Testicular ultrasound to stratify gonadal hormone references in a Norwegian study of male puberty

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BACKGROUND

Puberty in boys is associated with pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which stimulate gonadal production of sperm and testosterone, respectively (Fig. 1). Pubertal development in boys is traditionally classified using Tanner stages I-V based on clinical inspection of genitalia (Tanner G), pubic hair (Tanner P) and testicle size. Ultrasound-based references of testicular growth in Norwegian boys are now available and this technique may provide more reliable data than Prader orchidometry[1] (Fig. 2).

Altered timing of puberty may have profound implications for public health[2]. Although data on Norwegian children are currently lacking, others have demonstrated a secular trend towards earlier puberty timing in Western girls[3]. Epidemiological research suggest that an early onset of puberty in boys is associated a with higher risk of developing testicular cancer, adiposity, cardiovascular disease and diabetes in adult life[4,5,6].

Improved and up-to-date references for pubertal development are needed to monitor timing of puberty and to identify children with an abnormally early or late start of puberty.

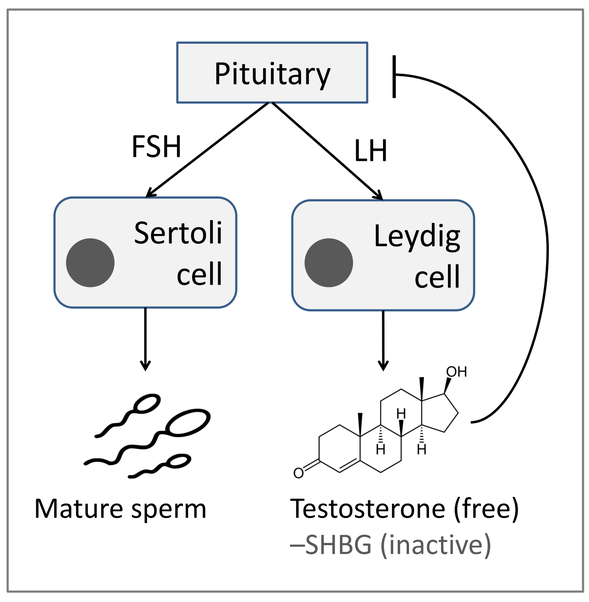

Figure 1. The male pituitary-gonadal axis

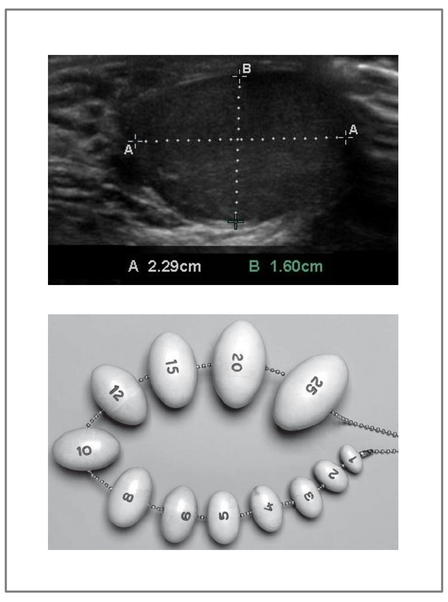

Figure 2. Testicular volume is quantifiable by ultrasound or traditional orchidometry

OBJECTIVES

- ❑ Main project «Bergen Growth Study 2» aims to thoroughly describe pubertal development in Norwegian children
- ❑ In this study, we establish references for key puberty hormones LH, FSH, SHBG and testosterone based on (i) age, (ii) ultrasound-determined testicular volume and (iii) Tanner P stages

METHODS

- ❑ Blood samples from n=451 boys 6-16 years of age were analyzed using LC-MS/MS (testosterone) and ILLUMINA-2000 (FSH, LH, SHBG)
- ❑ Metric testiclular volumes were determined by ultrasound[1]
- ❑ References were estimated with generalized additive models for location, scale and shape objects using GAMLSS package in *R*

RESULTS

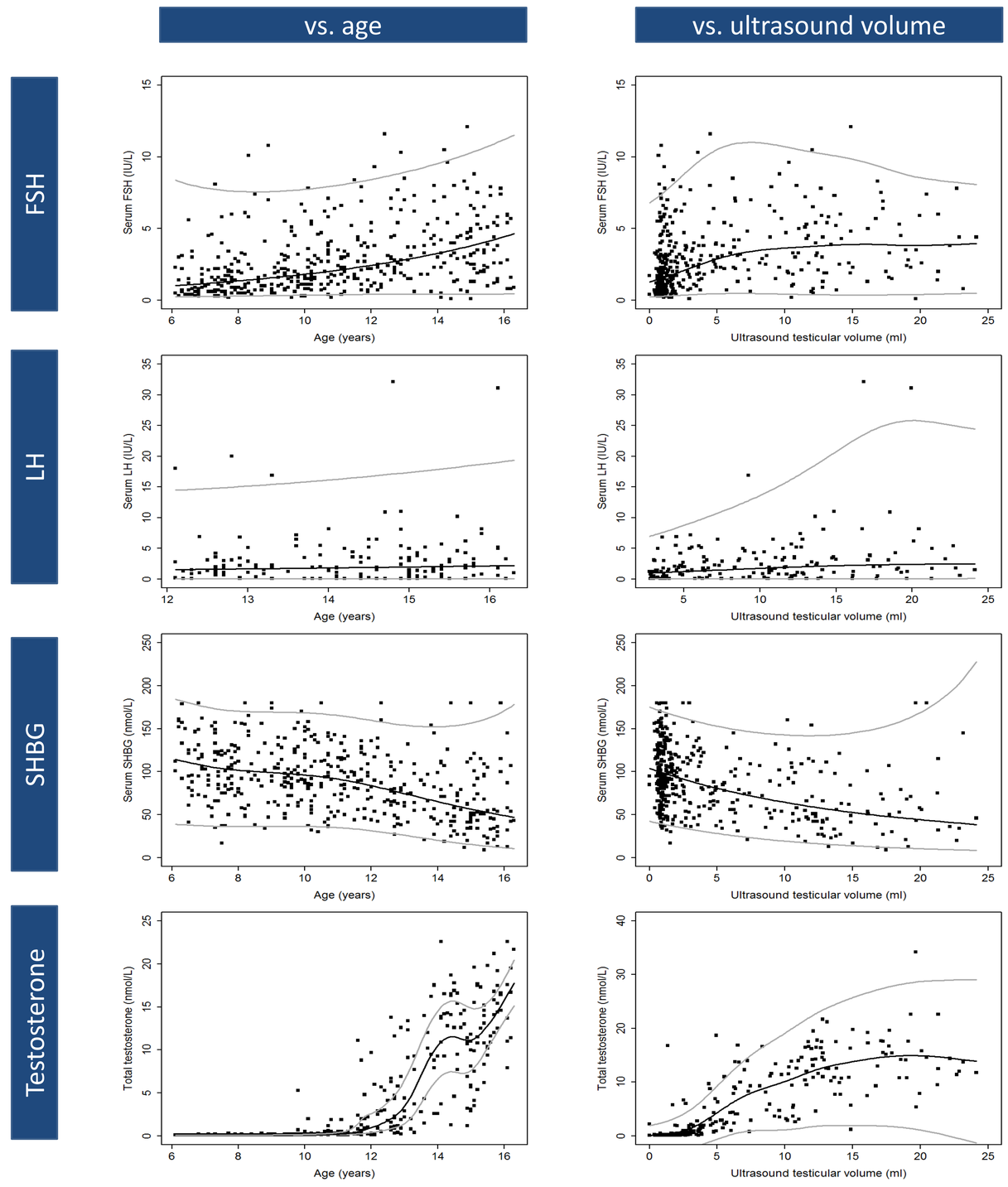

Figure 3. Generalized additive models describing hormone levels varying with (i) age and (ii) ultrasound testicular volume throughout puberty for n=420-451 boys. Continuous reference intervals are specified by median (black line) and 2.5 – 97.5 percentiles (gray lines). A cut-off of 12 years of age or pubertal-stage testicle volume ≥2.73 ml was used to fit models where indicated.

	Hormone reference intervals, Tanner P stages				
	I (n=252)	**II** (n=33)	**III** (n=29)	**IV** (n=28)	**V** (n=73)
FSH (IU/L)	1.6 (0.3-7.7)	2.5 (0.1-10.3)	3 (0.6-11.6)	3.8 (0.2-8)	3.9 (0.4-10.7)
LH (IU/L)	0.1 (0.1-6.9)	1.5 (0.1-20)	1.5 (0.1-6.9)	2.5 (0.1-16.9)	2.1 (0.1-33.4)
SHBG (nM)	99 (36-173)	89 (35-180)	74 (36-180)	52 (27-132)	53 (11-180)
TEST (nM)	0.1 (0.1-2.1)	1 (0.1-13.8)	2.8 (0.1-12.6)	11 (2.4-19.2)	14 (3.2-24.3)

Table 1. Hormone reference intervals for the five Tanner P stages, presented as median and 2.5 – 97.5 percentiles. Analytical coefficients of variation (CV) for FSH (6% @23 IU/L), LH (8% @27 IU/L), SHBG (8% @63 nM) and total testosterone (TEST; 6% @36 nM) were provided by the Hormone Laboratory.

CONCLUSIONS

- ❑ Updated hormone reference intervals are an important tool to assess children during pubertal development
- ❑ Biochemical analytes, endocrine profiles and ultrasound assessments of testicular volume are objective markers of puberty status and allow for better evaluation and clinical follow-up of children with deviating development

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