

# GnRH $\alpha$ STIMULATION TEST – A SERIES

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# Common indications

- Early sexual maturation.
- Delayed sexual maturation.
- Child on GnRH analogue therapy to assess adequacy of suppression.

CONVENTIONAL GnRH STIMULATION TEST	NEWER GnRH ANALOGUE STIMULATION TEST
<p data-bbox="389 596 672 638">BASAL LH, FSH</p> <p data-bbox="613 638 636 724">↓</p> <p data-bbox="389 769 792 817">IV GNRH (100ug/m<sup>2</sup>)</p> <p data-bbox="613 817 636 903">↓</p> <p data-bbox="389 948 757 989">30 MINUTE LH FSH</p> <p data-bbox="613 989 636 1075">↓</p> <p data-bbox="389 1120 815 1161">60 MINUTE LH FSH E2</p>	<p data-bbox="1169 596 1451 638">BASAL LH, FSH</p> <p data-bbox="1357 638 1379 724">↓</p> <p data-bbox="1169 769 1778 817">SC GNRH ANALOGUE (10ug/kg)</p> <p data-bbox="1357 817 1379 903">↓</p> <p data-bbox="1169 948 1451 989">4 hour LH FSH</p> <p data-bbox="1357 989 1379 1075">↓</p> <p data-bbox="1169 1120 1532 1161">24 hour LH FSH E2</p>

CONVENTIONAL GnRH STIMULATION TEST	NEWER GnRH ANALOGUE STIMULATION TEST
<p>COST OF GNRH = 6000 INR</p> <p>IV LINE</p> <p>½ day ADMISSION</p>	<p>COST OF GNRHa = 250 INR</p> <p>IV LINE FOR SAFETY</p> <p>OP procedure</p>

\* - Ref:

Rosenfield RL, Cooke DW, Radovick S. Puberty and its disorders in a female.

In: Sperling MA, editor. Pediatric Endocrinology. 3<sup>rd</sup> ed. Philadelphia: WB Saunders; 2008. p. 573-90



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**ORIGINAL ARTICLE**

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**Evaluation of GnRH analogue testing in diagnosis and management of children with pubertal disorders**

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Gnrh analogue given exogenously

4 hour assess pituitary reserve

24 hour assess gonadal sex hormone production

# Analogue testing\*

- 0 hours – baseline
- 4 hours – test the reserve of gonadotrophins – hence concentrate on the LH and FSH
- 24 hours – concentrate on the estrogen and testosterone – the gonadal steroidogenesis

\* - Ref:

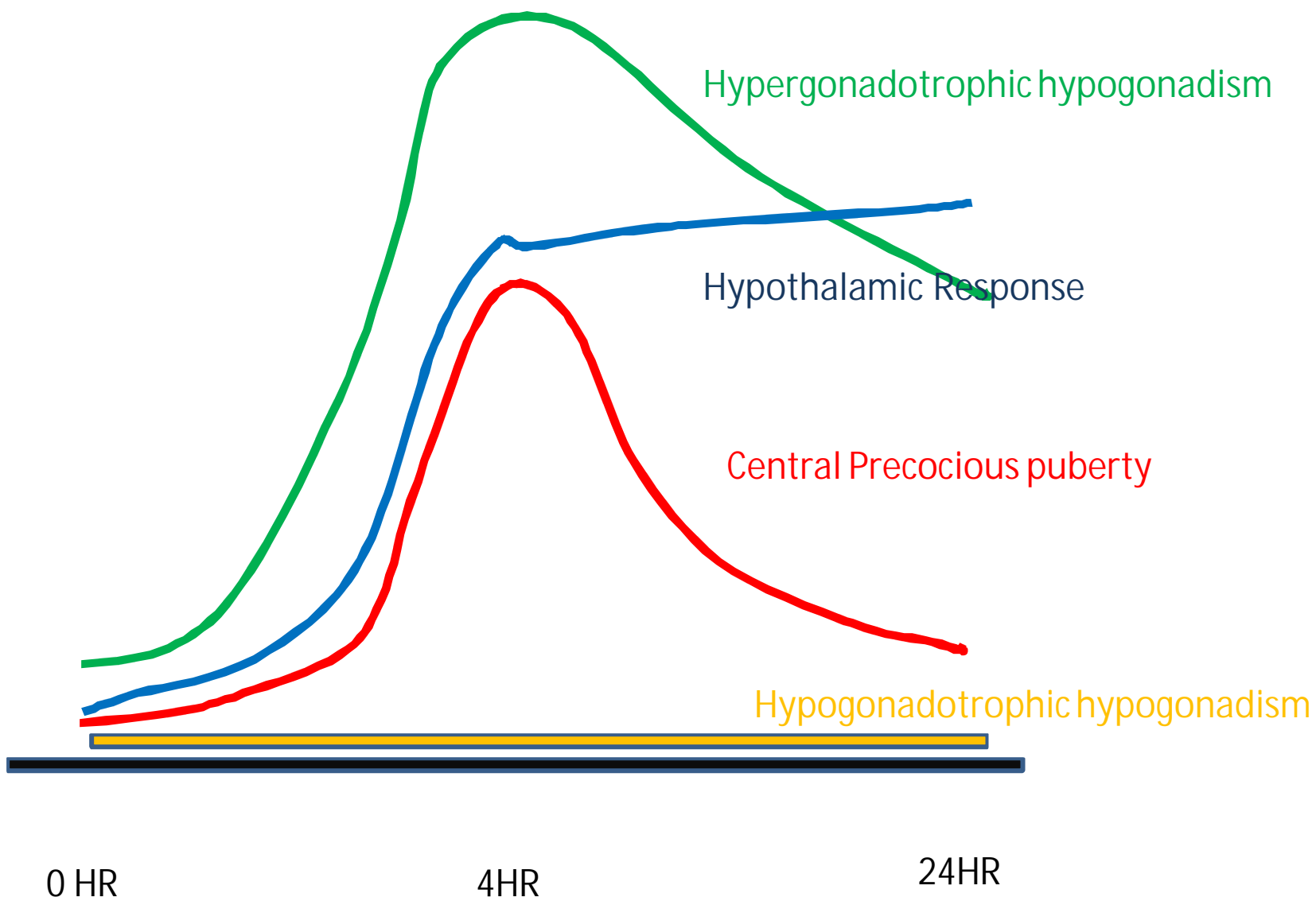
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# Use of GnRHa stimulation test

- Stimulated gonadotrophins score over basal gonadotrophin level in pubertal disorder.
- Assessment of pituitary status and ovarian reserve .
- Assess the degree of pubertal maturation.
- Stimulated gonadotrophins co-relate with the stage of puberty and the rate of pubertal progression.





# LHRH Test

## Why does my child need an LHRH test?

This test may be done for a number of different reasons. These include

- concern about early puberty
- concern about late puberty
- concern about a baby's physical development.

## What will this test tell us?

The pituitary gland is a tiny pea sized organ found underneath the brain which produces lots of different types of hormones. Hormones are chemicals which carry messages to different parts of the body through the bloodstream. Puberty hormones produced by your child's pituitary gland stimulate the release of the sex hormones (oestrogen and testosterone) from the ovaries or the testes. These sex hormones are responsible among other things, for 'switching on' puberty.

This test will tell us if the hormones produced by your child are at the normal levels for their age and development.

## What happens before the test?

Your child may eat and drink as normal before the test.

If your child is having any other test at the same time you will be given instructions about fasting if this is necessary.

We have a well-stocked playroom but do feel free to bring in your child's favourite toy or comforter.

## What are the risks of having the test?

Rarely a child may get a headache, facial flushing or mild sickness. These symptoms do not last for long.

## What happens during the test?

You must arrive on the Medical Day Care ward at 8.30am and you will have to spend the morning in hospital.

If your child is having any other test at the same time you may have to stay until the early afternoon.

When you arrive on the ward the nurse will check a few details like your child's name, address etc. They will also ask about your child's current state of health and whether they have any particular medical problems and if they have recently had or been in contact with anyone who has had an infectious

illness. They will also go over any questions you might have about the test. Your child will have his/her blood pressure, pulse and temperature taken. This is to check your child is well enough to have the test. We will also measure and weigh your child. This is so we can work out the right amount of medicine to give.

Ametop (local anaesthetic) cream will be placed on to the back of your child's hands and on the inner elbows. We call Ametop "magic cream" as it helps to numb the area before the cannula (small thin plastic tube) is put in. It takes about 30 minutes to numb the area. We will also place a clear dressing or cling film over the top to keep the cream in place.

Your child will have their cannula put in by a doctor or nurse, into a vein in the area that has been numbed. Do not worry if your child becomes upset. This is normal. It will depend on your child's age and how much they understand about what is happening. Being held in a certain way so the doctor or nurse can insert the cannula can also make them upset. It will help if you can explain to your child what is going to happen in a way they will understand. It will also help if you stay with your child so you can cuddle them. Reassure your child that they will be able to play on the ward as soon as it is over.

### LHRH (Male) Test – Assay Request Form

ID No:			
Surname:		Date of Birth:	
Forename(s):		Gender:	
Consultant:	Speciality		
Date of Test:	Ward:	Mehta ID	
Clinical Details:		Ht (cm):	
		Wt (kg):	

Time points	Time of collection		Tests requested	Sample sent (Tick and sign)
	due	actual		
0 minutes			FSH LH	
4 hours			FSH LH	
24 hours			FSH LH Testosterone	

### LHRH (Female) Test – Assay Request Form

BCH No:			
Surname:		Date of Birth:	
Forename(s):		Gender:	
Consultant:	Speciality		
Date of Test:	Ward:		
Clinical Details:		Ht (cm):	
		Wt (kg):	

Time points	Time of collection		Tests requested	Sample sent (Tick and sign)
	due	actual		
0 minutes			FSH LH	
4 hours			FSH LH	
24 hours			FSH LH Estradiol	



# CASE 1

- 17 year old girl child – No menarche.
- Delayed onset of sexual characteristics.
- Recurrent gut problems – abdominal pain and vomiting.
- Short (height at 3<sup>rd</sup> centile).
- Tanner stage: A2 P3 B3 B3 Mo.
- Arrested puberty.

# EVALUATION

- Normal thyroid function test.
- Normal prolactin.
  
- Basal LH 0.1
- Basal FSH 0.7
- Estradiol 12 pg/ml
  
- Blood values correspond to pre-pubertal status.

## QUESTIONS

THIS IS ARRESTED PUBERTY

IS IT HYPOGONADOTROPHIC  
HYPOGONADISM

IS IT OVARIAN FAILURE (EARLY)

IS IT SYSTEMIC DISEASE

DO WE NEED A MRI?

	BASAL	4 HOUR	24 HOUR
LH	0.1	5.9	6.9
FSH	0.7	9.9	15.7
E2	12		26.1



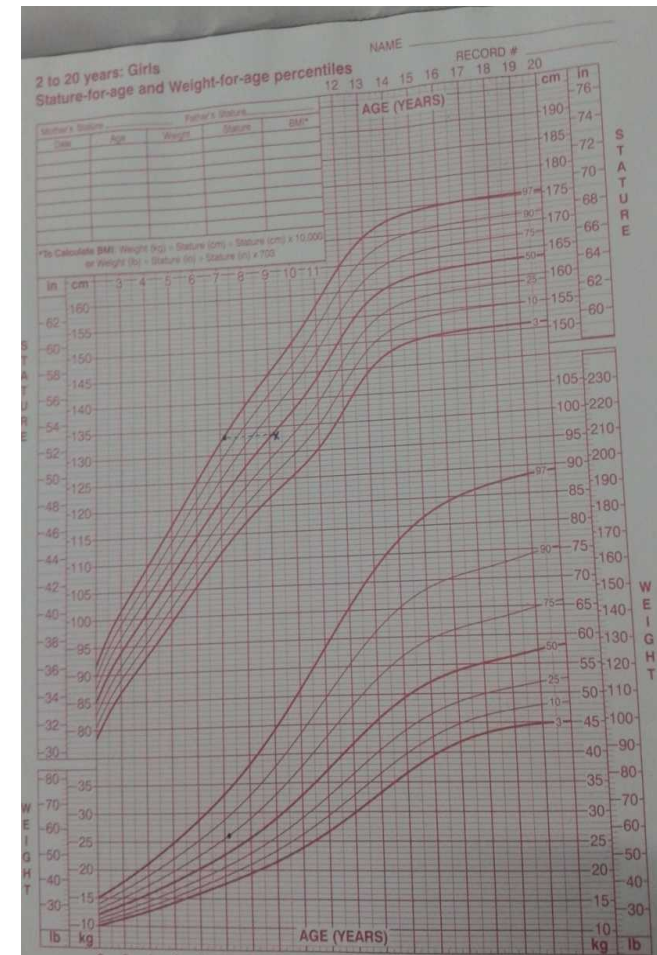
- Normal pituitary response to GnRH.
- Normal ovarian steroidogenesis (>25pg/ml)
  
- Lack of hypothalamic inhibition –
- ? ACUTE STRESS
- ? ACUTE ILLNESS
- ? ORGANIC

- CT abdomen showed focal thickening of small bowel.
- Ileal biopsy did not show any features of IBD.
- Persistent high CRP and Counts.
- Laprotomy showed stenotic distal jejunum and multiple nodes and thickened mesentery.
- HPE report = CROHNS DISEASE

QUESTIONS	ANSWERS
THIS IS ARRESTED PUBERTY	YES
IS IT HYPOGONADOTROPHIC HYPOGONADISM	NO
IS IT OVARIAN FAILURE (EARLY)	NO
IS IT SYSTEMIC DISEASE	YES – CROHNS DISEASE
DO WE NEED A MRI?	WAIT AND WATCH

# CASE 2

- 7.2 year old female child
- Onset of breast development at 6.5 years
- Height at 97<sup>th</sup> centile
- Height age 9 years
- Bone age 9.2 years
- Normal thyroid functions and prolactin
- LH 0.4, FSH 2.2, E2 <10pg/ml



# DIAGNOSTIC DILEMMA

WAIT – This is Simple Thelarche	BE AGGRESSIVE – This is Precocious puberty !
PREPUBERTAL UTERUS	LH 0.4
PREPUBERTAL ESTRADIOL <10	HEIGHT – 97 <sup>th</sup> centile
FSH 2.2	ADVANCED BONE AGE 9.2

**WILL SHE HAVE EARLY MENARCHE?**

**WILL SHE BE A SHORT CHILD?**

**SHOULD WE START GnRH ANALOGUES?**

# GnRHa stimulation test

	0hr	4 hr	24 hr
LH	0.4	0.6	0.3
FSH	1.1	6.4	4.3
E2	<20		<20

Stimulated LH > 5-10 OR

LH/FSH > 1 OR

ESTRADIOL > 50 pg/ml

Ref: Nelson Text book of pediatrics

WILL SHE HAVE EARLY MENARCHE?

NO

WILL SHE BE A SHORT CHILD?

NO

SHOULD WE START GnRH ANALOGUES?

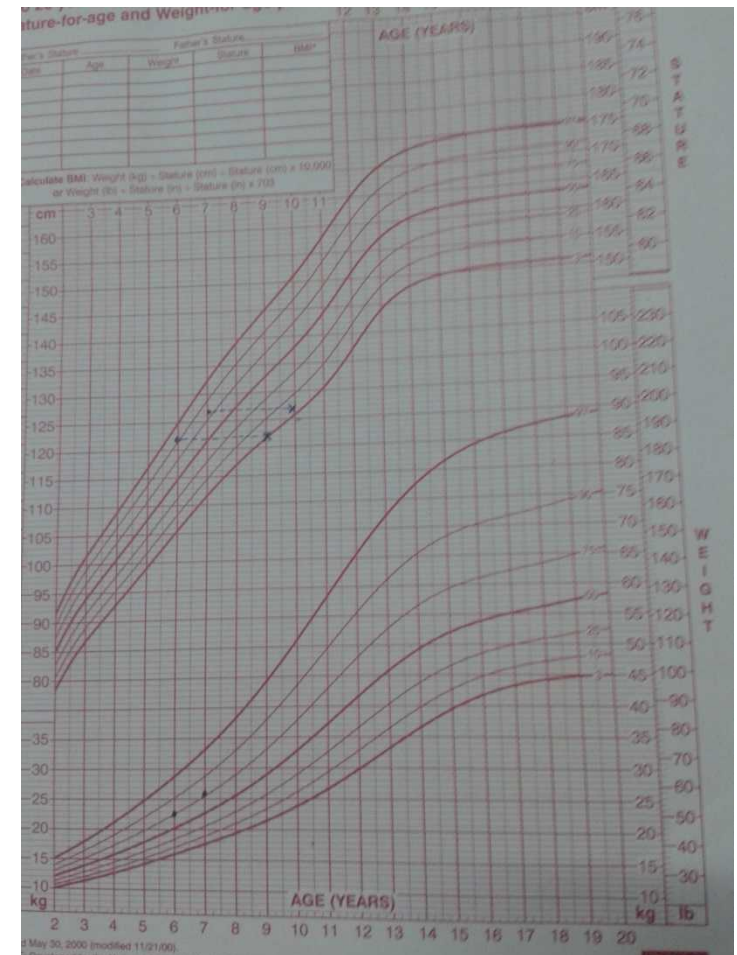
NO

# CASE 3

- 7 year old girl child with Idiopathic CPP
- On Inj Lucrin 11.25 mg sc every 12 weeks
- On good compliance
- Child weighs 25 kg
- Mother feels that the pubertal process is unsuppressed



	At diagnosis of CPP	1 year post GnRH analogue therapy
Height	122	127
Height age	7.5	8.2
Chronological age	6	7
Bone age	9.0	9.9
Tanner stage	2	3



SHOULD WE INCREASE THE DOSE OF GNRH ANALOGUES?



# Principle

- Luprolide – 2 parts – enclosed in microspheres as a co-polymer – slow release, 2 – some free leupride is also available
- Second part made use of in the test
- We check LH and E2 immediately after the therapeutic injection and assess adequacy of suppression

# Monitoring patients

	When to check	Cut off
Pituitary 2009	3 <sup>rd</sup> hour	No cut off
JCEM 2004	2hour	LH < 6.6
JPEM	40 min	LH <2
Archives of ped	2 hours	LH < 4
Sperling TB of ped endocrinology	2 hours	LH <6.6, E2 <10

- Acharya SV, Gopal RA, George J, Bandgar TR, Menon PS, Shah NS. Utility of single luteinizing hormone determination 3h after depot leuprolide in monitoring therapy of gonadotropin-dependent precocious puberty. *Pituitary* 2009;12:335-8
- Brito VN, Latronico AC, Arnhold IJ, Mendonca BB. A Single luteinizing hormone determination 2 hours after depot leuprolide is useful for therapy monitoring of gonadotropin-dependent precocious puberty in girls. *J Clin Endocrinol Metab* 2004;89:4338-42.
- Lawson ML, Cohen N. A single sample subcutaneous luteinizing hormone (LH)-releasing hormone (LHRH) stimulation test for monitoring LH suppression in children with central precocious puberty receiving LHRH agonists. *J Clin Endocrinol Metab* 1999;84:4536-40

- 3 hours post Injection - Check LH and estradiol
- Index child: LH = 0.1 IU/ml, Estradiol < 10 pg/ml

SHOULD WE INCREASE THE DOSE OF  
GNRH ANALOGUES?

NO

Rate of growth - Normal

LH and estradiol suppressed

CONTINUE THE SAME DOSE

# To summarise ...

	Case 1	Case 2	Case 3
DILEMMA BEFORE THE STIMULATION TEST	IS IT HYPOGONADOTROPIC HYPOGONADISM OR SYSTEMIC DISEASE?	IS IT PREMATURE THELARCHE OR PRECOCIOUS PUBERTY?	IS THE GNRH DOSE ADEQUATE OR INADEQUATE?
	Good gonadotrophin response, N estradiol response	FSH > LH  LH peak <10	Suppressed Lh and E2
CLARITY AFTER THE TEST	IT IS A SYSTEMIC DISEASE	THELARCHE ONLY	Adequate dose

# Take home message



- *GnRH analogue test as efficacious as conventional GnRH stimulation test*
- *Cost effective, feasible, OPD basis*
- *Must be used judiciously in pubertal disorders where there is a diagnostic dilemma*

Thank you.....