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A Case Study in Unethical Transgressive Bioethics: “Letter of Concern from Bioethicists” About the Prenatal Administration of Dexamethasone

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On February 3, 2010, a “Letter of Concern from Bioethicists,” organized by fetaldex.org was sent to report suspected violations of the ethics of human subjects research in the off-label use of dexamethasone during pregnancy by Dr. Maria New. Copies of this letter were submitted to the FDA Office of Pediatric Therapeutics, the Department of Health and Human Services (DHHS) Office for Human Research Protections, and three universities where Dr. New has held or holds appointments. We provide a critical appraisal of the Letter of Concern and show that it makes false claims, misrepresents scientific publications and websites, fails to meet standards of evidence-based reasoning, makes undocumented claims, treats as settled matters what are, instead, ongoing controversies, offers “mere opinion” as a substitute for argument, and makes contradictory claims. The Letter of Concern is a case study in unethical transgressive bioethics. We call on fetaldex.org to withdraw the letter and for co-signatories to withdraw their approval of it.

Keywords: bioethics, fetal treatment, human subjects research, methodological integrity, off-label use of medications, public advocacy, transgressive bioethics

On February 3, 2010, a “Letter of Concern from Bioethicists” was sent to report suspected violations of the ethics of human subjects research in the off-label use (i.e., not for purposes approved by FDA) of dexamethasone (a glucocorticoid steroid) during pregnancy “for the purposes [sic] of preventing genital virilization associated with CAH[congenital adrenal hyperplasia] in 46,XX females,” by Dr. Maria New, Professor of Pediatrics at Mount Sinai Medical Center in New York City (fetaldex.org 2010a; Appendix). The effort was organized by fetaldex.org, which continues to update this “action.” “We have organized a group of professional researchers in bioethics and allied fields to file formal letters of concern” (fetaldex.org 2010b). Copies of this letter were submitted to the U.S. Food and Drug Administration (FDA)

Office of Pediatric Therapeutics, the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protections, Mount Sinai Medical Center, Weill Medical College of Cornell University (“from which much of this treatment appears to have been administered, under Dr. New’s guidance” when she served on Cornell’s faculty), and Florida International University (“where Dr. New is Associate Dean for Clinical Research”).

The stated purpose of fetaldex.org, which was founded in 2010, is the following:

This website seeks to raise awareness regarding the prenatal use of dexamethasone, a Class C steroid, to attempt to prevent a female fetus from developing genitals that are more in-between a male and female type. (fetaldex.org 2010b)

Ellen Feder, Ph.D., of American University, appears as corresponding author, followed by 31 co-signatories and three “additional supporters of inquiry (offered to sign after letters had already gone in).”

The “Letter of Concern from Bioethicists” (hereinafter referred to as LoC) and the subsequent activities of fetaldex.org can usefully be characterized as an example of transgressive bioethics. Transgressive bioethics combines attention-getting tropes with traditional philosophical argument to challenge accepted clinical practice or research in a deliberately provocative fashion, to expose what is taken to be unethical practice and reform it. Transgressive bioethics can be understood as aiming to fulfill a traditional role of the humanities: to speak truth to power in a conspicuous fashion, to bring power to account. There is nothing intrinsically objectionable to transgressive bioethics, when it meets the intellectual and moral standards required to produce a public discourse of bioethics that is “reasonable” (Jonsen 1998, 353). The purpose of this paper is to show that the “Letter of Concern from Bioethicists” and the subsequent activities of fetaldex.org fail to meet these intellectual and moral standards, making this episode a case study in unethical transgressive bioethics.

DR. NEW’S RESEARCH

The target of the LoC is the research of Dr. New. The first requirement of sound bioethics, including transgressive bioethics, is reproducing empirically verifiable facts completely and accurately (De Grazia and Beauchamp 2001). We therefore start with an account of Dr. New’s research on prenatal use of dexamethasone to prevent virilization of the female fetus affected by congenital adrenal hyperplasia (CAH). CAH is a genetic hormonal disorder resulting in anatomic and physiologic masculinization of females.

Dr. New is one of the leading pediatric endocrinologists in the world, having made many contributions to our understanding and treatment of adrenal disorders. Many scholars have written about the most frequent adrenal disorder, i.e., CAH owing to 21-hydroxylase deficiency (21OHD). Indeed, the first anatomical description was

reported De Chrecchio (1865) in Italy. Grunberger and Boschitsch (1981) reported the case histories of 22 adult female patients aged 15 to 27 years before any prenatal therapeutic program had been developed. All treatment was at that time postnatal. Because of genital masculinization and, in the majority of cases, despite some form of corrective genital surgery (mostly clitorrectomy), 11 of the women could not engage in heterosexual intercourse. Menarche occurred spontaneously in only 10 cases. Because prenatal testing was not yet available, the diagnosis was made postpartum, at which time the treatment of choice was the administration of a corticosteroid. From the standpoint of ameliorating genital ambiguity (but one conspicuous effect of high levels of intrauterine androgen exposure), intervention at this stage is considerably less than efficacious.

With the advent of prenatal diagnosis of CAH through chorionic villus sampling or amniocentesis (depending on when the pregnant woman first presents for obstetric care) came the opportunity for earlier therapeutic intervention in pregnant women at high risk for carrying a child with CAH. The pioneer in prenatal treatment to prevent genital ambiguity was Maguelone Forest in Lyon, France, who reported the first prenatal treatment of CAH in 1987 (Forest, B'etuel, and David 1987). In 1986 Dr. New utilized Dr. Forest's protocol to initiate prenatal diagnosis and treatment in the United States (New 1990; Karaviti et al. 1992). Many other countries have now begun a program of prenatal diagnosis and treatment of CAH to prevent genital ambiguity. The protocol is as follows.

An obstetrician who performs chorionic villus sampling or amniocentesis requests prenatal diagnosis by sending a sample of tissue to Dr. New. The pregnant woman's obstetrician makes a referral to Dr. New for the purpose of tissue analysis for 21OHD. DNA is sent to Dr. New's laboratory for analysis. She often requires DNA from the father as well, unless it was obtained from a previous pregnancy consultation.

The pregnant woman has requested prenatal diagnosis and treatment because she has a member of her family who is affected with 21OHD and therefore the fetus is at risk. Prenatal treatment with dexamethasone for 21OHD must be initiated before the 9th week of gestation to be effective, because sexual differentiation of genitalia typically occurs between the 9th and 13th week of gestation and chorionic villus sampling or amniocentesis cannot safely be performed prior to this milestone. Once the presence of normal 21OHD is identified and/or the fetus is identified as male, dexamethasone therapy is discontinued. Male fetuses and unaffected female fetuses do not require prenatal treatment, but neither the referring physician nor Dr. New knows this until the genetic diagnosis is made. Therefore, treatment is initiated by the referring obstetrician blind until the status of the fetus is determined (male or female, affected or unaffected).

DNA diagnosis takes about 2–3 weeks, depending on whether the cells grow well enough. The dose of dexamethasone is 20 μ g per kilogram per day in three divided doses, based on prepregnancy weight, with a maximum dose of 1.5 mg of dexamethasone per day. When the genetic information becomes available, Dr. New's office immediately calls the referring obstetrician to report whether the fetus is a male or unaffected female and advises the doctor to stop the treatment. If it is a female that

is affected genetically, the woman is administered dexamethasone until term. Dr. New asks for a postnatal follow-up to be sure that the prenatal diagnosis is correct. Follow-up data are gathered by Dr. New under an institutional review board (IRB)-approved protocol with informed consent for data collection, analysis, and reporting (Trautman et al. 1995; New et al. 2001).

The short-term outcome of preventing genital ambiguity in the affected female is 100% effective, providing that the pregnant woman is compliant and the dexamethasone is administered properly. The referring obstetrician obtains consent and writes the prescription for dexamethasone. Frequently, Dr. New must provide advice as to the dose and the duration. It is of note that Dr. New herself has written the prescription for dexamethasone for only one patient: a pregnant woman who is herself a patient with a severe form of CAH who became pregnant with a female fetus who was also affected with a severe form of CAH (personal communication with Dr. New).

Dexamethasone is administered at a very low dose (20 $\mu\text{g}/\text{kg}/\text{day}$ of prepregnancy weight in 3 divided doses). At this low dose, dexamethasone does not have teratogenic potential, and furthermore, because the therapy does not begin until just before the ninth week of gestation, organogenesis of the major organs has been completed, so on both counts a risk for induced birth defects is not present.

To date more than 800 fetuses have been diagnosed by genetic analysis of fetal tissue worldwide, so that in many countries, including the United States, prenatal diagnosis and treatment has become the standard of medical care. It should also be pointed out that the regulatory agencies in some countries have approved this protocol. This status of prenatal use of dexamethasone as standard of care is reflected in the major obstetrics textbooks. *Danforth's Obstetrics* is illustrative:

Approximately 90% of patients with CAH during pregnancy have a partial or complete deficiency of the 21-hydroxylase enzyme. The resultant decrease in cortisol production leads to increased ACTH stimulation, which then results in both increased production of androgenic cortisol precursors . . . and decreased production of aldosterone. Because these androgenic steroids readily cross the placenta, pregnancies complicated by significant maternal 21-hydroxylase deficiency are at increased risk for fetal virilization. Such virilization is most apparent in female infants, although male infants also may have somewhat enlarged external genitalia. The risk of fetal virilization is reduced if pregnant patients with CAH receive adequate basal glucocorticoid replacement together with additional glucocorticoid in times of stress. Mineralocorticoid replacement should be continued as well. (Krakow 2008)

DR. NEW HAS “LONG PRESCRIBED” PRENATAL EXAMETHASONE:A FALSE CLAIM

The LoC states in its second paragraph:

It is our understanding that Dr. New has long prescribed dexamethasone for purposes of preventing genital virilization associated with CAH in 46,XX females.

Dr. New has prescribed dexamethasone prenatally in *only one case*, as we documented earlier. This central factual claim of the LoC is therefore false. That it could be advanced reflects the failure to undertake the research required to document this claim. Had such research been undertaken, the claim could not have been truthfully made. Making false claims as a consequence of the failure to meet the standard of reproducing empirically verifiable facts completely and accurately (De Grazia and Beauchamp 2001) is intellectually irresponsible and therefore unethical transgressive bioethics. By itself, this false claim discredits the LoC. However, there are multiple additional flaws in it that betray its systematically unethical nature. We address each in turn.

PRENATAL ADMINISTRATION FOR DEXAMETHASONE IS COSMETIC: FALSE REPRESENTATION OF THE POSITION OF A SCIENTIST

The second paragraph of LoC states:

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. (emphasis original)

No argument is made to support the clinical ethical judgment that genital virilization of females is a “cosmetic issue.” Instead, reference is made to a paper by Walter Miller (1999), a pediatric endocrinologist.

Miller reports the complications of virilization as “persistence of a urogenital sinus, labioscrotal fusion and clitoromegaly, which are surgically correctable. This fetal hyperandrogenism may also masculinize the brains of affected females” (Miller 1999, 537). The LoC mentions only one of these complications, clitoromegaly, without explanation.

Miller reports on the use of prenatal dexamethasone, “There is now sufficient clinical experience so that present dexamethasone protocols result in little or no masculinization of the female genitalia” (Miller 1999, 537), and cites work by Dr. New in support. Miller goes on to make the case that prenatal use of amethasone is “experimental.” He points out that unaffected fetuses “will receive at least 6 weeks of

dexamethasone treatment before a diagnosis is made” (Miller 1999, 537); that “only 1 in 8 pregnancies to a couple with a previously affected child has a theoretical chance to be helped by prenatal therapy” (Miller 1999, 538); that the dosages exceed normal fetal glucocorticoid levels by a factor of 10; that the mechanism by which virilization may be altered is not well understood; and that “the teratogenic effect of dexamethasone has not been evaluated definitively” (Miller 1999, 538). Miller emphasizes the point that the long-term risks are not well understood as “most difficult” (Miller 1999, 538). He concludes:

The genitalia of virilized females can be repaired surgically but adrenogenization of the brain is irreversible; hence, prenatal dexamethasone treatment may offer unique advantages. However, the ethics of needlessly subjecting 7 of 8 fetuses to an experimental therapy with unknown long-term consequences remain unresolved because the long-term safety and outcome have not been established. Therefore, prenatal treatment of CAH remains experimental. (Miller 199, 538)

Miller goes on to call for the administration of prenatal dexamethasone under protocols limited to “large centers that receive a large enough number of patients to yield meaningful research results” (Miller 1999, 538–539). Miller also sets out the domains of information that should be included in the informed consent process for such research.

Nowhere in his article does Miller use the word “cosmetic” or any of its cognates. The reference to the Miller paper in the LoC to support its claim that prenatal administration of dexamethasone is cosmetic is erroneous because it is inconsistent with the plain language of the Miller paper. Miller, as just quoted, characterizes virilized genitalia as surgically repairable but makes no mention that this is a cosmetic procedure. Instead, he treats such surgery as a medical issue “that should be of the primary concern of physicians,” to use the language of the LoC. Worse, Miller directly supports the *opposite* view when he acknowledges that virilization of the brain is an “irreversible” complication and thus of clinical significance. In summary, the LoC falsely represents Miller’s paper as stating that prenatal administration of dexamethasone is merely cosmetic.

SUBSEQUENT ADMISSION THAT PRENATAL ADMINISTRATION OF DEXAMETHASONE IS NOT COSMETIC

Hilde Lindemann, Ph.D., of Michigan State University, joined Drs. Feder and Dreger in a posting on the bioethics blog site of The Hastings Center, reiterating the claims advanced in the LoC (Lindemann, Feder, and Dreger 2010a). One response was from an interdisciplinary group from Harvard Medical School (Diamond et al. 2010). David Diamond and colleagues pointed out that virilization of females with CAH in its severe forms includes a persistent urogenital sinus, an anomaly in which the urethra and vagina form a single channel. They write: “Even without doing surgery on the enlarged clitoris, surgical reconstruction to separate the urinary and reproductive tracts

in childhood is necessary to prevent urinary incontinence and infections leading to renal damage as well as to allow normal urination and future sexual function” (Diamond et al. 2010). Diamond and colleagues also point out that Miller underestimates the complications of neonatal surgery to correct this problem. Prevention of this anatomic anomaly, they correctly add, is not cosmetic.

Drs. Lindemann, Feder, and Dreger responded as follows:

The reason we did not pay enough attention to this point is explained by our focus on New’s work on prenatal dex[amethasone], which appears after much review to stand out as atypical. In her promotion of prenatal dex to “at risk” women, New emphasizes the prevention of ambiguous genitalia as the most important aim of intervention. This has implied that ambiguous genitalia represent some kind of medical problem in and of themselves.

Obviously it would be good if medically necessary interventions (for example, surgery to correct a severe urogenital sinus) could be made unnecessary through prevention, as some interventions for neural tube defects have been prevented through increasing fertile women’s intake of folic acid. That said, we remain extremely concerned about the way that prenatal dex is being promoted and administered, and we do not see the potential for a postnatal urogenital sinus as a license to do what has been done. (Lindemann, Feder, and Dreger 2010b)

This response amounts to an admission that the attenuation of virilization with dexamethasone prevents more than just clitoromegaly; it also prevents clinically significant anatomic anomalies and therefore prevents “medically necessary interventions,” not just cosmetic procedures. As a result, they contradict and thus nullify one of the central claims in the LoC, that prenatal administration of dexamethasone for affected female fetuses is merely cosmetic.

MISREPRESENTATION OF CARES FOUNDATION WEBSITE

The LoC cites a CARES (Congenital Adrenal Hyperplasia Research Education & Support) Foundation document twice. The website is described as “online promotion of the treatment of dexamethasone administered by Dr. New’s clinic.”

The CARES Foundation was incorporated in 2001 as a 501(3)(c) nonprofit organization (CARES Foundation 2009). It is not associated with Dr. New’s clinic, as the LoC implies in its ambiguous wording. This website is also cited in the LoC to support its claim that Dr. New has recruited pregnant women “without the benefit of

IRB oversight.” The website makes no such claim. The CARES website is thus misrepresented twice.

PRENATAL ADMINISTRATION OF DEXAMETHASONE HAS SIGNIFICANT IATROGENIC RISK: FAILURE TO MEET THE STANDARDS OF EVIDENCE-BASED REASONING

The LoC makes two related claims about the risk of prenatal administration of dexamethasone. The LoC concludes its second paragraph with: “Furthermore, use of prenatal dexamethasone has been demonstrated to bear significant iatrogenic risk.” The LoC concludes its fifth paragraph with: “contrary to the apparent claims aimed at prospective patients, dexamethasone treatment cannot responsibly be characterized as benign.”

Claims about the clinical benefits and risks of any clinical intervention should be evidence based. Bioethics is held to this exacting intellectual standard no less than clinical practice and research (Sulmasy and Sugarman 2001). The accepted standard for establishing unacceptable risk of a clinical intervention is a systematic review of the literature. No such review is described in the LoC. Instead, five papers are cited and no search strategy is described, in a letter being sent to federal agencies committed to evidence-based advancement of biomedical science and clinical practice. The LoC has an intellectual obligation to rebut Dr. New’s work by appealing to an evidence-based analysis of her work in the context of the results of a systematic review. That the LoC fails to meet the fundamental standard of evidence-based reasoning is a fundamental error.

The LoC asserts that perinatal treatment with dexamethasone puts fetuses at risk for neurotoxicity. The LoC references a study performed on 8 rhesus monkeys (3 of which were given placebo) that were administered dexamethasone in doses of 5 mg/kg (Uno et al. 1994). For reference, the typical dose given to pregnant (human) women was 20 μ g/kg. The LoC provides no justification for its extrapolation from the results of a study of 5 rhesus monkeys that were administered a single, 200-fold higher dose of dexamethasone than that administered to human female fetuses affected by CAH.

In support of its claim about “significant iatrogenic risk” the LoC cites a 2000 NIH Consensus Development Conference Statement (National Institutes of Health Consensus Development Panel 2001). The LoC neglects to mention that this is a statement on the use of antenatal steroids to promote fetal maturation, a clinical entity very dissimilar from CAH. The NIH statement does not address prenatal administration of dexamethasone to prevent the clinical complications of CAH. Prenatal use of steroids to promote fetal maturity occurs later in gestation and at a much higher dose. This fundamental clinical disanalogy to prenatal use of dexamethasone for prevention of virilization is not acknowledged, much less addressed in the LoC.

Even if the NIH statement were clinically relevant, the statement does not support the claim of the LoC. This is because the LoC omits the conclusion of this statement, which reads: “The collective international data continue to *support*

unequivocally the use and efficacy of a single course of antenatal corticosteroids using the dosage and interval of administration specified in the 1994 Consensus Development Conference report” (National Institutes of Health Consensus Development Panel 2001, 144, emphasis added).

The fetaldex.org website refers to a summary (“Cognitive functions” 2009) that appeared in *Growth, Genetics, and Hormones* about a study to “show that this prenatal dex treatment may result in detrimental changes to the brains of children given the drug in the womb.” The “About the Journal” webpage for this publication (<http://www.gghjournal.com/atAGlance.cfm>, accessed April 22, 2010) does not describe this journal as peer reviewed. It is not listed in the Web of Knowledge journal citation reports and therefore has no impact factor. The fetaldex.org Web site does not report any of this information and does not report that it relies on a summary of an article cited in the LoC (Hirvikoski et al. 2007).

The fetaldex.org website does not portray the summary accurately. It states that there was no statistically significant difference reported for such cognitive functions as verbal comprehension and IQ but that there were statistically significant differences for memory function. The accompanying “Editor’s Comment” to this study suggests several more problems: “the sample size is small limiting statistical power; the assessment of school performance was self-reported and based on a measure of limited utility in detecting subtle learning problems; the generalizability of the findings are limited to children younger than 18 years, i.e., the pattern of neurocognitive effects may depend on chronologic age” (Sandberg 2009). Furthermore, in the study in question, the control-group children in the study were CAH-unaffected. That is, this study did not actually have a control arm of patients not altered by dexamethasone therapy, so that the null hypothesis of the study fails to be invalidated by virtue of a key methodological flaw of the study. These crucial methodological limitations are left unmentioned on the fetaldex.org website and in the LoC.

The LoC also cites a study (French et al. 2004) to support its claim that that prenatal administration of dexamethasone “results in detrimental changes to the brains of children.” The population studied was children whose mothers had been administered steroids for preterm births, not CAH-affected females. As in the case of its reference to the NIH Consensus Panel, analyzed earlier in this article, the LoC does not report this difference in populations, with the same disabling problems for the LoC. Worse, the paper reports a protective effect of fetal dexamethasone against cerebral palsy and an association with hyperactivity in children treated. These mixed results are not reported in the LoC and do not support its unequivocal claim about brain changes.

Finally, the usual evidence-based approach to judging the efficacy of an intervention in a population is based on the number needed to treat (NNT) and the number needed to harm (NNH). The NNT for prenatal dexamethasone administration is 8 (the number of fetuses exposed before genetic analysis is completed and one affected fetus is identified). Contrast this to the NNT for childhood influenza vaccination to prevent one hospitalization per year: between 1031 and 3050 for children 6–23 months and between 4255 and 6897 for children 24–59 months of age

(Lewis et al. 2007). The NNH for prenatal dexamethasone would have to be calculated on the basis of a systematic review of the literature that described statistically significant differences in harms between CAH-affected children who were prenatally treated with dexamethasone and CAH-affected children who were not. The peer-reviewed papers cited in support of the LoC's claim about "significant iatrogenic risk" are either human studies without the required control group or animal studies. Therefore, the NNH for prenatal dexamethasone for affected female fetuses cannot be calculated on the basis of the references in the LoC. The claim of the LoC that "prenatal dexamethasone has been demonstrated to bear significant iatrogenic risk" lacks empirical foundation and therefore violates the standards of evidence-based reasoning.

Were the authors of the LoC more charitably attuned to the substance of Dr. New's research, they would have found a number of studies over the years that examined, in great detail, concerns regarding neurotoxicity and all manner of other forms of potential teratogenicity. It turns out that Dr. New has pondered and studied the concerns regarding antenatal neurotoxicity in humans in publications going back to 1995 (Trautman et al. 1995) and she continues to study the hypothesis today. In one 2004 study (Meyer-Bahlberg et al. 2004), New and colleagues examined 174 children, newborn to age 12 years, who were exposed to dexamethasone perinatally, of which 48 had CAH. These children were compared to 313 unexposed children, including 195 with CAH. New and colleagues used four different developmental questionnaires chosen for age-appropriateness and found that exposure to dexamethasone demonstrated no statistically significant correlations between dexamethasone administration and developmental delay on any measure, in any of the groups. Dr. New has also authored studies demonstrating that dexamethasone-treated fetuses had no difference in birth weight, length, and head circumference and that the risk of fetal loss was not higher than the general population (New et al. 2001). Given the low prevalence of CAH, this is likely to be among the largest study populations ever available for this disease.

By contrast, the PREDEX study relied upon by the LoC has been enrolling patients prospectively in several European countries since 1999, and had only reported enrolling 14 patients through 2004 (Lajic 2004). The lead investigator for PREDEX, Dr. Svetlana Lajic, has published several studies on the neurocognitive effects of perinatal administration of dexamethasone over several years (Lajic 2004; Hirvikoski 2007; 2008). One study (Hirvikoski 2007) reported lower rates of verbal working memory and higher rates of social anxiety in CAH-unaffected patients treated with dexamethasone ($n = 26$), though this same index was measured and not identified as statistically significant by New and colleagues ($n = 174$). In a follow-up study, Hirvikoski and colleagues report that their previous findings were not able to be reproduced, and may have been the result of a Type I error due to small sample size (Hirvikoski, 2008), lending credence to the results of studying a larger sample size such as reported by New and colleagues. Regardless, the data cited by the authors of the LoC do not support the LoC's claim that "dexamethasone treatment cannot responsibly be characterized as benign." Indeed, the preponderance of evidence suggests that the therapy is benign.

It is a perennial challenge to study the long-term effects of a therapy for a condition that has a low incidence and prevalence, particularly when the effects being studied (neurocognitive behaviors) are affected by a vast array of factors. It is therefore all the more impressive that a dispassionate review of the empirical literature on the subject finds that Dr. New's work represents the most methodologically sound and statistically convincing evidence that significant adverse neurocognitive outcomes attributable to perinatal dexamethasone therapy have yet to be convincingly reported. Assertions to the contrary have no basis in the empirical literature on the subject.

OFF-LABEL ADMINISTRATION OF DEXAMETHASONE IS RESEARCH THAT SHOULD BE CONDUCTED ONLY WITH IRB OVERSIGHT: AN APPEAL TO A NONEXISTENT ETHICAL STANDARD

The third paragraph of the LoC states:

Off-label use of prescription medication is a long-time practice of medicine that has not been understood to constitute research requiring IRB oversight. We do 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 involving many hundreds of patients now among the targeted "subjects" of long-term research. In clear violation of established bioethical protocols, these pregnant women appear to have been recruited (and perhaps are still being recruited) without the benefit of IRB oversight.

The last sentence has a reference to the CARES website about Dr. New's research, which we addressed earlier.

Two claims are made in this paragraph of the LoC. The first is that off-label use of prenatal dexamethasone "appears to constitute a de facto clinical trial." The second is that Dr. New is conducting follow-up studies of the long-term outcomes of prenatal dexamethasone without IRB approval. The latter claim is demonstrably false, as is clear from the plain language in Dr. New's 2001 report on the follow-up, which states: "The study was approved by our institution's review board for human rights in research. Informed consent was obtained from mothers" (New et al. 2001, 5654; see also Trautman et al. 1995, which is cited in the LoC).

The claim that prenatal use of dexamethasone is a "defacto clinical trial" is neither clarified nor justified by the LoC. Assertion made without supporting argument, as Plato had Socrates teach us long ago, constitutes "mere opinion." "Mere opinions" are not valid argument forms, because they are conclusions in search of premises.

To determine whether supporting premises might be available, we performed a literature search in PUBMED using "off label use AND ethics" that yielded 68

citations (April 22, 2010). The oldest citation is from 1994. The absence of a literature on the topic means that there was no ethical analysis and argument, much less a consensus ethical standard, that off-label use of prescription medications is research. Thus, no ethical standard for off-label use of drugs existed when Dr. New began her treatment protocol in 1986. The LoC falsely assumes such a standard has always existed. To avoid this criticism, the LoC could have cited a consensus ethical standard. The LoC does not do so because, as our review of the 68 citations indicates, there is no such standard in the literature. Grant, for the sake of argument, that such a standard has just been created. To apply it to clinical practice from 25 years ago commits the terror of presentism, i.e., applying ethical standards of the present as if they applied throughout human history, against which historians rightly warn us (Pernick 2009). The claim that prenatal administration of dexamethasone constitutes a “de facto clinical trial” fails.

UNDOCUMENTED CLAIM THAT PREGNANT WOMEN MAY NOT HAVE PROVIDED INFORMED CONSENT FOR ADMINISTRATION OF DEXAMETHASONE

The sixth paragraph of the LoC states:

It does not appear that physicians prescribing this drug to hundreds of women have sought IRB approval for clinical trials of dexamethasone for the purposes of minimizing virilization [and that therefore] 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.

The LoC assumes that obstetricians prescribing dexamethasone in such cases would not adhere to ethical and legal standards of informed consent in clinical practice, simply because there was no IRB oversight. This is a non sequitur. Moreover, it calls into question the professional integrity of scores of physicians without a shred of evidence being offered for the plausibility of the hypothesis of systematic and widespread violation of the ethical and legal standards of informed consent in obstetric practice for the prenatal administration of dexamethasone.

A CALL FOR CLINICAL TRIALS: AN UNORIGINAL CLAIM THAT LACKS SUPPORTING ARGUMENT

The LoC states in its seventh paragraph:

Given the well-established risks to fetal development, physicians should initiate treatment of this type only through structured clinical trials with human subjects research protections in place.

This call for clinical trials under IRB oversight is not based on the earlier claim that off-label use of prenatal dexamethasone is by definition experimental, which we

addressed earlier. It is, instead, the claim that, because the long-term outcomes of prenatal administration dexamethasone are not known and because some risks have been reported, prenatal dexamethasone should be offered only under a clinical protocol. To be sure, the authors of the LoC trade heavily on the existence of uncertainty as regards the risks of dexamethasone, but the mere existence of disagreement does not speak to the merits of whether there is empirical support for disagreement about the risks of dexamethasone. We have suggested that much of this uncertainty is predicated on studies that either are not germane to the specific question regarding the administration of dexamethasone in this setting or are predicated on small clinical studies that are statistically underpowered compared to the data reported by Dr. New and in which tentative observations of potential harm are not reproduced in subsequent studies. The authors may have gleaned their argument from Miller (1999) in his 1999 paper cited by the LoC, but the Miller paper is not cited in this part of the LoC. Perhaps this is because Miller offers no more empirically substantive basis for his claims than the authors of the LoC proffer.

The LoC statement is not consistent with the 2002 consensus statement from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology, which the LoC does not cite. This statement reads: “There is substantial difference of opinion concerning whether prenatal treatment of CAH is a research endeavor” (Joint LWPES/ESPE CAH Working Group 2002, 4049). No position is taken on the matter, a fact that the LoC fails to report.

In bioethics when one asserts a position that is controversial, one is obligated as a matter of intellectual integrity to advance an argument for one’s position (De Grazia and Beauchamp 2001). The LoC offers as the single premise: “Given the well established risks to fetal development.” As we pointed out earlier, in the absence of a structured scientific review of the literature and an analysis of the NNT and NNH based on such a review, the use of “well established” lacks empirical justification. Grant, however, that it is a reasonable claim. This “premise” reflects an incomplete ethical analysis, because there is no comprehensive analysis of the outcomes. For the premise to reflect an adequate ethical analysis, one would have to show that, on balance, the well established risks are not offset by clinical benefits, especially the amelioration of virilization. The consensus statement from the Joint LWPES/ESPE CAH Working Group states that it is “clear” that such ameliorization is accomplished, a conclusion that we believe is readily sustained by an assessment of the totality of the literature, including the body of clinical studies published by Dr. New. The claim that there should be clinical trials lacks supporting argument.

CLINICAL TRIALS SHOULD NOT BE PURSUED: A CLAIM THAT CONTRADICTS THE CALL FOR CLINICAL RESEARCH

In the final paragraph of the LoC, which comes immediately after the paragraph in which the call for clinical trials is made, the LoC states:

Finally, we agree with Dr. Walter Miller, Distinguished Professor of Pediatrics and Chief of Endocrinology at the University of California San Francisco, who has written

that “this experimental treatment is not warranted and should not be pursued even in prospective clinical trials.”

The quoted passage is from a recent column by Miller in *EndocrineNews* (Speiser and Miller 2008). In it, he provides a condensed version of the argument that he made in his 1999 paper, cited in the LoC and discussed earlier. Miller concludes his *EndocrineNews* column with: “It is this author’s opinion that this experimental treatment is not warranted and should not be pursued, even in prospective clinical trials” (Speiser and Miller 2008, 17). Miller provides no argument for his opinion, which is required to justify the rejection of his earlier call for clinical trials (Miller 1999). In endorsing Miller’s opinion that clinical trials should not be undertaken the LoC contradicts its call, issued in the preceding paragraph, for clinical trials to be undertaken. The LoC thus violates the law of noncontradiction, the most fundamental requirement of argument-based reasoning.

MAJOR DIFFERENCES BETWEEN VERSION CIRCULATED TO SOLICIT CO-SIGNATORIES AND SUBMITTED VERSION

The original version circulated to solicit individuals to become co-signatories contained no references. Major changes were made after co-signatories added their names to the draft LoC. There was no indication that changes would subsequently be made after the agreement of co-signatories to add their names.

In an exchange on the bioethics listserv sponsored by the Medical College of Wisconsin, two of us (FAC and LBM) pointed out that numerous claims were made without substantiation in what turned out to be a draft version of the LoC. The initial response of the authors was that the LoC was not a scholarly paper and therefore was somehow exempt from accepted standards of scholarship. Such a position would disable transgressive bioethics. References were added in the submitted version. We addressed earlier the inadequacy, misuse, and false representation of the references. This substandard scholarship disables the LoC as transgressive bioethics that meets minimal standards of intellectual rigor and integrity.

The opening sentence of the circulated unreferenced draft reads: “We write to express our grave concern that a research group affiliated with your institution may be engaging in an unapproved, off-label pharmaceutical trial targeted at pregnant women and their fetuses.” This sentence does not appear in the submitted version. The sixth paragraph of the submitted LoC concludes with: “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.” This sentence does not appear in the draft circulated to solicit co-signatories. The final paragraph of this version of the LoC starts with: “We call for rigorous investigation by your institution into whether researchers associated with your institution are currently or have previously treated pregnant women with dexamethasone to prevent genital virilization.” The final paragraph of the submitted LoC begins with: “We call for rigorous investigation by the FDA into possible regulatory violations in this matter.”

There is no indication in the submitted LoC that the cosignatories were made aware of these major changes in the LoC. There is also no indication that the co-signatories read and approved the submitted version of the LoC.

CONCLUSION

Rebecca Dresser and Joel Frader (2009) recently called for “responsible self-regulation” of off-label use of drugs. This has been a common practice not only in obstetrics but also in pediatrics and adult medicine and surgery in general for decades. Specifically, there is ongoing discussion in the scientific community on whether the prenatal administration of dexamethasone to prevent the complications of CAH in affected females is experimental or standard of care (Joint LWPES/ESPE CAH Working Group 2002).

The LoC could have contributed to this important topic. Instead, the LoC makes false claims; misrepresents scientific publications and websites; fails to meet the fundamental standards of evidence-based reasoning; makes undocumented claims; treats as settled matters what are, instead, ongoing controversies; offers “mere opinion” as a substitute for argument; and makes contradictory claims. The LoC is therefore a case study in unethical transgressive bioethics.

We call on fetaldex.org as the self-proclaimed organizer of “a group of professional researchers in bioethics and allied fields to file formal letters of concern” (fetaldex.org 2010b), and the corresponding author to withdraw the LoC from the government agencies and academic institutions to which it was submitted and to announce the withdrawal publicly on its website and the bioethics listerv. We also call on the co-signatories to remove their names from the LoC, to report their decision to remove their names to the government agencies and academic institutions to which the LoC was sent, and to inform fetaldex.org of their decision. We call on fetaldex.org to post notices of withdrawal by co-signatories from the LoC on its website.

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APPENDIX: fetaldex.org LETTER OF CONCERN FROM BIOETHICISTS

The following letter has been sent to:

1. the FDA Office of Pediatric Therapeutics;
2. the HHS Office for Human Research Protections;
3. Mount Sinai Medical Center (Dr. New's current institution);
4. Weill Medical School of Cornell University (from which much of this treatment appears to have been administered, under Dr. New's guidance);
5. Florida International University (where Dr. New is Associate Dean for Clinical Research).

The preliminary FDA response is shown here; the Office of Human Research Protections preliminary response is shown here.

Dear Sir or Madam:

We write to express our grave concern over possible non-IRB-approved clinical research on pregnant women that has been conducted under the auspices of Mount Sinai Medical Center and Weill Cornell Medical College, Cornell University, under the direction of Dr. Maria New.

This work involves off-label administration of dexamethasone to pregnant women who may give birth to girls with Congenital Adrenal Hyperplasia (CAH). 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. 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]

Off-label use of prescription medication is a long-time practice of medicine that has not been understood to constitute research requiring IRB oversight. We do 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 involving many hundreds of patients now among the targeted “subjects” of long-term research. In clear violation of established bioethical protocols, these pregnant women appear to have been recruited (and perhaps are still being recruited) without the benefit of IRB oversight.[3]

In professional contexts among her peers, Dr. New has publicly resisted discussion of the details of the information pregnant women and their partners are provided. One online promotion of the treatment with dexamethasone administered by Dr. New's clinic nevertheless promised 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.”[4]

Human studies have demonstrated, on the contrary, that prenatal dexamethasone treatment results in detrimental changes to the brains of children,[5] over 90% of whom 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.) Children exposed prenatally to dexamethasone for CAH show problems with working memory, verbal processing, and anxiety.[6] Animal studies have also indicated reason to be very concerned about prenatal dexamethasone's effect on fetal brains.[7] Therefore, contrary to the apparent claims aimed at prospective patients, dexamethasone treatment cannot responsibly be characterized as benign.[8]

Despite knowledge of risks to fetal development, it does not appear that 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*. 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. 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.

Given the well-established risks to fetal development, physicians should initiate treatment of this type 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.

We call for rigorous investigation into possible regulatory violations 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. Finally, we agree with Dr. Walter Miller, Distinguished Professor of Pediatrics and Chief of Endocrinology at the University of California San Francisco, who has written that “this experimental treatment is not warranted and should not be pursued even in prospective clinical trials.”[9]

Citations:

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Signed:

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Source: http://fetaldex.org/letter_bioethics.html (accessed April 20, 2010).