg et al., "Relationship between semen production and medical comorbidity." *Fertil Steril*. 2015 Jan;103(1):66-71.

² Morrison, CD; and Brannigan, RE., "Metabolic syndrome and infertility in men." *Best Pract Res Clin Obstet Gynaecol*. 2014 Oct 24. pii: S1521-6934(14)00217-X.



Society also considers changes in fertility status across the lifespan and their impact on health, to be a critical gap that should be addressed by the workshop. For example, NICHD could support research on how teenage pregnancies impact overall health in the short and long-term. In addition, research is needed to evaluate how reproductive status and the endocrine system are affected by and recover from insults such as weight loss or androgen abuse. We note that cancer survivors in their reproductive years, both male and female, represent an increasing fraction of the overall population³. The effects of chemotherapy on fertility status should be included in research efforts. Finally, a comprehensive analysis of the comorbidities associated with infertility is a critical need, and NICHD and CDC would be well positioned to support research in this area.

Barriers to progress

There are important conceptual barriers to progress in the field that have implications for clinical care of both men and women. For example, discussion of infertility in males in clinical practice is frequently addressed in the context of testosterone levels, possibly precluding a more complete discussion of other components of male infertility and investigation of comorbidities such as obesity and endocrine disease. Addressing the normal range of male testosterone as a function of body mass index is critically necessary. In women, the menstrual cycle is an important indicator of overall health, and we are concerned that clinical care does not routinely include a discussion of this important “vital sign”⁴. In order to collect useful data that address the research gaps noted above, we recommend that NICHD use the workshop as a forum to consider optimal methods for measurements and monitoring of key indicators of fertility status during routine clinical care and how this information can be efficiently utilized by researchers.

A practical problem in researching infertility is the need to assess fertility status over relatively long time periods across the lifespan of individuals. These research projects may require funding that goes beyond the 3 to 5 year timeline typical of the R01 mechanism. Additionally, the development of resources such as biorepositories, cohort studies, and survey instruments analogous to the National Health and Nutrition Examination Survey (NHANES) would greatly assist researchers in efforts to understand how the reproductive axis is linked to overall health. Cohort studies in particular would be useful in efforts to understand how natural changes in fertility status, such as early or late puberty and menopause, are linked to overall health.

Epidemiological evidence that could inform downstream research efforts

Because fertility status is a critical indicator of overall health that is not consistently monitored in a clinical setting, we are potentially missing opportunities to answer questions in related areas such as maternal-fetal medicine. A proactive approach to surveying fertility status in individuals may help researchers draw links between the fertility status of parents and potential health consequences in children, such as obesity and metabolic syndrome. We suggest that the NICHD workshop develop

³ Jeruss et al., “Preservation of Fertility in Patients with Cancer” *N Engl J Med.* 2009 Feb 26; 360(9): 902–911.

⁴ <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Menstruation-in-Girls-and-Adolescents-Using-the-Menstrual-Cycle-as-a-Vital-Sign> Accessed March 10, 2015.



decision making tools and survey instruments to collect data on patients' fertility status. Tools for healthcare providers should consider how linked issues, such as obesity, should be addressed in the context of infertility; i.e., how does treatment of one of these conditions affect the other? In an ideal future, biorepositories with patient samples would be linked to accurate quality of life measurements and patient-reported outcomes.

Summary of Recommendations

In conclusion, the Endocrine Society recommends that the workshop on fertility status and overall health address the following topics:

- How changes in fertility status impact overall health;
- How infertility is linked mechanistically to comorbidities;
- What are priority areas that can be addressed best through human clinical research;
- Identify methods to encourage healthcare providers to address infertility in conjunction with associated health issues;
- Develop optimal clinical methods for monitoring and disseminating information about key indicators of fertility status; and
- Develop resources that will allow researchers to study fertility status and overall health across the lifespan.

We applaud the NICHD and CDC for investing time and resources in this important research area and look forward to the outcomes of the workshop. We would be happy to assist the NICHD and CDC in your efforts and to disseminate any information or products developed in the course of the workshop. Thank you for considering the Endocrine Society's comments. If we can be of any additional assistance in your efforts, please do not hesitate to reach out to Dr. Joseph Laakso, Associate Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

Lisa Fish, MD

President, Endocrine Society