Assessing the diagnostic value of testosterone, basal luteinising hormone and luteinising hormone-releasing hormone test in predicting pubertal progression in boys

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Introduction

Central precocious puberty (CPP) in boys:

- considered the onset of puberty (testicular enlargement) before 9 years of age
- much less common in boys than in girls
- current gold standard for diagnosis is luteinising hormone-releasing hormone (LHRH) testing

There is limited evidence base for interpreting LHRH for boys[1]

Current recommendations:

- LHRH test: positive for puberty if stimulated LH >4.1 IU/L[1,2]
- basal LH: pre-pubertal cut off <0.2 IU/L[1,2]

Objectives and hypothesis

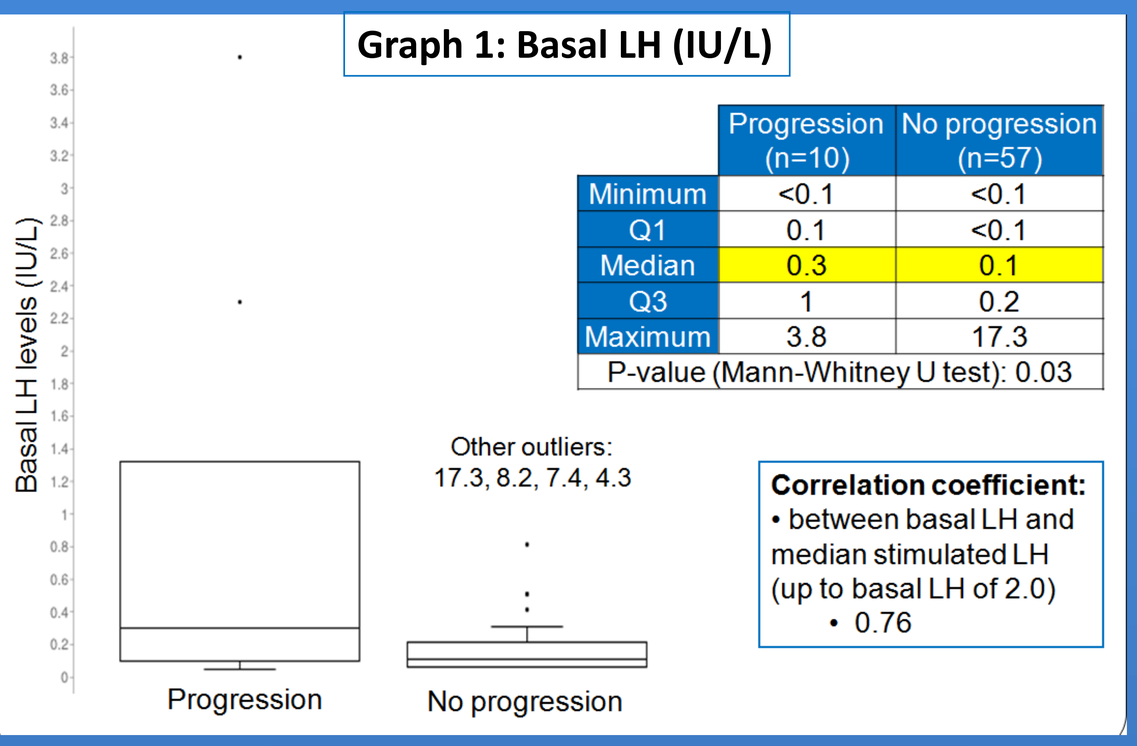
1. Test efficacy of using basal LH as well as basal testosterone for predicting CPP in boys
2. Establish diagnostic cut-offs for LHRH testing in boys

Method

- Retrospective data collection of basal gonadotropin, testosterone and LHRH test results from a regional paediatric centre between 1st January 2005 to 31st December 2013
- 67 boys: aged 2 to 10 years old
- Measure of progression into puberty was based on clinician's judgment following LHRH testing
  - 10 boys in progression group
  - 57 boys in non-progression group
- Compare differences between the two groups

Results

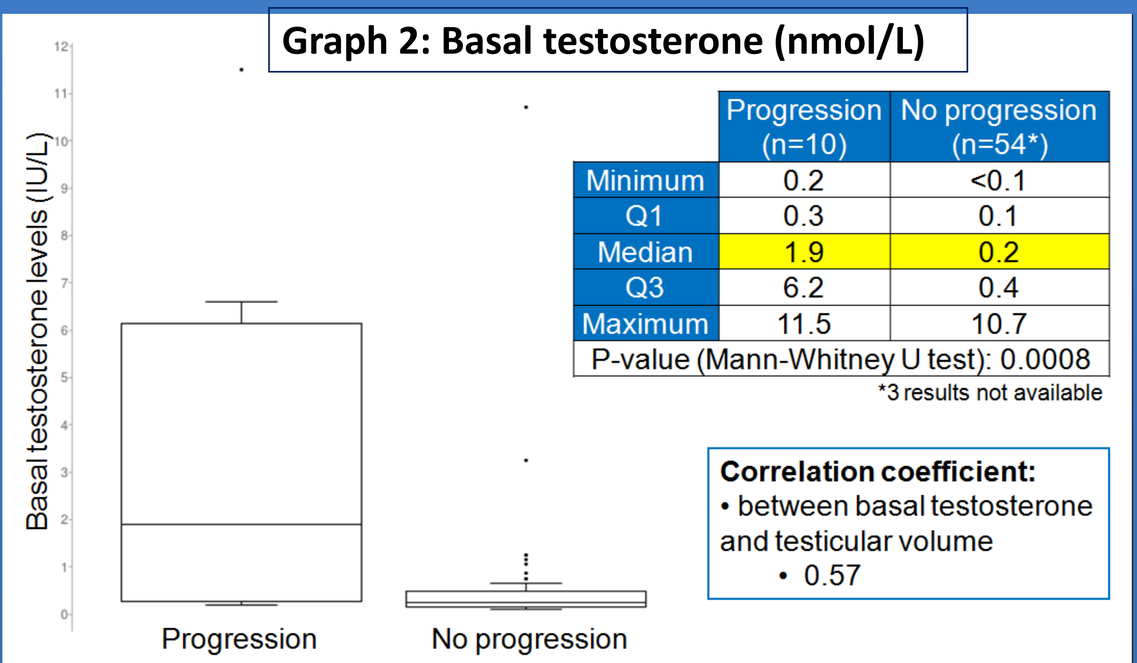
Graph 1: Basal LH (IU/L)



	Progression (n=10)	No progression (n=57)
Minimum	<0.1	<0.1
Q1	0.1	<0.1
Median	0.3	0.1
Q3	1	0.2
Maximum	3.8	17.3
P-value (Mann-Whitney U test): 0.03		

Correlation coefficient:
- between basal LH and median stimulated LH (up to basal LH of 2.0)
  - 0.76

Graph 2: Basal testosterone (nmol/L)

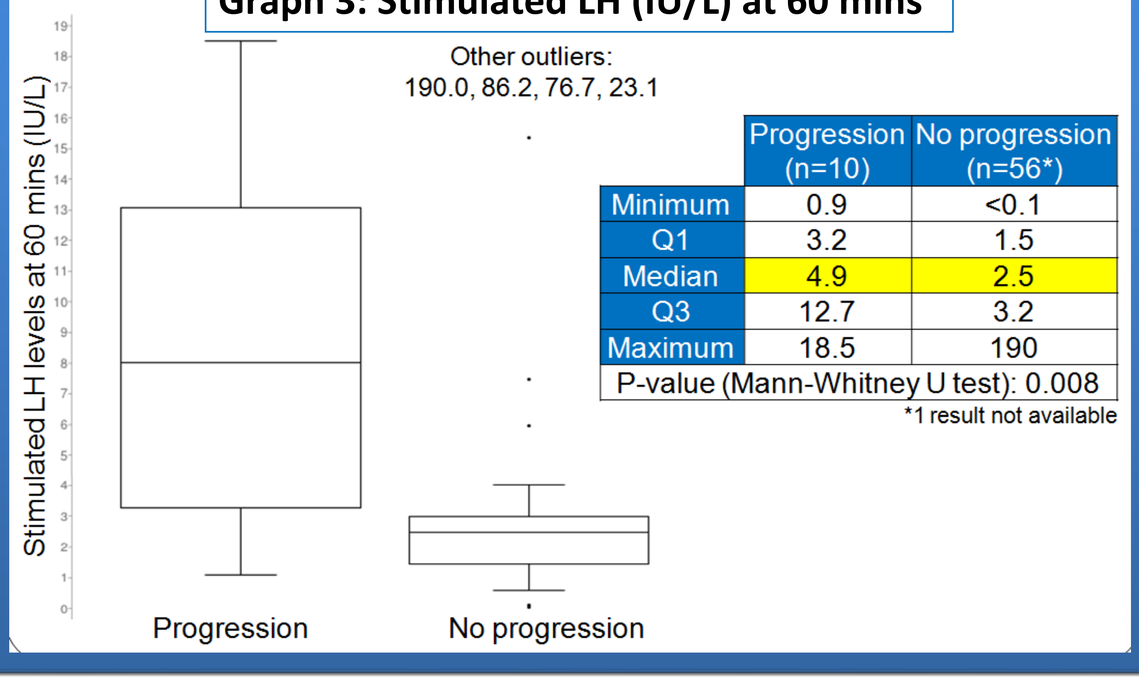


	Progression (n=10)	No progression (n=54*)
Minimum	0.2	<0.1
Q1	0.3	0.1
Median	1.9	0.2
Q3	6.2	0.4
Maximum	11.5	10.7
P-value (Mann-Whitney U test): 0.0008		

*3 results not available

Correlation coefficient:
- between basal testosterone and testicular volume
  - 0.57

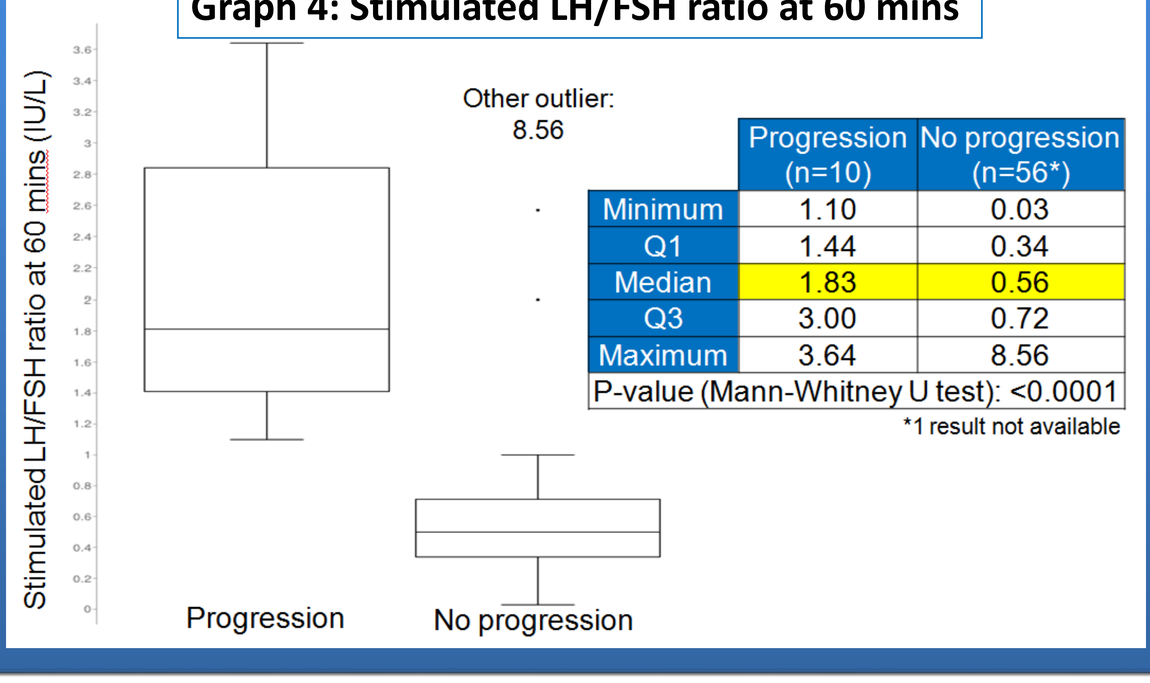
Graph 3: Stimulated LH (IU/L) at 60 mins



	Progression (n=10)	No progression (n=56*)
Minimum	0.9	<0.1
Q1	3.2	1.5
Median	4.9	2.5
Q3	12.7	3.2
Maximum	18.5	190
P-value (Mann-Whitney U test): 0.008		

*1 result not available

Graph 4: Stimulated LH/FSH ratio at 60 mins



	Progression (n=10)	No progression (n=56*)
Minimum	1.10	0.03
Q1	1.44	0.34
Median	1.83	0.56
Q3	3.00	0.72
Maximum	3.64	8.56
P-value (Mann-Whitney U test): <0.0001		

*1 result not available

	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Basal LH ≥0.3 IU/L	60.0% (26.4%- 87.6%)	80.7% (68.1% - 89.9%)	35.3% (14.3% - 61.7%)	**92.0% (80.8% - 97.7%)**
Testosterone ≥3.3 nmol/L	50.0% (23.7% - 76.3%)	**98.2% 90.1% - 99.7%**)	83.3% (36.1% - 97.2%)	**91.4% (81.0% - 97.1%)**
Basal LH ≥ 0.3 IU/L **AND** Testosterone ≥3.3 nmolU/L	**75.0% (40.9% - 92.9%)**	81.5% (69.2 – 89.6%)	37.5% (18.5% - 61.4%)	**95.7% (85.5% - 98.8%)**
Peak LH at 30 mins >5.3 IU/L	60.0% (23.4% – 87.6%)	**87.5% (75.9% – 94.8%)**	46.2% (19.3% – 74.8%)	**92.5% (81.8% – 97.9%)**
Peak LH at 60 mins >3.5 IU/L	60.0% (23.4% – 87.6%)	**87.5% (75.9% – 94.8%)**	46.2% (19.3% – 74.8%)	**92.5% (81.8 – 97.9%)**
Peak LH/FSH at 30mins >1.26	**100.0% (70.0% – 100.0%)**	**89.3% (78.1% – 95.9%)**	62.5% (38.5% – 84.7%)	**100.0% (92.8% – 100.0%)**
Peak LH/FSH ratio at 60 mins >1.0	**100.0% (69.0% – 100.0%)**	**94.6% (85.1% – 98.8%)**	76.9% (46.2% - 94.7%)	**100.0% (93.2% – 100.0%)**

Table 1: Table showing the clinical utility of different diagnostic cut-offs

Conclusion

Using basal LH and testosterone together can be a very useful screening test to rule out central precocious puberty in boys.
If a LHRH test is required; we report new diagnostic cut-offs, and have shown that the stimulated LH/FSH ratio provides the greatest diagnostic value.

Recommendations: Pre-pubertal

1) Basal LH < 0.3IU/L
2) Basal testosterone <3.3nmol/L

3) Stimulated LH at 30 mins <5.3 IU/L
4) Stimulated LH at 60 mins <3.5 IU/L
5) Stimulated LH/FSH ratio at 30 mins <1.26
6) Stimulated LH/FSH ratio at 60 mins <1.0

Pubertal response

1) Basal LH ≥ 0.3 IU/L AND Basal testosterone ≥3.3 nmol/L

2) Stimulated LH/FSH ratio at 30 mins ≥ 0.6

3) Stimulated LH/FSH ratio at 60 mins ≥ 1.0

References

[1]Carel JC et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009 Apr;123(4):e752-62

[2]Resende EA, Lara BH, Reis JD, Ferreira BP, Pereira GA, Borges MF. Assessment of basal and gonadotropin-releasing hormone-stimulated gonadotropins by immunochemiluminometric and immunofluorometric assays in normal children. *J Clin Endocrinol Metab.* 2007 Apr;92(4):1424-9