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Preoperative Testosterone for Hypospadias: What's the Goal?

In this issue of The Journal, Mittal et al (page 1314) present a well-researched and well-organized study on the effects of preoperative androgen stimulation (PAS)—specifically parenteral testosterone given either 1 or 2 times preoperatively—on glans width (GW) in patients undergoing hypospadias surgery.[1] They should be applauded for the diligence demonstrated on an institutional level to capture data regarding these patients. Even with the difficulty at the beginning of the study cited by the authors in terms of patient accrual, data on over 500 subjects were analyzable, leading to what appears to be the largest study of its kind. Although it suffers from the typical shortcomings of retrospective cohort analysis—lack of treatment randomization and inconsistencies in data capture—the sheer size of the group makes the finding of increased GW after parenteral testosterone compelling. It is also in line with prior studies assessing changes in penile measurements after testosterone treatment in patients with hypospadias,[2,3] so the findings themselves are not surprising. However, as the debate regarding PAS in hypospadias patients continues, objective measures such as GW will be important parts of the decision-making process.

While objective changes in penile measurements in response to PAS have been demonstrated in this study as well as multiple prior ones, the literature surrounding improvement in surgical outcomes that PAS is supposed to achieve is far murkier. A recent analysis of the state of the relevant literature by Li et al identified 14 studies addressing the impact of preoperative testosterone,[4] including 5 randomized controlled trials. In the higher quality studies (ie randomized controlled trials), PAS was not associated with higher complication rates in pooled analysis, though in the observational studies the effect of PAS tended towards causing more complications. The authors also found a very low fragility index amongst the included studies, an indication of a lack of statistical robustness. As with most of these types of pooled analyses, lack of standardization of treatment delivery and treatment indication amongst the included studies led to an apples-to-oranges scenario, limiting what conclusions may be drawn.

Of course, the aim of PAS is to decrease complications—anything less than a clear benefit would be exposing children to systemic androgen unnecessarily. Effects on long bone growth[5] and penile androgen receptors have both been pointed out as potential risks of this therapy, though, again, these studies are plagued by the apples-to-oranges issue, as much of the data involve different disease states[6] or different species.[7] But that does not absolve the treating physician of wrestling with the potential impact of these treatments, especially in light of no clear evidence of improved surgical outcomes.

Specifically, with respect to future studies, a question that should be asked is: what is success? Is any improvement in complication rate a reason to give PAS? If not, how do we determine what is "worth it"? Does the risk analysis change in proximal hypospadias, where the complication rates are higher? And what should we tell parents about all of this, especially considering the ongoing (and escalating) debates regarding childhood interventions of all types? The reader may feel that all will become clear with more study, but I would point to the fact that the first paper on parenteral testosterone in genital reconstruction was written in 1987[8] as an argument against unbridled optimism in future progress.

So what is to be done? In his wonderfully titled review article "Fat, demented and stupid: an unrecognized legacy of pediatric urology?" Chris Cooper points out the emerging (and disturbing) health trends associated with common interventions in pediatric urology, and gently encourages the reader to reflect on their usage.[9] I would echo that here, but with a further difference, and encourage the reader to ask herself (by inverting a well-known metaphor): in the setting of treatment effect, when does absence of evidence become evidence of absence?

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