

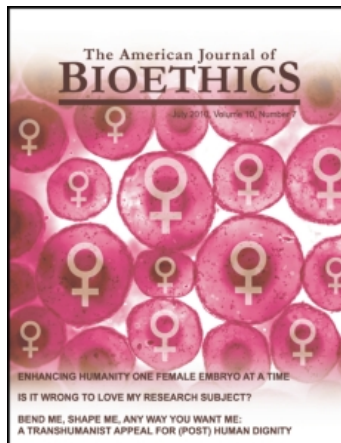
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Description and Defense of Prenatal Diagnosis and Treatment With Low-Dose Dexamethasone for Congenital Adrenal Hyperplasia

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Description and Defense of Prenatal Diagnosis and Treatment With Low-Dose Dexamethasone for Congenital Adrenal Hyperplasia

Maria New, Mount Sinai School of Medicine

BACKGROUND

Much speculation as to the conduct of my research has been made by scholars and the media, particularly by the authors of fetaldex.org and in the article in this journal by McCullough and colleagues (2010). It is important to clarify the facts about my research protocols and the process by which I currently study congenital adrenal hyperplasia (CAH) (New et al. 1999; Wajnrajch and New 2010).

I have been conducting prenatal diagnosis of CAH since 1986. I have utilized the current invasive method for prenatal diagnosis and treatment developed in Lyon, France, by Dr. Maguelone Forest in 1978 (David and Forest 1984). Following the steps shown in Figure 1, I have conducted about 600 prenatal diagnoses in the United States in patients with CAH. Of these, 70 were affected female fetuses, of which 59 were prenatally treated until term (New et al. 2001) (Figure 2). I have advised outside physicians on the dexamethasone treatment. Biosynthesis of steroids in patients with 21 hy-

droxylase deficiency is shown in Figure 3. The algorithm for prenatal diagnosis and treatment as shown in Figure 1.

THE GOAL OF TREATMENT

Congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic disorder that results in genital ambiguity in females with the classical form of this disease. Genital ambiguity in females occurs in several forms of the disorder, including 21-hydroxylase deficiency (21OHD), the most common form of CAH, and 11 β -hydroxylase deficiency (11BOHD). The genital ambiguity is owed to the excessive fetal androgen production, with results as shown in Figure 4, and it is preventable by prenatal low-dose dexamethasone administration to the mother. Prenatal treatment with dexamethasone must begin before the ninth week of gestation to prevent genital ambiguity in the affected female, yet prenatal diagnosis by current invasive methods such as chorionic villus sampling (CVS) or amniocentesis

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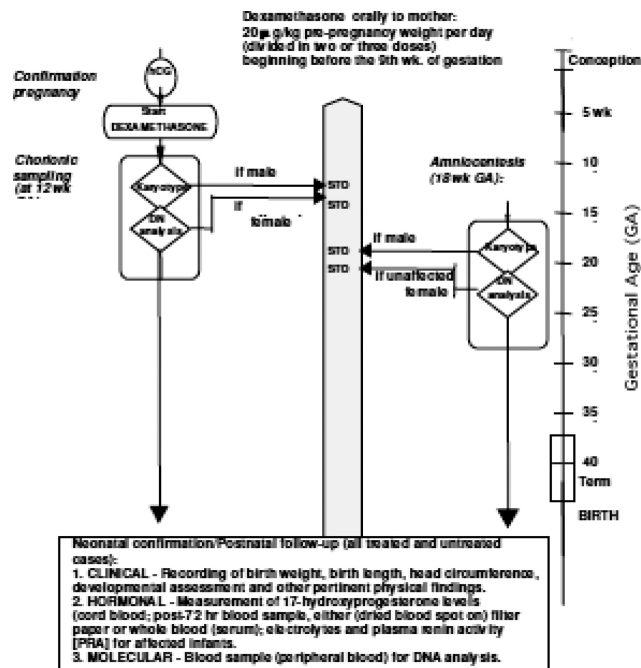


Figure 1. Current Algorithm for Prenatal Diagnosis and Treatment (Nimkarn and New 2009)

The mother presents to her physician because she is pregnant and the fetus is at risk for CAH. Ideally, the parents are counseled by a team consisting of her physician, obstetrician, a genetic counselor, a pediatric endocrinologist, and a molecular geneticist. The risks and benefits of prenatal diagnosis and treatment are thoroughly explained. The options of prenatal treatment, postnatal surgery, or no treatment are given to the mother and the father, and the short-term and long-term outcome of prenatal treatment are described. When the patient is part of Dr. New's clinic, which is unusual as most of the patients are not from New York, this is performed by Dr. New and her team. Otherwise, the physician may call Dr. New for further advice about diagnosis and treatment. The treatment is begun according to the algorithm in this figure. Oral dexamethasone treatment to the mother is initiated at 20 µg/kg prepregnancy weight per day in three divided doses. The mother undergoes chorionic villus sampling at 10–12 weeks of gestation or amniocentesis at 16 weeks of gestation to obtain fetal DNA. The DNA is analyzed for fetal sex; if male, the prenatal treatment is terminated. If the fetus is proven to be female, treatment is continued until genetic analysis of the DNA indicates the fetus is unaffected, and prenatal treatment is then terminated. If the female fetus is affected, prenatal treatment is continued until the baby is born. A blood sample is obtained from the newborn to confirm the prenatal genetic diagnosis and the newborn genitalia are scored according to Prader and Gurtner (1955); see Figure 1.

to obtain fetal DNA cannot be performed before the 10th week of gestation. Males and unaffected females at risk for classical CAH do not require prenatal treatment; however, with current methods all fetuses at risk of CAH must be treated for several weeks before their sex and/or affection status is known. In addition, the mother must undergo invasive diagnostic procedures such as CVS or amniocentesis to obtain fetal DNA in order to determine whether the fetus is affected with the disorder. *The goal of treatment is to prevent genital ambiguity in the affected female fetus.*

A new noninvasive method of prenatal diagnosis and treatment is under development. It will allow detection of the fetal male sex and the unaffected genetic status of the female fetus at 6 to 7 weeks of gestation. Thus, only affected female fetuses will be treated.

IN DEFENSE OF PRENATAL DIAGNOSIS AND TREATMENT OF CAH

Despite recent claims made by Dreger and colleagues (2010) and reported in the popular media (*Time* 2010; *Newsweek* 2010) to the contrary, I have no interest in preventing lesbianism or homosexuality nor have I ever proposed it.

When the sex of a newborn is uncertain because of genital ambiguity, a sex is usually assigned on the basis of physical examination and it becomes the delivery-room sex that is then entered onto the birth certificate. If later in the child's life, symptoms and signs appear that do not conform to the assigned sex, a change in the sex assignment and birth certificate may be attempted. The later the physician-imposed sex reassignment is made, the more doubtful will a long-term gender identity be stable.

Prenatal Diagnosis Referrals 1986-2007

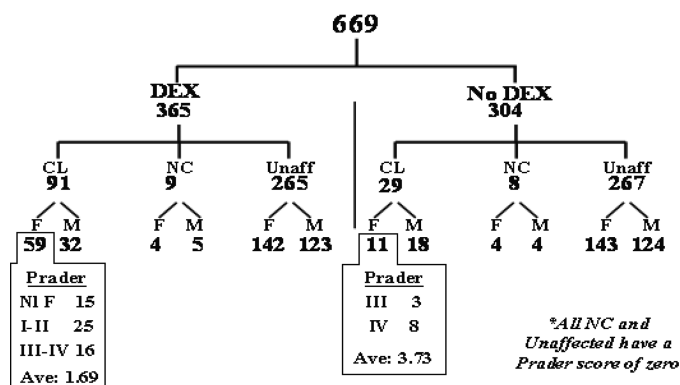


Figure 2. Diagram depicting prenatal dexamethasone treatment outcome by Prader scores (Figure 4) in fully and partially treated affected female newborns with CAH. Prader scores indicate the degree of masculinization. Prader scores 1 to 2.5 are considered typical female genitalia. Prader scores 3 to 5 may require surgical correction. Males, fetuses with non-classical 21OHD, and unaffected females were partially treated with dexamethasone from the 9th to the 18th week of gestation, while female fetuses affected with the classical form of CAH (59 fetuses) were treated until birth. The 16 females with Prader scores of III-IV were prenatally treated late or only partially treated. Dex = dexamethasone; F = female; NI = normal; CL = classical CAH; NC = non-classical CAH; Unaff = unaffected (New 2001).

Changes in sex assignment and birth certificates are difficult. Many will require extensive psychiatric care.

If prenatal treatment is rejected or the affected female with 21 hydroxylase deficiency is born before prenatal treatment was developed or is unavailable, parents usually seek surgical correction of the genital ambiguity (clitoroplasty/vaginoplasty). This surgery involves two distinct procedures. One is the clitoral reduction and the other is the reconstruction of a vaginal introitus, which is inapparent owing to labial fusion (Prader and Gurtner 1955; Figure 4). This correction even in the most experienced hands sometimes results in poor long-term outcome. Adult females who have had genitoplasty in infancy are at risk for impaired sexuality. They have difficulty with intercourse because the vaginal opening is fibrotic and have reduced child bearing. Of even more concern is the complication of

a fistula between the vagina and the urethra. I have met several adult women with CAH with a fistula who have urinary leakage and chronic urinary-tract infections. These women are forced to wear pads to soak up constant urine leakage (Nordström et al. 2010).

However, the surgical treatment of genital ambiguity has not been studied as well as prenatal treatment with dexamethasone for CAH. In my experience (which is one of the largest) if the dexamethasone is properly administered to the mother and the mother is compliant, prenatal dexamethasone treatment results in normal or near normal female genitalia compatible with sexual intercourse, normal fertility, and no urinary leakage and infections. These patients do not require genitoplasty. The preliminary data of medical and psychological outcome of males and females who have been treated prenatally with dexamethasone and

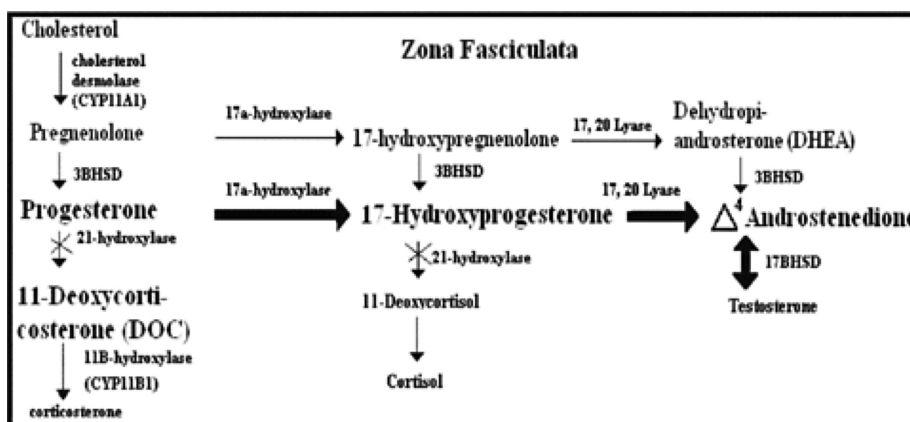


Figure 3. Pathways for the biosynthesis of steroids in patients with 21-hydroxylase deficiency.

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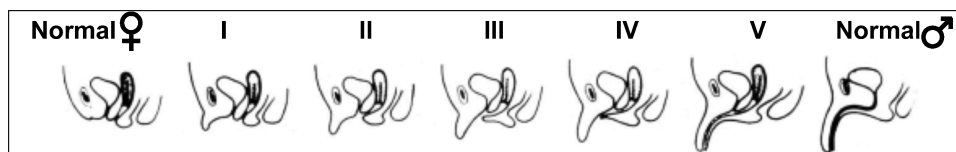


Figure 4. Degree of virilization of the external genitalia of females as modified from Prader. In Type I, the only abnormality is a slight enlargement of the clitoris. In Type V, there is a markedly enlarged phallus with a penile urethra (Prader and Gurtner 1955).

who are now 12 years and older were studied and thus far have shown no adverse affects in 149 subjects with respect to diabetes, obesity, fractures, hypertension, gender, behavior, cognition, and memory (New 2010).

The outcome for patients who received neither surgical treatment nor prenatal treatment for CAH is unsatisfactory for a number of medical and psychological reasons. Among the several patients I have treated who are 46, XX males who have CAH, and have been reared as males, (1) they inevitably are very short because of the overproduction of androgens, which are converted to estrogens, which cause early fusion of the growing ends of the bones, (2) these males are obliged to have lifelong treatment with testosterone to have male puberty, while their adrenal disorder must be treated and the adrenal androgens are suppressed, (3) they need to have a hysterectomy and oophorectomy to avoid menses, and (4) if they have mineralocorticoid deficiency, they need extra salt and salt-retaining hormones as treatment in addition to hydrocortisone to replace their own missing secretion of cortisol and aldosterone from the adrenal.

Even if one remains unpersuaded that prenatal dexamethasone is the best option available, the ad hominem attacks against me and my research are astonishing.

Dreger and colleagues (2010) write that I “apparently did not seek IRB permission to treat the drug administration *itself* as experimental.” However, all of my studies have been conducted under IRB approval. I have also received permission from the FDA to administer dexamethasone prenatally.

Finally, I have been in contact with almost all the families in which a member was treated for CAH. Not one family has described any enduring dissatisfaction with prenatal treatment. All mothers with whom I have spoken who desired future pregnancies would have accepted future dexamethasone treatment, even utilizing invasive prenatal diagnosis. The two mothers who did not desire prenatal treatment in the next pregnancy did not want additional children. I am sure that the satisfaction will be as good if not better with noninvasive prenatal diagnosis, which will be more acceptable to women and offers less risk. It is my goal to do good in the world and help children. It is my belief that this research does that. ■

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