

An Attempt to Shut Down Discourse About a Controversial Practice Will Not Benefit Patients, Human Subjects, the Bioethics Community, or the Research Community

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DOI: 10.1080/15265161.2010.499587

Publication Frequency: 12 issues per year

Published in: *The American Journal of Bioethics*, Volume 10, Issue 9
September 2010 , pages 64 - 66

First Published on: 01 September 2010

To cite this Article: Tamar-Mattis, Anne 'An Attempt to Shut Down Discourse About a Controversial Practice Will Not Benefit Patients, Human Subjects, the Bioethics Community, or the Research Community', *The American Journal of Bioethics*, 10:9, 64 - 66, First published on: 01 September 2010 (iFirst)

The article by [McCullough, Chervenak, Brent, and Hippen \(2010\)](#) is strongly worded, but fails to address the most significant ethical questions raised by Dreger and colleagues in their Letter of Concern (LoC). It also does not address the legal concerns raised in my letter, submitted to the universities and federal agencies at the same time as the LoC, on behalf of Advocates for Informed Choice, a nonprofit organization providing legal advocacy on behalf of children with differences of sex development (including congenital adrenal hyperplasia [CAH]) and their families ([Tamar-Mattis 2010a](#)). The major legal concerns raised in my letter are not about off-label prescription; they are about whether Dr. New's activities meet legal standards for human subject research and informed consent.

Dr. New (perhaps in collaboration with others, as the target article suggests) is administering dexamethasone to pregnant women with the intention of creating generalizable knowledge about its effects. Her own grant applications to the National Institutes of Health (NIH) state that her team is "routinely carrying out prenatal diagnosis and treatment" of CAH and that the team has thereby "accumulated a large population of prenatally-treated infants to study" ([New 2003](#)). Indeed, she reports developing a "database describing the longitudinal

data of patients with CAH followed by Dr. New for over 30 years” enabling study of “long term effects of prenatal treatment of CAH with dexamethasone on cognition and behavior” (New 2003). This database is not simply a repository of data gathered retrospectively. The Maria New Children's Hormone Foundation website continues advertising her clinic's services (stating that “she has treated over 600 pregnant women at risk for the birth of a CAH-affected child”) and inviting inquiries from the public (Maria New Children's Hormone Foundation 2010). It is reasonable to infer that she is continuing to treat pregnant women with dexamethasone with the intention of studying the results. This is the “de facto clinical trial” to which both the LoC and my letter refer (Feder and Dreger 2010; fetalDex.org 2010; Tamar-Mattis 2010a). Such activity is “research” as defined at 45 CFR 46.102(d), and therefore requires IRB approval and other legal protections for vulnerable human subjects whether or not there is also a treatment purpose (Tamar-Mattis 2010a; 2010b).

McCullough and colleagues assert that they have discredited the LoC and undermined its central factual claim by demonstrating (via citation to an undated “personal communication with Dr. New”) that she has only written one patient's dexamethasone prescription herself. However, this assertion in fact does nothing to address the questions the LoC raises—it only indicates that New was part of a larger research endeavor. This endeavor includes Weill-Cornell Medical College, where Dr. Chervenak, the second author of the article, is Chairman of Obstetrics and Gynecology. McCullough, Chervenak, et al. call on the bioethicists who wrote the LoC to withdraw their complaints to the Food and Drug Administration and the Office of Human Research Protection (OHRP). Surely they know, however, that the LoC authors cannot call off federal investigators now that they have determined that the concerns raised are sufficient to merit investigation (Borrer 2010). Indeed, the OHRP already knows the way to Cornell, having previously determined that there were serious deficiencies in Cornell's institutional review board (IRB) system during New's tenure (Office of Human Research Protections 2004).

While it seems that Dr. New obtained IRB approval for research, it is not clear whether this approval was for the actual treatment of pregnant women with dexamethasone, or just for the post facto chart review and follow-up studies (Advocates for Informed Choice 2010; Feder and Dreger 2010; Tamar-Mattis

2010a). Therefore, it remains unclear whether the subjects have received the benefit of standard and legally required protections for vulnerable human research subjects, such as heightened requirements for informed consent, *before* taking the drug (Tamar-Mattis 2010b). Dr. New and her associated institutions have reportedly resisted repeated appeals to offer assurances that these subjects were adequately informed and protected (Advocates for Informed Choice 2010; fetaldex.org 2010).

We do know, however, that Dr. New has repeatedly stated that “the treatment has been found safe for mother and child” (fetaldex.org. 2010; Maria New Children's Hormone Foundation 2010; Tamar-Mattis 2010a). In addition to being a possible violation of 21 CFR 312.7(a) (prohibiting promotion of an investigational new drug as safe or effective for the purposes for which it is under investigation; Tamar-Mattis 2010a), these public statements are certainly enough to raise concerns about whether the pregnant subjects are receiving full information about the risks and unknowns of dexamethasone. These confident public statements also raise questions about her objectivity as a researcher who is studying whether the treatment is indeed safe. McCullough and colleagues and New may be certain that this treatment represents the standard of care, but many experts in the field dispute this view (Feder and Dreger 2010; fetaldex.org 2010; Frias et al. 2001). The authors also seem certain that New's research is sufficient to discount the concerns raised by others' research. However, prevailing standards of informed consent require that providers disclose all the information a reasonable patient needs in order to make an informed decision for herself.

As an attorney, I am confident that a court could find that a pregnant woman offered dexamethasone has a right to know about the controversy over this treatment in the field. If a court finds that women or their fetuses treated through New's clinic were harmed by dexamethasone treatment for suspected CAH, and the women were not given full information about the risks and unknowns of treatment, any of the physicians responsible for treatment as well as their institutions could face liability (Advocates for Informed Choice 2010). Legal liability aside, the ethical principle of respect for autonomy requires that these patients be informed of the widespread concerns over this unproven treatment.

The central ethical problem raised by the LoC is that Dr. New and her

associates are engaged in administering a controversial and unproven prenatal drug, partly for research purposes, and will not answer questions about the protections extended to vulnerable human subjects/patients. Was there IRB oversight for the use of dexamethasone in a research endeavor? If so, what was the IRB's reasoning in determining the risk to be acceptable? And what were the pregnant women told when they were given this drug? It is deeply troubling that such questions would be met with anything other than complete transparency. Certainly there is no reason that anyone should be called unethical for asking them.

It is the responsibility of bioethicists as professionals and as members of the human family to raise questions if they believe that vulnerable human subjects are being exposed to unwarranted risk. Neither good intentions nor strong convictions have historically proven sufficient to protect human research subjects. Transparency and disinterested oversight provide far stronger assurance. Any researcher who believes she should be above scrutiny is demonstrating the kind of hubris that can lead to tragedy in human subjects research.

In his commentary Dr. [Lantos \(2010\)](#) suggests that the call for IRB oversight is an overreaction. Where the administration of dexamethasone is part of a research endeavor, however, standard rules for research should apply. This includes IRB oversight for the protection of human subjects, because we as a society have recognized that researchers and subjects have inherent conflicts of interest. We do not allow researchers using human subjects to self-regulate ([Tamar-Mattis 2010b](#)).

Where dexamethasone is administered purely for treatment purposes, and not to produce generalizable knowledge, there is more room for negotiation about what constitutes adequate protection for mothers and their fetuses. In negotiating this framework, however, it is important to recognize that this is not a mundane medical decision. Prenatal treatment in general is an area that calls for great caution. As Lantos points out, genital anomalies in babies seem to create strong emotions that muddy many people's thinking. Parents balancing the potential risks of prenatal steroids against the potential need for medically necessary genital surgery are also making decisions about the appearance of their child's genitals and the possibility that she will have

“masculinized” (lesbian?) behavior. It is reasonable to suggest that some extra protections are needed here, and reliance on the professionalism of a single treating physician is not enough. For decades, many in the medical profession exempted themselves from the regular rules of medical ethics when children with differences of sex development (DSD) were involved, resulting in numerous public and private tragedies (Tamar-Mattis 2006). Clearly, the habit has not yet disappeared.

As the executive director of Advocates for Informed Choice and an advocate for children with CAH, I call on Dr. McCullough, Dr. Chervenak, and their co-authors to add their voices to the many demanding full and open explanation of Dr. New's informed consent protocols. Children with CAH and their families deserve the same legal protection and ethical standards as any other children who might be subjects of off-label or experimental treatment.

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The definitive version was published in *The American Journal of Bioethics*, Volume 10 Issue 9, September 2010.

doi:10.1080/15265161.2010.499587

(<http://dx.doi.org/10.1080/15265161.2010.499587>)