CAPE News

Newsletter of The Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)

JUNE 2025
Volume 29 - Issue 2

CONTENTS

PUBERTY

Next Issue: Thyroid Disorders

To follow official ISPAE social accounts click below icons

JUNE 2025
Volume 29 - Issue 2

CAPE News | ISPAE

EDITOR'S MESSAGE

Dear Readers,

Greetings from the CAPE News Editorial team.

We are delighted to bring to you the Second issue of CAPE News 2025. The development in puberty disorders has been well highlighted by the compilation work done by the CAPENEWS Team.

The work done by the IDEALite community, a part of ISPAE, is worth praising. We thank all the members who have contributed. We also acknowledge the support from Mr Akhtar, our designer, who has been very prompt and punctual in helping us with the issue. The keen eye of Dr Anju Virmani & Dr Aashima Dabas has been praiseworthy.

The theme of the next issue is “Thyroid Disorders”. We look forward to your contributions.

We will be glad to have suggestions/ feedback for improvements, at editor.capenews@gmail.com.

Regards,

Nikhil Lohiya, Team CAPE News

JUNE 2025
Volume 29 - Issue 2

CAPE News | ISPAE

ISPAE PRESIDENT- MESSAGE

Dr Anurag Bajpai- on behalf of ISPAE 2025-2026

Dear friends

Congratulations to the CAPE News team for producing a fantastic issue on puberty disorders that covers the entire topic. The readership will gain a lot from this publication. In line with our goal of creating inclusive, multidisciplinary care systems, ISPAE has formed dedicated working groups for ten important pediatric endocrine disorders. These groups serve as active platforms to raise awareness, develop care pathways, promote research, and support families. By connecting clinicians and the community, we strive to foster a well-informed, supportive environment for children with chronic endocrine conditions. We encourage ISPAE members to participate in these working groups.

Another major achievement has been launching a Fellowship in Pediatric Endocrinology accredited by the National Board of Examinations (NBE). This marks a historic step in standardizing and expanding specialized training across India. I thank the many educators, clinicians, and institutions whose tireless efforts have made this vision a reality. I am also pleased to announce the formalization of the ISPAE Type 1 Diabetes Registry, a crucial step in understanding the burden and geographic distribution of Type 1 Diabetes Mellitus among Indian children. This national registry will aid in epidemiological mapping and support advocacy, funding, and policy development. We actively invite participation from centers across the country, including district hospitals, teaching institutions, and private practices. Our strength is in our collective effort—clinicians, researchers, families, and advocates working together to make sure no child with an endocrine disorder is left behind. I thank each of you for your unwavering dedication and invite you to stay actively involved in ISPAE's care, education, and transformation journey. Let us keep dreaming, collaborating, and serving with purpose and passion.

Happy reading,

Dr Anurag Bajpai.

Welcome New Members

Life Members

• Naveen Kannur, Bengaluru • Suma Uday, Bengaluru • Bhavishya Desai, Bengaluru • Kirandeep Kaur, Sri Ganga Nagar, Rajasthan • Shyam Sunder, Vellore, TN	• Hima Bindu Kurnool, AP • Rupali Rokade, Nagpur, Maharashtra • Sruthi Ratakonda, Bengaluru • Sweta, Hajipur, Bihar • Mainak Sarkar, Hooghly, West Bengal	• Rahul M, Amravati, Maharashtra • Sudip Chowdhury, Gurgaon, Haryana • Arsh Gill, Bathinda, Punjab • Kashish Gupta, Delhi

WINNER- March 2025 Quiz

Dr Reshma M
Assistant Professor, Pediatrics, Government Medical College, Alappuzha, Kerala

Congratulations!

JUNE 2025
Volume 29 - Issue 2

CAPE News | ISPAE

CLINICAL PRACTICE GUIDELINES FOR THE CARE OF GIRLS AND WOMEN WITH TURNER SYNDROME PROCEEDINGS FROM THE 2023 AARHUS INTERNATIONAL TURNER SYNDROME MEETING

Dhanya Soodhana, *Consultant Pediatric and Adolescent Endocrinologist, Aster Malabar Institute of Medical Sciences, Kozhikode, Kerala*

Turner syndrome (TS), which affects 50 per 100 000 females, impacts multiple organs through all stages of life, necessitating multidisciplinary care. The following summary is based on a recent guideline which extends previous ones and includes important new advances, within diagnostics and genetics, estrogen treatment, fertility, co-morbidities, neurocognition and neuropsychology. Exploratory meetings held in 2021 in Europe and United States, culminated with a consensus meeting in Aarhus, Denmark in June 2023. Prior to this, eight groups addressed important areas in TS care:

Diagnosis and genetics:

- A diagnosis of TS should be considered in individuals with female phenotype with a karyotype containing one X chromosome and complete or partial absence of the second sex chromosome, associated with one or more typical clinical manifestations of TS.
- The new general surveillance management guideline applies to TS individuals with any karyotype and also to individuals with 45,X/46,XY mosaicism with either ambiguous or male external genitalia, regardless of sex of rearing.
- In an individual with typical signs of TS, it is recommended that a minimum of 30 metaphases should be counted if chromosome analysis is the first-line test.
- When a rapid test result is needed (e.g., prenatally, newborn), other methods can be used as a first-line test. These include microarray, fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), with chromosome analysis as a second line confirmatory test.
- Fetal echocardiography should be performed in case of prenatal diagnosis of TS.
- Prenatal diagnosis of TS should be confirmed by postnatal karyotyping on blood.
- When sex chromosomes are included as part of non-invasive prenatal testing (NIPT), counseling should include information about the clinical validity/performance.
- If NIPT indicates a high risk for TS, thorough non-directive genetic counselling (informed decision-making) is recommended. A detailed ultrasound should be performed, and invasive diagnostic testing should be offered.
- Preimplantation testing should be offered to individuals with TS who want to use their own oocytes for pregnancies. TS individuals with mosaicism (45,X/46,XX) who become pregnant spontaneously, should be offered prenatal diagnostic testing.
- Screening for Y chromosomal material by PCR or other molecular method is recommended in TS individuals with a 45,X karyotype and signs of virilization.

Growth disorders and their management:

- Growth hormone (GH) treatment should be offered early, because growth failure in TS starts before birth and is rapid during the first years of life - early GH treatment can prevent loss of height potential. Treatment may be offered from as young as 2 years of age in the evidence of growth failure, short stature, or likelihood of short stature.
- GH treatment may be offered in older individuals as long as epiphyses remain open, and may be continued until bone age ≥14 years and/or height velocity <2 cm/year.
- A starting GH dose of 45-50 µg/kg/day or (1.3-1.5 mg/m^2/day) is recommended in most instances, increasing to a maximum of 68 µg/kg/day (2.0 mg/m^2/day) if response is suboptimal and/or adult height potential remains substantially compromised.
- To monitor response to growth-promoting treatment, height should be measured every 6 months and plotted on a standard (reference female population) and/or TS-specific height chart. Maintenance of height percentile equivalent to, or greater than, the pre-treatment height percentile on a female population-based growth chart or increasing percentile on a TS-specific height chart, provides evidence of treatment effect.

- Monitoring GH therapy should include IGF-I measurement, at least annually. IGF-I should be within the normal range for age, pubertal stage, and sex. GH dose reduction may be warranted for persistently high IGF-I values.
- Estrogen supplementation, even in very low doses, should not be added routinely in the prepubertal years to promote growth.

Puberty and sex hormone treatment:

- Luteinizing hormone (LH), follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH) measurements are recommended at 8-9 years and annually until 11-12 years to enable timely referral for fertility preservation if appropriate.
- Initiation of low dose estrogen replacement should begin between 11-12 years of age, if FSH is elevated on at least two sequential measurements. Estrogen dosage should be increased slowly to adult replacement dosage over 2-4 years.
- In individuals with a later diagnosis (>12 years) who have short stature and remaining growth potential, initiating treatment with low dose 17β-estradiol (E2) simultaneously with GH is recommended.
- E2 transdermal (TD) route when possible is preferred, with oral E2 as second choice. Ethinyl estradiol has more risks but is better than no treatment.
- Cyclic progesterone should be added once breakthrough bleeding occurs. This usually occurs after about 18-24 months of unopposed estrogen exposure, but can be later, based on pubertal stage, serum E2, uterine growth and endometrial thickness, and estrogen dose. The preferred option is micronized progesterone 200 mg for 10-12 days per month.
- Combined sequential E2 and progesterone dosing in young women is recommended to avoid experiencing abnormal uterine bleeding. A combined continuous regimen is an option when the endometrium is more stable.
- To optimize uterine growth during puberty and bone health in adulthood, multiple assessments of treatment effect are suggested. These should include height, breast development, uterine ultrasound, bone density, and serum E2 levels (aiming for E2 levels of 100-150 pg/ml at full adult replacement).
- In adolescents experiencing abnormal uterine bleeding, endometrial thickness and serum E2 levels should be measured, to adjust E2 and/or progesterone doses.
- Cyclic estrogen and progesterone treatment should be continued until the usual age of menopause (approximately 50-55 years). Replacement should be individualized, taking patient preference into account, to aid adherence.

Cardiovascular Health:

- The newborn with prenatally diagnosed or suspected TS should be examined with transthoracic echocardiography (TTE) at day 2-3 of life; sooner if CHD is suspected: even if the fetal echocardiogram (echo) or postnatal clinical examination was normal.
- Cardiovascular Magnetic Resonance (CMR) scan should be performed, in addition to/ instead of, initial screening echo, in all adolescents and adults newly diagnosed with TS. Imaging should ideally be completed within 12 months, with the exact interval based on initial echo findings (if echo completed first), presence of additional risk factors, and clinical judgement.
- Computed tomography (CT) is a reasonable alternative when CMR is not tolerated or available. Both CT and CMR scans should include electrocardiogram (ECG)-gated or ECG-triggered assessment of the thoracic aorta.
- Individuals with TS require lifelong cardiovascular surveillance at a frequency that should be determined by their risk factors for aortic dissection.
- Annual assessment of blood pressure is recommended, preferably using ambulatory blood pressure monitoring (ABPM), and initiation of medical therapies if hypertension is confirmed.
- Routine screening for blood clotting disorders before initiation of female sex hormone replacement therapy (HRT) is not recommended.
- Regular aerobic physical activities are recommended as part of a heart healthy lifestyle.

Transition from pediatric to adult care:

- An intentional, defined, individualized pathway to transition from pediatric to adult care for adolescents with TS should begin in early adolescence.
- Developmentally appropriate, organ systems-based assessment and counseling should occur during transition, ensuring that these are documented upon transfer.

Fertility assessment, monitoring and counselling:

- Developmentally appropriate disclosure of the potential for reduced fertility should be made to individuals with TS; disclosing that the probability to conceive and spontaneous menarche is primarily associated with the presence of a 46, XX cell line, and that there is increased risk of maternal and fetal complications in pregnancy compared to the general population.
- Counselling of TS girls and parents, as early as possible after diagnosis, by the primary care provider, pediatric endocrinologist, or gynecologist, as appropriate, regarding family building options such as fertility preservation, foster care, adoption, surrogacy, egg or embryo donation or the choice to remain childless should be discussed.
- Referral to a fertility specialist with specific expertise in TS care should be offered to all individuals with TS (or their parents/guardians), when developmentally appropriate, at the time of diagnosis and intermittently over time.
- AMH measurements should be offered to all girls with TS from diagnosis. AMH should be monitored annually if fertility preservation is considered, along with pre- and post-test fertility counselling.
- Thorough cardiac screening and appropriate counselling by maternal–fetal medicine specialists and cardiologists with expertise in managing women with TS is recommended prior to planning a pregnancy.
- Controlled ovarian stimulation and oocyte cryopreservation should not be offered to premenarcheal children or individuals not mature enough to understand and undergo the procedure.

Health Surveillance for Comorbidities throughout lifespan:

- Girls and women with TS should attend specialist interdisciplinary or multidisciplinary clinics, when available, for health surveillance in addition to their primary care provider.
- A comprehensive physical examination with particular attention to hip stability and lymphedema, echo, and renal ultrasonography should be obtained regardless of prenatal imaging results, ideally prior to discharge.
- Monitoring pre-feeding blood glucose levels in the first 48 hours of life and ensuring that the infant is euglycemic prior to discharge is recommended. Heightened awareness for the symptoms of hypoglycemia in the early years of life is suggested.
- In the first year of life, counseling on, and monitoring for, feeding difficulties and poor weight gain is needed.
- A renal ultrasound is necessary, at the time of diagnosis, to identify congenital anomalies of the kidney and urinary tract.
- A comprehensive ophthalmologic examination between 6-12 months of age, or at the time of diagnosis if older, is recommended.
- Annual otoscopy evaluation for detection of middle ear disease, including effusion and cholesteatoma, in childhood and in those with symptoms is recommended.
- Age-appropriate behavioral audiometric evaluation should be conducted every 2-3 years in childhood and adolescence, starting as soon as developmentally able (1-2 years of age), every 5 years in adults, and any time decreased hearing is suspected.
- At least annual dental care is needed, from the first tooth eruption throughout the lifespan, with particular attention to periodontal health.
- Screening for hypothyroidism is needed from diagnosis, continuing through adulthood, with measurement of TSH every 1-2 years or sooner if suggestive symptoms occur. An elevated TSH should be confirmed, and replacement started.
- Screening for obstructive sleep-disordered breathing is required, through history and/or validated instruments throughout the lifespan.

- Annual skin assessment and use of compression garments, lymphatic massage, and referral to specialists in lymphedema care for any compromising lymphedema, is suggested.
- Promotion of healthy lifestyle, including exercise, is important to address modifiable risk factors of cardiovascular disease and screening for diabetes with measurement of hemoglobin A1c or fasting glucose every 1-2 years, starting at age 10-12 years, or sooner with symptoms of diabetes.
- Assessment of diabetes autoantibodies at diagnosis of diabetes may help determine the type of diabetes, as it is not easy to differentiate Type 1 and Type 2 diabetes in this population.
- Counseling on healthy lifestyle should include encouraging dietary intake of calcium and vitamin D, weight-bearing activity, and importance of estrogen replacement for bone health.
- Routine screening for vitamin D deficiency (serum 25 (OH) vitamin D levels) between 9-11 years of age and then every 2-3 years, with standard vitamin D supplement as necessary, is important.
- Measuring liver enzymes (alanine aminotransferase (ALT) at minimum) in childhood and every 1-2 years should start at the age of 10 and continue throughout the lifespan.
- HRT should be continued in the presence of liver function abnormalities.
- Measure complete blood count to evaluate for anemia every 1-2 years in adolescents and adults.
- Screen for celiac disease if there are gastrointestinal symptoms, poor growth, weight loss, osteoporosis, skin changes, anemia and/or other symptoms present at any age.
- Dual energy X-ray absorptiometry (DXA) scan should be obtained after completion of growth but prior to 21 years of age and every 5-10 years throughout adulthood.
- Screening for orthopedic anomalies (such as scoliosis, genu valgum, Madelung deformity) which in severe cases, may lead to pain and improve with intervention is recommended at diagnosis and then at least annually until skeletal maturation, is recommended.
- In girls and women with TS and Y chromosome material identified on standard karyotyping or FISH analysis, individualized decision-making about gonadectomy/salpingo-oophrectomy is needed. This also includes a discussion of the timing of the procedure, weighing the risk of gonadoblastoma or dysgerminoma, against the potential benefit of gonadal function and fertility.

Neurocognition and its implications for mental health and well-being:

- Cognitive/ neuropsychological evaluation and screening for behavioral/ social/ emotional issues should be integrated into the care of individuals with TS across the lifespan.
- A “support plan” can be prepared by the specialist providers as a tool to empower individuals and their caregivers in advocating for all necessary support outside the medical environment (e.g., schools, community), to achieve optimal educational and socioemotional development.
- Girls and women with TS should receive counseling regarding sexual health and sexual well- being.

Reference

Gravholt CH, Andersen NH, Christin-Maitre S, Davis SM, Duijnhouwer A, Gawlik A, Maciel-Guerra AT, Gutmark-Little I, Fleischer K, Hong D, Klein KO, Prakash SK, Shankar RK, Sandberg DE, Sas TCJ, Skakkebæk A, Stochholm K, van der Velden JA; International Turner Syndrome Consensus Group; Backeljauw PF. Clinical practice guidelines for the care of girls and women with Turner syndrome. *Eur J Endocrinol*. 2024 Jun 5;190(6):G53-G151.

MONOGENIC CENTRAL PRECOCIOUS PUBERTY: GENETICS BASIS

Sohini Pradhan, *Senior Resident, Dept of Pediatrics, All India Institute of Medical Sciences, New Delhi;* **Sangita Yadav**, *Head, Dept of Pediatrics, HIMSR & HAHC Hospital, New Delhi.*

Central Precocious Puberty (CPP) is defined as the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. It results from the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis. Although most girls have idiopathic CPP, especially in certain ethnicities, the discovery of underlying genetic mutations in recent years has refined our understanding of the pathophysiology of CPP. In a recent analysis of patients with apparently idiopathic CPP, genetic etiology was found in 12.6% patients - 22.2% boys and 12.1% girls. Monogenic

causes, which are especially relevant in familial cases, provide valuable insight into the neuroendocrine control of puberty. Understanding these mechanisms can not only contribute to early diagnosis and personalized treatment strategies, but also offers prognostic information that is relevant for long-term care planning.

Genetic Landscape of CPP

The landscape of CPP genetics has evolved dramatically, with identification of key monogenic contributors. The Table summarizes the genetic patterns of CPP. MKRN3, the most commonly implicated gene, is located on chromosome 15q11.2 and encodes a zinc-finger protein functioning as an E3 ubiquitin ligase. It is maternally imprinted and paternally expressed, meaning mutations passed down from the father lead to phenotypic expression. MKRN3 mutations lead to disinhibition of GnRH secretion, initiating early puberty. DLK1, another imprinted gene on chromosome 14q32, has been linked to CPP and metabolic consequences in adulthood, including obesity and type 2 diabetes. Rare activating mutations in KISS1 and its receptor KISS1R also result in premature stimulation of GnRH secretion. Other potential candidates, such as MECP2 and PROKR2, are under investigation. Out of the four primary genes identified, two are imprinted, suggesting that additional imprinted genes involved in CPP may yet be discovered, offering a rich area for future research.

Table showing Genetic patterns of Familial Central Precocious Puberty

Gene	Inheritance	Function	Effect in CPP	Clinical note
MKRN3	Paternal	Inhibits GnRH via ubiquitin	Loss of function→ CPP	Most common monogenic cause
DLK1	Paternal	Regulates Notch signaling	Loss of function→ CPP	Adult obesity/ DM risk
KISS1	AD	Stimulates GnRH	Gain of function→ CPP	Rare, sporadic
KISS1R	AD	Kisspeptin receptor	Gain of function→ CPP	Very rare
MECP2	X-linked	Epigenetic regulator	Possible modifier	Seen in girls with neurodegenerative diseases (Rett syndrome)

Pathophysiology and Inheritance

The onset of puberty is marked by the reactivation of the HPG axis after a quiescent period during childhood. This reactivation involves increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. GnRH stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn act on the gonads to produce sex steroids—testosterone in males and estrogen in females—leading to the development of secondary sexual characteristics and fertility.

In CPP, this process is initiated earlier than normal. Among the inhibitory influences on GnRH neurons, MKRN3 plays a critical role. It acts via ubiquitin-mediated degradation of upstream activators of GnRH. Loss-of-function mutations in MKRN3 reduce this inhibitory control, causing premature activation of GnRH secretion. DLK1, another imprinted gene, also negatively regulates neuroendocrine signaling via the Notch pathway. Abnormalities in this gene similarly diminish inhibitory signaling.

Kisspeptin, encoded by KISS1, and its receptor KISS1R, are potent stimulators of GnRH secretion. Gain-of-function mutations in these genes lead to hyperactivity of the stimulatory pathway, promoting early pubertal onset. The intricate interplay between these stimulatory and inhibitory forces is further

influenced by epigenetic mechanisms, including DNA methylation and genomic imprinting, particularly evident in MKRN3 and DLK1, both maternally imprinted and paternally expressed genes.

Clinical Features and Diagnostic Approach

Clinically, CPP is characterized by early onset of pubertal signs such as thelarche (< 8 years in girls), testicular enlargement (< 9 years in boys), pubarche, accelerated linear growth, and advanced bone age. In monogenic cases, a positive family history, particularly paternal, is a key clue.

Diagnostic evaluation begins with thorough history and physical examination. The bone age confirms advanced skeletal maturation. The biochemical hallmark is pubertal level of LH, or a pubertal response on the GnRH stimulation test: peak LH >5 IU/L and LH:FSH ratio >1 are diagnostic of CPP. Imaging with MRI of the brain, including focus on the pituitary, is essential, in all boys or in girls < 6 years, to exclude CNS lesions such as hypothalamic hamartomas. If clinical suspicion and family history point towards a genetic cause, targeted next-generation sequencing (NGS) gene panels or whole exome sequencing (WES) may be employed. Genetic testing is particularly useful in familial cases or when neuroimaging is normal. Imprinting and methylation studies can provide additional insight in select scenarios, especially for MKRN3 and DLK1.

Management Implications

The cornerstone of CPP treatment remains suppression of the HPG axis using long-acting GnRH analogs such as leuprolide acetate or triptorelin. These agents act by downregulating pituitary GnRH receptors, thereby reducing LH and FSH secretion, which halts progression of secondary sexual characteristics, helps preserve adult height potential, and mitigates the psychological effects of early puberty. Treatment is typically continued until the appropriate chronological and bone age is reached (>11 years in girls; >12 years in boys). Monitoring of treatment includes tracking growth velocity and bone age every 6–12 months, with periodic re-evaluation of LH and FSH levels. Psychosocial support is equally vital as early physical development may cause distress, particularly in girls.

In monogenic CPP, identification of the underlying genetic cause adds value by guiding therapy and predicting recurrence risk and implications for siblings or future offspring. Thus, genetic counseling can be offered to families with heritable mutations. Awareness of associated risks helps; for instance, patients with DLK1 mutations require additional metabolic surveillance for insulin resistance, obesity, and dyslipidemia. Public awareness campaigns can promote early identification and referral.

Future Perspectives

Studies continue to discover novel imprinted genes and regulatory variants through advanced genomics. As new genes involved with the onset of CPP are being identified, there is a better understanding of their role in the control of puberty, with potential for innovations in the diagnosis and treatment of the pubertal disorders. The integration of genetic testing into routine endocrinology practice will guide clinicians towards specific management strategies. Collaborative multicenter studies across diverse populations can help build comprehensive gene panels and develop context-specific guidelines for diagnosis and care.

References

1. Abreu AP, Kaiser UB. Pubertal development and regulation. *The Lancet Diabetes & Endocrinology*. 2016 Mar 1;4(3):254-64..
2. Canton AP, Macedo DB, Abreu AP, Latronico AC. Genetics and Epigenetics of Human Pubertal Timing: The Contribution of Genes Associated With Central Precocious Puberty. Journal of the Endocrine Society. 2025 Feb;9(2):bvae228.
3. Roberts SA, Kaiser UB. Genetics in endocrinology: genetic etiologies of central precocious puberty and the role of imprinted genes. *E J Endocrinol*. 2020 Oct;183(4):R107-17.
4. Moise-Silverman J, Silverman LA. A review of the genetics and epigenetics of central precocious puberty. *F Endocrinol (Lausanne)*. 2022 Dec 2;13:1029137.
5. Fanis P, Morrou M, Tomazou M, Michailidou K, Spyrou GM, Toumba M, Skordis N, Neocleous V, Phylactou LA. Methylation status of hypothalamic Mkrn3 promoter across puberty. *Front Endocrinol (Lausanne)*. 2023 Jan 13;13:1075341.

JUNE 2025
Volume 29 - Issue 2

CAPE News | ISPAE

FERTILITY PRESERVATION IN CHILDREN AND ADOLESCENTS

Pinky Meena, *Assistant Professor, AIIMS, Rajkot;* **Aashima Dabas**, *Professor, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi.*

Fertility preservation has become an increasingly important aspect of pediatric and adolescent healthcare, especially in the context of rising cancer survival rates and the expanding use of gonadotoxic therapies for various non-malignant conditions. There is risk of infertility due to exposure to chemotherapy, radiotherapy, surgery, or genetic disorders.

Causes of Fertility Impairment in Children and Adolescents

Oncologic Treatments

- **Chemotherapy-** Alkylating agents are highly gonadotoxic, and associated with accelerated activation and atresia of primordial follicles, leading to premature ovarian insufficiency (POI) and premature menopause. Depending on agents and regimes, impact on fertility may be broadly classified as:
  ** low (<20%: vincristine, methotrexate, dactinomycin, bleomycin, mercaptopurine, vinblastine),
  ** medium (20-80%: cisplatin, carboplatin, doxorubicin), or
  ** high (>80%: cyclophosphamide, ifosfamide, busulfan, melphalan, procarbazine, chlormabucil).
- **Radiotherapy** to the pelvis, abdomen, spine, or brain (affecting the hypothalamic-pituitary-gonadal axis) may compromise gonadal function. Ovarian radiation has been shown to cause 50% follicle depletion at the dosage of 2 Gy and 60% chances of ovarian insufficiency at 2.5-5 Gy.
- **Surgical procedures** involving reproductive organs can directly impact fertility.

Non-Oncologic Conditions

- Autoimmune disorders.
- Bone marrow failure syndromes treated with hematopoietic stem cell transplant (HSCT).
- Genetic disorders- Turner syndrome, Klinefelter syndrome, fragile X syndrome.
- Others gonadal disorders- endometriosis, ovarian/ testicular torsion, benign ovarian tumors.
- Patients with DSDs or gender dysphoria may require tailored fertility preservation options.

Fertility Preservation Options: The choice of fertility preservation technique depends on the patient's sex, age, pubertal status, diagnosis, urgency of treatment, and risk of infertility.

For Females

1. Oocyte Cryopreservation: is indicated for post-pubertal girls with adequate ovarian reserve. It involves controlled hormonal stimulation to retrieve mature oocytes, followed by vitrification. The challenge is that it requires minimum of 10–14 days of stimulation, which may not be feasible in urgent cases. Another risk is temporary exposure to high estradiol levels, which is undesirable in certain cancers. Another method requiring less time for ovarian stimulation is cryopreservation of *in vitro* matured immature cumulus-oocyte-complex (COCs). Additionally, immature COCs can be obtained while harvesting ovarian tissue for cryopreservation. Thawed oocytes are utilized for *in vitro* fertilization with intracellular sperm injection, resulting in live birth rates per transfer varying between 39% and 52%. Oocyte degeneration may occur after thawing that leads to inferior outcomes as compared to embryo conservation.

Cryopreservation by vitrification results in significantly higher survival rate of vitrified oocytes (73.6-92.7%), than that of slow freezing (58-72.3%), and superior outcome in rates of fertilization, implantation, and live birth. Clinical efficacy of long-term freezing has been less studied, with a multicenter study showing comparable outcomes of oocytes cryopreserved for up to 48 months with those preserved for shorter periods. Preliminary data from large cohorts reports good offspring safety in terms of rate of congenital malformations (0.005-5.6%), being comparable to the USA national birth record in 2019 (3%). However, long-term studies are required on offspring safety indicators.

2. Ovarian Tissue Cryopreservation (OTC): is indicated for prepubertal and pubertal girls who are not producing mature oocytes or those requiring immediate treatment. It involves surgical removal of ovarian cortex containing primordial follicles, followed by cryopreservation for future auto-transplantation. Slow-freezing cryopreservation is currently the preferred modality for preservation of ovarian tissue, unlike vitrification in case of oocyte cryopreservation.

Auto-transplantation to orthotopic sites (OTT) (broad ligament and ovarian medulla) provides a chance for spontaneous conception, whereas transplanting to heterotopic sites (skin of arm, back) necessitates assisted reproductive techniques. The overall live birth rates after OTT range from 18.2 to 43.3%. The duration of ovarian function after grafting depends on the quantity of primordial follicles at the time of transplant and the proportion that survive the grafting process. The mean duration is approximately 4-5 years in humans. The major risk of OTC remains reinduction of malignancy after transplantation.

3. Gonadotropin-Releasing Hormone (GnRH) Analogues: GnRH can be used to temporarily suppress ovarian function during chemotherapy and OTC. It is stipulated to reduce ovarian damage by downregulating the pituitary and minimizing follicular recruitment. However, there is conflicting evidence on effectiveness, and it is not a substitute for cryopreservation.

For Males

1. Sperm Cryopreservation: is indicated for post-pubertal boys capable of producing a semen sample. This method is the easiest and most reliable method for fertility preservation for pubertal boys. It involves collection of sperm by masturbation or electroejaculation and testicular sperm extraction (TESE), followed by cryofreezing of semen. Cryopreserved sperm from patients with a previous malignancy have shown comparable potential to obtain a clinical pregnancy with evolution of ART.

2. Testicular Tissue Cryopreservation (TTC): is indicated for prepubertal boys not having spermatogenesis. It involves cryopreservation of immature testicular tissue (ITT) containing spermatogonial stem cells (SSCs), extracted surgically before gonadotoxic chemotherapy or radiation exposure. Slow freezing cryopreservation protocols have shown better results.

Potential methods for fertility restoration include autologous graft of immature testicular tissue, injection of testicular stem cells (TSCs) into the testis, and *in vitro* maturation of TSCs. The main advantage of ITT graft is the preservation of TSCs within their original niche which enable preferable cell and paracrine interaction for tissue maturation, stem cell self-renewal, and differentiation. However, the autograft is marred with increased risk of malignancy relapse, especially in testicular cancer, leukemia, and lymphoma, which are prone to metastasize to the testes.

Ethical and Legal Considerations: Fertility preservation in children, particularly prepubertal patients, raises unique ethical and legal challenges as parents need to give consent, with assent from the child if they can understand the implications. Many procedures, such as TTC and OTC for prepubertal children, are considered experimental in some countries. The mean age of these procedures ranges from 7-14 years, being lower in countries where healthcare is covered by insurance. There are additional costs with these techniques; and yet-unanswered questions about storage duration, ownership, and disposition in the event of patient death or incapacity.

Psychosocial Impact: Fertility preservation discussions can be emotionally charged for families already coping with a life-threatening illness. While it can provide a sense of hope for a future beyond illness, adolescents may struggle to comprehend long-term implications or may feel embarrassed or overwhelmed by discussions of reproduction. Professional counselling is essential to support informed, family-centered decisions.

Therefore, effective fertility preservation requires a proactive, compassionate, and multidisciplinary approach. The team typically includes Oncologists/ Hematologists, Reproductive Specialists, Pediatric Surgeons, Psychologists or Social Workers, Ethicists and Legal Advisors. As per American and German recommendations, the potential gonadotoxicity with chemotherapy, and the fertility preservation options should be discussed with all families before commencing therapy. Access to fertility preservation may be considered as limited in India due to lack of awareness, limited availability of cryopreservation facilities, high costs and sociocultural taboos. However, it is time we embraced technology for a better future outlook for our children.

References:
1. Chen L, Dong Z, Chen X. Fertility preservation in pediatric healthcare: a review. *Front Endocrinol.* 2023; 14:1147898.
2. Pasten González A, Salvador AC, Mora J, et al. Current Status of Fertility Preservation in Pediatric Oncology Patients. *Children.* 2024; *11:* 537.
3. Emrich NLA, Einenkel R, Färber CM, et al. Ovarian tissue cryopreservation for fertility preservation: a two-decade single-center experience with 451 children and adolescents. *Reprod Biol Endocrinol*. 2025;23:51.

DRUG CORNER

DRUG CORNER: A PRACTICAL GUIDE TO ESTROGEN USE FOR PUBERTAL INDUCTION IN GIRLS

Swathi Padmanaban, *Consultant Pediatric & Adolescent Endocrinologist, Rainbow Children's Hospital, Chennai, Tamil Nadu;* **Dhanya Soodhana**, *Pediatric & Adolescent Endocrinologist, Aster MIMS, Kozhikode, Kerala.*


Girls with primary or secondary ovarian insufficiency or delayed puberty require carefully planned pubertal induction with incremental estrogen replacement therapy. A gradual approach helps ensure optimal growth, psychological readiness, and uterine development.

Pharmacological Rationale and Preferred Estrogen Preparations

17β-estradiol is the preferred form of estrogen for pubertal induction. It more closely mimics natural physiology, particularly when delivered transdermally, bypassing hepatic first-pass metabolism and providing a favorable cardiovascular profile.

In India:

- Transdermal 17β-estradiol (e.g., Estraderm MX 50: 1.5 mg patch) is now available and preferred for its physiological delivery.
- Oral 17β-estradiol or estradiol valerate is a widely used, cost-effective alternative. However, tablets often need to be split to achieve the lower starting doses required for induction.

Therapeutic Goals of Pubertal Induction

1. Initiate development of secondary sexual characteristics (e.g., breast development),
2. Stimulate uterine growth to adult size,
3. Promote an adolescent growth spurt,
4. Achieve peak bone mass by late 20s,
5. Support psychological and emotional development.

Induction is best started at 11–12 years. In girls diagnosed after 13 years, a faster 2-year induction protocol may be considered to support peer alignment. Oral 17β-estradiol is available as 1 mg tablets, which are approximately equivalent to 10 mcg ethinyl estradiol. Since the starting doses for induction are much lower, tablets need to be cut or carefully dissolved, although solubility and consistency may vary between brands.

For clinical reference, the following daily doses are considered approximately equivalent:
- 50–100 mcg of transdermal 17β-estradiol
- 2 mg of oral 17β-estradiol
- 20 mcg of ethinyl estradiol.

- It is generally agreed that starting doses for pubertal induction should be about 10% of adult replacement doses. High dose oestrogen, early in puberty, or rapid escalation of doses, may result in reduced final height and poor breast development, with nipple development but poor supporting breast tissue, which cannot be reversed later.
- Induction regimens should use 17β-estradiol rather than synthetic estrogens, partly for physiological reasons but also so that serum levels can be measured. Weight-based doses rather than fixed doses are better, consistent with other forms of pediatric endocrine replacement therapy, such as thyroxine, GH and cortisol.
- At the beginning of year 4, when the adult estradiol dose had been reached, serum estradiol should be checked to enable dose modification. With transdermal estrogen, a range of 150–450 pmol/L should be aimed for.

Transdermal Estrogen Protocol

Transdermal patches are available in India as Estraderm MX 50: 1.5 mg patch (approximate cost INR 5,400/ 8 patches). They can be cut to the desired size, and cut pieces stored in the original sachet at room temperature.

Year 1–2:
- Apply a small patch overnight (10-12 h)
- Cut Estraderm patches as needed (Fig.)
- Rotate application sites (buttocks, belly, lower back)
- Dosage according to weight (Table 1).

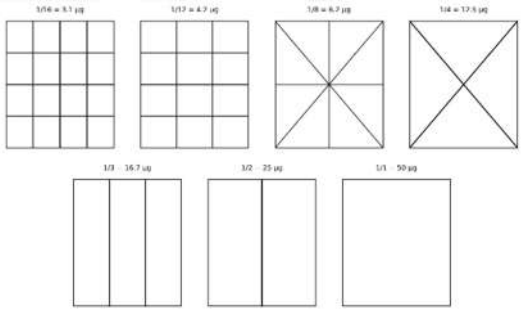


Fig: Examples of how to cut different types of patches

Year 3:
- Split the total dose over 24 hours
- Apply two half- doses overnight, remove one in the morning

Year 4:
- Target serum estradiol levels at full dose 150–450 pmol/L

Table 1: Dose protocol for transdermal 17β-estradiol over 3 years with weight-wise adjustments.

Year	Weight (kg)	50 ug patch fraction	Dose (ug)	Duration
Year 1	<40	1/16	3.1	10-12h (overnight)
	40-55	1/12	4.2	10-12h (overnight)
	>50	1/8	6.2	10-12h (overnight)
Year 2	<40	1/8	6.2	10-12h (overnight)
	40-55	1/6	8.3	10-12h (overnight)
	>50	¼	12.5	10-12h (overnight)
Year 3	<50	1/3	16.7	
	50-65	3/8	18.8	
	>65	½	25	
Year 4 post-induction	-	-	50-75 (up to 100)/ 24h (~1 ug/kg/24h)	

Oral Estrogen Protocol

Available in India as estradiol valerate 1mg and 2mg (approximate cost INR 500/28 tab). Evening administration is recommended to mirror the transdermal regimen. A regimen using 1mg estradiol valerate tablets is given in Table 2.

Duration	Dose
First 12 mo	0.5 mg (½ tab) on alternate days
Next 6 mo	0.5 mg daily
Next 6 mo	Alternate 0.5 mg and 1 mg daily
Final 6 mo	1 mg daily
Post-induction	Transition to adult estrogen + progestogen

Clinical Criteria for Dose Escalation

The timing of dose escalation during pubertal induction should be guided by the clinical response. Key factors to consider include:

- The extent of breast development
- The patient's linear growth rate
- Whether the child is receiving concomitant growth hormone therapy.

Timing and Initiation of Progestogen Therapy

• Introduce after 3 years of estrogen monotherapy, or earlier if breakthrough bleeding occurs
• Options:
  - Medroxyprogesterone acetate: 5–10 mg/day for 10–12 days/month
  - Micronized progesterone: 100–200 mg/day for 10–12 days/month.

Monitoring Parameters and Long-Term Follow-Up

To ensure safety and effectiveness of pubertal induction, structured & periodic monitoring is essential.

- Baseline assessment:
  - Growth velocity and blood pressure
  - Pelvic ultrasound to evaluate uterine size and morphology
- During induction & every 6 months:
  - Height velocity
  - Tanner staging
  - Blood pressure
- Annually:
  - Bone age assessment
- At completion of induction:
  - A repeat pelvic ultrasound is recommended once the final estrogen supplementation stage is reached, to assess uterine maturity.

References

1. Donaldson M, Kriström B, Ankarberg-Lindgren C, et al, on behalf of the European Society for Paediatric Endocrinology Turner Syndrome Working Group. Optimal Pubertal Induction in Girls with Turner Syndrome Using Either Oral or Transdermal Estradiol: A Proposed Modern Strategy. *Horm Res Paediatr*. 2019;91(3):153-163.
2. Matthews D, Bath L, Högler W, Mason A, Smyth A, Skae M. Hormone supplementation for pubertal induction in girls. *Arch Dis Child*. 2017 Oct;102(10):975-980.

BIOCHEMISTRY CORNER: INHIBIN B

Ajinkya Patil, *Consultant Pediatric Endocrinologist, Hormocare Pediatric Endocrinology Clinic, Jalgaon*

Inhibin B (INHB) is a glycoprotein hormone belonging to the TGF-β superfamily, composed of 1α subunit linked to 1βB subunit by a disulphide bridge. It is produced by Sertoli cells in males and granulosa cells of developing antral follicles in females, with its primary physiological function within the hypothalamic-pituitary-gonadal (HPG) axis being to inhibit FSH secretion via negative feedback. In healthy males, INHB levels mark pubertal development, with a postnatal peak (up to 270 pg/ml), followed by low levels through childhood, rising during early puberty,

2-3 years before clinical pubertal onset. Levels rise from ~ 109 pg/ml at Tanner Stage G1 to 134 pg/ml at Tanner Stage G4. In healthy females, it surges sharply during Tanner stage 2 as dormant ovaries begin to mature, to median levels by stage 3, before declining in late puberty, likely reflecting menarche. This pubertal surge makes it a valuable marker of gonadal maturation, serving as a robust diagnostic tool in differentiating between pubertal variants including constitutional delay in puberty (CDP), congenital hypogonadotropic hypogonadism (CHH), and precocious puberty.

Role in Precocious Puberty

Premature activation of the HPG axis, with subsequent stimulation of ovarian granulosa cells, produces INHB inappropriate for the chronological age. This helps in girls in diagnosing central precocious puberty (CPP), and differentiating between progressive and non-progressive forms, and also for monitoring the therapeutic response to GnRHa therapy. INHB has not been studied in CPP in boys.

Role in Delayed Puberty

INHB, tested along with other hormones, is useful in helping distinguish Constitutional Delay of Growth and Puberty (CDGP) from Idiopathic Hypogonadotropic Hypogonadism (IHH), avoiding long periods of watchful waiting, which increased patient anxiety and delayed therapeutic interventions.

A. Basal Inhibin B:

Basal INHB achieves good sensitivity for diagnosing IHH, with rates of 85.7% in males and 83.8% in females, along with high specificity of 93.3% in males and 100% in females. However, stimulated INHB levels (both FSH and GnRHa) are more reliable than single basal measurements in distinguishing between functional and non-functional gonadal tissue.

B. GnRH Agonist stimulated Inhibin B (GnRH-iB):

The standard protocol involves measurement of INHB levels after administration of GnRHa triptorelin, most commonly 24 hours post-injection. Using sex-specific cut-off values of 113.5 pg/ml for boys and 72.6 pg/ml for girls, GnRH-iB achieved 100% sensitivity and specificity for documenting pubertal onset.

C. FSH stimulated Inhibin B (FSH-iB):

FSH, being less tightly regulated than LH, is present in circulation even during the prepubertal period. In children with CDGP, INHB levels rise in response to FSH stimulation even when basal levels may be low; while in cases of permanent hypogonadotropic hypogonadism, the response is blunted or absent. The test protocol typically involves measuring INHB levels before and after FSH administration, usually given as multiple doses. A recent study identified specific FSH-iB cut-offs of 116.14 pg/ml in males and 116.50 pg/ml in females for onset of puberty with 100% sensitivity and specificity demonstrated in both exploratory and validation cohorts.

The fundamental distinction between FSH-iB and GnRHa-iB lies in the level of axis stimulation, with FSH providing direct gonadal stimulation, while GnRHa testing evaluates the integrated response of the entire HPG system. From the perspective of diagnostic accuracy, both have demonstrated comparable outcomes, albeit with limited cohort size. The simplicity and convenience of test administration favors the use of GnRHa-iB over FSH-iB.

Other Clinical Implications:

- Tumor detection & monitoring: Granulosa cell tumors in girls and Sertoli cell tumors associated with Peutz-Jeghers syndrome in boys can be detected and monitored using serial INHB levels.

- CPP treatment monitoring: GnRHa therapy suppresses the HPG axis, leading to decreased INHB levels. Monitoring these low INHB levels is a useful method for assessing the effectiveness of the therapy.

Conclusions

INHB represents a valuable biomarker for understanding and managing pubertal development, offering insights into gonadal function that complement traditional hormone assessments. The development of stimulated testing protocols represents a major advancement, but further studies are needed to establish optimal stimulation protocols, timing, and interpretation criteria.

References

1. Kelsey TW, Miles A, Mitchell RT, Anderson RA, Wallace WH. A normative model of serum inhibin B in young males. *PloS One*. 2016 Apr 14;11(4):e0153843.
2. De Filippo G, Rendina D, Nazzaro A, Lonardo F, Bouvattier C, Strazzullo P. Baseline inhibin B levels for diagnosis of central precocious puberty in girls. *Horm Res Paediatr*. 2013 Sep 17;80(3):207-12.
3. Chaudhary S, Walia R, Bhansali A, Dayal D, Sachdeva N, Singh T, Bhadada SK. Basal and FSH-stimulated Inhibin B in Precocious Puberty. *Indian Pediatr*. 2024 Aug;61(8):756-9.
4. Sahoo BK, Kumar PR, Pattanaik SR, Dash DK, Patro D, Telagareddy R. Role of Inhibin B, AMH, GnRHa Test and HCG Stimulation Test to Distinguish Isolated Hypogonadotropic Hypogonadism (IHH) from Constitutional Delay in Growth and Puberty (CDGP). *Indian J Endocrinol Metab*. 2024 Mar 1;28(2):153-9.
5. Gao Y, Du Q, Liu L, Liao Z. Serum inhibin B for differentiating between congenital hypogonadotropic hypogonadism and constitutional delay of growth and puberty: a systematic review and meta-analysis. *Endocrine*. 2021 Jun;72:633-43.
6. Chaudhary S, Walia R, Bhansali A, Dayal D, Sachdeva N, Singh T, Bhadada SK. Unravelling a novel, promising and convenient tool for differential diagnosis of delayed puberty: GnRHa-stimulated inhibin b (GnRH-iB). *J Endocrinol Invest*. 2022 Dec;45(12):2265-73.
7. Chaudhary S, Walia R, Bhansali A, Dayal D, Sachdeva N, Singh T, Bhadada SK. FSH-stimulated inhibin B (FSH-iB): a novel marker for the accurate prediction of pubertal outcome in delayed puberty. *J Clin Endocrinol Metab*. 2021 Sep 1;106(9):e3495-505.

PEDSENDOSCAN

Arpita Bhriguvanshi, *Professor Junior Grade, King George Medical University, Lucknow*

Marie C, et al. Contribution of clinical and biological mini-puberty and genetic analysis in 57 46,XY differences of sex development: A monocentric retrospective cohort. Horm Res Paediatr. 2025 Jan 17.

A retrospective monocentric cohort study at CHU Bicêtre Hospital, Paris, involving 57 infants with 46,XY differences of sex development (DSD) was conducted. Hormonal assessments (anti-Müllerian hormone [AMH], inhibin B, follicle-stimulating hormone [FSH], luteinizing hormone [LH], testosterone) were performed at birth and monthly up to four months of age. Genetic analysis was performed using a targeted next-generation sequencing (NGS) panel of 60 DSD-associated genes. Genetic mutations were identified in 49% of infants, predominantly NR5A1, AR, and WT1 genes. At 2 months, predictive hormonal thresholds were AMH <235 pmol/L (PPV 80%, p=0.02), inhibin B <189 pg/mL (PPV 66%, p=0.02), and FSH >4 IU/L (PPV 71%, p=0.44). **The combined use of AMH and inhibin B increased predictive accuracy (PPV 88%, p=0.007), suggesting early hormonal testing at two months is a reliable approach to guide genetic analysis in 46,XY DSD.**

European Society for Paediatric Endocrinology (ESPE). Puberty suppression in adolescents with gender dysphoria: ESPE guidelines review. Horm Res Paediatr. 2024.

ESPE conducted a detailed systematic review addressing puberty suppression in transgender and gender-diverse adolescents. The criteria for initiating treatment included a confirmed diagnosis of gender dysphoria, psychological maturity, and onset of puberty (Tanner stage ≥2). Treatment options primarily involved GnRH analogs (GnRHa) to halt development of secondary sexual characteristics. Documented side effects included mild hot flashes, mood fluctuations, fatigue and headaches, rarely leading to discontinuation. The review emphasized regular monitoring of bone mineral density (BMD) with dual-energy X-ray absorptiometry scans, as treatment could temporarily decrease BMD z-scores. Treatment did not negatively impact neurodevelopmental or psychosexual development, with evidence suggesting stable cognitive functions and increased romantic and sexual experiences post-treatment. Fertility considerations were essential, with emphasis on reversible GnRHa and ongoing fertility counseling, especially before initiating irreversible treatments. Alternatives to GnRHa for late adolescents included continuous progestins or oral contraceptives for menstrual suppression. **The guidelines recommended treatment initiation and monitoring by experienced multidisciplinary teams, underlining a comprehensive approach, detailed informed consent, and regular psychological support throughout treatment.**

Trevisani V, et al. The assessment of urinary sexual hormones within mini-puberty and correlations with anthropometrics in healthy term children. J Endocrinol Invest. 2025;48:731-42.
In this prospective longitudinal study of 165 healthy term infants from birth to 6 mo in Modena, Italy, urinary gonadotropins (uFSH, uLH) and sex hormones (uT, uE) were analyzed at birth, 3 mo, and 6 mo using electrochemiluminescence assays. There was significant positive correlation of uLH with penile length at birth (ρ=0.323, $p<0.05$) and at 3 mo (ρ=0.371, $p<0.01$). Female infants demonstrated significant negative correlations between uFSH at birth and anthropometric percentiles at 3 mo (length: ρ=-0.505, weight: ρ=-0.478, $p<0.01$). **This study validated urinary hormone assessments as a practical, accurate diagnostic method for early pubertal evaluation and growth**

Zhang Y, et al. Efficacy and safety of different doses of GnRH analogues in precocious puberty: A meta-analysis. Transl Pediatr. 2025;14(1):92-102.
Zhang et al. performed a meta-analysis of randomized controlled trials comparing low-dose and standard-dose GnRH analogs in central precocious puberty (CPP). Analysis included growth velocity (GV), bone age (BA) advancement, and predicted adult height (PAH). No significant differences were found in GV (mean difference: -0.07 cm/year, 95% CI: -0.36 to 0.22, p=0.64), BA advancement (mean difference: -0.05 years, 95% CI: -0.18 to 0.08, p=0.47), or PAH (mean difference: 0.15 cm, 95% CI: -0.62 to 0.92, p=0.70). Low-dose treatment was associated with fewer adverse events, suggesting enhanced safety. **This supports low-dose GnRH analogues as an effective, safer, cost-efficient therapeutic**

Rhys-Evans M, et al. Combined Gonadotropin Therapy to Replace Mini-Puberty in Male Infants with Congenital Hypogonadotropic Hypogonadism. Ann NY Acad Sci. 2024
This interventional study used recombinant human luteinizing hormone (rhLH) and follicle-stimulating hormone (rhFSH) to replicate mini-puberty in infants with congenital hypogonadotropic hypogonadism (CHH). The treatment significantly increased testicular volume ($p<0.001$) and penile length (mean increase: 1.2 cm, $p<0.001$), and normalized serum testosterone and inhibin B levels. Hormonal normalization was sustained during follow-up, suggesting lasting benefits for reproductive maturation and sexual health. **This innovative gonadotropin replacement highlights a significant therapeutic advance in early CHH management, with potential to improve future fertility and sexual development outcomes.**

LISTENING TO THE STALWARTS

Nikhil Lohiya, *Division of Growth & Endocrinology, Silver Lining Pediatric Super Specialty Center, Nagpur*

Dr Vijaya Sarathi HA is Professor, Dept of Endocrinology, Vydehi Institute of Medical Sciences & Research Center, Bangalore. After MD in Pediatrics, he did DM Endocrinology from KEM Hospital, Mumbai. One of the most dynamic persona in the field of Pediatric & Adult Endocrinology, he has a keen interest in pubertal and adrenal disorders. His work is a testimony of the contribution he has made in the field of Endocrinology.

The CAPE News team is delighted to present a conversation with him regarding his experience in the field of puberty as a Pediatric Endocrinologist.

1. *What inspired you to pursue DM Endocrinology after completing MD in Pediatrics?*

During my pediatric training, I encountered several children with growth and pubertal disorders, diabetes mellitus, and atypical genitalia, who lacked expert care. At a time when DM programs in pediatric subspecialties were limited, I had to opt for a general super specialty program. I appreciated that Endocrinology was a discipline in which adult superspecialists showed a greater interest in managing pediatric patients than adult ones. Most importantly, among all the general super specialty departments in Maharashtra, Endocrinology was the one which was led by a Pediatrician (Prof. Nalini Shah). She was also an accomplished pediatric Endocrinologist. I found the Department of Endocrinology at KEM Hospital, Mumbai, an ideal place to gain expertise in a pediatric subspeciality (endocrinology), which aligned with my passion of serving pediatric patients with chronic disorders.

2. *How does the training and practice of DM Endocrinology differ from that of pure Pediatric Endocrinology?*

DM Endocrinology offers a broader exposure across all age groups, including adult and geriatric endocrinology. As some of the rarest disorders in childhood are not uncommon in adults, experience in managing such diseases in adults strengthens the management of these rare pediatric endocrine disorders. In addition, transition from pediatric to adult clinics happens under a single roof in DM Endocrinology, thereby allowing us to

understand the outcomes of management of chronic endocrine disorders of pediatric-onset. However, some centers may lack a specific focus on pediatric endocrine disorders. On the other hand, pure Pediatric Endocrinology training offers a greater exposure to emergencies in pediatric endocrinology and endocrine manifestations of pediatric systemic illnesses.

In practice, managing pediatric endocrine disorders is time-intensive, and dedicating sufficient time to these cases can be challenging while also caring for a large number of adult patients.

3. *What are the key gaps in pediatric endocrinology training in India?*

There are limited centers in India for dedicated pediatric endocrinology training. Moreover, in most of these centers, the programs run for approximately one year, which limits comprehensive training in pediatric endocrinology. However, the recently initiated DM programs and FNB programs in pediatric endocrinology are expected to gradually address these limitations. Notably, the most high-volume pediatric endocrinology training centers are in the government sector, where advanced diagnostic and therapeutic interventions are often used restrictively due to cost constraints. This deprives fellows of exposure to these advances in the field.

4. *What drew you to focus on pubertal and adrenal disorders?*

Pubertal and adrenal disorders are areas where clinical acumen truly matters. The interplay of hormones during puberty, the psychosocial impact of early or delayed development, and the challenge of diagnosing rare adrenal conditions make these fields intellectually stimulating. My early mentors encouraged me to explore these niches, and over time, they became a natural focus of both research and clinical care.

5. *How common are pubertal disorders in India? Are we diagnosing them effectively?*

Pubertal disorders are fairly common, but often missed. With changing trends toward earlier puberty in girls, many parents now seek care for their daughters' early pubertal development. Although it is recognized in a timely manner in many cases, it is not uncommon to encounter girls presenting with menarche at 9–10 years and reduced growth potential. In contrast, delayed puberty is more common in boys and is often underreported or dismissed as constitutional.

6. *If we are missing some cases, what needs improvement?*

Lack of awareness among parents, inadequate school health programs, and delayed referrals from primary physicians contribute to underdiagnosis. To enable early diagnosis of pubertal disorders, we need better community awareness, school-based screening programs, and sensitization of primary care providers. Creating clear referral pathways and training pediatricians to identify red flags in growth and puberty can significantly improve early diagnosis and management.

7. *What challenges do children and families face when precocious puberty is diagnosed?*

There is emotional distress for both the child and the family. Children may face bullying or body image issues, while parents often struggle with fear and misinformation. Many parents of children with progressive precocious puberty face challenges in affording investigations such as magnetic resonance imaging and GnRH analog therapy. Notably, with changing trends in pubertal onset, some girls develop pubertal features only slightly earlier than expected. In such scenarios, both parents and treating physicians often face challenges in making decisions regarding the extent of investigations and management options. It is not uncommon in current practice for girls with slightly early puberty to undergo unnecessary investigations and sometimes even unwarranted therapies.

8. *What should clinicians keep in mind when dealing with delayed puberty from the patient's perspective?*

Delayed puberty often carries a social stigma, especially for adolescent boys who may be teased for their short stature or immature appearance. It can affect self-esteem and peer relationships. Clinicians must provide reassurance, avoid unnecessary delays in intervention, and work closely with families to ensure emotional support and realistic expectations.

9. *Among patient care, research, and teaching, what do you enjoy the most?*

Each offers its own form of fulfillment. Patient care offers the joy of watching children grow and thrive under my treatment. Research keeps me inquisitive and contributes to the wider medical community. Teaching

allows me to give back and shape the next generation of endocrinologists. If I had to choose, teaching gives me the most satisfaction, as I believe that the percolation of my knowledge exponentially enhances the patient care.

10. *Pros and cons of working in a medical college vs. private practice in Pediatric Endocrinology?*

Medical colleges provide academic stimulation, research opportunities, and the joy of teaching. Medical colleges offer ample opportunities to stay updated with recent advances in the field. Moreover, patient management can be optimized, as evaluation and treatment decisions are often made by a multidisciplinary team rather than an individual clinician. On the other hand, private practice offers flexibility to physicians and is often more convenient and time-saving for patients. Ideally, a hybrid model—consulting in both setups or collaborating with academic institutions—is the best of both worlds.

11. *Any message for budding pediatric endocrinologists?*

Stay curious and compassionate. Pediatric endocrinology is a rewarding field that demands patience and a long-term perspective. Keep up with advancements, focus on holistic care, and never underestimate the value of listening to the concerns of parents and children. Most importantly, believe that every child you help will carry forward a healthier, happier life—and that is a legacy worth building.

CASE REPORT: "The Triad Unfolded: A Classic Case of McCune-Albright Syndrome"


Sahana N, Vani HN, *IGICH, Bengaluru*

A 5y4m girl presented with history of fall from a height of 2 feet while playing, followed by limping and hip pain in 2023. MRI of the hips revealed multiple small cystic lesions in bilateral acetabuli and femoral necks. Bone biopsy confirmed fibrous dysplasia. On further inquiry, the mother reported two episodes of vaginal bleeding and progressive bilateral breast enlargement over the past year. On examination, she weighed 18 kg (0.14 SD), height 109 cm (-0.27 SD), and had hyperpigmented patches over the right temporal area, neck, buttock, and posterior thigh. Gait was antalgic. Tanner staging showed breast stage 3, pubic and axillary hair stage 1. Thyroid, calcium, and liver function tests were normal. Bone age was 6 years. Pelvic ultrasonography (USG) revealed a uterine length of 4.1 cm with 3 mm endometrial thickness, right ovary 1.9×1 cm, and left ovary 1.5×1.1 cm. On leuprolide stimulation test, at 60 minutes LH was 2 µIU/ml, & FSH was 14.91 mIU/ml; at 24 hours estradiol was 51.26 pg/ml, consistent with peripheral precocious puberty (PPP). Tc^{99m} MDP bone scan showed increased uptake in multiple skull bones, facial, humeral, vertebral, rib, and hip bones, consistent with polyostotic fibrous dysplasia. She was treated with tamoxifen, advised regular follow-up, and planned for corrective osteotomy and fixation.

Discussion: McCune–Albright syndrome (MAS) is a rare, non-inherited, complex genetic disorder classically defined by a triad of clinical features: polyostotic fibrous dysplasia, café-au-lait macules, and multiple hyperfunctioning endocrinopathies. These endocrinopathies include gonadotropin-independent precocious puberty, growth hormone excess, non-autoimmune hyperthyroidism, hyperprolactinemia, and, less commonly, neonatal hypercortisolism. MAS was initially described in 1936–1937 by Donovan McCune and Fuller Albright. The estimated prevalence ranges from 1 in 100,000 to 1 in 1,000,000 live births, with a marked female predominance (F:M ratio approximately 9:1). The condition arises sporadically due to postzygotic activating mutations in the *GNAS1* gene, which encodes the stimulatory G protein alpha subunit (Gsα). This leads to constitutive activation of adenylyl cyclase, resulting in excessive cyclic AMP (cAMP) production, downstream pathway activation, and unregulated cellular proliferation and hormone secretion.

The most frequent endocrine manifestation is PPP in females, characterized by autonomous ovarian estrogen production. This is mediated through intermittent formation of large functional ovarian cysts, resulting in fluctuating yet markedly elevated serum estradiol concentrations. Clinically, patients typically present with isolated episodes of vaginal bleeding, which may precede or coincide with thelarche. Unlike central precocious puberty (CPP), growth acceleration and bone age advancement are usually modest due to the intermittent and peripheral nature of estrogen exposure. Pelvic USG typically reveals unilateral ovarian cysts with significant asymmetry in

ovarian volume, a distinguishing feature from CPP. In some cases, an enlarged uterus with a visible endometrial stripe and no cystic structures may also be observed.

Biochemically, estradiol concentrations are elevated—often 2-3 times above age-appropriate norms—while gonadotropins remain suppressed at baseline and following GnRH stimulation, confirming a GnRH-independent mechanism. Spontaneous cyst resolution leads to abrupt declines in estrogen levels, inducing estrogen withdrawal bleeding and reduction in uterine size.

Management of MAS is symptom-directed and necessitates a comprehensive, multidisciplinary approach involving pediatric endocrinology, orthopedics and rehabilitation. Therapeutic strategies for PPP include the use of aromatase inhibitors (e.g., letrozole), selective estrogen receptor modulators (e.g., tamoxifen), estrogen receptor antagonists (e.g., fulvestrant), and anti-androgens, aimed at mitigating hyperestrogenism and preventing premature epiphyseal fusion. Fibrous dysplasia is typically managed with analgesia and intravenous bisphosphonate therapy to reduce bone pain and lesion progression. Given the progressive nature of MAS-related endocrinopathies, long-term surveillance is essential for early detection and management of evolving hormonal dysfunction.

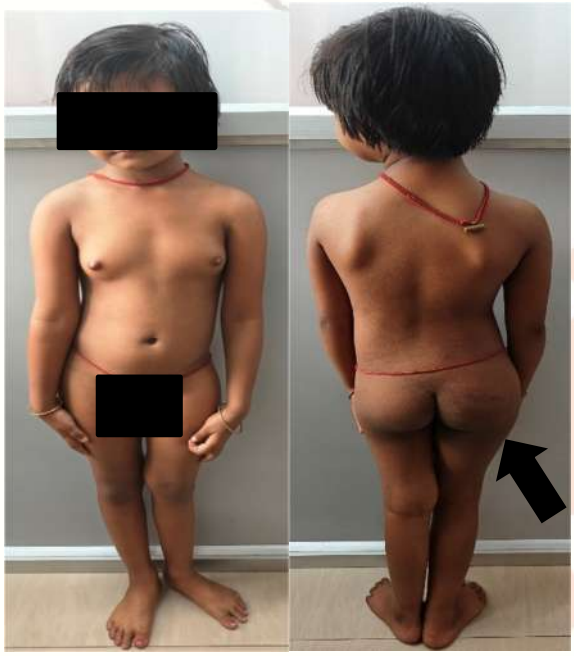


Fig. 1: 5y old girl with breast Tanner stage 3, hyperpigmented patches over right buttocks, posterior thigh with left hip deformity

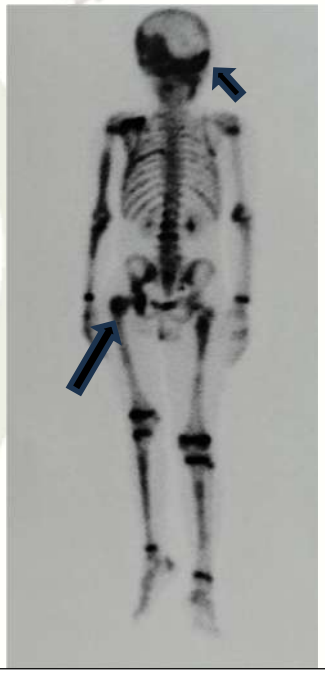


Fig 2: Tc99m Bone scan showing increased radiotracer uptake cranio-facial bones, ribs, right humerus, hip joint, lumbar vertebrae

References:

1. Faria AG, Montenegro LR, Jorge AAL, et al. Peripheral precocious puberty in girls with McCune-Albright syndrome: a case series. *Arch Endocrinol Metab*. 2025 May 14;69(2):e240459.
2. Nicolaides NC, Kontou M, Vasilakis IA, Binou M, Lykopoulou E, Kanaka-Gantenbein C. McCune-Albright syndrome: a case report and review of literature. *Int J Mol Sci*. 2023 May 9;24(10):8464.
3. Gryngarten M, Comar H, Arcari A, Boulgourdjian E, Escobar ME, Domené H. McCune-Albright syndrome, a rare form of precocious puberty: diagnosis, treatment, and follow-up. *Arch Argent Pediatr*. 2021 Oct;119(5):e420-e427.
4. Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extra-skeletal manifestations of fibrous dysplasia. *Orphanet J Rare Dis*. 2012;7(Suppl 1):S4. doi:10.1186/1750-1172-7-S1-S4.

JUNE 2025
Volume 29 - Issue 2

CAPE News | ISPAE

CASE REPORT- AN INTRIGUING CASE OF CENTRAL PRECOCIOUS PUBERTY


Deepali, Subramanian Kannan. *Dept of Endocrinology, Diabetes & Metabolism, Narayana Health Hospitals, Bangalore*

Case Summary:

Kumari A, presented to us at age 8y2m, with complaints of accelerated increase in height over the past 3 months. She was the 2nd born child of non-consanguineous parentage, delivered at term by vaginal delivery with birth weight 2.9 kg. Her perinatal period was uneventful and developmental milestones were normal. Her mother noted her tall stature since early childhood, and at age 3y, when she noted breast development, sought medical attention. At that time, the child was 106 cm tall (+2.5 SDS) and > 97th centile cf. mid parental height of 157.5 cm, which is 50th centile; with thelarche (Tanner B2). Pooled samples showed undetectable LH (<0.01 IU/L) at 3.5y and again at 4.5y. Parents were reassured and advised observation. There was gradual progression in breast development, with development of pubic and axillary hair by age 8y. At her first visit to us, she was 149 cm (+3.3 SD), Tanner staging B3 P3 A+. She was thoroughly examined for neurocutaneous markers, with the only positive finding being a small (2cm) cafe-au-lait spot over the left iliac region, with no bony deformities. Throughout the entire duration, history was negative for exposure to oral/ topical sex steroids/ cosmetics (lavender oil, tea tree oil)/ other probable endocrine disruptors. There were no features of hyperthyroidism; no complaints of headache, seizures, laughing spells or radiation exposure. Her sister had attained menarche at the age of 12y and mother at the age of 10y. Her labs are summarised in Table 1: LH was detectable, consistent with Gonadotropin-dependent precocious puberty. The bone age (BA) was significantly advanced at 11y, cf. height age 12y3m, vs. CA 8y2m. In view of the cafe-au-lait spot and elevated alkaline phosphatase, a ^{99}Tc MDP bone scan was done and was normal. MRI brain including pituitary gland was normal. Her IGF-1, corrected for her BA and with reference Indian standards, was normal. The 2-hour post glucose GH was suppressed, ruling out pituitary gigantism.

She was started on GnRH-analog Leuprolide depot 11.25 mg (Brand: Lupride), administered deep intramuscularly in July 2024, followed by a second dose in October 2024. After her second dose, she developed a left gluteal abscess necessitating incision and drainage in November 2024. In January 2025, she presented with further progression of puberty, with vaginal bleeding. At that time she was Tanner B4, P2 with pale vaginal mucosa, height of 151cm (Height SDS+3.3), having grown 2 cm over 4 months, BA was 11.5y, and LH was still detectable at 0.861 mIU/ml. She received the third dose of leuprolide depot 22.5 mg in February 2025.

At her latest visit in May 2025, age 9y, she had grown 3.8 cm over 6 months, she had developed a sterile abscess 3 months post her last injection (Fig 1); serum LH was undetectable. After a detailed discussion with her parents, it was decided to stop leuprolide and proceed with natural progression of puberty.

Discussion:

The etiology of central precocious puberty (CPP) is multiple and heterogeneous, including congenital and acquired causes that can be associated with structural or functional brain alterations. In the past decade, genetic and epigenetic causes of CPP have been documented, by the identification of rare pathogenic gene variants causing perturbation of specific hypothalamic pathways.

In 2008, a rare heterozygous activating mutation of KISS1R (p.Arg386Pro) was identified in a girl with CPP. This mutation, located in the C-terminal tail of the receptor, led to prolonged activation of intracellular signaling pathways in response to kisspeptin in mammalian cells. A rare kisspeptin variant, p.Pro74Ser, was subsequently identified in the heterozygous state in a boy who developed sporadic CPP at the age of 1 year. The capacity to stimulate signal transduction was prolonged for p.Pro74Ser mutant kisspeptin compared with wild type, suggesting that this variant might be more resistant to degradation.

In 2017, a complex genetic defect (14 kb deletion associated with a 269 bp insertion) involving another maternally imprinted gene, Delta-like homologue 1 (DLK1, located on chromosome 14q), was identified in a family with CPP. In the past 3y, new, rare frameshift mutations of DLK1 in girls with CPP or precocious menarche (age <9y) have been identified. Notably, metabolic conditions, such as overweight or obesity and insulin resistance, are found to be more prevalent in individuals with CPP associated with DLK1 mutations than in those with idiopathic CPP.

MKRN3 is an important neuroendocrine player in the control of pubertal timing, acting as an upstream inhibitor of GnRH secretion. A systematic review and meta-analysis of 14 studies, evaluating 857 patients with sporadic or

familial CPP, showed a pooled overall MKRN3 mutation prevalence of 9% in quantitative analyses. In 2021, in a multi-ethnic cohort of 716 children with CPP, there were 71 cases with different types of loss-of-function MKRN3 mutations. Patients with more severe MKRN3 mutations (i.e., frameshift, nonsense, or promoter mutations) had greater BA advancement and higher basal LH levels at presentation compared with patients with mis-sense mutations. CPP due to loss-of-function mutations of MKRN3 is clinically indistinct from idiopathic CPP; however, the type of genetic defect might affect the severity of the phenotype.

We suspected our case could have a genetic alteration, particularly loss-of-function of MKRN-3 gene, and have advised the parents to get the genetic tests done. We welcome comments and views from the experts.

Table 1: Summary of Labs

DATE	Range (units)	July 2024	Feb 2025	Mar 2025
FSH	mIU/ml	5.8		
LH	mIU/ml	0.93	0.86	<0.216
TSH	0.729-4.402 µIU/ml	0.904		
fT4	0.76-1.33 ng/dl	1.27		1.33
PRL	3 - 18.6 ng/ml	8.7		
ALP	143.0-318.0 U/L	785		440
Ca	9.34-10.7 mg/dl	10.34		
Phos	4.37-6.25 mg/dL	4.88		
Vit D	20-50 ng/ml	31		
PTH	15-65 pg/ml	60.1		
IGF-1	88-452 ng/ml (up to 526 corrected for BA)	329		
2H Post-glucose load GH	<0.4 ng/ml	0.189		

30th ISPAE ACES MEETING – 22nd MARCH 2025- MONOGENIC DIABETES

Zalak Upadhyay, *Pediatric & Adolescent Endocrinologist, Endocare for Kids, Rajkot, Gujarat*

The 30th ISPAE ACES meeting was successfully conducted on 22nd March: 7-9 pm. Topic: monogenic diabetes. We thank the case presenters, moderators and speakers for their contribution.

Next meeting: 21st June: topic Hypogonadotropic hypogonadism in boys. Pearls will be shared in the next issue.

LEARNING PEARLS:

- Urinary C-peptide to creatinine ratio serves as a non-invasive marker to assess residual insulin secretion in individuals with diabetes.
- There may not be definitive clinical features that guarantee MODY diagnosis, but there are certain clinical pointers that raise suspicion and may favour Maturity-Onset Diabetes of the Young (MODY) –

- *Diagnosis of diabetes before 25–35 years of age*
- *Strong family history of diabetes in successive generations (autosomal dominant pattern)*
- *Persistent C-peptide levels (suggesting preserved insulin secretion- at least 2y post diagnosis)*
- *Negative pancreatic autoantibodies*
- *Non-obese phenotype*
- *Good glycemic control with low-dose oral drugs or insulin*
- *Absence of features of metabolic syndrome*
- *Mild or asymptomatic hyperglycemia, often detected incidentally*

The MODY Probability Calculator is a clinical tool (not a diagnostic tool, but a decision-support tool to prioritize patients for genetic testing) designed to help healthcare providers estimate the likelihood that a patient with diabetes has MODY, rather than type 1 or type 2 diabetes (T2DM). The calculator uses clinical features such as:

- Age at diagnosis
- Body Mass Index (BMI)
- Family history of diabetes
- Current treatment (e.g., insulin, oral agents)
- Glycemic control (e.g., HbA1c levels)
- Sex
- Ethnicity

These factors are used to generate a probability score.

- GCK MODY (autosomal dominant) presents as mild fasting hyperglycemia, often with history of three generations being affected. Usually the finding is incidental, most commonly detected during pregnancy. It is useful to diagnose, as there is no progression to complications, and treatment may be ineffective and unnecessary.
- Neonatal diabetes (NDM) is rare, with an incidence of approximately 1 in 90,000 to 160,000 live births. It should be suspected and investigated for if hyperglycemia without known risk factors lasts beyond 3-5 days, and requires insulin. Intrauterine growth retardation (IUGR) is common because insulin is required for fetal growth. Up to 50% of babies will present in diabetic ketoacidosis (DKA).
- Due to the presence of fetal hemoglobin, HbA1c is unreliable in babies younger than 6 months, but HbA1c > 6.5% points towards the diagnosis of diabetes.
- Because 80% of children with NDM have genetic etiology, in suspected NDM, genetic testing is a must:
  - It is mandatory for all infants < 6 months of age diagnosed with diabetes,
  - Should also be done in infants age 6–12 months with negative pancreatic autoantibodies,
  - Desirable in infants with syndromic features, IUGR, or developmental delay.
- When a Variant of Uncertain Significance (VUS) is found in a suspected NDM, parental testing is recommended to determine whether the variant is inherited or de novo. This helps in interpreting pathogenicity — a *de novo* mutation (not present in either parent) may support clinical relevance, especially if it fits the phenotype.
- When interpreting parental results, if the same variant is found in a parent who is normoglycemic (i.e. no diabetes), this reduces the likelihood of the variant being causative/pathogenic, and suggests the variant may be benign or have incomplete penetrance.
- 90% of infants with activating KATP mutations can be successfully transitioned from insulin to oral sulfonylureas (e.g., glibenclamide). Benefits include
  - Improved glycemic control
  - Easier administration
  - Neurological benefits in some cases (e.g., DEND syndrome).

- Trial of sulfonylureas without the molecular diagnosis should be avoided.
- For infants not responsive to sulfonylureas, insulin is the standard treatment.
- Transient NND due to 6q24 abnormalities usually present in the first week of life with IUGR, may resolve, and relapse after puberty. Presentation in DKA is less common.
- Umbilical hernia or omphalocele can be a pointer to transient NDM.
- NDM may show any of the following courses
  - Permanent remission,
  - Hyperglycemia during illness,
  - Hyperinsulinemic hypoglycemia during infancy, or
  - Recurrence mimicking T2DM in adolescence or pregnancy.
- Periodic monitoring of HbA1c is mandatory in transient NDM.
- DiabetesGenes.org is an excellent and reputable resource for clinicians and researchers dealing with monogenic forms of diabetes.

LEARNING PEARLS: PEPP PEDIATRIC OBESITY

Chetan Dave, *Consultant Pediatric Endocrinologist, Rajkot, Gujarat*

- Pediatric obesity is increasing day by day, the most common cause being nutritional excess.
- Age-appropriate BMI cutoffs should be used to diagnose pediatric obesity.
- Blood pressure should be measured, and metabolic screening (including SGPT, lipid profile, and glucose tolerance test) should be done in all obese children.
- Lifestyle measures are the first line of management in pediatric obesity.
- Avoiding high-carbohydrate and high-fat processed foods and dietary management under the supervision of professional dietitian are advisable.
- Daily 60 minutes of brisk exercise; restriction of screen time, and timely good sleep are vital for weight loss.
- Pharmacotherapy is approved for selected patients with specific age groups; orlistat is the first-line weight-loss drug approved above 12 years of age.
- Early treatment of metabolic complications is necessary.
- Endocrine causes of obesity are very rare but dangerous.

LEARNING PEARLS: PEP GROWTH DISORDERS

ISPAE-PEP Meeting on Growth Disorders – 21st May 2025

Contributors: **Jaivinder Yadav, Vijay Jaiswal, Raghupathy P**



The ISPAE-PEP session on growth disorders held on 21st May 2025 featured valuable case contributions from teams based in Karnataka and Delhi. The first case, focusing on endocrine-related short stature, was presented by Dr Sahana N (Clinical Fellow, Pediatric & Adolescent Endocrinology, Indira Gandhi Institute of Child Health, Bangalore), under the mentorship of Dr Amarnath Kulkarni, and examined by Dr Vaman Khadilkar (Senior Pediatric & Adolescent Endocrinologist, Jehangir Hospital, Pune). The second case, of acquired hypothyroidism, was presented by Dr Ankita Soni (3rd year MD resident, Maulana Azad Medical College, Delhi) under the guidance of Dr Aashima Dabas (Professor of Pediatrics, MAMC) and examined by Dr Anju Seth (Director-Professor of Pediatrics & Principal, Lady Hardinge Medical College, Delhi). An OSCE session on the topic was conducted by Dr Nikhil Lohiya.

Key Learning Points: Growth Assessment and Monitoring:

- Comprehensive growth monitoring, including weight, height, head circumference during infancy, and Tanner's Sexual Maturity Rating (SMR) staging, is essential for all children.
- Monitoring should occur during immunization visits, at 9 mo, 12–15 mo, and every 3–6 mo thereafter until growth is complete (up to 18y).

- Standardized tools such as non-stretchable measuring tape, accurate weighing scale, stadiometer, and orchidometer should be used for accurate assessments.
- Growth should be plotted using appropriate charts: Intergrowth-21 for preterm infants, WHO growth charts for ages 0–5y, and IAP charts for 5–18y.
- For preterm infants, corrected gestational age should be used till age 2y to account for catch-up growth.
- WHO and updated IAP charts include color-coded z-score lines to facilitate early detection of growth failure.
- Growth velocity, a sensitive marker for growth impairment, should be evaluated using two height measurements taken at least six months apart and plotted on IAP growth velocity charts.
- Anthropometric assessments should include weight-for-age, height-for-age, weight-for-height, BMI, waist circumference, mid-parental height (MPH), and bone age, all of which assist in identifying growth abnormalities.
- The new IAP charts provide user-friendly tools to calculate MPH and diagnose short stature, overweight, and obesity.
- Mobile applications such as the IAP growth app offer accurate z-score calculations, allowing objective monitoring of growth deviations.

Approach to Short Stature:

- Non-endocrine causes of short stature are more prevalent than endocrine causes.
- Parental information about stature in comparison to siblings and peers, and clothing size, can provide diagnostic clues.
- Normal growth variants, including familial short stature and constitutional delay in growth and puberty, should be differentiated through detailed history, examination, and growth trends, to avoid unnecessary investigations.
- Children with height and weight below growth reference (-2 Z score or <3rd centile), in relation to MPH (genetic potential) require evaluation.
- A thorough history should include birth parameters (especially for SGA), neonatal events (e.g., hypoglycemia, jaundice), screening for systemic illnesses (e.g., celiac disease), growth trends, nutritional and medication exposure (especially steroids).
- Physical examination should assess for dysmorphic features, body proportions, thyroid enlargement, rickets, truncal obesity, systemic signs of chronic illness, and neurocutaneous markers (e.g., multiple nevi, café-au-lait spots).
- Nutritional or systemic illnesses typically affect weight more than height, whereas endocrine disorders primarily impact height with preserved weight-for-height or BMI.
- Investigations should be guided by clinical suspicion. Initial (Level I) investigations include CBC, renal and liver function tests, T4 and TSH, urine and stool examination, bone age assessment, and celiac serology. Further evaluation includes IGF-1 levels and growth hormone (GH) stimulation testing to assess the GH-IGF axis. Single GH test is of no use. Karyotype should be done in girls with unexplained short stature.
- Addressing the underlying cause—whether endocrine or non-endocrine—usually improves growth velocity and leads to upward centile shifts.
- Indications for GH therapy include GH deficiency, SGA with growth failure, and syndromic short stature (e.g., Russell-Silver, Turner, Noonan, and Prader-Willi syndromes).

JUNE 2025
Volume 29 - Issue 2

CAPE News | ISPAE

SENSOR STORAGE MATTERS: A SUMMER WARNING

In April, Mr Harsh Kohli, batch 1 IDEALite, shared a timely reminder about the importance of **proper storage of glucose sensors** in the refrigerator, especially during the scorching Indian summer. This season often sees a **spike in sensor malfunction complaints**, a key reason for which is **heat exposure** during storage or transit.

With sensors now widely available—even at local chemist shops—there's growing concern that many vendors may **lack awareness of the storage guidelines**, risking the quality of the product.

Particularly in **summer**, families are strongly advised to purchase sensors **only from verified distributors**, and to **avoid online orders** where exposure during shipping is unpredictable. Proper storage is not just a technicality—it's critical to ensure sensor accuracy and safety.

BEST PROGRAM

BEST PROGRAM UPDATE – ADVANCING TYPE 1 DIABETES EDUCATION

Preeti Singh, *Professor, Lady Hardinge Medical College & Kalawati Saran Hospital, New Delhi*

We are delighted to share the continued progress of the BEST (Basic Education Series in Type 1 Diabetes) program, an ISPAE-led initiative designed to empower caregivers, allied health professionals and school personnel with essential knowledge for the ambulatory management of children and adolescents living with T1D. Now entering its 10th batch, the program has trained more than 300 participants across India, fostering greater confidence and competence in diabetes care beyond the clinical setting. The structured, interactive format: delivered online over 4 weeks: has been appreciated for its accessibility, clarity, and relevance.

We are pleased to announce that registrations are now open for the upcoming Batch 10, commencing August 5, 2025. Sessions will be held every Tuesday evening (7–9 pm) and will cover eight focused topics delivered by a dedicated faculty team. Applications are open to caregivers, trained nursing staff, school personnel, and adults with T1D interested in strengthening their understanding of daily diabetes management. The last date to apply is 21st July, 2025. To apply, please visit:

 BEST Batch 10 Online Registration Form. https://docs.google.com/forms/d/1yaavQg-C1dIJMxUHFPvLuUiKMKCzY_J_5OOsmRszAqs/edit

For any queries, please get in touch with Mr. Ankit at 9041493138 or abukoushal@gmail.com.

Please share this information widely with your T1D families, to strengthen this shared journey in building a well-informed, empowered T1D community.

ACTIVITIES BY ISPAE MEMBERS

PRADER WILLI SYNDROME (PWS) MONTH AWARENESS ACTIVITIES- MAY 2025

N Kavitha Bhat, Shruti Sastry, Namratha Upadhya, Jahnavi M, *Aster Cluster, Bengaluru*

The Department of Pediatric Endocrinology at Aster Hospitals, Bangalore, observed Prader-Willi Syndrome (PWS) Awareness Month in May 2025 with a series of impactful initiatives aimed at raising awareness and supporting families of children living with this rare genetic condition. A key feature of the campaign was the creation and dissemination of informative PWS awareness videos by our dedicated team of specialists: Dr Bhat, Dr Sastry, Dr Upadhya, Dr Jahnavi, and department coordinator Ms Vineetha Prabhath (MBA in Hospital Administration). These videos addressed various aspects of PWS, including early diagnosis, growth and hormonal concerns, behavioral challenges, and comprehensive care strategies. To sustain engagement throughout the month, the Dept circulated daily awareness flyers via an online platform, educating families on various topics including medical management, nutrition, behavioral support, and early intervention strategies.

The Dept. also hosted a live interactive session on PWS, during which Dr Upadhya, Dr Sastry, and Clinical Geneticist Dr Nemmani Laxmi Kaveri responded to queries from parents and caregivers. Additionally, Ms Prabhath shared a brief overview of the multidisciplinary PWS clinic conducted regularly at Aster Hospitals. The session fostered meaningful dialogue and helped address real-life challenges faced by families.

The initiative was widely appreciated by the PWS community, with many families expressing gratitude for the knowledge shared and the sense of connection fostered by these activities. Through such events, we aim to raise awareness among parents and caregivers of children with PWS.

Learning point: Early diagnosis and multidisciplinary care in PWS can significantly improve quality of life by enabling better management of growth, behavior, and metabolic health.

IDEAL CORNER

Shruti Arora, *Certified Pediatric Diabetes Educator*

Congratulations! IDEALite Rekha Negi awarded #dedoc° Voices Scholarship for IDF World Congress 2025

Rekha Negi, a Batch 4 IDEALite from Chamba, Uttarakhand, was awarded the prestigious #dedoc° Voices Scholarship to attend the International Diabetes Federation (IDF) World Congress 2025 in Bangkok, Thailand, April 7–10.

This global recognition celebrates Rekha's dedication to T1D advocacy, particularly her efforts to improve access to care, education, and empowerment for people living with diabetes in remote areas in Uttarkhand. Her selection underscores the impact of community-driven advocacy in shaping the future of diabetes care. As a #dedoc° Voice, she proudly represented the UDAI (Uttarakhand Diabetes Awareness Initiative) Society, bringing grassroots perspectives to a global platform.

"I am honored to receive the #dedoc° Voices Scholarship… Thank you to the #dedoc° Voices team for ensuring that voices like mine are heard where it matters most" Rekha shared.

Congratulations! IDEALite Vaishali Vakil honored with Rangoli Award at Unimo 2025

Unimo, a community of over 1 lakh moms, recognized Vaishali Vakil for her unwavering commitment and impact as a Counselor and Diabetes Educator for children with T1D. She was awarded the prestigious Rangoli Award at Unimo 2025, held on 29th March at Taj Santa Cruz, Mumbai, for her outstanding work.

Living with T1D for over 37 years and a batch 1 IDEALite, Vaishali has transformed her personal journey into a mission of support. Through her work with the Juvenile Diabetes Foundation, she has guided over 500 children and families to manage life with T1D with confidence and care.

Mann Ki Baat: Heartfelt Conversations for T1D Families

Mann Ki Baat is a new online initiative launched by Dr Shuchy Chugh, Mr Harsh Kohli, Mr Alex Fernandes, and Ms Beenu Singh to support families navigating life with T1D. This informal series creates a safe, empathetic space for parents and individuals living with T1D to share experiences, ask questions, and connect.

The first session, on 19th April, focused on the emotional impact of a new T1D diagnosis. Parents opened up about common fears and questions — *"Why did this happen to my child?"*, *"Is there a cure?"*, *"What did we do wrong?"* The conversation helped normalize these concerns and reminded families that they are not alone in their journey.

The second session, on 17th May, addressed the theme "*Travelling with T1D.*" Participants shared practical tips, travel checklists, and personal stories,

covering everything from packing supplies to managing insulin across time zones. The session empowered families to travel with confidence and preparedness.

Mann Ki Baat continues to foster connection and understanding within the T1D community—one conversation at a time.

Type 1 Run – Bengaluru: 6th April 2025 Cubbon Park, Bengaluru

Organised by Ms Beenu Singh and the Type 1 Diabuddies of Karnataka on a regular basis, the T1 Run brings together children, adults, and parents living with T1D for a morning of fun, fitness, and fellowship. The run is followed by a community breakfast, when participants check their BG levels and take insulin together —celebrating shared journeys and mutual support. On 6th April, children and parents enjoyed a morning of healthy fun!

DCS Quarterly Camp Held in Visakhapatnam: 27th April 2025 AMCOSA Hall, Visakhapatnam

Diabetic Child Society (DCS), in partnership with India Youth for Society (IYFS), conducted its quarterly camp for children with T1D, welcoming 203 children from 6 districts of Andhra Pradesh.

The half-day event provided insulin, syringes, pen needles, and included on-site HbA1c testing and retinal screening by Visakha Eye Hospital. Newly diagnosed children received awareness kits, while parents and children shared inspiring personal stories. In a step towards sustainability, participants also practiced waste segregation, responsibly handing over used medical supplies and e-waste for safe disposal, supported by IYFS.

Dept of Pediatric Endocrinology, Rainbow Hospital, Bangalore, hosts World Wish Day with Insulin Pump Workshop & Special Wish Fulfilment

On 30th April**,** the Dept of Pediatric Endocrinology, Rainbow Children's Hospital, Bangalore organized a special event to mark World Wish Day, focusing on care, education, and emotional support for children living with T1D. One of the children who benefitted was 11-year-old Amirah Patel, whose heartfelt wish to meet actor Mr Salman Khan was fulfilled in collaboration with Make-A-Wish India. Accompanied by her mother Ms Sabeera Begum and Mr AB Bosco from the Bangalore Chapter, Amirah traveled to Mumbai, where she was warmly welcomed by the Make-A-Wish team and had the opportunity to present a hand-drawn portrait to Mr Khan.

The event featured an insulin pump workshop**,** equipping families with practical knowledge on advanced diabetes management. Rainbow Bangalore continues to blend clinical excellence with compassionate initiatives—creating meaningful experiences for children with T1D and their families.

Friends Forever – Peer Support Group Meet for Children with T1D

R Bhuvaneshwari, *Senior Executive Dietitian, Dr Mohan's Diabetes Center*

On 18th May, Dr Mohan's Diabetes Specialities Centre, Tanjore, hosted the "Friends Forever" peer support group meeting for children with T1D. The event aimed to educate, empower, and emotionally support children and their families in managing T1D effectively.

Deputy Mayor and Gynaecologist Dr Anjugam Boopathy inspired participants with her keynote address, emphasizing the vital role of insulin therapy and self-monitoring in maintaining a balanced, healthy life. Educational sessions by Dr Killivalavan, Consultant Diabetologist, and Senior Dietitians Ms R Bhuvaneshwari and Ms NM Bhuvaneshwari covered insulin adjustments, carbohydrate counting, types of insulin, and injection techniques.

Interactive role plays on emergency preparedness enhanced practical understanding, while children actively participated in solution-focused team presentations. The day concluded with demonstrations of insulin pumps, CGMS, and a sample T1D-friendly diet plan. Family queries were addressed, and participants left with new knowledge, confidence, and gifts of appreciation, making the event both informative and deeply encouraging for young Type 1 Warriors.

T1D Myths & Facts Session: Ahmedabad

Savita Agarwal, *JDPF, Ahmedabad*

An interactive event on "Myths and Facts about T1D" was held on 25th May at the Health and Care Foundation, Ahmedabad. With 21 children participating, parents and kids presented short skits to debunk common myths, making the session both educational and engaging.

A script was prepared in which 10 pairs of parents put forward the myths about T1D and their kids explained to them the facts to debunk the respective myths. We named this session "Diabetes ki School", where the parents were the students and the kids were their teachers. It was conducted in Hindi and Gujarati. This was followed by an interactive Q&A round between the kids and the doctors. Education and awareness are more effective if imparted in a fun way. Also, involving the kids and parents themselves makes them feel involved, with the kids learning to embrace their diabetes.

Diabetes Besties Summer Camp: Date: 26 May 2025: Venue: Karnataka Institute of Endocrinology & Research

The Diabetes Besties Summer Camp brought together almost 50 children with T1D for a fun-filled and educational day, with creative activities like a drawing competition, group songs, a talent show, and awareness sessions on safe sharp disposal and hypoglycemia management.

The day concluded with a cheerful group photo, healthy lunch, and distribution of certificates and gifts, leaving the children with smiles, memories, and valuable learning.

First-Ever T1D Awareness Campaign held at Pravara Institute, Loni

On June 13, 2025, the Pravara Institute of Rural Medical College, Loni (Maharashtra) hosted its first-ever T1D Awareness Campaign**.** Led by Dr Bhakti Katariya Dugad**,** Pediatric Endocrinologist from Nashik, the event brought together almost 40 children with T1D and their families**.** Highlights included:

- Educational sessions for children and parents
- A quiz competition with prizes for parents
- A talent show by children with T1D
- A skit on diabetes performed by the medical team
- Local language materials, snack boxes, and takeaway gifts.

The event fostered learning, joy, and a sense of community support—marking a meaningful milestone for diabetes care in this rural setting.

Yog Dhyan Foundation (YDF) Quarterly Report: April – June 2025

Anil Vedwal, Chief Functionary, YDF

YDF continued its committed journey of care and empowerment for children with T1D through impactful health camps and educational sessions.

April: The 2nd Quarter HbA1c & Health Camp on 12th April had esteemed guests from Rotary Club, Delhi South-End Next, with YDF Core Members Mr Rummy Chhabra, Ms Bindia Chhabra, and Ms Taruna Seth, sharing insights on the importance of CGM in T1D management, and the Rotary Club kindly sponsoring one year of diabetes supplies for one child. On 13th April, the "Look! One Virtual Event" session on "Working together leads to great impact" had Hero Ms Bindia Chhabra (Vice President, YDF), and panelists Ms Aruna Sharma, Mr Jitesh Wadhwa, and Ms Bhumika Khurana, emphasizing unity and teamwork in T1D care.

May: 1st May saw sessions on bio-waste management; and meditation and mindfulness; by Dr Anil Vedwal & Ms Riddhi Modi. The "Look! One Virtual Event" session on 11th May on "Understanding T1D in children: a guide for teachers" featured Hero Ms Ashu and panelists Ms Aruna Sharma, Ms Chhavi, and Ms Amrita Rupani, highlighting the essential role of teachers in supporting children with diabetes at school. On 18th May, a special Sunday camp educated caregivers about financial planning and savings, ensuring improved access to basic diabetes care.

June: The YDF Monthly Camp on 1st June, attended by over 175 children and families, had diabetes education, wellness yoga, bio-waste awareness, birthday celebrations, distribution of diabetes supplies, topped by a delicious lunch supported by the Bigger Picture Foundation. On 7th June, YDF (Dr Anil Vedwal, Ms Chhavi, Mr Jitesh Wadhwa, Mr Naman Sharma and Mr Siddharth) participated in the Patients Conclave at GIMS Hospital, Greater Noida organized by Dr Saurabh Srivastava and Mr Rohan Arora (Founder, Diabloom). The event addressed challenges faced by low-income families of children with T1D: YDF committed providing of glucometers with glucostrips and organizing of quarterly camps at GIMS. On 15th June, "Look! One Virtual Event" on "Diabetes management across different phases of life" featured Hero Mr Rohan Arora, Speaker Dr Shruti Arora, and panelists Ms Kashis, Mr Naman Sharma, Mr Jitesh Wadhwa and Ms Amarjeet Kaur. Special guests Mr Rajiv Kaickar, Ms Bindia Chhabra & Dr Anju Virmani joined in. The month concluded with the International Yog Day celebration on 22nd June.

HOMAGE: Mr Rajiv Kaicker, a pillar of support and inspiration in the Indian T1D community, sadly passed away on 26th June. Mr Kaicker lived with T1D for 65 years from onset at age about 4 years, and was always there to help and guide. We will miss him.

TRAINEES SECTION

Vikas Mehrotra, *Director, Kilkari Hospitals, Aligarh*

Please answer the questions below on Puberty. Correct answers and individual quiz scores will be mailed to the respective email address after the quiz closes.

https://forms.gle/9HVfQposQ3uqvLXGA

Last Date 10th July 2025

ISPAE 2025 Nagpur

9th Biennial Meeting of

Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)

14th to 16th November 2025 | Nagpur

ABSTRACT SUBMISSION DETAILS

The Scientific committee invites delegates to submit their original work and interesting cases to expert national and International faculty in ISPAE 2025 meeting in Nagpur

The Scientific committee encourages: Pediatric Endocrine fellows, DM trainees, pediatricians with interest in Pediatric endocrinology, Physicians with interest in Pediatric Endocrinology, Diabetologists, young consultants and registrars to submit their work to renowned experts

Papers can be submitted as short structured abstracts through the website. The top 5 scoring abstracts would be selected for oral presentation. The modality of presentation shall be communicated to the submitting author. Authors can also submit full papers for the Young investigator award through the the website.

Important Dates

Submission opens	**01/07/2025**
Submission closes	**31/08/2025**
Notification of selection	**01/10/2025**
Presentation	**15/11/2025 and 16/11/2025**

Prizes will be awarded for following categories

- Young investigator award
- Best oral presentation
- Best poster presentation

Get ready to showcase your work in the city of oranges in ISPAE 2025 and win attractive prizes !

Guidelines for abstract submission:

A blinded structured abstract of 250 words in the format: Introduction, Aim, Methods, results and conclusion should be submitted. All authors and their affiliations should be submitted separately in the website. During submission they should have an option to select the abstract category as well from a drop box: Growth, Diabetes, Thyroid, Puberty, Bone, Systemic disease, Obesity, DSD, Neonatal endocrinology

Guidelines for YI award submission:

Submission should be made through the website. Title page and study manuscript should be submitted separately. A title page should contain: study title, co-authors and their affiliations, word count, study center, details of submitting author, funding details, necessary ethical clearances. The blinded manuscript should contain blinded abstract, study manuscript (upto 2000 words excluding references), upto 4 illustrations (figures and tables). There should not be mention of authors or center in the manuscript

Before submission the author has to tick the following:

a) Submitting author has taken the permission to submit the paper on behalf co-authors

b) There are no Conflicts of Interest (If there are – there should be a provision to declare the same

c) Necessary ethical clearances have been obtained

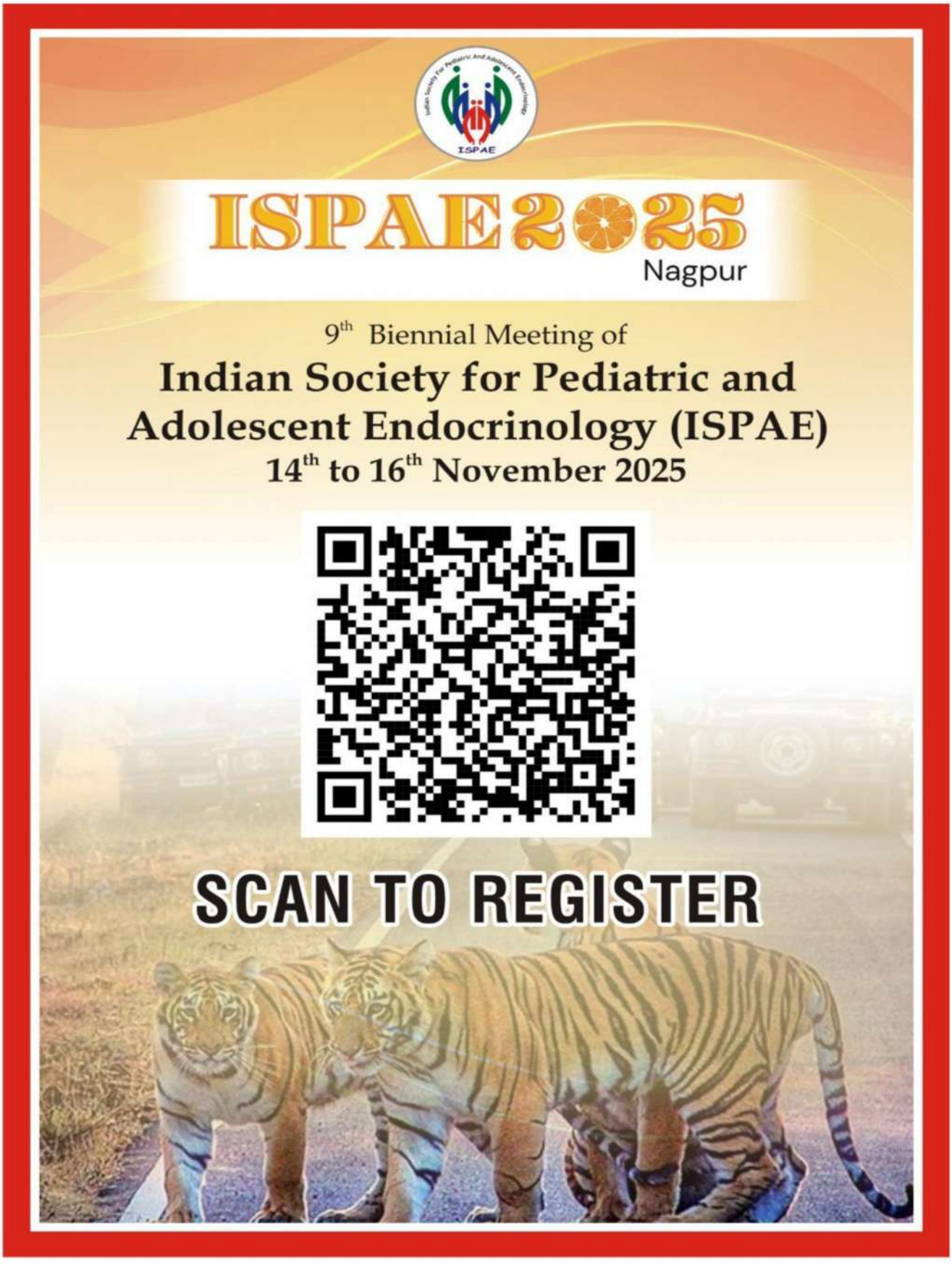
Scientific Committee

Dr. Vaman Khadilkar Chair	**Dr. Shaila Bhattacharyya**	**Dr. Sudha Rao**
Dr. Anurag Bajpai	**Dr. Hemchand Prasad**	**Dr. Rahul Jahagirdar**

CLICK TO SUBMIT ABSTRACT

ispae2025@gmail.com

www.ispae2025.com


ISPAE2025
Nagpur
9th Biennial Meeting of
Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)
14th to 16th November 2025
SCAN TO REGISTER