EDITORIAL

Research into outcomes of treatment for children with differences of sex development demands caution

Special consideration of patients' needs is warranted.

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Over the past 15 years, there has been a growing chorus of voices — medical professionals, parents and affected adults — calling for more research into long-term effects of medical treatment of children with differences of sex development.

After decades of treatment, two of the most commonly voiced concerns are that we still lack evidence-based guidelines for making decisions about elective genital surgery or about prenatal treatment with dexamethasone to prevent genital virilization in girls with congenital adrenal hyperplasia. This forces parents and physicians to make difficult decisions without needed information about the long-term effects on personality development, sexual or mental function, and overall quality of life.

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As an advocate for children with differences of sex development (DSD) and their families, I support these calls for research to support development of patient-centered, evidence-based care. However, the idea of more research also gives me a feeling of trepidation. History shows that medical research is fraught with risks for the subjects, and that many of these hazards have only been perceived with hindsight. I worry that a rush into research without consideration of the specific needs of children with DSD may cause more harm than good.

Inherent conflict of interest

At the core of most ethical problems with research is that the researcher has an inherent conflict of interest with the research subject. I am not just talking about financial conflicts of interest, the effect of research outcomes on the researcher's career or the influence of ego in scientific inquiry — all well-documented moral hazards for researchers. Even when a researcher has the noblest of intentions, the researcher's goal is the production of knowledge. This goal may not be congruent with the subject's best interest. When the subject is also the researcher's patient, the conflict becomes more complex.

In the case of DSD, there has been such vociferous criticism of past practices and such great need for more information that providers may feel an urgent need to gather data. This can make it difficult for a researcher or physician to maintain clinical judgment about what is best for the patient.

For this reason, the scientific community has developed special protections that should apply whenever humans are the subjects of research. Although we cannot cover the entire regulatory framework in this article, there are some basic protections that are legally mandated in most cases and are certainly ethically required any time human subjects are used. These include requirements for enhanced informed consent, for assent when children are the subjects of research that will not benefit them individually and for an institutional review board (IRB) to approve the research plan.

This last requirement is arguably the most important because the IRB is an independent body whose role is to examine the specific context of the proposed research, ask probing questions about potential harms to subjects and ensure that the rights of subjects are fully taken into account.

When is it necessary to consult with an IRB? One good answer is that if you think it might be necessary, go ahead and consult. The IRB can tell you if your work does not require its oversight.

Another sign that IRB consultation is needed is when the line is crossed from treatment of a patient into research. If a physician undertakes an intervention or examination with the intention of contributing to generalizable knowledge, it is likely to be considered research. This is true whether or not the patient stands to benefit from the procedure. So for example, genital exams are sometimes necessary for patient care. But if a surgeon does follow-up exams years after surgery on multiple DSD patients with the intention of aggregating data to improve future surgical treatment, the activity is likely to require IRB approval.

Special concerns

Even diligent IRB oversight may not be enough to protect children with DSD if the IRB is not educated about the special concerns affecting these children. One of the tasks of the IRB is to assess the risk of harm that proposed research poses to the subjects and weigh that against any potential benefit. In most situations, for instance, an IRB might consider the risk of harm from a single genital exam to be relatively low. But adults with DSD have reported that they experienced such exams as deeply shaming and painful in childhood, even if they did not protest.

Children with DSD are likely to have been exposed already to multiple genital exams, and it is well-documented that these children can suffer psychological harm from excessive genital exams. An IRB must be accurately informed about the effect such procedures may have specifically for children with DSD to accurately assess whether proposed research is ethically warranted, construct procedures for meaningful patient assent and inform parents of the risks involved in the research.

When proposed research involves innovative treatment, such as new surgical techniques or off-label prescription, the IRB needs accurate information about the knowns and unknowns of current treatment outcomes to evaluate potential harms and benefits of innovative treatment. For example, many treatment protocols for children with DSD assume that some surgical intervention is necessary for genital ambiguity — it is just a matter of figuring out which surgical techniques are best. However, an IRB considering a surgical protocol must know about the lack of evidence that any surgery is necessary for healthy psychosocial development and about the potential to delay surgical treatment until consent or assent is possible.

Given the many ethical questions about treatment of DSD, the IRB must also be sure to independently consider whether the goals of treatment are ethically justified. For example, many published studies on the use of dexamethasone prenatally in 46,XX fetuses with congenital adrenal hyperplasia have offered the possibility of a reduction in "masculine behavior" as a possible benefit of this experimental treatment. However, the idea of using prenatal interventions with the goal of changing nonpathological behavior traits is ethically troubling. This outcome should not be considered a potential benefit to be weighed against risk of harm in evaluating a proposed study.

Research is critically needed into outcomes of treatment for children with DSD. I applaud the researchers and clinicians who are turning their attention to this important matter. Remembering the mistakes of the past, however, with clinical research and with treatment of DSD, I also beseech them to proceed with caution.

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For more information:

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