Klinefelter Syndrome and Cryptorchidism

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JAMA. 2009;301(14):1436-1437 (doi:10.1001/jama.2009.443)

http://jama.ama-assn.org/cgi/content/full/301/14/1436

survival[1-3] and 1 trial in which follow-up time was not significantly different between the bevacizumab group (median, 13.3 months; range, 0-25.6 months) and controls (median, 12.8 months; range, 0-24.2 months).[4] We found that the RR of VTE with bevacizumab from these 4 RCTs was 1.39 (95% confidence interval [CI], 0.97-2.01). In addition, the RR was 1.32 (95% CI, 1.10-1.59) from 10 RCTs in which the follow-up time was not specified for bevacizumab group and control, and bevacizumab was associated with significantly prolonged time to progression. Thus, it appears that the potential bias may be limited.

We speculate that VTE may develop during the early phase of the treatment. However, we also conducted a meta-analysis correcting for exposure time using progression-free survival data, as suggested by Minor. The RR of VTE from these trials was 1.10 (95% CI, 0.89-1.36). This analysis was limited by the assumptions that exposure time is equivalent to progression-free survival time and that VTE events occur evenly over time. Further studies will be needed to investigate the time course of VTE associated with bevacizumab.

We agree with Cortes et al that the increased risk of bevacizumab-induced VTE was observed only in patients receiving combination chemotherapy or cytokines. However, this does not imply that bevacizumab as a single agent may not increase the risk of VTE. The authors cited a small RCT in which bevacizumab was used as a single agent to treat metastatic renal cell cancer in which VTE was not significantly observed. As shown in our analysis, the incidence of VTE in renal cell cancer was low (3%; 95% CI, 1.6%-5.5%); thus, the study was not powered to detect the contribution from bevacizumab. Currently, the trials using bevacizumab as a single agent are sparse, and it is difficult to assess its effect on VTE.

We acknowledge that RRs of VTE were not statistically significant in the AVADO trial for breast cancer and the breast cancer trials included in our meta-analysis. Risk of VTE did indeed vary among tumor types, with the highest risk seen in patients with aerodigestive malignancies and the lowest incidence in renal cell cancer and breast cancer. The reason for this variation remains unclear, but Drs Kilickap and Arslan suggest a viable explanation for the high incidence of VTE in colorectal cancers: a higher incidence of VTE in this subset of patients may be related to their treatment with 5-fluorouracil via a central venous catheter. Because the location of each VTE was not specified in each RCT, our study was limited in addressing this issue, and further studies will be needed to understand the role of bevacizumab in catheter-related VTE.

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Financial Disclosures: Dr Wu reported being a speaker for Pfizer, receiving honoraria from Onyx Pharmaceuticals and Wyeth, and being partially supported by the Research Foundation of the State University of New York. Dr Chu reported no financial disclosures.

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Klinefelter Syndrome and Cryptorchidism

To the Editor: The study by Dr Ferlin and colleagues[1] advances understanding of the genetic contributions to cryptorchidism. In their study, the prevalence of Klinefelter syndrome, the most common genetic cause of cryptorchidism, was almost identical to that in a 1969 study in which the prevalence of Klinefelter syndrome among 600 boys with cryptorchidism was 1.1%.[2]

Long-term follow-up of 29 pediatric patients with Klinefelter syndrome (16 prepubertal and 13 pubertal)[3] has highlighted the differences in clinical manifestations of Klinefelter syndrome during early childhood and puberty. While in the prepubertal group 11 children (69%) had cryptorchidism (5 bilateral and 6 unilateral) and 5 (31%) were unaffected, among the pubertal patients with Klinefelter syndrome 4 patients (31%) had cryptorchidism (1 bilateral and 3 unilateral) and 9 (69%) had normal descended testes. Moreover, although the Sertoli function remained unaffected during childhood, a mild Leydig cell dysfunction was seen at this early stage in Klinefelter syndrome. However, Sertoli function deteriorated significantly during late puberty, rendering most of the patients with Klinefelter syndrome subfertile or infertile.

Notwithstanding the availability of early diagnosis of Klinefelter syndrome, the genetic abnormality that results in complex testicular alterations and infertility presents difficult challenges for the treating physician. Consideration should be given to obtaining genetic studies in all patients presenting with cryptorchidism.

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Financial Disclosures: None reported.
Disclaimer: The contents of this letter represent the authors' views and do not constitute an official position of the Department of Health and Human Services.

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In Reply: As Dr Gottlieb and colleagues noted, one of the main findings of our study was the frequency of detection of Klinefelter syndrome, especially in boys with persistent bilateral cryptorchidism (5/120 [4.2%; 95% confidence interval, 1.8%-9.7%]). This finding is of particular interest because the availability of early diagnosis of Klinefelter syndrome would allow better management of affected persons during puberty and early adulthood in relation to preservation of fertility and initiation of androgen replacement therapy before symptoms and signs of hypogonadism develop.

Boys with this chromosomal alteration have a progressive testicular failure with spermatogenic failure and reduced testosterone concentrations in late adolescence and early adulthood.[1] During childhood and early puberty, pituitary-gonadal function in persons with Klinefelter syndrome is relatively normal, but from midpuberty onwards a hypergonadotropic hypogonadism develops.[1] With a decrease in androgen production, secondary sexual characteristics might not completely develop, and features of eunuchoidism and gynecomastia can develop. Androgen insufficiency might then lead to reduced bone mass, anemia, and other pathological conditions typical of hypogonadism. Furthermore, patients with Klinefelter syndrome are at increased risk of mental retardation, breast cancer, metabolic syndrome, obesity, diabetes mellitus, hypothyroidism, and autoimmune and other systemic diseases.[2]

Although patients with prepubertal Klinefelter syndrome have preservation of seminiferous tubules with reduced numbers of germ cells, the testes in an adult with Klinefelter syndrome are characterized by extensive fibrosis and hyalinization of the seminiferous tubules with few residual foci of spermatogenesis.[1] Diagnosis of Klinefelter syndrome early in childhood would allow cryopreserving spermatozoa from the semen or from the testes during late puberty or early adulthood, and then starting androgen replacement therapy before symptoms and signs of hypogonadism develop.

However, we caution against genetic screening in all boys presenting with cryptorchidism, as Gottlieb et al suggest. Our study indicates that routine screening at birth was probably unnecessary because the majority of cases of cryptorchidism spontaneously resolved and were not associated with genetic anomalies. Genetic analysis could be recommended for boys with normal birth weight and gestational age affected by bilateral cryptorchidism that does not spontaneously resolve by 12 to 24 months.

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Financial Disclosures: None reported.

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Biodiversity, Medicine, and Shakespeare

To the Editor: Drs Bernstein and Ludwig[1] write well of the need to preserve planetary biodiversity and of the many drugs derived from nature. I was reminded of a passage in Shakespeare's *Romeo and Juliet*, in which Friar Lawrence talks about much the same thing:

O, mickle is the powerful grace that lies
In plants, herbs, stones, and their true qualities;
For naught so vile that on the earth doth live
But to the earth some special good doth give . . .
Within the infant rind of this weak flower
Poison hath residence, and medicine power;
For this, being smelt, with that part cheers each part;
Being tasted, slays all senses with the heart.

(Act II, scene 3)

The poet's words, written more than 400 years ago, still ring true—perhaps more now than ever, as species become endangered and extinct at an alarming rate.

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Financial Disclosures: None reported.

1. Bernstein AS, Ludwig DS. The importance of biodiversity to medicine. *JAMA*. 2008;300(19):2297-2299.

In Reply: We thank Dr Boxer for his comment. We would not attempt to gild this lily, for as the Bard observed, brevity is the soul of wit. Suffice it to say that artists have, since time immemorial, revered the natural world. For the sake of ourselves and our children, we would do well to follow their example.

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Financial Disclosures: Dr Bernstein is coauthor of a book on biodiversity for which he receives no royalties. Dr Ludwig reported no disclosures.