Review Article

Leuprolide Vs triptorelin: The recent trends in GnRH analogues in precocious puberty

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Abstract

Precocious puberty resulting from hypothalamic-pitiutary-gonadal axis activation is increasing problem in children and early institution of therapy for the axis suppression allows the patients to attain target adult heights. The review evaluates and compares the efficacy of the most commonly used two GnRH analogues: leuprolide and triptorelin; and the recent trends in their dosages.

Key words

Early puberty, GnRH analogue, Leuprolide, Triptorelin.

Introduction

Precocious puberty (PP) is an increasingly common problem in children causing significant psychosocial problems and hence requires timely diagnosis and intervention. Precocious puberty results due to the activation of the hypothalamic-pitiutary-gonadal axis resulting from the increasing amplitude of gonadotropin- releasing hormone (GnRH) and luteinizing hormone (LH) pulses signals for increased gonadal sex steroid production, causing early onset secondary sexual characteristics [1].

PP is defined as onset of secondary sexual characteristics in girls before 8yrs of age and is mostly thelarche stage II Tanner. In boys it is before 9yrs in boys with increase in testicular volume stage II [2]. However, it can sometimes be a case of isolated thelarche or pubarche, where all the secondary sexual characteristics do not develop.

We conducted an extensive search of pubmed using the words precious puberty, GnRH analogues, leuprolide, triptorelin. The articles included in the study were:

- Articles in English
- Only used in precocious puberty
- Studies with Final height estimation done
- With only LH suppression done
- Mentioned use of single drug, no combinations
- Excluded case studies

HPA axis

A varied array of stimuli like photoperiod, nutrients, stress, infection, metabolic products, environmental exposures, many hormones are integrated to the hypothalamus to regulate the synthesis and secretion of gonadotropin-releasing hormone (GnRH) [3]. This acts on the GnRh receptors in the pituitary for the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which in turn act on the gonads to produce gametes, steroids and peptide proteins [4].

This cascade of hormone production is regulated by a systematic positive and negative feedback loop between the pituitary, gonads and hypothalamus.

The inactivating mutations of two GnRH regulator neuropeptides kisspeptin and neurokinin B in the hypothalamus result in delayed puberty by delayed degradation of the ligand–receptor complex within the cell membrane [3].

Other modulators regulating GnRH neuron activity are neuropeptide Y, products of the pro-opiomelanocortin protein, gonadotropin-inhibitory hormone (GnIH) and neurotransmitters (such as γ-amino butyric acid and glutamate).

The common mutations affecting these neuropeptides are KISS1, MKRN3, single nucleotide polymorphisms of FSHB gene and LHB gene [5].

GnRH analogues

GnRH is released in a pulsatile manner into the hypophyseal portal system, which stimulates the pituitary to release LH, and FSH. These GnRH pulses occur every 60-120 min and cause a pulsatile LH surge, which allows the receptor concentrations to be replenished between pulses [4, 6].

GnRH analogues disrupt this pulsatility of GnRH and provide continuous levels that result in reduced gonadotropin production and reversal of pubertal changes by downregulating the receptor concentrations, which desensitizes the pituitary to continued stimulation.

Hence they are the mainstays of treatment in CPP. The agonists are derived from native GnRH by substitution of a D-amino acid for the native L-amino acid at position 6 in the decapeptide, this makes them resistant to degradation and prolongs their half-life [7].

GnRH agonists are best administered intramuscular or intravenous. The drug if given subcutaneously needs higher doses and the smaller blood peaks takes slower to develop and much longer to wean off. If given orally the drug get degraded. By the intravenous and intramuscular routes 75% are rendered hypogonadal by 4 weeks and by 8weeks all are rendered hypogonadal. Other routes are intranasal and long term implants [8].

Indications in CPP

Therapy with GnRH is indicated in children with CPP with:

- accelerated bone age
- height advancement
- psychosocial stress

The two most commonly used GnRH analogues worldwide are leuprolide and triptorelin and there have been multiple studies evaluating the efficacies of both the analogues.

Leuprolide was FDA approved in 1985 for medical use in the United States. It may be used for hormone receptive tumors such as prostate and breast cancer, estrogen dependent conditions like endometriosis and uterine fibroids. Leuprolide and triptorelin are FDA approved for treating precocious puberty.

Table - 1: Leuprolide studies.

S. No.	Study	Number	Age group	Study duration (mean)	Bone age advanced/ mean	Height gain (mean)	Drop outs	Dose	Side effects	Mean LH Suppression
1	Parker et al 1989 (Pennsylvania) [9]	6	3.6-7.9yrs	3months	8.85yrs		-	:3,75mg/4weeks :6mg/4weeks	-	8.3+-3.3ug/L
2	Clemens, et al. 1993 (Arizona) [10]	10		1.6-3.5yrs	> 1.4+-0.1yrs (than CA)	3.4cm	Nil	3.75mgX28days	Nil	2.4+-0.2IU/L
3	Carel, et al. 2002 (France) [11]	44	8.2+-0.7yrs	6months	>2.9+-0.9yrs(than CA)		16%	11.25mg/3months S/C	Nil	1.3+-0.9IU/L (95%)
4	Baradu, et al. 2006 (California) [12]	30	<8yrs	12months	:5.8cm/yr :3.6cm/yr :5.3cm/yr		2	:3,75mg/4weeks :7.5mg/4weeks :11.25mg/3months	Nil	:1.73+-0.99IU/L :1.30+-0.70IU/L :2.13+-1.41IU/
5	Y.C. Tung, et al. 2007 (Taiwan) [13]	11	8+-1.5yrs	4.7+-1.8yrs	>14yrs	19+-10cm	-	3.75mg X 28days	-	1.3+-1.5mIU/ml
6	Meriq V, et al. 2009 (USA) [14]	14	6.5-10.2yrs	12months	11.39+-1.04yrs (mean)	2.8+-1.9cm	Nil	:3.75mg/28days :11.25mg/3months :22.5mg/3months	Nil	: 0.69+-0.12 :1.24+_0.2 :0.84+-0.08
7	Neely, et al. 2010 (USA) [15]	55	<8yrs	3.9+-2yrs	>1yr (than CA)	-	Nil	7.5-15mg/month	Nil	1.98 IU/L
8	Fuld, et al. 2011 (USA) [16]	54	7.8+-1.9yrs	24months	10.3+-2.4yrs	5.3+-1.6cm-	Nil	:7.5mg/28days :11.5mg/3months :22.5mg/3months	Nil	:1.56+-0.94 :2.52+-1.13 1.63+-0.76
9	Peter lee, et al., 2011 (USA) [17]	39	<10yrs	3.9+_2yrs	> 3yrs (than CA)	4cm	-	3.75mg X 28days	Nil	-
10	Kim Jin, et al. 2013 (korea) [18]	54	<8yrs	24 weeks	>1.27+-0.7yrs (than CA)	-	Nil	3.75mgX28days	Urticaria, Pain, swelling	<3IU/L in (52/54)
11	Peter Lee 2014 (Chicago) [19]	65	2-11yrs	36months	11.15yrs (mean)		48	11.25/30mg X3months	Several???	2.2mIU/ml

12	Kendirici, et al. 2015 (Ankara) [20]	62	<8yrs	12months	7.7-11.2yrs (range)	-	6	3.75mg X 28days	Nil	-
13	Borges, et al. 2015 (Brasil) [21]	62	1.3-8.9yrs	1.8=_0.1yrs	>3yrs(than CA)	6.7cm	-	3.75mg X 28days	Nil	-

Studies using leuprolide are as per **Table – 1**.
Leuprolide has been used for treatment of PP in various studies from the age group ranging from 1.3 to 11yrs [19, 21]. It has been used in varying dosages by pediatric endocrinologist all over the world; 3.75 mg every 28 days, 6-7 mg/4 weeks, 11.25 mg/3 months, 22.5 mg/3 months.

NICE guidelines recommend to start Triptorelin initially at a dose of 3.75 mg every 2 weeks for 3 doses, to be administered on days 0, 14, and 28 of treatment, then 3.75 mg every 3–4 weeks, discontinue when bone maturation consistent with age over 12 years in girls and over 13 years in boys.

Most of the studies have evaluated the efficacy of the dose 3.75mg/4weeks for suppressing the HPA axis [9, 10, 13, 17, 18, 20, 21]. The starting dose is higher in studies from the US using either 300 mcg/kg/day or 7.5 mg minimum and 15 mg maximum every 28 days, while a starting dose of leuprolide acetate 3.75 mg administered intramuscularly or subcutaneously every 28 days is widely accepted in Europe and Asia.

Two studies by Fuld and Meriqcompared the efficacy of three different dosing schedules using 3.75mg/28days,7.5mg/28days, 11.25mg/3months, 22.5mg/3months in PP [16, 14].

Suppression of stimulated LH is considered the single best short-term measure of treatment adequacy and the study by Fuld found no differences in LH suppression between the 7.5-mg 1-month and 22.5-mg 3-month doses and 11.25-mg 3-month dose results in marginally inferior LH and FSH suppression compared with monthly leuprolide [16]. However, they reasoned that lesser degree of LH suppression associated with the 11.25-mg 3-month dose was not clinically meaningful. They did not find any differences in E2 level, growth velocity, bone age advancement, or change in the predicted adult height in either year of treatment. Their study proposed two approaches:
a) beginning all subjects on 22.5-mg 3-month DL, which more closely approximates the total dose delivered by monthly therapy, or
b) starting on the 11.25-mg dose, which is sufficient in most cases, then increasing the dose if there is persistent hormonal or clinical criteria requirement.

In the study by Meriq, et al.; LH was suppressed to less than 2 IU/l in all patients on 22.5 mg by 3 months, in all patients on 7.5 mg monthly by 9 months and in all patients on 11.25 mg by 12 months. They demonstrated suppression of luteinizing hormone occurs sooner in the 3-month 22.5 mg leuprolide acetate dose compared to the 3-month 11.25 mg [14].

Similar results were seen in the study by Baruda in which stimulated LH and FSH levels were significantly higher during therapy with both the 3.75 mg and 11.25 mg-3 month depot leuprolide doses when compared with 7.5 mg monthly, and values with 11.25 mg were relatively higher than 3.75mg [13]. However these differences were not accompanied by detectable changes in sex steroid concentrations in any of the groups.

All the other studies showed adequate LH suppression with 3.75mg/ 28 days dose. Only in a study by Brito et al adequate suppression was not achieved by 3.75mg and had hence had to be increased to 7.5 mg [22].

Study by Carel, et al. with 11.25 mg leuprorelin 3-month depot efficiently inhibited the pituitary gonadal axis in 95% of children they studied with CPP during a 6-month trial, but a short-term

evaluation was a drawback of this study.

It was noted in the studies that maximum pubertal suppression evidenced by the LH levels were achieved only by the third month of starting leuprolide mostly by 3.75 mg every 28 days [11, 20].

Leuprolide has proven to be a relatively well-tolerated drug in the patients of precocious puberty. The most common side effects noted were local site pain, rhinorrhea, headache, cough, arthralgia, pyrexia, nasal congestion, gastero intestinal symptoms [18, 19]. In Peter Lee's study side effects were observed more in the study group receiving 11.25 mg as compared to 3.75mg and 30 mg [18]. The incidence of injection site pain was 29.4% (10 of 34) in the 11.25-mg dose group and 23.7% (9 of 38) in the 30-mg dose group and very few in the 3.75 mg group.

Ji Woo Lee reported some few rare side effects with leuprolide: anaphylaxis, sterile abscess at injection site and unilateral slipped capital femoral epiphysis, there were however extremely rare reported only in one patient each in a study group of over 654 [23].

Triptorelin

Triptorelin studies are as per **Table – 2**.

Triptorelin has been widely used for precocious puberty at the dose of 3.75mg intramuscularly every four to suppress the secretion of sex hormones and has shown adequate suppression of both basal and stimulated LH values [27, 28, 29, 32, 34, 35, 37].

Liang et al studied the efficacy of 3.75mg given subcutaneously every 6weeks. They rationalized that even though the intramuscular route results in a higher plasma Triptorelin concentrations, subcutaneous injection maintains a sustained drug level after administration [31]. All their patients achieves prepubertal LH values after 6-8weeks of initiating treatment and hence reported comparable effects with IM regimen at 4-week intervals. There were some reported side effects associated with the hypoestrogenism induced by it, such as headache, sweating, and depression and also prolonged duration of menstruation recovery implying longer ovarian suppression. Hence the need for longer interval of the injection.

However all the patients taking subcutaneous injections developed a nodule about 1 cm in diameter at the injection site, which disappeared after 6-12 weeks. Liang, et al. implied that they could overcome this side effect by increasing the interval of giving the injection.

Several studies have efficacy of the 3-month triptorelin 11.25 mg formulation in children with CPP [26, 32, 33, 35]. These studies revealed that that 87.6% had suppressed LH response to the GnRH test (<3 IU/L), 3 months after initiating treatment and 92.8% of children had after 6 months. The proportion of boys and girls with LH suppression at 3 months was similar. The most frequent adverse effects noted were headache, rhinitis, and abdominal pain.

One of the benefits of starting GnRH therapy is to allow the child to achieve the target height. Several factors have been attributed to affect the end results like [28]:

- early age at treatment
- greater difference between BA and CA at the initiation of treatment
- greater decline in this difference during the course of treatment
- longer duration of treatment and lower bone age at the end of treatment

The study by Bajpai, et al. stated that girls less than 6yrs and with lower bone advancements achieved better final heights than the older girls [28].

In a study by Arrigo the best statural outcome were observed in the patients who stopped treatment at a bone age ranging from 12.0 to 12.5 years, in comparison to girls who stopped with more advanced bone age [26].

Table - 2: Triptorelin Studies.

S. no	Study	Numbers	Study duration	Age group	Bone age (mean)/ advanced	Height gain (mean)	Drop outs	Dose	Side effects	Mean LH suppression
1	Swaenepoel, et al. 1991 (Paris) [24]	35	5yrs	0.75-8.5 yrs	8.8+-6.6yrs	5.5+-1.8cm/yr	-	60ug/kg 28days	-	-
2	Hummelink, et al. 1991 (multicentric) [25]	40	3yrs		9.5+-2yrs	>2cm than predicted ht	-	75ug/kg/4weeks	-	-
3	Arrigo, et al. 1999 (Italy) [26]	71	3.9+-1.9 yrs	2.6-9.2 yrs	9.8+-1.4yrs	2.5-6cm-	-	60µ/kg every 28days	-	-
4	Cassio, et al. 1999 (Italy) [27]	46	25 months	7.5-8.5 yrs	10.2yrs	:5.4cm/yr :6.9cm/yr	2	3.75mg/28days :no treatment	-	-
5	Bajpai, et al. 2002 (India) [28]	35		2.7-7.3 yrs	8.9-10.7yrs	8.7+-1.6cm		3.75mg/28days	Nil	-
6	Carel, et al. 2004 (France) [29]	58	2 yrs	6.5+-1.5yrs	10.1+-1.5yrs	5cm/yr	-	3.75mg/28days (<20kg 1.87mg)	-	-
7	Martinez-Aguayo, et al. 2005 [30]	20	24 months	7.5 +/-0.2 years				11.25mg/3months		
8	Liang, et al. 2006 (China) [31]	46	12 months	2-yrs	6-11.5yrs	:4+-0.6cm :3.2+-1.2cm	-	:3.75mg/SC/6weeks :3.75mg/IM/4weeks	:1cm papule at site(all) :skelalgia(few)	;0.2mIU/ml :0.2mIU/ml
9	Carel, et al. 2006 (French) [32]	64	12months	8.3+-0.9 yrs	10.7+-1.1yrs	6.2+-1.7cm/year	Nil	11.25mg/3months	Headache, rhinitis, GI discomfort	<3IU/L (95%) at 12months
10	Chiocca, et al. 2012 (Italy) [33]	17	12 months	7.9+-0.9 yrs	9.8+-1.2yrs	6.4+-1.2cm	Nil	11.25mg/90 days	Headache (22%) Flushes (1%)	<3IU/L
11	Strich, et al. 2013 (Israel) [34]	32	4 yrs	4.6-11.6 yrs	>6months than CA	-	Nil	3.75mg/28days	Nil	2.7+-1.9IU/L (30/32)
12	Bertelloni, et al. 2015 (Italy) [35]	25	3.1+0.9 yrs	7.9+-0.9 yrs	10.4+_0.9yrs	2.8+-5.6cm 2.4+-4.1cm		3.75mg/28days 11.25mg/90 days	Nil	-
13	Klein, et al. 2015 (USA multicentric) [36]	45	48 weeks	2-9 yrs	140.32months	6.8cm/year	Nil	22.5mg/6months	75% nasopharyngeal, headache, URI, cough	<4.2IU/L 93% at 6months
14	Zung, et al. 2015	17	22		20.5+-	-	-	3.75mg/28d		0.59±0.33

	(Israel) [37]		months		9.3months			ays		IU/L
15	Glab, et al. 2016 (Poland) [38]	40	3.3 ± 2.3 years	>6.0 ± 1.9	9.56 ± 2.14	PAH >in less 7yrs	-	3.75mg/28d ays	-	
16	Faienza, et al. 2017 (Italy) [39]	94	3.4+-0.6 yrs	7+-0.6 yrs	10.1+-1.6yrs	8.1+-1.5yrs	-	3.75mg/28d ays	-	-

Other studies have defined the most appropriate time for stopping treatment at a bone age of 11.5 years [40]. They also reported improved height in children when GnRH analogue treatment was started before 6yrs of age.

Other studies have suggested that patients with lower LH levels had greater predicted adult height. Reasoning that greater oestradiol suppression is theoretically better, resulting in slow bone maturation, less pubertal progression and greater increases in final height [14].

While some studies have stated that use of GnRH analogues have no positive impact on the final height achieved. Cassi, et al. stated LHRH analogue have no apparent effect on final height in subjects with onset of puberty between 7.5 and 8.5 years [27]. A Spanish study also reiterated the fact that GnRH analogues do not improve the height of the subjects when used in precocious puberty [41].

However the numbers of studies not showing are far fewer than the ones benefitting from all over the globe, and hence it can be safely said that treatment with GnRH analogues do improve the final height in precocious puberty.

Some studies have evaluated the changes in weight and body composition that accompany suppression of the pituitary-gonadal axis by administration of GnRH agonists and have reported both positive and negative impact on weight gain when on therapy. Palmert, et al. used BMI, triceps fold thickness, body fat percentage using DXA analysis and correlated an increase weight gain in children treated with GnRHa, however 50% of the their study population was overweight prior to starting therapy [42].

A Turkish study showed a slight increase in BMI and moderate increase in total body fat percentage. It was interesting to find an exaggerated elevation in trunk fat mass and insulin resistance. None of the children were overweight prior to therapy in this study [43].

However few studies have contradicted this data that the study population was not properly matched [44, 45]. Wolter's study attempted to distinguish between normal-weight and overweight children and a control group of overweight children without GnRHa treatment and found no side effect of weight gain in overweight children treated with GnRHa.

A study by Robert Lanes in 2004 compared the efficacy of triptorelin and leuprolide in early puberty on the impact on final height [46]. They reported better LH suppression and more skeletal maturation delay in children treated with triptorelin, which translated to increased adult height in that group. This was attributed to the better gonadotropin suppression by triptorelin. This is the only study that compared the two drugs in a study to the best of our knowledge.

Conclusion

Our review found out that leuprolide 3.75 mg every 28 days and 22.5 mg every 3months had similar efficacy and fewer side effects compared to 11.25 mg every 3 months. However, both leuprolide and triptorelin were equally effective in suppressing puberty at 3.75 mg every 28 days, but the local side effects reported like site pain, redness and sterile abscess, were relatively more with leuprolide. Literature also reports sleep disturbances, mood swings and memory loss with leuprolide. The most commonly encountered side effect with triptorelin was weight gain in comparison to leuprolide. It has been observed that the timing of initiation of

treatment early age at treatment, greater difference between BA and CA at the initiation of treatment, greater decline in this difference during the course of treatment result in better outcomes.

While the main focus for initiation of treatment has been to achieve final target height in almost all the studies, it also equally important to take into account the emotional and social implications of early onset puberty on the child and the parents. Hence this should also be strongly considered and evaluated while deciding to initiate treatment.

After a thorough review of all the data we gathered we recommend that both leuprolide and triptorelin are at par for treatment of early puberty, either one can be used based on the ethnicity or country specific sensibilities, keeping in mind the common side effects reported and prescribing the agonist accordingly. However it is the timely diagnosis and treatment that is mandatory in such cases.

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