February 8, 2010

Dr. Harry Lander
Associate Dean for Research Administration
Weill-Cornell Medical College, RASP
1300 York Avenue
New York, NY 10065

Dear Dr. Lander:

I am the Executive Director of Advocates for Informed Choice (AIC), a non-profit organization that advocates for the legal and human rights of children born with disorders of sex development (DSD) and their families. I write to express AIC's grave concern over possible non-IRB-approved clinical research on pregnant women that has been reportedly conducted under the auspices of Mount Sinai Medical Center and Weill-Cornell Medical College, Cornell University, under the direction of Dr. Maria New. I am referring to the off-label use of dexamethasone on pregnant women for the purpose of preventing genital virilization in fetuses who might be 46,XX fetuses affected by 21-hydoxylase deficiency, a form of Congenital Adrenal Hyperplasia (CAH). On behalf of the children and families who form AIC's constituency, pregnant women who are now being urged to undergo this unproven treatment, and the American public generally, AIC requests a prompt investigation into this matter to ensure that pregnant women are not being subject to ethically problematic or explicitly prohibited practices.

Dexamethasone treatment in pregnancy for prevention of genital virilization in the fetus is an unapproved use that carries significant risk of iatrogenic harm.

It is our understanding that Dr. New has long prescribed dexamethasone for purposes of preventing genital virilization associated with CAH in 46,XX females. This indication is not approved by the FDA. While we recognize that off-label prescription can be beneficial, there are serious clinical and ethical concerns about this particular treatment practice. Genital virilization is a cosmetic issue, one that has been recognized within Dr. New's field as independent of the genuine medical concerns—often serious and life-threatening in some forms of CAH—*unaddressed by prenatal dexamethasone treatment*. That is to say, prenatal treatment with dexamethasone is intended to avoid a cosmetic issue associated with CAH, rather than to treat the medical issues that should be the primary concern of physicians.[1] Furthermore, use of prenatal dexamethasone has been demonstrated to bear significant iatrogenic risk.[2]

[1] Miller WL. "Dexamethasone treatment of Congenital Adrenal Hyperplasia in utero: an experimental therapy of unproven safety." J Urol 1999;162:537-40.

[2] National Institutes of Health Consensus Development Panel, "Antenatal Corticosteroids Revisited: Repeat Courses. National Institutes of Health Consensus Development Conference Statement, August 17-18, 2000." Obstet Gynecol 2001;98:144-50.

Human studies have demonstrated that prenatal dexamethasone treatment results in detrimental changes to the brains of children.[3] Children exposed prenatally to dexamethasone for CAH show problems with working memory, verbal processing, and anxiety.[4] Animal studies have also indicated reason to be very concerned about prenatal dexamethasone's effect on fetal brains.[5] Severe and long-lasting adverse effects on treated pregnant women have also been reported.[6] Dexamethasone treatment in this context cannot responsibly be characterized as benign.[7]

This treatment raises significant ethical dilemmas that have gone unaddressed for over 20 years, involving a vulnerable population.

Treatment of pregnant women who may be carrying a 46,XX fetus with dexamethasone in order to prevent genital virilization raises several significant ethical problems. Pregnant women are considered a vulnerable population in the research context, and they are being exposed to risky and experimental treatment in order to potentially benefit the fetus. Furthermore, 90% of fetuses so treated will receive no benefit from this treatment. (Only 1 in 8 fetuses started on this treatment are actually 46,XX CAH, and of the 1/8 who are, 20% will not benefit from the treatment.) Finally, fetuses are being exposed to significant risk of harm, including neurological damage, to address a cosmetic issue for which there is little evidence of increased psychosocial risk. This off-label use continues in spite of strong criticism from several prominent specialists, including Dr. Walter Miller, Distinguished Professor of Pediatrics and Chief of Endocrinology at UCSF, who has said this drug should not be used in this way, even in a clinical trial, because so many unaffected mothers and fetuses will be exposed to dexamethasone and because widely-accepted clinical alternatives exist which would only target affected children.[8]

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[3] French NP, Hagen R, Evans SF, Mullan A, Newnham JP. "Repeated antenatal corticosteroids: effects on cerebral palsy and childhood behavior." Am J Obstet Gynecol 2004: 190:588-95.

[4] See, for example: [a] Hirvikoski T, Nordenstrom A, Lindholm T, et al. "Cognitive functions in children at risk for congenital adrenal hyperplasia treated prenatally with dexamethasone." J Clin Endocrinol Metab. 2007;92:542-8; and [b]Trautman, PD, Meyer-Bahlburg HF, Postelnek J, New MI. "Effects of early prenatal dexamethasone on the cognitive and behavioral development of young children: results of a pilot study." Psychoneuroendocrinology 1995;20:439-449.

[5] Uno H, Eisele S, Sakai A, et al. "Neurotoxicity of glucocorticoids in the primate brain." Horm Behav 1994;28:336-48.

[6] Frias J, Levine L, et al. "American Academy of Pediatrics Technical Report: Congenital Adrenal Hyperplasia." Pediatrics 2000;106:6:1511-18.

[7] Lajic S, Nordenstrom A, Hirvikoski, "Long-term outcome of prenatal treatment of congenital adrenal hyperplasia." In Fluck CE and Miller WL (eds): Disorders of the Human Adrenal Cortex. Endocr Dev. Basel: Karger, 2008, vol. 13:82-98. Available at http://74.220.219.62/~katrinak/wp-content/uploads/2008/08/prenatal_tx_cah.pdf

[8] Miller W. "Prenatal treatment of classic CAH with dexamethasone: pro vs. con." Endocrine News Tri-Point Series 2008: 16-18. Available through http://www.endo-society.org/endo_news/tri_point_series.cfm

Dr. New's off-label treatment may constitute research involving human subjects as defined in 45 CFR 46.102, without the protections for human subjects outlined in Subpart A of 45 CFR 46, or the additional protections for pregnant women and fetuses outlined in Subpart B of that section.

AIC does not take issue here with the practice of off-label prescribing in general. We are concerned instead with a particular instance of what appears to constitute a de facto clinical trial. Dr. New is described by a colleague as treating hundreds of pregnant women over decades with the apparent intention of follow-up and study to determine long-term effects.[9] This would appear to constitute "research" with human subjects under the definition in 45 CFR 46.102(d), because there is an intention to develop or contribute to generalizable knowledge. It has also come to our attention that Dr. New is on the board of directors of the Maria New Children's Hormone Foundation, which describes its mission as being, "to support the research of renowned pediatric endocrinologist, Dr. Maria New."[10] The Maria New Children's Hormone Foundation website claims that "Dr. New maintains contact with all children treated prenatally [with dexamethasone], and has found not permanent adverse effects of treatment on mother or fetus."[11] This claim also seems to indicate that Dr. New is and has been treating pregnant women with the intention of developing generalizable knowledge.

Based on reports from Dr. New's own clinics,[12] the foundation that supports her research,[13] and the reports of prominent researchers and bioethicists who have attempted to communicate with her and with Mount Sinai,[14] it appears that these pregnant women may have been recruited (and perhaps are still being recruited) without the benefit of IRB oversight or the special informed consent requirements afforded to pregnant human subjects and fetuses outlined in Subparts A and B of 45 CFR 46.

We are particularly concerned that, although Dr. New appears to have consistently had IRB approval to do post-natal follow-up observational and survey studies of women and children exposed to prenatal dexamethasone, she may have conducted no proper clinical trials and thus obtained no IRB oversight for the actual prenatal treatment of the 600+ pregnant women and their fetuses. In public correspondence with Dr. New in 2001, a committee of the American Academy of Pediatrics urged that "prenatal glucocorticoid therapy for CAH should be confined to centers doing controlled prospective, long-term studies.," pointing out that "[t]he memory of the tragedies associated with prenatal use of … thalidomide demands no less."[15] Unfortunately, we cannot verify that she heeded this advice. We have been unable to find conclusive evidence

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[9] Kitzinger E (Weill Medical School of Cornell University). "Prenatal Diagnosis & Treatment for Classical CAH." CARES Foundation, Winter 2003. Copy attached. Also available at http://www.caresfoundation.org/productcart/pc/news_letter/winter02-03_page_9.htm

[10] http://www.newchf.org/

[11] http://www.newchf.org/testing.php. Copy attached.

[12] Kitzinger E (Weill Medical School of Cornell University). "Prenatal Diagnosis & Treatment for Classical CAH." CARES Foundation, Winter 2003. Copy attached. Also available at http://www.caresfoundation.org/productcart/pc/news_letter/winter02-03_page_9.htm

[13] http://www.newchf.org/testing.php

[14] *See* www.fetaldex.org.

[15] Frias J, Levine L, et al. "Reply: Prenatal Treatment of Congenital Adrenal Hyperplasia: Author Differs with Technical Report." Pediatrics 2001:107:4:804.

in her published work or any evidence at clinicaltrials.gov that Dr. New has been administering dexamethasone to pregnant women as part of a controlled clinical trial.

Dr. New's off-label treatment may constitute investigational use of an approved, marketed drug, without the submission of an Investigational New Drug Application (IND) as required by 21 CFR 312.

Dr. New's off-label treatment may constitute investigational use of an approved, marketed drug as defined in 21 CFR 312.3(b), because dexamethasone is not approved for this use. This treatment does not meet the standard for an exemption under 21 CFR 312.2(b)(1) because it "involves a route of administration" (fetal treatment via the pregnant woman) and "use in a patient population" (pregnant women) and "other factor[s] that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product" (i.e., treatment of unaffected fetuses, treatment of cosmetic issues). 21 CFR 312.2(b)(1)(iii). Dr. New's treatment does not clearly meet the exception under 21 CFR 312.2(d), because she may not be prescribing the treatment solely in the course of practice of medicine, but rather in the context of an ongoing investigation as described above. However, as far as we can determine, she has not filed an IND.

Dr. New may be actively promoting off-label use of an investigational new drug as safe and effective to prospective patients, a violation of 21 CFR 312.7(1).

While off-label use of prescription medications by physicians is permissible, under 21 CFR 312.7(1) investigators are not permitted to actively promote off-label uses of investigational drugs to prospective patients, and such off-label uses should not be described as safe and effective to prospective patients. In a recent notice of violation, the FDA reprimanded an investigator after national magazines published her statements suggesting that the drug she was investigating was safe and effective before it was approved.[16]

Dr. New appears to have engaged in similar promotional behavior. As an example, I enclose a copy of the Maria New Children's Hormone Foundation webpage, which states that "Dr. New pioneered prenatal diagnosis of CAH and prenatal treatment of classical CAH. She has the only clinic in the United States which routinely provides this service," and refers the reader to Dr. New's clinic and to www.marianew.com "for more information about our laboratory services."[17] The webpage goes on to claim that "with nearly 20 years' experience, the treatment has been found safe for mother and child." [18] I have also enclosed an article from the CARES Foundation newsletter (a publication targeting parents of children with CAH) which seems to claim to "at risk" women, on behalf of Weill-Cornell and particularly Dr. Maria New, that prenatal

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[16] Notice of Violation Letter to Dr. Leslie Bauman. Division of Drug Marketing, Advertising and Communications of the U.S. Food and Drug Administration. January 11, 2010. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM198400.pdf.

[17] http://www.newchf.org/testing.php

[18] *Id.*

dexamethasone is safe and effective for prevention of virilization. The article echoes the language on the Maria New Children's Hormone Foundation webpage, stating that follow-up with hundreds of children treated prenatally over 20 years "has found no adverse developmental consequences….the treatment appears to be safe for mother and child," and it also seems to suggest that all at-risk women should consider a consultation specifically with Dr. New's clinic.[19] Taken together, these statements appear to constitute promotion to prospective pregnant patients of an off-label use, aimed specifically at their fetuses, as "safe and effective."

Even if no legal violation has technically occurred, the practice of prescribing dexamethasone to pregnant women who may be carrying a 46,XX fetus with CAH without adequate clinical trials or IRB approval raises significant ethical concerns and threatens to further erode public trust in research.

Despite knowledge of risks to fetal development, it does not appear that Dr. New or other physicians prescribing this drug to hundreds of women have sought IRB approval for clinical trials of dexamethasone for the purposes of minimizing genital virilization in 46,XX females at risk for CAH *in utero*. Given the risks and ethical concerns enumerated above, physicians should initiate treatment of this type, if at all, only through structured clinical trials with human subjects research protections in place. Registered clinical trials ensure that women and their families make fully informed decisions with respect to the risks they assume for themselves and on behalf of their future children. Studies such as these also ensure that adverse effects will be noticed as soon as possible, and that any harm that comes to women and their children provide the benefit of increased scientific knowledge that can subsequently protect other women and babies from the same harms.

Our concern was deepened when several professional researchers reported to us that Dr. New had publicly resisted answering questions in a professional setting about her informed consent procedure for this treatment, and that Mount Sinai Medical Center had not answered their questions about IRB approval of her protocol.[20] Public descriptions of this drug as safe and effective may have misled some women to believe the use is FDA-approved, when it is not. Pregnant women who have been prescribed dexamethasone external to IRB-approved trials may not have provided fully informed consent as would happen formally under an IRB-approved trial. Furthermore, AIC believes that transparency is critical when an institution undertakes systematic experimental treatment of vulnerable human subjects. The public has a right to know what institutional controls and informed consent processes are protecting human subjects. To do otherwise risks ethical catastrophe and the further erosion of public trust in medical research.[21]

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[19] Kitzinger E (Weill Medical School of Cornell University). "Prenatal Diagnosis & Treatment for Classical CAH." CARES Foundation, Winter 2003. Copy attached.

[20] www.fetaldex.org.

[21] *See* NIH Council of Public Representatives. "Human Research Protections in Clinical Trials: A Public Perspective." October 2001. Available at http://copr.nih.gov/reports/human_research.pdf.

Conclusion

AIC calls for rigorous investigation by Weill-Cornell Medical College into possible ethical violations associated with your institution in this matter. We also believe that women who have been treated without the protection of IRBs should now be advised of the information that may not have been made available to them at the time of treatment, and that they should be given the most recent information from studies indicating long-term risks to women and children. We are also raising these concerns to Dr. New's current institutions (Mount Sinai Medical School and Herbert Wertheim College of Medicine of Florida International University), the FDA Office of Pediatric Therapeutics (asking them to look especially into ongoing claims of safety and efficacy when, in fact, this drug is not FDA approved for this use), and with the Office for the Protection of Human Subjects, the National Institutes of Health Office of Rare Diseases (which has funded follow-up studies), and the institutions which employ Dr. New's grant collaborators.

Finally, we agree with Dr. Walter Miller, Distinguished Professor of Pediatrics and Chief of Endocrinology at the University of California San Francisco, who asserts that "this experimental treatment is not warranted and should not be pursued even in prospective clinical trials."[22]

Sincerely,

Anne Tamar-Mattis, J.D.
Executive Director

[22] Miller W. "Prenatal treatment of classic CAH with dexamethasone: pro vs. con." Endocrine News Tri-Point Series 2008: 16-18.