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Case Report

Prenatal Virilization Associated with Paternal Testosterone Gel Therapy

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Transdermal testosterone gels are used in the treatment of hypoandrogenism of males. Virilization due to exposure to testosterone gels has been reported in children resulting in a US Food and Drug Administration (FDA) warning about secondary exposure to these products. At present, we are unaware of prenatal virilization associated with unintentional testosterone gel exposure. We report prenatal virilization in a female infant due to secondary maternal exposure to the father's testosterone gel. We also describe postnatal virilization of the child's twin sister.

1. Introduction

Transdermal testosterone gels are used in the treatment of hypoandrogenism of males [1]. Virilization due to exposure to testosterone gels has been reported in children ranging from 9 months to 5 years of age [2–6]. In May 2009, the US Food and Drug Administration (FDA) issued a warning for testosterone gel products (AndroGel 1% and Testim 1%), alerting prescribers about secondary exposure to these products [7]. Based on interrogation of medical literature databases, at present we are unaware of prenatal virilization associated with unintentional testosterone gel exposure. We now report prenatal virilization of a female infant due to secondary maternal exposure to the father's testosterone gel. We also describe postnatal virilization of the child's twin sister.

2. Case Presentation

Dizygotic twin girls were born after a 30-week gestation. Pregnancy was complicated by premature labor at 26 weeks of gestation requiring 12 mg betamethasone treatment for two days. Medications taken during pregnancy were Wellbutrin, Pepcid, Procardia, and Indocin. The birth weight for Twin A was 1700 gm and Twin B was 1660 gm.

Twin A required intubation and mechanical ventilation for 4 days followed by continuous positive airway pressure (CPAP) until day of life 8. Twin B required CPAP for 8 days. Both infants had apnea of prematurity and mild hyperbilirubinemia. The infants were discharged to home at 37 weeks post conception age.

At birth, Twin A was found to have clitoromegaly (2.3×1.7 cm) [8] and was Prader Stage 2. Twin B did not have clitoromegaly (0.3×0.1 cm). The urethral openings of the twins were at the base of the phallus.

At 96 hours of age, the total testosterone of the virilized twin was 9.8 ng/dL (0.4 nM), androstenedione was 71 ng/dL (2 nM), and the 17-hydroxyprogesterone was 82 ng/dL (2.4 nM) (Table 1; hormonal determinations performed at Esoterix Laboratory Services, Casablanca Hills, CA).

Transabdominal ultrasound showed normal Mullerian structures with no evidence of persistent Wolffian structures. The uterus measured $2.9 \times 0.67 \times 1.2$ cm with normal endometrial stripe for age measuring of 0.6 cm. The karyotype was 46, XX. An adrenocorticotropic hormone (ACTH) stimulation test yielded normal results at 10 days of age.

At 12 months of age, the circulating testosterone level was 103 ng/dl (4 nM). A pelvic ultrasound showed no adrenal or ovarian masses. An ACTH stimulation test revealed an elevated baseline testosterone level but no other abnormalities.

Table 1: Diagnostic test results for twin A.

Chronologic age Twin A (months)	Ref. Range #	0.1	12	18	22	23*	25**	29	34	38
Total testosterone ng/dL (nM)	<3–10 (0.07–0.4)	9.8 (0.4)	103 (4)	46 (1.8)	129 (5.2)	115 (4.8)	217 (8.7)	4.6 (0.18)	13 (0.5)	2.3 (0.09)
Androstenedione ng/dL (nM)	<10–17 (0.3–0.6)	71 (2.0)	64 (1.9)	46 (1.4)			55 (1.6)	<10 (<0.03)		
17-Hydroxyprogesterone ng/dL (nM)	3–90 (0.1–3)	82 (2.4)	17 (0.5)		15 (0.45)	14 (0.42)		<10 (<0.3)		
17-Hyroxypregnenolone ng/dL (nM)	14–207 (0.4–7)		135 (4)							
Dehydroepiandrosterone ng/dL (nM)	20–130 (0.6–4)		20 (0.6)		47 (1.4)	83 (2.5)				
5-Dehydroepiandrosterone-sulfate mcg/dL (nM)	<5–57 (<0.1–1.4)			11 (0.44)			<10 (<0.4)	22 (0.88)		
Cortisol ng/dL (nM)	3–21 (0.9–7)		3 (0.9)							
Renin ng/mL/hr (<10)	1–6.5		6.0							
Estradiol ng/dL (nM)	<15 (<0.4)				<0.10 (<0.003)					
Deoxycorticosterone ng/dL (nM)	2–34 (0.6–1.0)				<2.0 (<0.06)					
DHT ng/dL (nM)	<3 (<0.3)						35 (1.4)			
Bone Age (mo)			15	18	24					36

Prepubertal reference ranges from Esoterix Laboratory Services, Casablanca Hills, CA.
*After 0.25 mg of dexamethasone per day for 2 weeks.
**AndroGel exposure revealed at 25 months of age.

At 22 months, the testosterone level was 129 ng/dl (5 nM). An MRI showed normal adrenal gland and ovaries. A trial of dexamethasone was given to suppress potential adrenal gland androgen production (0.25 mg per day for 2 weeks), but testosterone levels did not decrease (155 ng/dl; 6 nM).

At 25 months of age, Twin B presented with clitoromegaly and a few pubic hairs. The testosterone level was 50 ng/dl (2 nM) (Table 2). An ACTH stimulation test and adrenal pelvic ultrasound studies were normal. A bone age was the same as the chronological age.

Shortly thereafter, after not previously revealing usage, the father stated that he had been using AndroGel three times a day for several years. The gel was applied on the forearms, and he cradled the children when they slept in their parent's bed.

The father was advised about proper precautions in using AndroGel. At 29 months, testosterone levels had decreased to 4.6 (0.16 nM) and 7.6 ng/dl (0.3 nM), respectively, in Twin A and B. At 34 months, testosterone levels increased to 13 (0.5 nM) and 18.0 ng/dl (0.7 nM), respectively, in Twin A and B. It was recommended that AndroGel be discontinued in favor of parenteral administration.

At 36 months, the parents separated and the mother and children moved to a new residence. At 38 months, testosterone levels were 2.3 (0.09 nM) and 3.1 ng/dl (0.09 nM), respectively, for Twin A and B. Bone ages were the same as the chronological age.

3. Discussion

Testosterone products are used in the treatment of hypogonadism, which is associated with decreased libido, erectile dysfunction, reduced muscle mass, and reduced bone density [1, 9]. It is estimated that about 4 million men suffer from this condition in the US, and [9] 1.8 million prescriptions are written for topical testosterone products annually [10].

When used in the household, children and women are at risk for secondary, unintentional testosterone gel exposure [9, 10]. Enlargement of genitalia, precocious pubic hair development, bone age advancement, and inappropriate aggressive and sexual behavior have been reported in children with secondary testosterone gel exposure [2–6]. Although, some children have reversal of virilization following elimination of exposure, advance bone ages and clitoromegaly have been found to persist [2–6]. Of note, although the testosterone exposure was significant enough to induce virilization in both girls, it did not result in bone age advancement. These observations suggest that the genitalia are more sensitive to effects of testosterone exposure than the skeletal system.

Table 2: Diagnostic test results for twin B.

Chronologic age Twin B (months)	Ref. Range #	25**	29	34	38
Total testosterone ng/dL (nM)	<3–10 (0.07–0.4)	50 (2)	7.6 (2.3)	18.2 (0.7)	3.1 (0.12)
Androstenedione ng/dL (nM)	<10–17 (0.3–0.6)	31 (0.93)	<10 (0.3)		
17-Hydroxyprogesterone ng/dL (nM)	3–90 (0.1–3)	14 (0.42)	<10 (0.3)		
5-Dehydroepiandrosterone-sulfate mcg/dL (nM)	<5–57 (<0.1–1.4)	20 (0.8)	21 (0.84)		
Bone Age (mo)		24			36

#Prepubertal reference ranges from Esoterix Laboratory Services, Casablanca Hills, CA.
**AndroGel exposure discovered at 25 months of age.

Secondary exposure of women to testosterone gels has been observed [10]. Women exposed to testosterone gel can show hirsutism, irregular menses, and mood changes [10]. The mother of the children in this report, though, did not manifest signs of androgen excess, including acne or hirsutism.

Support for the notion that bystander testosterone exposure resulted in prenatal and postnatal virilization comes from the exclusion of intrinsic causes of virilization. ACTH stimulation testing on two occasions was normal, dexamethasone did not suppress testosterone levels, and there was no structural ovarian or adrenal pathology. Most importantly there was reduction of testosterone levels in both girls when they moved to a new environment.

At present we are not aware of other cases of prenatal virilization associated with transdermal testosterone exposure. It is interesting that only one of the twins developed intrauterine clitoromegaly suggesting that individual differences in placental testosterone transmission or sensitivity to the hormone played a role here. This notion is supported by other studies showing variable female infant virilization born to women with androgen producing tumors or conditions [11–13].

Our observations suggest that transdermal testosterone exposure during pregnancy can result in virilization of the fetus. In addition to concerns about postnatal childhood secondary testosterone exposure, adverse effects on the fetus following maternal exposure need to be considered.

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