had a statistically significant gain in PAH after 3yrs of treatment: Group A +10.3 cm (1.53 SD), p<0.001, and group B +7.1 cm (1.06 SD), p=0.007. Thus, group A exceeded their TH by +3cm (0.45 SDS) and group B reached -0.8cm (-0.11 SDS) from their TH, p=0.03. The reduction of BA advancement was statistically significant in both groups (p<0.05), with superiority of the anastrozole-treated group: at 3yrs in group A BA advancement was +0.48 yrs, and at group B +1.24 yrs (p<0.001). No clinical adverse events or abnormal tests were noted in any of the groups. Bone density and vertebral morphology was not affected within or between groups. **Conclusions:** Aromatase Inhibitors may have a place in managing exaggerated adrenarche in boys, showing superiority to traditional low-dose hydrocortisone in improving predicted adult height and delaying bone age maturation, but notably by overcoming quality of life and compliance issues associated with hydrocortisone therapy (mandatory 6-8 am).

Pediatric Endocrinology
DISORDERS OF PUBERTY

Exploring the Potential Role of DLK1 in Pubertal Initiation

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The mechanisms that orchestrate the initiation of puberty are not well understood. *DLK1* encodes a transmembrane protein that interacts with NOTCH1 receptor to negatively regulate NOTCH signaling. Loss-of-function mutations in *DLK1* cause central precocious puberty, suggesting that DLK1 normally inhibits the reproductive axis centrally. The soluble form of DLK1, which is generated by proteolytic cleavage of the DLK1 extracellular domain, is measurable in human serum. We hypothesized that serum soluble DLK1 concentrations decline with age and that the decline, either in circulating levels or in tissue expression, contributes to the physiological mechanisms triggering pubertal initiation. Serum DLK1 was measured by immunoassay in 102 healthy subjects (age newborn - 26 yrs, 54 male). DLK1 concentrations did not differ by sex, BMI SDS, height, or status of fasting. DLK1 concentrations declined overall with age (R^2=0.04, P<0.001). However, there was not a substantial decline in the peripubertal period (mean± SEM, at Tanner stage 1, 2, 3, 4, 5: 14.8 ± 1.9, 16.4 ± 1.2, 17.0 ± 5, 13.6 ± 3, 9.7 ± 0.9 ng/mL). Serum DLK1, measured in 12 subjects (2 male) with a previous history of idiopathic central precocious puberty, did not differ from healthy controls. We next hypothesized that declining expression of *Dlk1* or increasing expression of competing canonical NOTCH ligands in hypothalamus contributes to pubertal onset. The preoptic area (POA) was microdissected from rat brains (age 4 d, 2 w, 6 w, and 8-16 w, n=5 each) and expression was measured by RT-PCR. *Dlk1* expression increased with age in both female and male rats (P<0.001). *Notch1* expression did not change with age. Expression of two ligands, *Jag1* and *Dll4*, showed a peak at age 6 w, around the time of puberty, but only in males, and none of the other ligands (*Jag1*, *Dll1*, and *Dll3*) showed increasing expression at the age of puberty. In conclusion, we did not find evidence that declining serum soluble DLK1 concentrations in humans, declining *DLK1* expression in rat preoptic area, or increasing NOTCH ligand expression in rat preoptic area contribute to pubertal onset.

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FSH Stimulated Inhibin B in Disorders of Puberty

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Background: Predicting puberty is a clinical challenge. Available tests include basal gonadotropins, GnRH and GnRH analogue stimulation test, hCG stimulation test and basal inhibin B(INHB). Unlike GnRH and GnRH analogue stimulated LH, no study has investigated for possibility of rapidly releasable pool of inhibin B from gonads so far. Therefore, in quest of a better diagnostic test present study was undertaken to explore stimulability of inhibin B and if found stimulable, potential role of FSH stimulated inhibin B(FSH-INHB) as marker of entry into puberty. **Methods:** A total of forty-two subjects fulfilling eligibility criteria were enrolled into this prospective interventional study. Study cohort was divided into Cohort A (Healthy children in puberty; n=26) and Cohort B (Patients of hypogonadotropic hypogonadism; n=16). All participants were subjected to FSH stimulation test and GnRHa stimulation test as per study protocol. Data was analysed for male and female separately. **Results:** Mean delta change between INHB and FSH-INHB in cohort A (Male; n=18) was 188.8 pg/ml (p value-0.002) while in cohort B(Male; n=8) was 16.64 pg/ml (p value-0.076). Mean delta change in cohort A(Female; n=8) was 1065 pg/ml (p value- 0.023) while in cohort B (Female; n=8) was 9.8 pg/ml (p value-0.128). On ROC analysis, INHB of 68.88 pg/ml in male had 94.4 % sensitivity and 87.5% specificity while 51.47 pg/ml in female had 75% sensitivity and 100% specificity for entry into puberty. Cut off for FSH-INHB were 116.14 pg/ml and 116.50 pg/ml for male and female respectively (100% sensitivity/100% specificity).
Conclusion: Inhibin B was stimulable in both male and female after entry into puberty, highlighting the presence of rapidly releasable pool in ovaries and testes. FSH stimulated inhibin B may emerge as promising tool for entry into puberty.

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Infigratinib in Children With Achondroplasia (ACH): Design of PROPEL2 - A Phase 2, Open-Label, Dose-Escalation and Dose-Expansion Study

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Background: ACH, the most common non-lethal form of skeletal dysplasia, is characterized by defective endochondral ossification resulting from gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene, a negative regulator of endochondral bone formation. Current treatment options are non-targeted, ineffective, or painful interventions aimed at preventing or treating complications. Infigratinib is an orally bioavailable and selective FGFR1-3 tyrosine kinase inhibitor in development for FGFR-related conditions. *In vitro* data with infigratinib showed inhibition of FGFR1-3 activity with reversal of established growth arrest in chondrocytes. *In vivo* studies revealed dose-dependent improvements in foramen magnum and long bone length in *Fgfr3*$^{Y367C/+}$ mice following treatment with infigratinib. **Methods:** PROPEL2 is a prospective, phase 2, open-label study of infigratinib in children with ACH. Children 3-11 years of age with ACH who have completed at least 6 months of observation in the observational PROPEL study are eligible to participate. PROPEL2 consists of dose escalation with an extended treatment phase, designed as dose finding, followed by a dose-expansion phase to confirm the selected dose and to provide evidence of efficacy. The primary endpoints of the dose-escalation/extended treatment phase are treatment-emergent adverse events and change from baseline in annualized growth velocity. Subjects (n=40) will be enrolled in ascending dose cohorts of approximately 10 subjects/cohort (4 cohorts planned) and treated for 6 months at their assigned dose, continuing for an additional 12 months with dose modifications as required. Up to 20 new subjects will be enrolled in the dose-expansion phase and receive infigratinib (mini-tablets, administered orally once daily) for 12 months. Secondary objectives include: safety/tolerability of infigratinib; changes from baseline in anthropometric parameters, including body proportions; and the pharmacokinetic/pharmacodynamic profile of infigratinib. An exploratory objective is evaluation of changes in ACH disease burden. **Current Status:** PROPEL2 is currently enrolling - the first subject was entered in July 2020. The planned total enrollment is 60 children with ACH (n=40 in the dose-escalation/extended treatment phase; n=20 in the dose-expansion phase). Following completion of PROPEL2, subjects have the opportunity to enroll in an open-label long-term extension study to assess the safety and efficacy of long-term administration of infigratinib in children with ACH.

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Late Endocrine Effects After HSCT in Children With Nonmalignant Diseases; A Single Center Cohort Analysis

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Endocrine complications are amongst the most frequent late effects after pediatric hematopoietic stem cell transplantation (HSCT) for malignant diseases. Little is known about the prevalence and risk factors of endocrine complications in children transplanted for nonmalignant diseases. This retrospective study included 134 males and 63 females transplanted for a non-malignant disease between 1997 and 2018 with at least 2 years of follow up. Endocrine late effects and growth were evaluated. Gonadal dysfunction was defined as transient or permanent elevation of gonadotropins or hypogonadotropic hypogonadism.

Median age at HSCT was 5.7 years (IQR 2.8-11.3) and median follow-up was 6.2 years (IQR 3.0-10.4). Underlying diseases were inborn errors of immunity (n=74), hemoglobinopathies (n=66) and bone marrow failure (n=57). The majority of patients had received busulfan-based conditioning (46%) or treosulfan-based conditioning (34%).

Gonadal dysfunction occurred in 24/44 (post)pubertal female patients (55%) and was permanent in 19/44 (43%). 22/44 received hormonal substitution, which could be discontinued in 7. In females who received busulfan-based conditioning 16/17 (94%) developed gonadal dysfunction compared to 5/15 (33%) patients with treosulfan-based conditioning; the odds ratio for permanent gonadal dysfunction was 18.7 (3.61-135, p=0.001).

Gonadal dysfunction occurred in 28/66 (post)pubertal male patients (42%) and was permanent in 23/66 (35%). 6/66 received hormonal substitution, which could be discontinued in 1. Gonadal dysfunction was more common in males (post)pubertal at HSCT, 14/21 (67%), compared to those prepubertal at HSCT, 14/45 (31%), p=0.014. 3/15 treated with a treosulfan-based regimen (20%) developed gonadal dysfunction, all transient, versus 19/39 with a busulfan-based regimen (49%), with 2 transient.

29/187 patients developed hypothyroidism (16%), 7 patients received thyroxine treatment (4%). All patients with persistent primary hypothyroidism (n=6) had positive TPO-antibodies.

17 patients received growth hormone treatment and were excluded from analysis. In patients without growth hormone treatment near adult height (NAH) was -1.2 SDS (median, IQR -2.0- -0.3) below mean parental height (MPH) in males and -0.4 SDS (median, IQR -1.6-0.3) in females. NAH below -2 SDS was seen in 13/43 males (30%) and 2/36 females (6%). The majority of these patients already had a height below -2 SDS before HSCT (73%).

In conclusion, this study on late endocrine effects after HSCT in children with nonmalignant diseases indicates frequent gonadal dysfunction, present in 55% of females and 42% of males. In this cohort, risk of gonadal dysfunction in females was higher after busulfan-based conditioning than treosulfan-based conditioning. Careful long-term endocrine follow-up is indicated.