

# Challenges and controversies in diagnosis and management of gonadotropin dependent precocious puberty: An Indian perspective

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### ABSTRACT

Managing precocious puberty (PP) has been a challenge due to lack of standardized definition, gonadotrophins assay, gonadotrophin stimulation, timings for blood sampling, and parameters for assessing outcomes. This review evaluated available literature to simplify the algorithm for managing gonadotrophin dependent/central PP (CPP), with an Indian perspective. CPP is one of the commonest forms of PP and mimics the normal course of puberty, at an age <8 and 9 years for girls and boys respectively. Basal and post gonadotrophin hormone releasing hormone analog (GnRHa) luteinizing hormone (LH)  $\geq 0.3$ – $0.6$  IU/L and  $\geq 4$ – $5$  IU/L (30–60 min after GnRH/GnRHa administration) respectively, using modern ultrasensitive automated chemiluminescence assays, can be considered positive for central puberty initiation. Uterine length of >3.5 cm and uterine volume of >1.8 ml are two most specific indicators for true CPP. Therapy is indicated in children with CPP with accelerated bone age, height advancement, or psychosocial stress. Treatment goal is to halt puberty progression to a socially acceptable age, allowing the child to attain optimal height potential. GnRHa is the treatment of choice, with best height outcomes when initiated <6 years age. Treatment is recommended till 11 years age. LH suppression to <3 U/L may be a reasonable target in patients on GnRHa therapy. Medroxyprogesterone acetate holds an important place in managing PP in India, cause of high costs associated with GnRHa therapy. There is an urgent need for clinical trials from India, for establishing Indian cut-off for diagnosis, treatment and follow-up of children with PP.

**Key words:** Adrenarche, gonadotropin releasing hormone analog, gonadotrophins, medroxyprogesterone acetate, menarche, precocious puberty, pubarche, thelarche

## INTRODUCTION

Onset of development of secondary sexual characteristics (as the first step toward attaining reproductive capacity) before the age of 8 and 9 years in girls and boys respectively has traditionally been used for defining precocious puberty (PP).<sup>[1]</sup> PP is a spectrum disorder, which may manifest

with either development of all the secondary sexual features (progressive PP) or may occasionally present as isolated premature thelarche, adrenarche or menarche.

Optimal management of PP is an important cause of its considerable long-term biological, psychosocial and health implications. Early onset of puberty and untreated PP has been linked to compromised adult height, increased occurrence of metabolic syndrome, dyslipidemia, dysglycemia, cardiovascular events, hyperandrogenism, increased risk of breast cancer, increased psychological disturbance, risk taking behavior and sexual activity.<sup>[2]</sup> However, the diagnosis and management of PP is complicated by lack of standardized age cut-offs for clinical diagnosis, the varied clinical presentation, lack of

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internationally standardized gonadotrophins (especially luteinizing hormone [LH]) assay, lack of standardized agents for gonadotrophin stimulation, timings for sampling for post-stimulatory LH, a large plethora of available pharmacologic agents, lack of standardized biochemical parameters for monitoring response to therapy and assessing long-term outcomes.

This article aims to review the available literature to simplify the algorithm for diagnosis and management of PP (especially gonadotrophin dependent PP), keeping in mind the resources available in India currently.

## METHODS

### Search strategy and selection criteria

References for this review were identified through searches of PubMed, Medline and Embase for articles published till October 2014, by use of the terms “PP” [MeSH Terms] OR “pubertal onset” [All Fields] OR “puberty” [All Fields]. The reference lists of the articles thus identified were also searched. The search was not restricted to English language literature.

## RESULTS

The prevalence of PP among Indian children is not known. The prevalence of PP is about 10 times higher in girls than boys with estimated register-based population prevalence of approximately 0.2% in girls and below 0.05% in boys (Denmark).<sup>[3]</sup> Secular trends from industrialized European countries and USA over the past 150 years have suggested a constant decline in the age of menarche, at a rate of about 2–3 months per decade.<sup>[4]</sup> Accordingly, in some developed countries, the ages of 7 years for white girls and 6 years for black girls have been proposed to define onset of PP from the more universally accepted cut offs of 8 and 9 years for girls and boys respectively. This decline in age of onset of puberty has also been associated with increased occurrence of children presenting with PP across the globe.<sup>[5,6]</sup> Improvement in nutritional status, better control of infections, better quality of life, increased childhood obesity, low birth weight followed by rapid gain of weight, genetic, ethnic factors, international adoption, increased exposure to endocrine disrupting chemicals are believed to have some role.<sup>[5,6]</sup>

The earliest clinical sign suggestive of onset of puberty is breast enlargement (thelarche) in girls and increase in testicular volume in boys, with the entire process of maturation completing within 4 years of onset.<sup>[1,7,8]</sup> Kisspeptin produced by arcuate nucleus and anteroventral periventricular area of the hypothalamus is critical to

puberty initiation. Neurokinin B and dynorphin from the same neurons stimulate and inhibit the release of kisspeptin respectively, and hence these kisspeptin, neurokinin and dynorphin neurons have now been recognized to be central to puberty initiation.<sup>[9,10]</sup>

### Etiology

Etiology of gonadotrophin releasing hormone (GnRH) dependent PP (central PP [CPP]), one of the most common forms of PP, remains undetermined in a majority of children (girls > boys), with idiopathic CPP comprising 90% of cases in girls, as per western literature.<sup>[7]</sup> However, idiopathic CPP is believed to be less common in India, both in girls as well as boys. Central nervous system (CNS) infections are an important secondary cause of CPP in India. In a series of 140 patients with PP from Mumbai, a definitive cause for CPP could be established in 56% (10 out of 18) boys and 21% (16 out of 77) girls, with hypothalamic hamartoma followed by neurotuberculosis being the two most common causes.<sup>[11]</sup> Some of the common causes of PP have been elaborated in Table 1.

### Clinical diagnosis

Evaluation of PP should include complete family history (age at onset of puberty in parents and siblings) patient’s details of age at onset of puberty and progression of pubertal manifestations. Any evidence suggesting possible CNS dysfunction, like recurrent vomiting, headache, increased head circumference, visual impairment, or seizures should be noted. Growth pattern and velocity should be meticulously recorded. Sexual maturity is assessed using Tanner’s staging. CPP in contrast to peripheral PP (PPP) classically mimics the normal

**Table 1: Common causes of precocious puberty**

GnRH dependent precocious puberty (central precocious puberty)	GnRH independent precocious puberty (peripheral precocious puberty)
Idiopathic	Congenital adrenal hyperplasia
Hypothalamic hamartoma	Adrenal adenoma/carcinoma
CNS infections (tuberculosis, postmeningitis)	McCune-Albright syndrome
Post-CNS insults (hydrocephalus, postcranial surgery, irradiation, trauma)	Human chorionic gonadotropin-secreting tumor
Craniopharyngioma, arachnoid cysts, optic glioma, meningioma	Ovarian tumors
Syndromes (neurofibromatosis-1, Sturge-Weber syndrome, tuberous sclerosis)	Van Wyk-Grumbach syndrome
Secondary activation of hypothalamic pituitary gonadal axis in congenital adrenal hyperplasia	Leydig cell tumors
Mutations (gain of function mutation of kisspeptin/kisspeptin receptor)	

CNS: Central nervous system, GnRH: Gonadotrophin hormone releasing hormone analog

course of pubertal development of thelarche, followed by adrenarche and menarche, and is associated with height acceleration and advancement of bone age (BA). Documentation of height velocity and BA is important cause certain incomplete variants of PP may be associated with normal height velocity and BA (isolated premature thelarche, premature adrenarche), and these children do not warrant therapy with GnRH analogs (GnRHa). Development of acne, oily skin, and apocrine body odor support the development of adrenarche.

Examination of testicular volume is important in males, as boys with CPP typically have symmetric enlargement of bilateral testis in pubertal range ( $>4$  ml, or  $>2.5$  cm in length), in contrast to PPP, which typically have disproportionately small testis, as compared to the degree of virilization.<sup>[12]</sup> Exceptions to this include PPP due to human chorionic gonadotropin secreting tumors and familial male limited PP (testotoxicosis, due to mutation in LH receptor).

Perhaps the most common cause of PPP is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Diagnosis is easy and early in females, even in the absence of salt wasting crisis, due to the varied degree of virilization of external genitalia at birth. Males with 21-hydroxylase deficiency, in the absence of salt wasting, often present at a later age with PP. Testicular volume though typically small (prepubertal) in these children, a small proportion will develop secondary CPP (due to long-term exposure to sex steroids, through mechanisms not well understood), resulting in increase in testicular volume. This has also been observed in other causes of PPP, and typically occurs once the chronic exposure to sex steroids is eliminated, like after initiation of treatment for CAH. In addition, development and enlargement of the adrenal rests may also be responsible for increased testicular volume in CAH. These adrenal rests can be made out separately from testis, on careful testicular palpation.

### Investigations

The main aim of biochemical evaluation is to confirm the diagnosis of CPP (GnRH dependent), distinguish incomplete nonprogressive forms of PP like premature thelarche, premature adrenarche from true PP. This involves estimation of LH in the basal state, as well as post GnRH/GnRHa stimulation. Various studies have reported different cut-offs of basal LH for the diagnosis of hypothalamic pituitary gonadal (HPG) axis activation (puberty initiation), a result of usage of different assay systems for LH estimation, having different sensitivity and assay coefficient of variation [Tables 2 and 3]. In general a basal LH  $\geq 0.3$ – $0.6$  IU/L using modern

ultrasensitive automated chemiluminescence assays (now available in India in most tertiary care centers), can be considered to be positive for HPG axis activation.<sup>[7,8]</sup> GnRH is not available in India. Triptorelin (100 mcg) followed by leuprolide (20 mcg/m<sup>2</sup>) are the 2 most commonly available GnRHa for GnRHa stimulation test in India. These preparations are usually administered subcutaneous or intramuscular. There is no available standard for timing of blood sampling for LH estimation post GnRHa administration. Generally an early sampling 30–60 min after GnRH/GnRHa administration is considered to be highly sensitive and specific for diagnosis, and a late sampling between 2 and 4 h may also be done, especially when a GnRHa are used for stimulation.<sup>[13-15]</sup> Different studies have again reported different levels of post-GnRHa stimulated LH for the diagnosis of HPG axis activation [Tables 2 and 3]. In general a stimulated LH  $\geq 4$ – $5$  IU/L using modern ultrasensitive automated chemiluminescence assays can be considered to be positive for HPG axis activation.<sup>[7,8]</sup> Follicle stimulating hormone (FSH) estimation is in general not helpful cause of the considerable overlap of prepubertal values with puberty, and cause of its elevation in premature thelarche. However, a peak LH/peak FSH  $> 1$  ( $>0.6$  in some studies) is also helpful in differentiating true CPP from premature thelarche, which has a predominant FSH response.<sup>[4,8]</sup>

Ultrasonography of uterus and ovaries by an experienced radiologist is a very useful investigation in affected females. An uterine length of  $>3.5$  cm, followed by uterine volume of  $>1.8$  ml are believed to be the 2 most specific indicators for true CPP, and are useful in differentiating CPP from premature thelarche or adrenarche.<sup>[12,20]</sup> Ovarian cysts can be found in both CPP and PPP, but cysts  $>9$  mm are also highly suggestive of CPP.<sup>[21]</sup>

As per standard textbooks, all boys with CPP and girls only with suggestive symptoms should undergo MRI brain for evaluation of secondary sinister causes of CPP.<sup>[4,8]</sup> However, it may be a good practice to do MRI brain in all children of CPP  $< 6$  years age, irrespective of sex. MRI may be avoided (not cost effective) in children  $>6$  years age, especially girls who do not have symptoms suggestive of secondary underlying pathology.

Ancillary investigations are always recommended as per the clinical presentation of the patient, to establish the etiology of CPP or PPP [Table 1]. It has been suggested that the children with mild pubertal development with ambiguous biochemical report may be monitored closely for 3–6 months for growth and BA acceleration before treatment initiation, at the cost of perhaps compromising on the final height outcome.<sup>[22]</sup> Therapy is indicated

**Table 2: Studies showing basal and poststimulated LH levels diagnostic of hypothalamic pituitary gonadal axis activation and puberty initiation in girls**

Study group	Assay used	Basal LH ≥ (IU/L)	Sensitivity (%)	Specificity (%)	Agent used	Peak LH ≥ (IU/L)	Sensitivity (%)	Specificity (%)
Brito <i>et al.</i> <sup>[15]</sup>	IFMA	0.6	62.7	100	100 mcg GnRH iv	6.9	92.2	100
Houk <i>et al.</i> <sup>[16]</sup>	Architect <sup>y</sup>	0.83	93	100	-	-	-	-
	Delfia <sup>y</sup>	1.05	100	100				
Sathasivam <i>et al.</i> <sup>[17]</sup>	ICMA	0.3	35	100	Leuprolide 20 mcg/kg sc	5.0	78	100
Resende <i>et al.</i> <sup>[18]</sup>	ICMA	0.2	89.61	100	100 mcg GnRH iv	3.3	100	100
	IFMA	0.6	83.12	100		4.2	84.61	100
Bizzarri <i>et al.</i> <sup>[19]</sup>	ICMA	>0.2	89	99	100 mcg GnRH iv	5	100	64

<sup>y</sup>3<sup>rd</sup> Generation chemiluminescent immunoassay. LH: luteinizing hormone, GnRH: Gonadotropin releasing hormone, ICMA: Immunochemiluminescent assay, IFMA: Immunofluorometric assay, iv.: Intravenous

**Table 3: Studies showing basal and poststimulated LH levels diagnostic of hypothalamic pituitary gonadal axis activation and puberty initiation in boys**

Study group	Assay used	Basal LH ≥ (IU/L)	Sensitivity (%)	Specificity (%)	Agent used	Peak LH ≥ (IU/L)	Sensitivity (%)	Specificity (%)
Brito <i>et al.</i> <sup>[15]</sup>	IFMA	0.6	71.4	100	100 mcg GnRH iv	9.6	100	100
Resende <i>et al.</i> <sup>[18]</sup>	ICMA	0.3	100	100	100 mcg GnRH iv	4.1	82.35	100
	IFMA	0.6	88.24	100		3.3	94.11	100

LH: luteinizing hormone, GnRH: Gonadotropin releasing hormone, ICMA: Immunochemiluminescent assay, IFMA: Immunofluorometric assay, iv.: Intravenous

in children with definitive diagnosis of CPP, rapid advancement of height and BA (>2.5 standard deviation for chronologic age), serum testosterone >75 ng/dl (in males <8 years age), estradiol (>10 pg/ml in females), or in the setting of parental anxiety, psychosocial stress.<sup>[12]</sup> Serum estradiol however has a high overlapping range in normal and PP limiting its use. In addition, estradiol assays are notorious for having poor reliability and reproducibility.

### Treatment

The main goals of treatment of PP are to halt/delay the process of puberty progression, till an age commensurate with peers of the child, to allow for normal social, psychological and intellectual development of the child, relieve the parents of the associated anxiety, and importantly allow the child to attain the optimal height potential, as untreated PP is associated with accelerated and advanced epiphyseal fusion, resulting in height loss.

Gonadotrophin releasing hormone analog is the mainstay of treatment as they help in achieving all the treatment goals when used in the appropriate clinical setting. Adult height preservation with GnRHa is best when initiated in children diagnosed before 6 years age, variable when initiated between 6 and 8 years age, and probably has little benefit when initiated after 8 years age.<sup>[7]</sup> Good predictors of height outcomes, include younger chronological age (CA), younger BA, greater height standard deviation score for CA at initiation of therapy and a higher predicted adult height using Bayley–Pinneau tables.<sup>[23,24]</sup> GnRHa should generally be continued till 11 years age, when pubertal progression

is more likely to commensurate with peers at school and neighborhood. Continuing use of GnRHa beyond CA of 11 years and/or BA of 12–12.5 years has been shown to have conflicting effect on final height outcomes in different studies.<sup>[22,24,25]</sup>

Gonadotrophin releasing hormone analog discontinuation is associated with initiation of menses within 1–2 years.<sup>[26,27]</sup> The authors frequently observed the occurrence of polycystic ovarian syndrome (PCOS) in a large majority of children following cessation of GnRHa therapy. GnRHa however is believed to have no impact on long-term menstrual regularity, reproductive potential, number of pregnancies and pregnancy outcomes.<sup>[28,29]</sup> Bone mineral density generally dips with the start of GnRHa but normalizes after discontinuation of therapy, with no impact on long-term outcomes.<sup>[2]</sup>

Concern for long-term metabolic outcomes (metabolic syndrome) and PCOS remains a concern in patients with PP, with currently available literature showing conflicting outcomes.<sup>[28,30]</sup> Interpreting these studies has been a challenge in view of use of different diagnostic criteria, race/ethnicity and several biases.<sup>[2,28-30]</sup> GnRHa therapy does not modulate the hyperandrogenism in later life associated with PP.<sup>[2]</sup> Limited data (only two studies) is suggestive of no impact of GnRHa therapy on psychologic outcomes of girls with CPP.<sup>[31,32]</sup>

Height outcomes with different GnRHa therapy across the globe have been elaborated in Table 4. The different GnRHa and their dosages currently available in India

**Table 4: Height outcomes of different gonadotrophin hormone releasing hormone analogs in managing central precocious puberty**

Study	GnRHa	Age at puberty onset	BA at start of therapy	CA at start of therapy	Treatment duration	Adult height (cm)	Height gain (cm)
Oostdijk <i>et al.</i> <sup>[25]</sup> (n=31)	Triptorelin 3.75 mg every 4 weeks	6.0 (2.0)	10.8 (0.7)	7.7 (0.8)	3.4 (1.1)	161.6 (7.0)	3.5 (4.2)
Bouvattier <i>et al.</i> (1999) <sup>[38]</sup> (n=20)	Triptorelin 3.75 mg every 4 weeks	9.3 (0.5)	10.9 (0.5)	9.5	2.0	157.6 (4.0)	3.5
Galluzzi <i>et al.</i> <sup>[39]</sup> (n=22)	Triptorelin 60-120 mcg/kg every 28 days; 5 patients first received Buserelin 20 mcg/kg/day	NA	10.25 (0.84)	7.32 (1.06)	3.99 (1.07)	158.49 (5.27)	3.27
Bertelloni <i>et al.</i> <sup>[40]</sup> (n=19)	Triptorelin 60 mcg/kg/26-28 days; 7 patients first received Buserelin 1600 mcg/daily	NA	9.6 (1.6)	6.2 (1.8)	NA	158.1 (5.2)	4.6*
Heger <i>et al.</i> <sup>[41]</sup> (n=50)	Triptorelin 75 mcg/kg/28-32 days	5.2 (2.1)	9.3 (2.5)	6.7 (2.0)	4.4 (2.1)	160.5 (8.0)	5.9 (8.5)
Arrigo <i>et al.</i> <sup>[24]</sup> (n=71)	Decapeptyl depot 60 mcg/kg/28 days	NA	9.8 (1.4)	7.0 (1.3)	3.9 (1.3)	158.4 (5.8)	2.9 (6.0)
Cassio <i>et al.</i> <sup>[42]</sup> (n=23)	Triptorelin 3.75 mg every 4 weeks	7.7 (0.5)	10.6 (0.8)	8.5 (0.6)	2.08	158.1 (6.2) <sup>#</sup>	NA
Carel <i>et al.</i> <sup>[43]</sup> (n=58)	Triptorelin 3.75 mg/28 days in children >20 kg and 1.87 mg/28 days in <20 kg weight	6.3 (1.5)	10.1 (1.5)	7.5 (1.3)	3.7 (1.5)	161.1 (5.9)	4.7*
Leger <i>et al.</i> <sup>[44]</sup> (n=9)	Triptorelin 3.75 mg every 4 weeks	6.5 (0.9)	11.1 (0.4)	8.7 (0.4)	2.1 (0.7)	160.2 (6.7) <sup>§</sup>	NA
Klein <i>et al.</i> <sup>[45]</sup> (n=80)	Deslorelin 4 mcg/kg/day or histrelin 4-10 mcg/kg/day	NA	10.0 (2.7)	5.4 (1.9)	5.7 (2.1)	159.8 (7.6)	9.8 (9.0)
Kempers and Otten <sup>[46]</sup> (n=17)	Triptorelin 3.75 mg every 4 weeks	6.4 (0.7)	NA	7.0 (1.35)	3.41 (1.79)	166.2 (2.25)	2.0
Adan <i>et al.</i> <sup>[47]</sup> (n=43)	Decapeptyl 3.75 mg/24-24 days; Dose reduced to half in children <20 kg	6.4 (0.2)	10.3 (0.2)	7.9 (0.2)	NA	159.5 (0.8)	3.4
Pasquino <i>et al.</i> <sup>[48]</sup> (n=87)	Triptorelin 100-120 mcg/kg/21-25 days	5.6 (1.6)	11.1 (1.6)	8.4 (1.5)	4.2 (1.6)	159.8 (5.3)	9.5 (4.6)
Lazar <i>et al.</i> <sup>[49]</sup>	Decapeptyl administered im. Every 4 weeks at calculated dose 1.5-3.0 mcg/kg/day	4.6 (1.2) 7.0 (0.4) 8.5 (0.7)	NA NA NA	6.4 (1.2) 7.5 (0.6) 8.9 (0.5)	4.8 (1.3) 2.8 (0.7) 2.1 (0.4)	162.8 (5.0) 157.9 (5.1) 153.9 (4.6)	8.2* 4.2* 1.1*

BA: Bone age, CA: Chronologic age, GnRHa: Gonadotrophin releasing hormone analog, NA: Not available, all ages have been mentioned in years, values in parenthesis represent standard deviation, \*Calculated from data available as final height gain is not mentioned in original article, <sup>#</sup>Data of only 20 out of 23 patients was available in original article, <sup>§</sup>Current height was the final height in only 5 of 9 cases

for treatment of PP have been elaborated in Table 5. Leurpolide depot is perhaps most commonly used followed by triptorelin depot preparation. No preparation of GnRHa has any added advantage over another. Buserelin and histrelin, available in Europe and USA, are not currently available in India. Monthly depot injections of leuprolide and triptorelin are most commonly used. Recently, 3 monthly depot preparations are also available in the market, with the advantage of reduced annual cost of therapy. However, concerns have been raised about the duration of efficacy of the 3 monthly preparations, with fears of wearing off of efficacy in the last of the 3 months (unpublished data). The first injection of GnRHa is associated with a transient surge in LH and FSH resulting in a transient increase in estradiol levels, which then rapidly reduces following down regulation of GnRH receptor, usually within a fortnight.<sup>[12]</sup> This transient surge in estradiol may result in vaginal spotting/bleeding in a small fraction of female patients following the first injection. Hence, it may be important to counsel

the parents regarding the same beforehand to allay any anxiety. Co-injection of depot medroxy-progesterone acetate (MPA) only with the first dose of GnRHa may be a reasonable option to prevent this estradiol surge and the associated vaginal bleed. Vaginal bleed if noticed following subsequent injections are more likely due to lack of adequate gonadotropin suppressing warranting more frequent LH levels monitoring, increase in dose/frequency of GnRHa injections. However, there are no guidelines or recommendations for timing of estimation of serum LH (basal/post stimulated, agent for stimulation), as well as level of serum LH during follow up of GnRHa therapy for therapy modulation. The only study done in India in patients on 11.25 mg leuprolide depot intramuscular injections has suggested 3 h LH post injection of depot leuprolide, to be useful for monitoring therapy in patients with CPP cause of its convenience and cost effectiveness.<sup>[33]</sup> Ideally, serum LH should be suppressed to undetectable levels in patients on GnRHa therapy, which may however be not practically feasible in the majority of

**Table 5: Gonadotrophin hormone releasing hormone analog depot preparations available in India**

Agent	Preparations available	Doses
Leuprolide	3.75 mg monthly im 11.25 mg 3 monthly im	Half dose is recommended in children with weight <20 kg Dose may need to be doubled/tripled in children with increased body weight, as per LH levels post injection
Triptorelin	3.75 mg monthly im 11.25 mg 3 monthly im	Half dose is recommended in children with weight <20 kg Dose may need to be doubled/tripled in children with increased body weight, as per LH levels post injection
Goserelin	10.8 mg 3 monthly	Available as subcutaneous implant

All depot preparations are available as lyophilized power along with separate reconstituting fluid in a composite syringe. It is important it inject the preparation immediately after re-constitution, to avoid solidification and injection failure. Injection should always be administered deep im., preferably in the gluteal region. Injection site sterile abscess have been reported with all agents in about 5% cases. LH: Luteinizing hormone, im.: Intramuscular

the patients. A suppression of LH to <3 U/L may be a reasonable target in patients on GnRHa therapy,<sup>[34]</sup> with few studies reporting LH <4 U/L also as an acceptable LH suppression cut-off.<sup>[35-37]</sup> Studies are warranted to evaluate the LH levels not only after administration of GnRHa depot injection, but also perhaps a few days before the next scheduled dose of GnRHa. A persistently suppressed serum LH on both occasions may be an important predictor of response to therapy.

However, use of GnRHa in managing CPP in India may be limited cause of the associated costs, making it unaffordable to a large fraction of the population. MPA or cyproterone acetate (CPA) should be used for managing PP in children who cannot afford GnRHa. MPA may be a reasonably good option for managing CPP in children >6 years of age, where use of GnRHa has been associated with minimal gains in height outcomes. MPA/CPA are useful in halting puberty progression, but have no beneficial impact on final height outcomes.<sup>[12]</sup> Advantages of MPA include its low cost, ease of administration, and established efficacy in halting puberty progression.

MPA has multiple mechanisms of actions. It inhibits central gonadotropin release by acting on hypothalamic pulse generator, and it also directly inhibits gonadal steroidogenesis by inhibiting 3-beta hydroxysteroid dehydrogenase 2 enzyme.<sup>[37]</sup> Its glucocorticoid mimetic action is responsible for adrenocorticotrophic hormone (ACTH) suppression, hypertension and development of cushingoid habitus. MPA use is associated with bone mineral loss, especially if used for a long period.<sup>[8,37]</sup> CPA has advantages and disadvantages similar to MPA, except for its ACTH

and cortisol suppressing effect leading to symptoms of iatrogenic adrenal insufficiency in a subset of patients. MPA is usually initiated in the form of depot deep intramuscular injections, at a low dose of 50 mg per month, which can be increased up to 400 mg per month, or the dosing frequency can be reduced to fortnightly.<sup>[8,37]</sup>

### Future directions

There is an urgent need for clinical trials from India, for the establishment of Indian cut-offs for diagnosis, treatment and follow up of children with PP. Trials should focus on evaluating the reliability of measurement of uterine length and volume, and ovarian volume (cheap and easy to do measure) in predicting puberty onset, and their relationship with more costly and less reproducible biochemical tests like basal and stimulated LH.

## CONCLUSION

Precocious puberty is a common problem seen in endocrinology practice. Diagnosis and management of PP remains a challenge in the absence of standardized guidelines. GnRHa is the agents of choice for managing CPP. MPA still holds an important place in the management of PP in India, especially in children >6 years age.

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