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Letter to the Editor From [Giovanelli] et al.: “DISTINGUISHING SELF-LIMITED DELAYED PUBERTY FROM PERMANENT HYPOGONADOTROPIC HYPOGONADISM: HOW AND WHY?”

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Dear Dr. Cangiano:

The editors and reviewers have completed their review of your manuscript, "New and consolidated therapeutic options for pubertal induction: in-depth review of the literature", er.2021-00117R1. It has been accepted for publication and scheduled to appear in an upcoming issue of *Endocrine Reviews*.

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The Associate Editors and I appreciate the work you have put into this manuscript and look forward to having it appear in *Endocrine Reviews*.

Congratulations!

Daniel J. Drucker, MD
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It is oft repeated how challenging it can be to distinguish between constitutional delay of growth and puberty (CDGP) and congenital hypogonadotropic hypogonadism (CHH) in adolescents with delayed puberty (DP). Although these conditions share several clinical, biochemical and radiological features, they diverge widely in management and outcomes: CDGP is self-limiting and may need no treatment, whereas CHH requires prompt intervention to induce or complete pubertal development and mitigate adverse psychosexual and mental health outcomes [1,2].

In their article, Harrington and Palmert [3] highlight persistent shortcomings in this area and focus on the most newly proposed diagnostic tests, encompassing kisspeptin-stimulated LH levels and FSH-stimulated inhibin B concentrations. Although these advances appear promising, the authors fail to emphasize other important measures, such as the evaluation of pre-test probability and the value of Bayesian analysis in determining management.

There is facile assumption that CDGP is the more common condition, but this assumes clinical presentation in early-mid teenage years and the absence of characteristic reproductive and non-reproductive clinical phenotypes - labelled as "red flags" - that are far more prevalent in CHH than in CDGP [1]. However, in older teenagers, or those having one or more red flag features, CDGP becomes the least likely diagnosis. In boys, neonatal cryptorchidism (especially when bilateral) and microphallus may indicate CHH-related absent mini-puberty [4]. Non-reproductive hallmarks include anosmia (*i.e.* Kallmann syndrome), craniofacial clefting, deafness, digital abnormalities, dental agenesis, renal aplasia and neurologic anomalies such as synkinesis (mirror movements).

Notably, a retrospective web-based study of "all-comers" with CHH [5] showed pubertal induction was undertaken at the median age of 18 ± 6 years in males and 19 ± 5 years in females, with clinicians' inexplicable blindness to obvious "red flags" being one of the core reasons behind this unacceptable delay.

The age at presentation is another key point overlooked by the authors [3]; whilst among younger teenagers, at least 30% of girls and up to 65% of boys with DP have CDGP [6,7], pathological forms of hypogonadism become exponentially more likely with increasing age; becoming the default diagnosis beyond 18–20 years, or indeed when linear growth is preserved.

In conclusion, we commend the authors for turning the spotlight on the novel developments regarding differential diagnosis of DP, which represents to date a tricky challenge. Indeed, the failure to distinguish between CHH and CDGP can lead to crippling psychological discomfort among patients and their caregivers [5,8].

We also wish to highlight the role of Bayesian logic, which is underutilised in the biosciences, whereby the absolute probability of a finding being true or false is tempered by knowledge of the likely consequences of false-positive and false-negatives. For teenagers with CHH, the adverse

consequences of a false-negative diagnosis (of CDGP) last for decades, whereas for those with CDGP it is hard to perceive any meaningful adverse outcomes arising from a false-positive CHH diagnosis, leading to treatment that is eventually set aside few years' later.

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