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Lack of evidence for feminization of males exposed to spironolactone in utero: A systematic review

To the Editor: Because of its antiandrogen properties, spironolactone is accepted and used as a therapeutic option for hormonal acne. Its risk in women of childbearing potential is conflicting. While it has been shown to cause feminization of male animals exposed in utero, it is also approved by the US Food and Drug Administration to treat edema in pregnant women (25-200 mg/day).[1]

To help dermatologists understand the risks of spironolactone use in pregnancy, we performed a qualitative systematic review to identify cases of male animals and humans exposed to spironolactone in utero.

In May 2018, a search in the PubMed database using the terms "spironolactone," "human/male/boy/mouse/mice/rat/rabbit/animal," and "pregnancy/in utero" generated 178 unique results. Manuscripts were included in our final analysis if male subjects were exposed to spironolactone during the human- or animal-specific period of genital development, and if they described the final development of the exposed offspring. Of these publications, 8 met the criteria, and they were combined with 5 animal studies reported in the spironolactone product insert.

Using US Food and Drug Administration guidelines, doses in animals were converted to equivalent daily human doses by body surface area, which accounts for variations in metabolism and drug distribution.[2]

Feminization of exposed males was observed in 6 of 9 animal studies (Table I). Of these, 5 studies used dosing greater than the human equivalent of 200 mg per day. The severity of genital dysmorphism in male animals was often dose dependent.

In humans, 5 males were born to mothers with renal disease who were treated with spironolactone before and during their pregnancies (Table II). There was no evidence of feminization despite exposure to doses as high as 400 mg a day. One of these boys was re-examined at puberty and was noted to have appropriate genital development.

We found 1 report of a male born with ambiguous genitals who was exposed to spironolactone until week 5.[11] However, the medication was stopped before genital development started, and spironolactone has a half-life of <17 hours.[1]

In the reviewed data, spironolactone at doses greater than the human equivalent of 200 mg daily caused feminization of male animal offspring, while doses <100 mg did not. Between these doses, the data are mixed.

In humans, genital differentiation starts at week 6 and is complete by weeks 12 to 14.[12] Because most women do not realize they are pregnant until gestational week 6,[13] it is likely that many male fetuses have been exposed to spironolactone while undergoing genital differentiation. Although we

Table I. Studies of animals exposed to spironolactone in utero

Study subject	Study no.	Maximum daily dose	Equivalent human dose,* mg	Results	Reference
Mouse					
	1	20 mg/kg	97.6	No feminization of offspring observed	Aldactone insert[1]
Rabbit					
	1	20 mg/kg	387	Feminization of male offspring	Aldactone insert[1]
Rat					
	1	40 mg	2581	Feminization of male offspring	Hecker et al[3]
	2	200 mg/kg	1935	Feminization of male offspring	Aldactone insert[1]
	3	20 mg	1296	Feminization of male offspring	Jaussa et al[4]
	4	100 mg/kg	972	Feminization of male offspring	Aldactone insert[1]
	5	20 mg/kg	194	Feminization of male offspring	Aldactone insert[1]
	6	20 mg/kg	194	Normal development of all organs	Seassaro et al[5]
	7	6 mg/kg	58	No feminization of offspring observed	Rose et al[6]

*By body surface area.

Table II. Cases of human males exposed to spironolactone in utero

Case no.	Maximum daily dose, mg	Results	Reference
1	400	Normal genitals at birth and puberty	Groves et al[7]
2	400	Normal genitals at birth	Groves et al[7]
3	200	Normal genitals at birth	Neerhof et al[8]
4	50	Normal genitals at birth	de Arriba et al[9]
5	25	Normal genitals at birth	Rigo et al[10]

identified 5 males exposed to spironolactone in utero without genital feminization, retrospective examination of patient databases may help us identify more cases. Additional human data showing an absence of feminization at acne doses would have a profound impact on how we counsel patients.

Given the limited number of animal studies and human cases in this study, there are insufficient data to safely argue that spironolactone does not have the potential to cause feminization of male offspring. However, with more data, this recommendation could change.

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High-throughput sequencing of the T-cell receptor β chain gene distinguishes 2 subgroups of cutaneous T-cell lymphoma

To the Editor: Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of T-cell neoplasms of the skin. Mycosis fungoides is an indolent form, and the leukemic variant, Sézary syndrome, portends a much worse prognosis. In current practice, the blood tumor burden is determined by morphologic assessment and enumeration of peripheral blood lymphocytes or quantification of $CD4^+CD26^-$ and $CD4^+CD7^-$ cells by flow cytometry.[1] These methods readily identify patients with advanced blood involvement but can be ambiguous in patients with earlier stage disease. Here, we used T-cell receptor (TCR) Vβ CDR3 high-throughput sequencing (HTS)