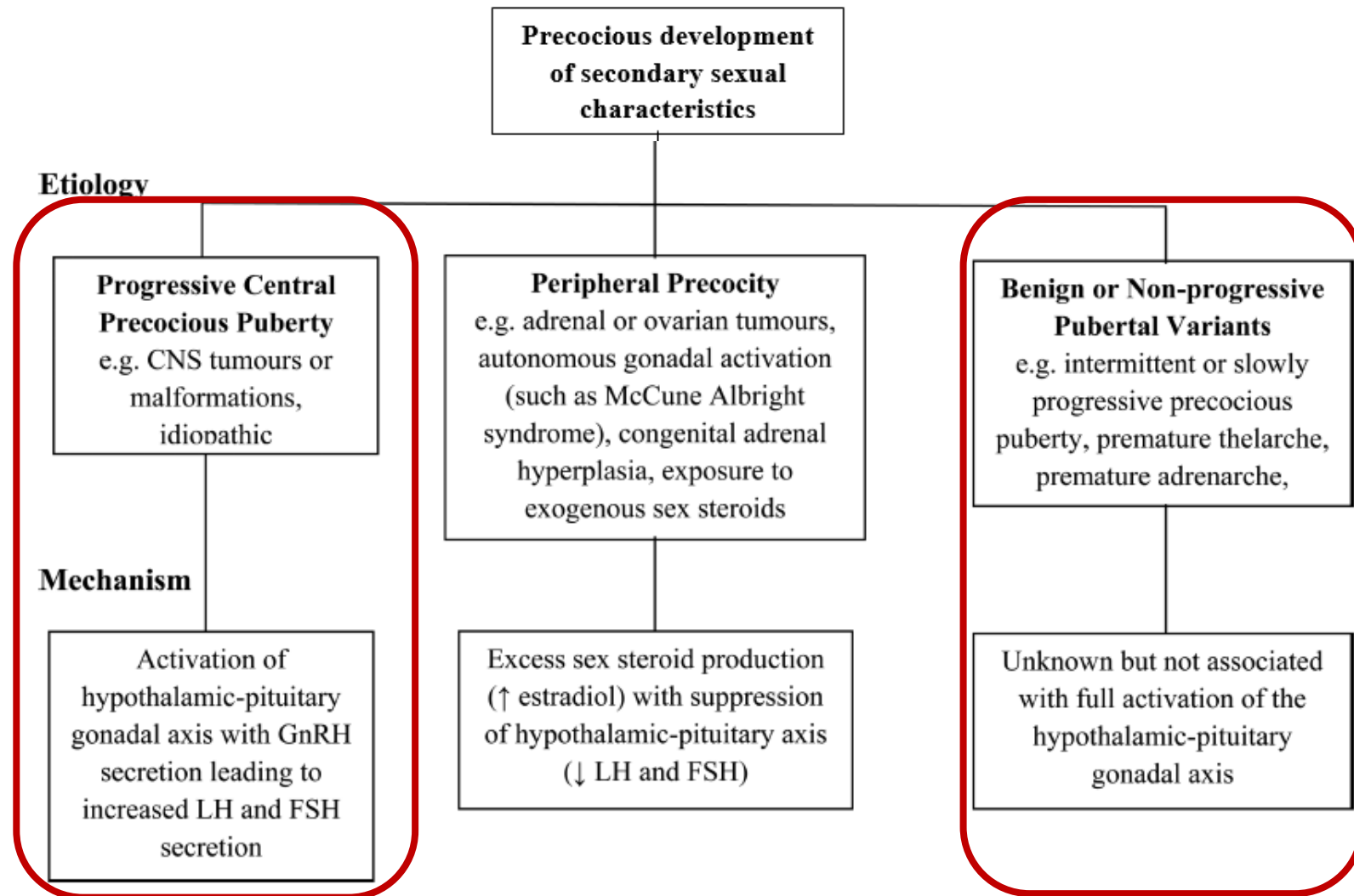


GnRH stimulation tests in the diagnosis
and management of precocious puberty:
one stimulus too many?

Disclosures

- I have no disclosures or conflicts of interest

General Paradigm



Assessment of activation of the HPG axis

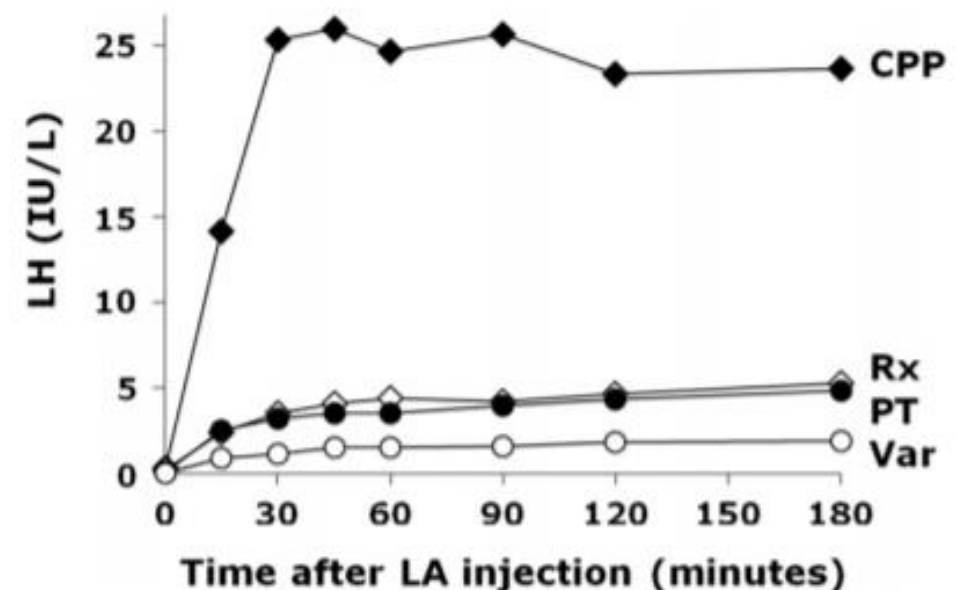
- Gold standard in distinguishing between CPP and benign variants
 - Clinical pubertal progression
- Basal LH measurements
- GnRH / GnRHa stimulation tests

Utility of GnRH/GnRHa stimulation tests in the assessment of CPP

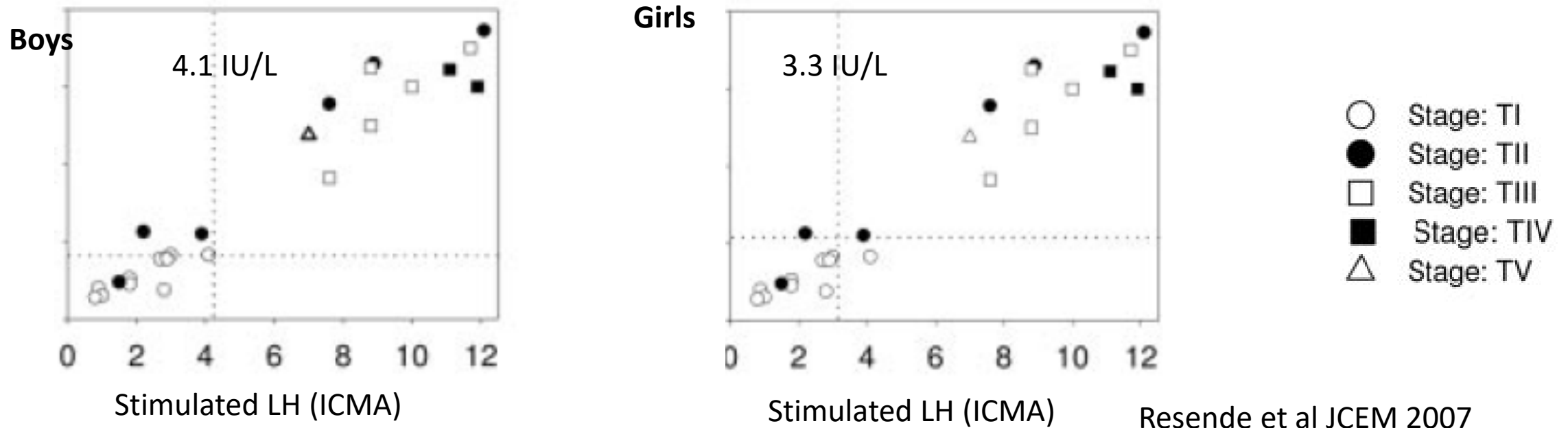
- Method

- Baseline LH, FSH, estradiol / testosterone measurement
- Leuprolide acetate (20mcg/ kg) or GnRH (100mcg)
- LH, FSH measured at 30 - 60 minutes

- Estradiol or testosterone 24 hours post



Stimulated LH levels 3.3-5 IU/L may indicate HPG activation



Resende et al JCEM 2007

- Stimulated LH of >5 IU/L 78% sensitivity and 100% specificity for pubertal progression
Sathasivam A et al Clin Endo 2010
- Stimulated LH/FSH ratio >0.66 typically seen with progressive central puberty
Oerter et al JCEM 1990

Utility of Basal LH concentrations

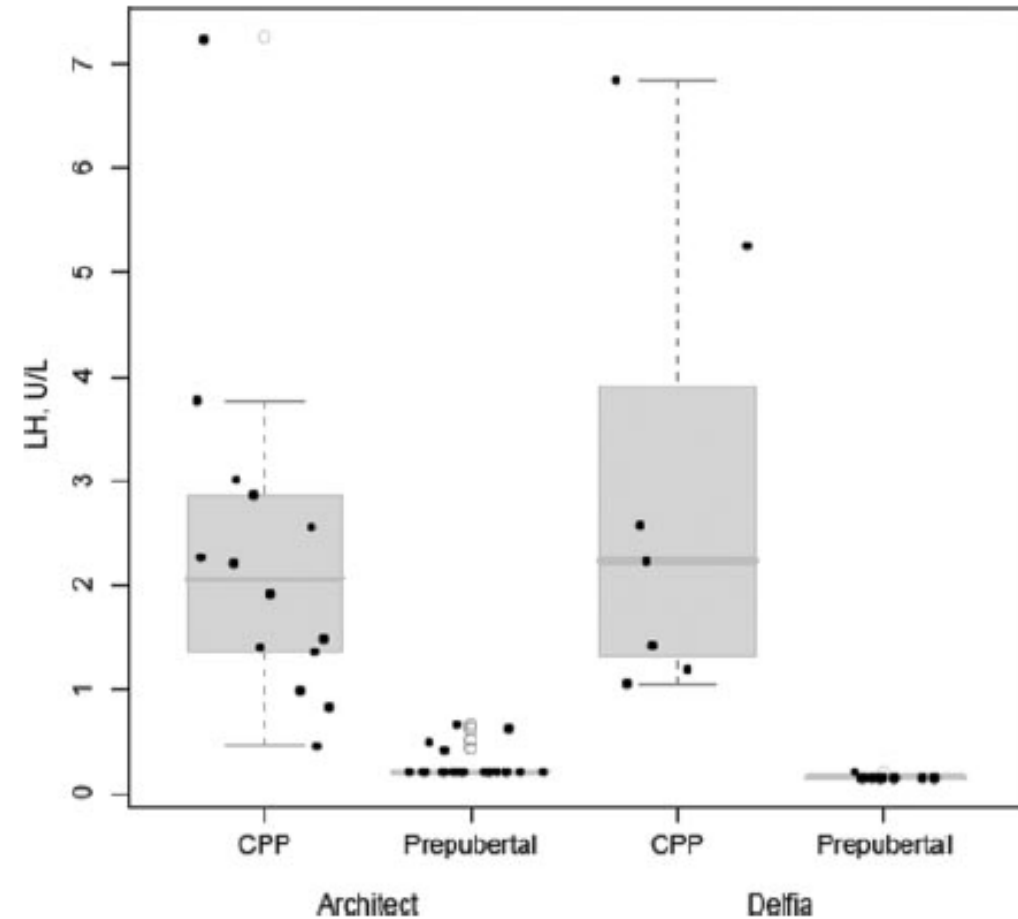
- Basal LH measurements
 - Radioimmunoassay (RIA), immunofluorometric assay (IFMA) measurements of LH have limited diagnostic sensitivity

Neely et al J Ped 1995

- Introduction of immunochemiluminescence assays (ICMA) allowed for improved discrimination

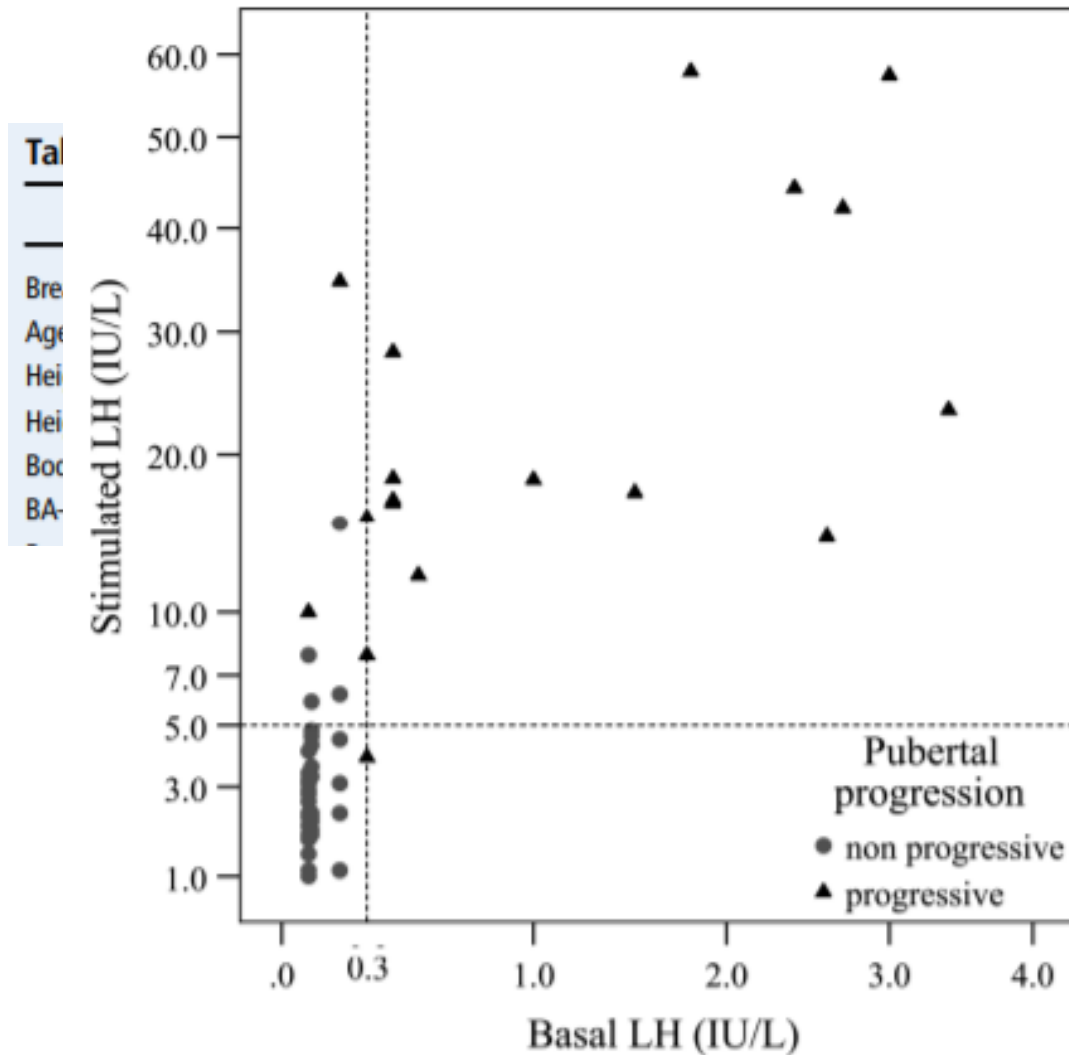
25 girls

- CPP was defined by a stimulated LH response > 5 IU/L
- Basal LH < 0.3 IU/L : prepubertal
- Basal LH > 0.83 IU/L: pubertal



Basal LH ≥ 0.3 IU/L is highly suggestive of activation of HPG axis

Harrington et al. Arch Dis Child 2013



imulation test

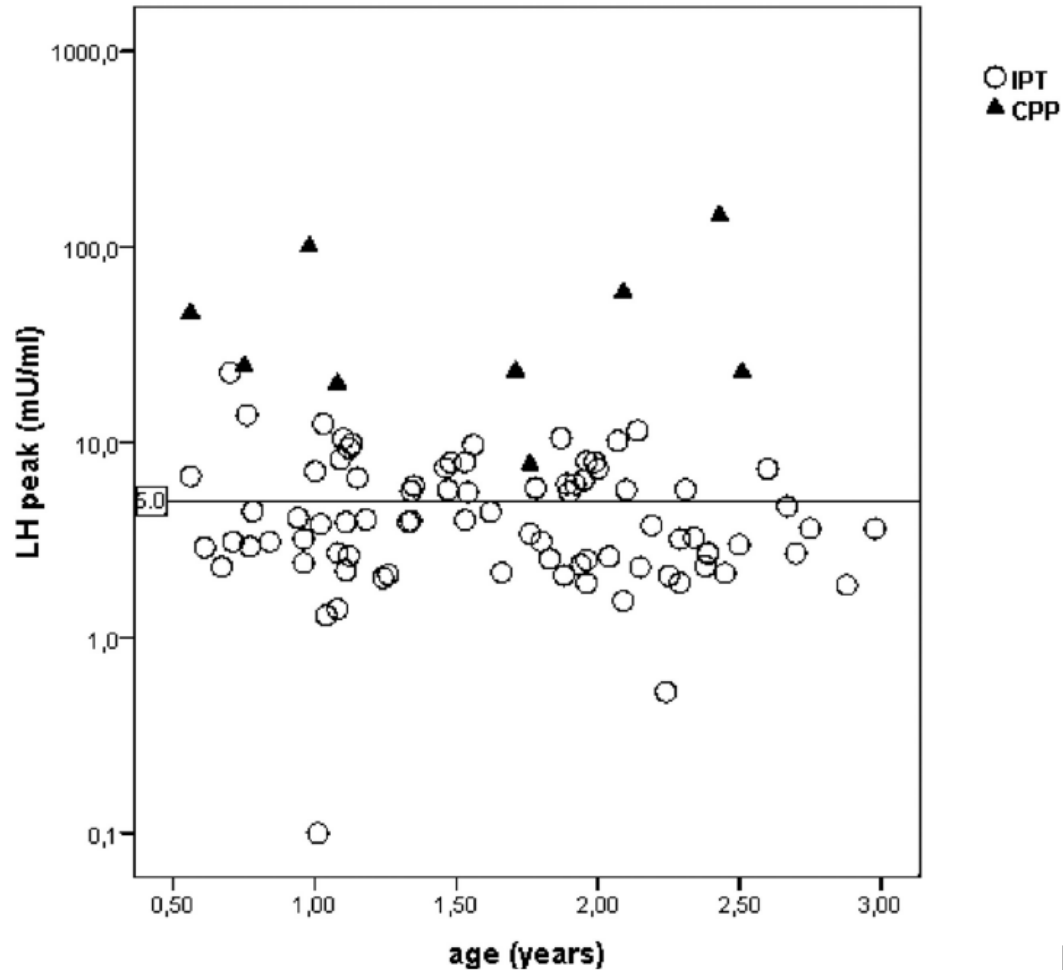
Non-progressive puberty (n=20)

n Value

Variable	Sensitivity	Specificity
Basal LH ≥ 0.3	89%	100%
Stim LH >5	95%	89%



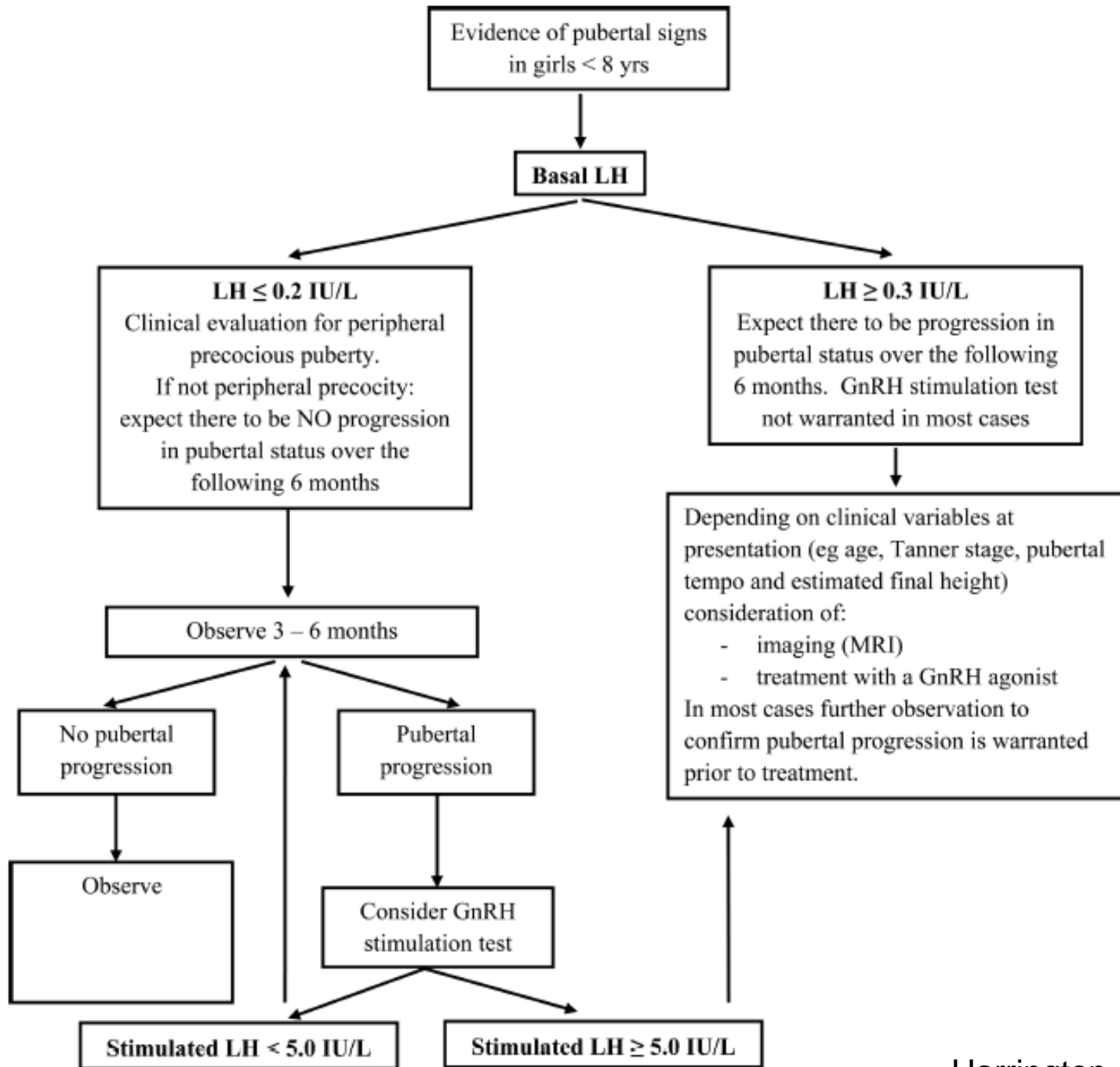
Interpretation of LH concentrations for pubertal onset can be difficult in children <2 yrs of age



IPT = idiopathic
premature thelarche

LH peak >5 to identify patients
with CPP

- Negative predictive value 100%
- Positive predictive value 23%



Choosing wisely
 2007-2010: average of 65 tests / year for investigation of precocious pubertal development
 2018-2019: average of 4 tests / year

GnRH stimulation tests to assess GnRHa effectiveness

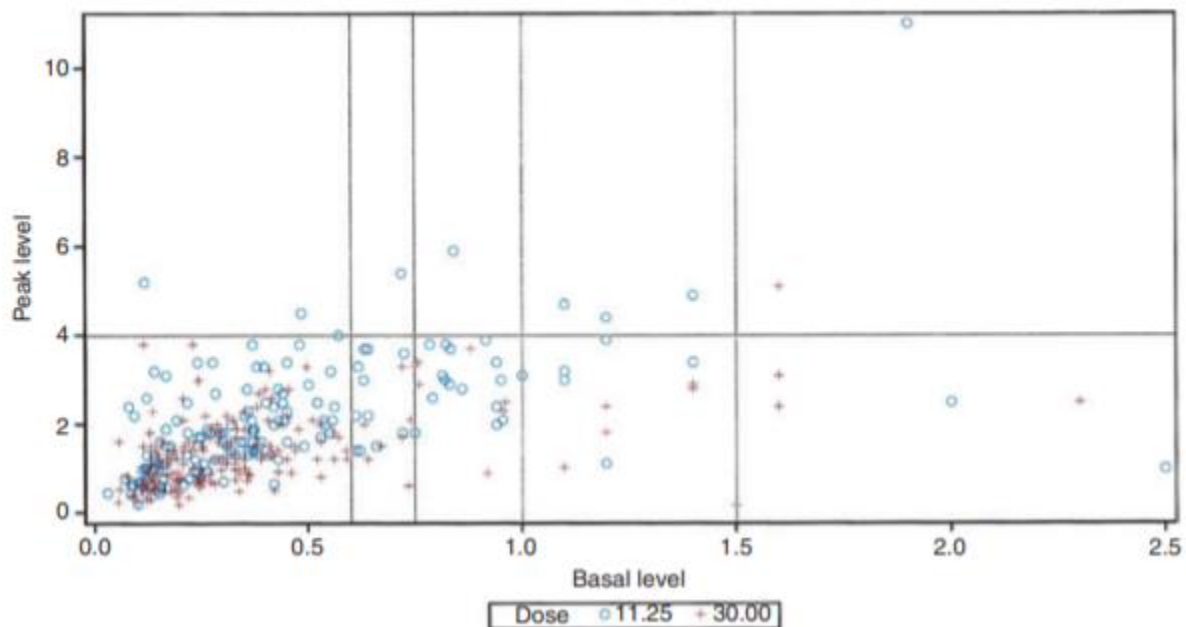
Goals of GnRHa treatment

- Slow or halt pubertal progression
 - Optimize adult height
 - Potentially alleviate associated psychosocial stress of early pubertal signs

Biochemical monitoring for suppression of pituitary-gonadal axis

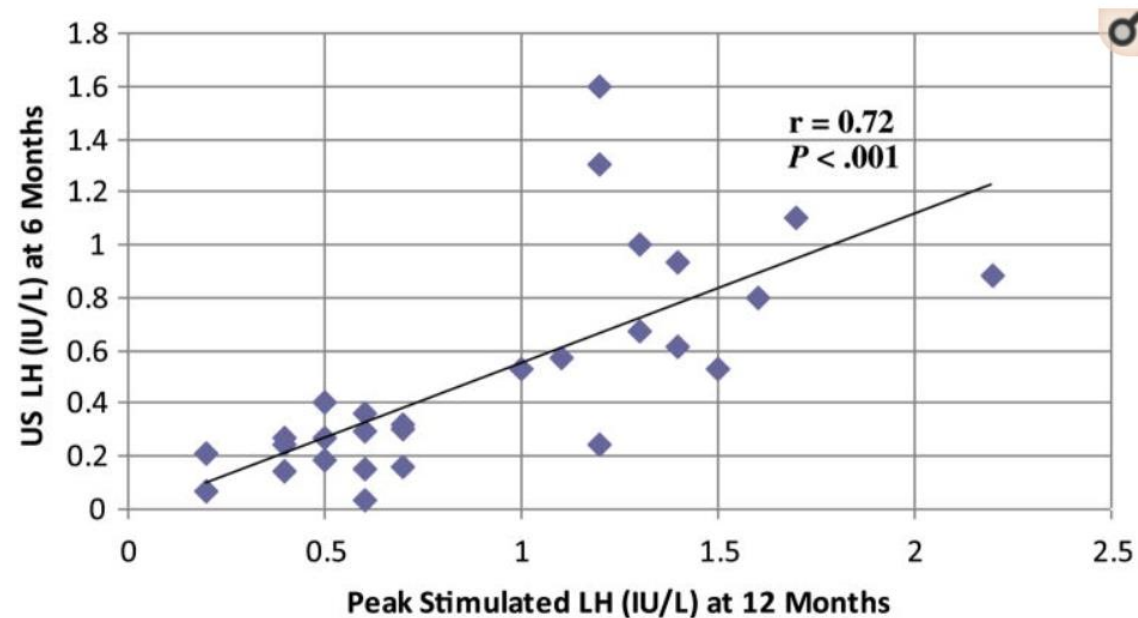
- Random LH and sex steroid concentrations
- Stimulated LH and sex steroid concentrations
- Urinary gonadotropins

Limited utility of basal LH levels to assess GnRHa effectiveness



Unstimulated LH concentration <0.6 associated with stimulated LH >4, 70% time

Lee et al. J Ped Endo Metab 2016



In children with CPP on Histrelin, random LH levels frequently remain “pubertal”

Lewis et al. J Ped 2014

Stimulated LH levels to assess GnRHa efficacy

- Stimulated LH of < 3-4 following GnRH/ GnRHa stimulation test used as end-point in dose efficacy studies.

Lee et al. JCEM 2012

Eugster et al JCEM 2007

Stimulated LH levels post GnRHa therapy

142 girls monthly Leuprolide

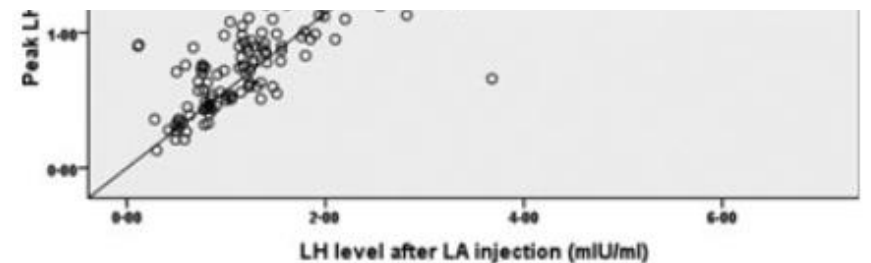
18 girls on 3.75 mg depot Leuprolide monthly

	During therapy	
	Classical GnRH test (100 µg, iv)	2 h after depot leuprolide (3.75 mg)
Basal LH (IU/liter)	<0.6	<0.6
LH peak (IU/liter)	<2.3	<6.6

Brito et al JCEM 2004



Stimulated LH 90 minutes after depot <2.5 100% sensitivity and 88% specificity



Demirbilek et al. Clin Endo 2012

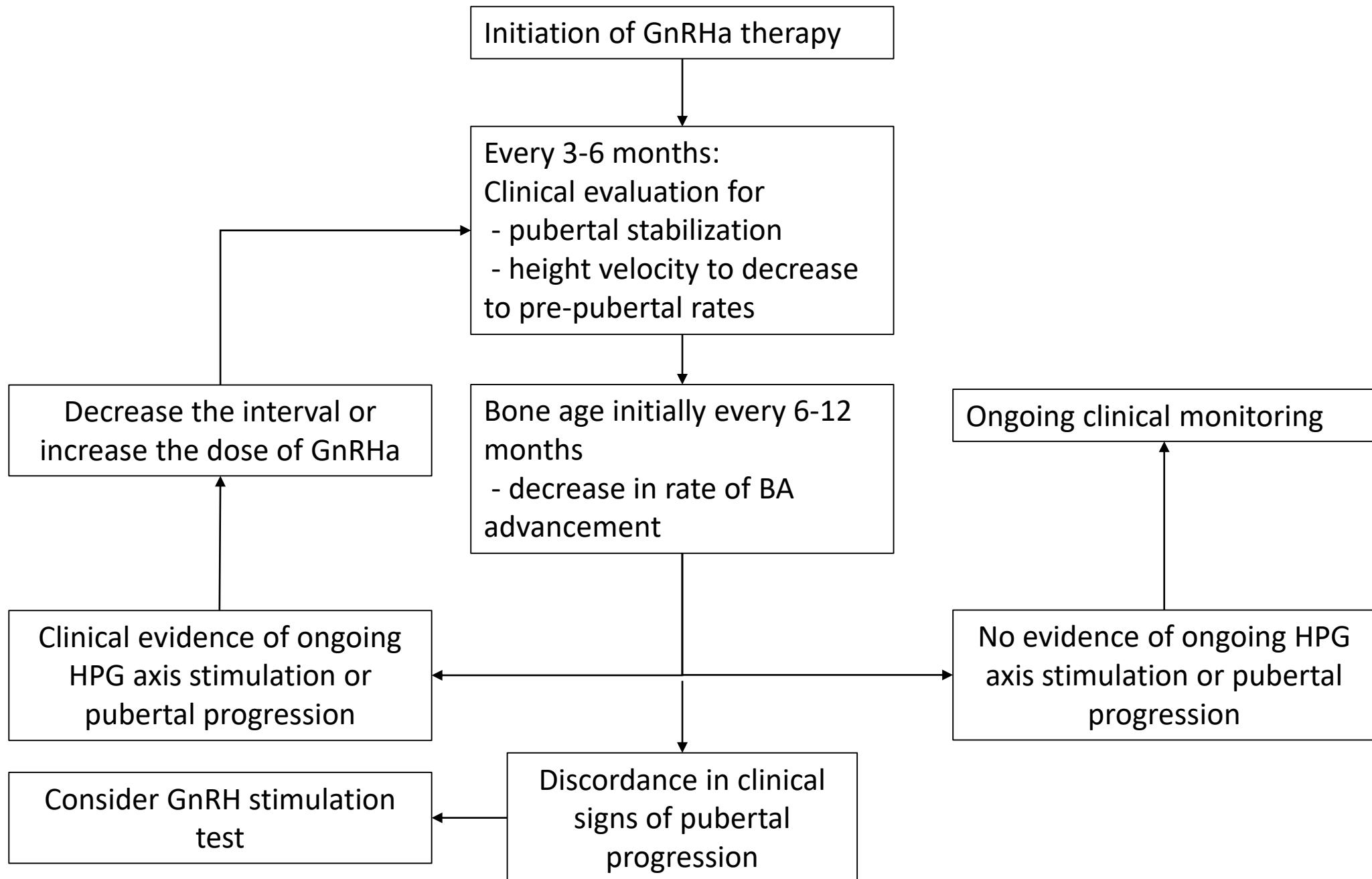
Lack of tight correlation between stimulated LH levels and clinical pubertal suppression

- Dose comparison studies

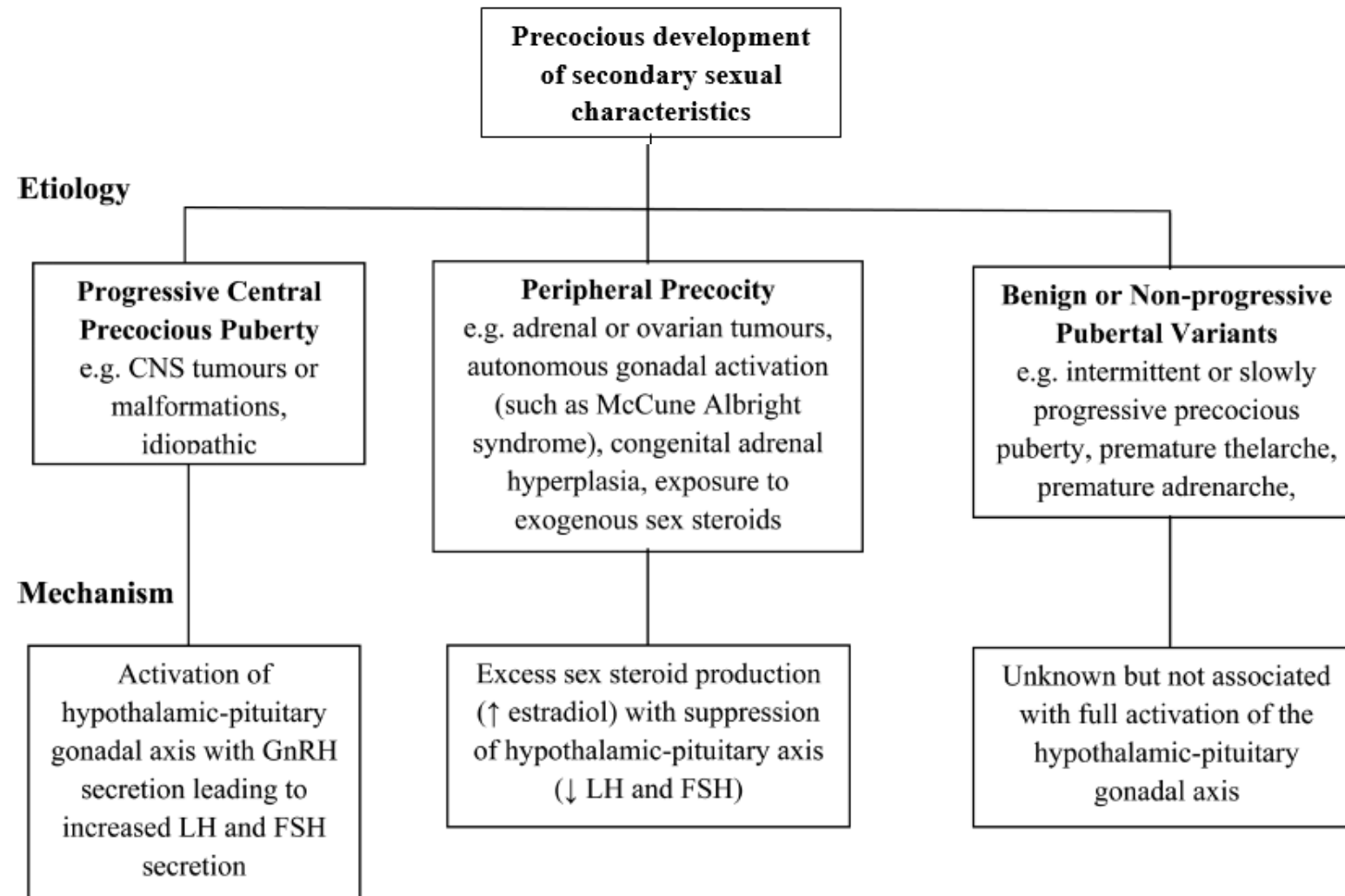
- 84 children with CPP: 11.25 mg versus 30 mg Leuprolide every 3 months
 - 9% of 11.25 mg and 18% of 30 mg group had evidence of clinical pubertal progression
 - Stimulated LH in all was <4 IU/L

Lee et al. JCEM 2012

- Lack of data demonstrating increased pituitary-gonadal suppression as measured using biochemistry correlates with increased adult height.



General Paradigm



Take home points

- Basal LH levels in children with precocious pubertal development are a good predictor for activation of HPG axis and subsequent pubertal progression
 - ≤ 0.2 IU/L likely non-progression
 - ≥ 0.3 IU/L likely progression
- Main consideration of GnRH stimulation tests is if clinical picture is not in keeping with basal LH levels
- Caution in interpreting basal and stimulated LH levels in children <2 years of age
- In children on GnRHa therapy, clinical assessment/ bone age can be the primary means to assess efficacy.

Thank you