Hypothalamus-pituitary-gonadal axis in cryptorchid boys

G. Verkauskas

Vilnius University, Lithuania

Institute of Cryptorchidism Reseach, Liestal, Switzerland

Disclosures

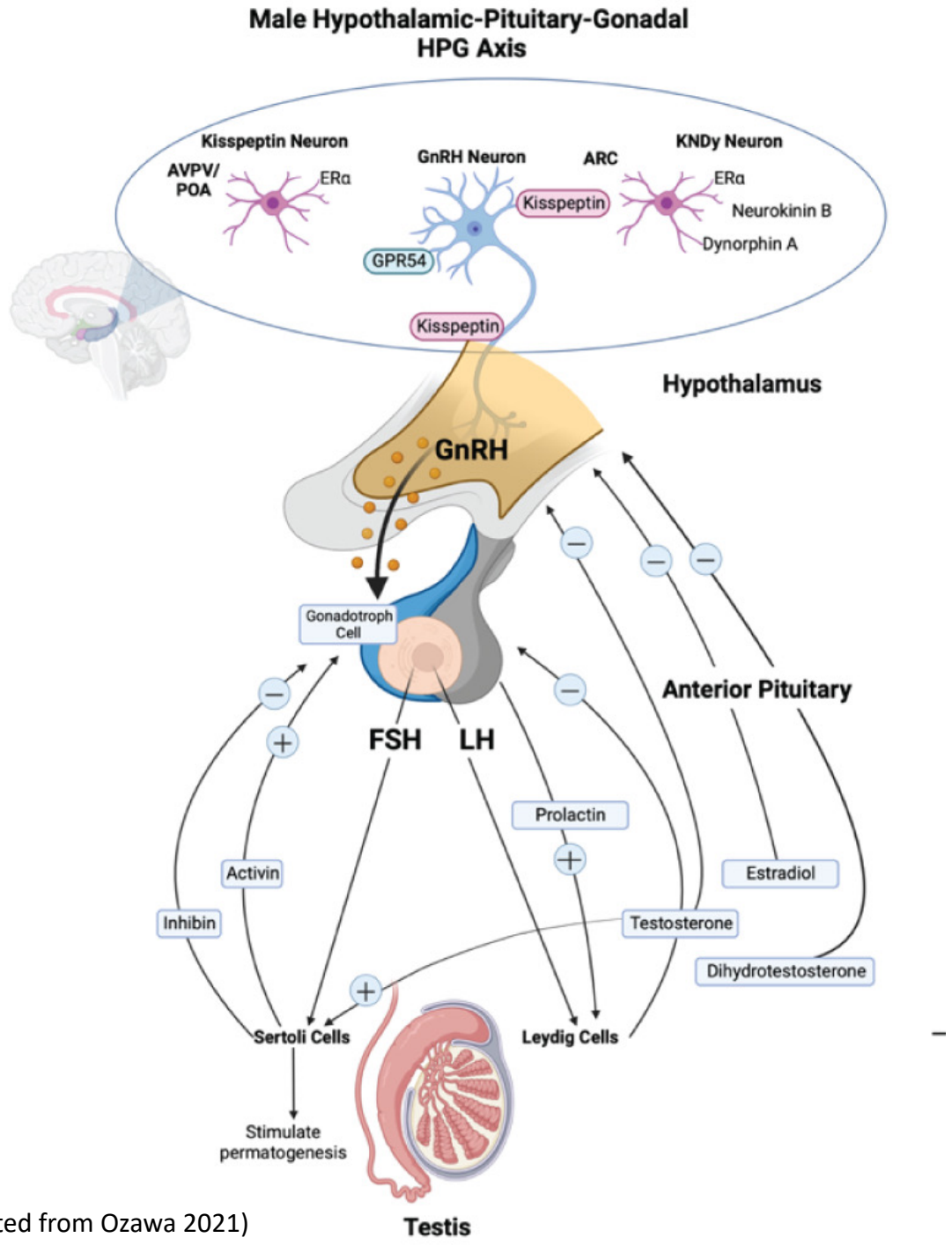


Vilnius University



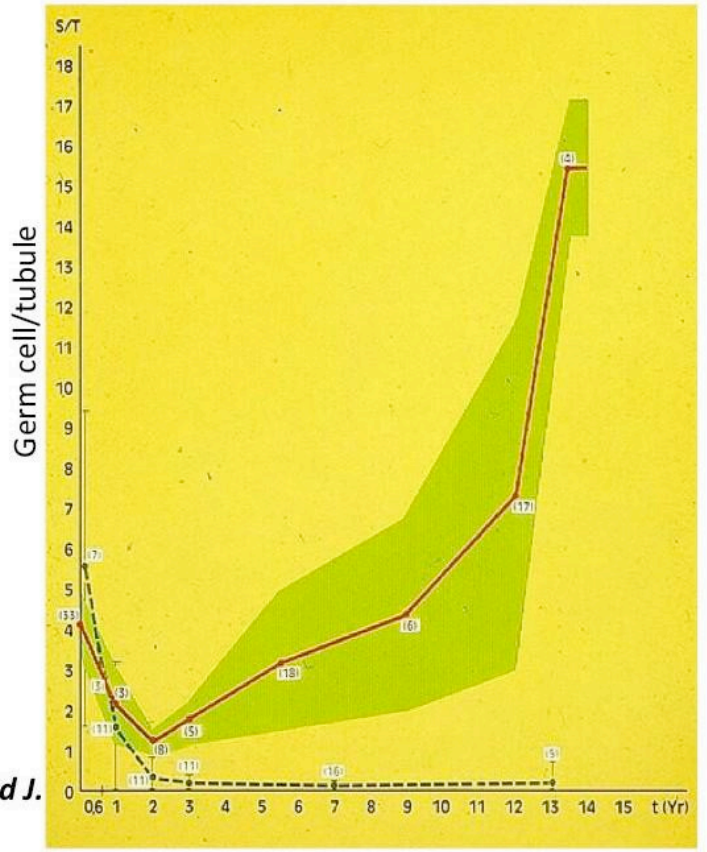
Funded by the European Union

Hypothalamus-pituitary-gonadal axis



(Image created with Biorender.com, adapted from Ozawa 2021)

Is isolated cryptorchidism a form fruste of hypogonadotropic hypogonadism or primary testicular dysgenesis?



-normal

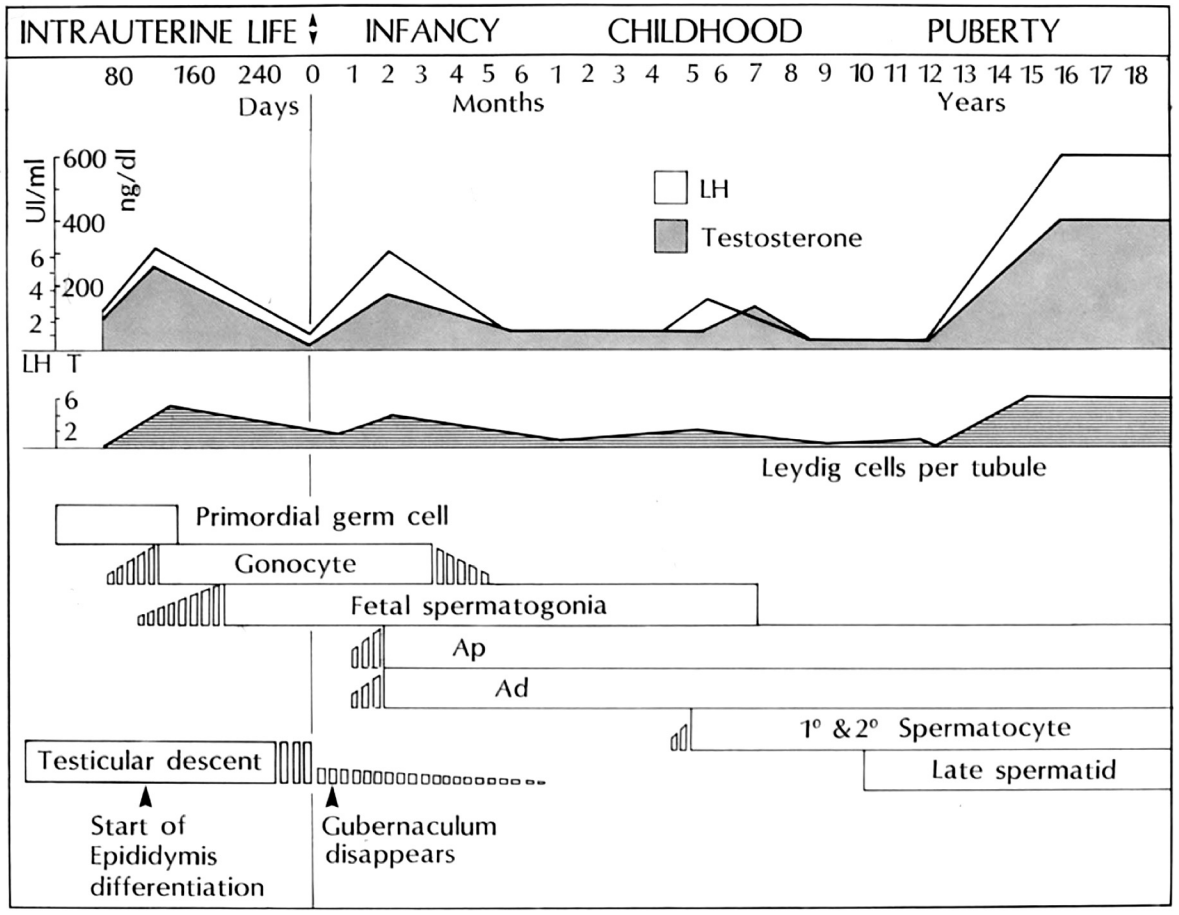
..intraabdominal

Hadziselimovic F, Girard J.
Horm Res. 1977;8(2):76-83

Dysgenetic gonad- high gonadotropins

	2 mo			1-2 years		
	FSH (IU)	LH	T (nmol/l)	FSH	LH	T
46XY partial gonadal dysgenesis (a streak and a dysgenetic testicle)	9	16.4	2,4	7,4	0,2	
Ovotesticular disorder (one ovotestis remaining)				62,7	3,7	0,08

Hypogonadotropic hypogonadism…



Similarities between isolated cryptorchidism and congenital hypogonadotropic hypogonadism

(rare heterogenous genetic disorder, deficiency in gonadotropin-releasing hormone)

Cryptorchidism	CHH
Cryptorchidism	Cryptorchidism and micropenis
Defective minipuberty	No minipuberty
Smaller testicles	Small testicles and undervirilisation
Reduced fertility	Infertility

Postpubertaly

- Both HIR and IIR groups with oligoazoospermia have been found with normal basal LH levels and the LIR group with LH levels in the hypogonadotropic range [Hadziselimovic F, Hoecht B, 2008)]. This relative FSH and LH deficiencies observed in the majority of cryptorchid patients.

Unilateral cryptorchidism- bilateral disease

- 49% of undescended testicles and 21% of contralateral had unfavorable histology. Eleven percent of boys had no Ad bilaterally at a median 39 mo.
- At the median age of 14 years- no normal testes on the cryptorchid side and only 17.4% normocellular testes on the contralateral side (Schindler AM et al 1982)

Damage is reversible

Treatment of infertility risk by GNRHa in isolated cryptorchidism at 1-6 years of age is **effective**

- Prospective randomised studies- confirmation of effectiveness after GnRH treatment (Vincel B; Spinelli C; Bica DT)
- Long term results of restored fertility in HIR cryptorchidism (Hadziselimovic F)

Minipuberty- the transient sex-specific activation of the hypothalamic-pituitary-gonadal (HPG) axis during the first 6 months of life in boys

- serum testosterone concentration at 3 months of age is a positive predictor of adult total sperm count (Scheutz Henriksen L 2022)

Minipuberty abnormal in cryptorchidism?

- Minipuberty is abnormal in true cryptorchid boys- lower LH and testosterone (Gendrel D et al)
- Unilaterally undescended testes fail to establish an adequate adult stem cell pool which normally occurs at 2-3 months of age (Huff et al)
- Postnatal exposure to androgens may be reduced in boys with cryptorchidism during minipuberty (Raivio T et al)
- Blunted LH and T responses after GnRH stimulation (Job 1977)

?

- It is not different from controls, but small heterogeneous group (Barthold JS et al)
- No functional insufficiency of the hypothalamo-pituitary-gonadal axis or disorders in T biosynthesis (De Muinck Keizer-Schrama SM et al, 1988)
- Higher FSH [1.59 (0.50–3.53) *vs.* 1.30 (0.49–2.92) at 3 months old, LH higher only in Finnish but not Danish cryptorchid boys [1.97 (0.77–5.91) *vs.* 1.75 (0.58–4.04) IU/liter and no difference in testosterone in a large cohort of Finish and Danish boys (Suomi AM)

Did historical surgery help

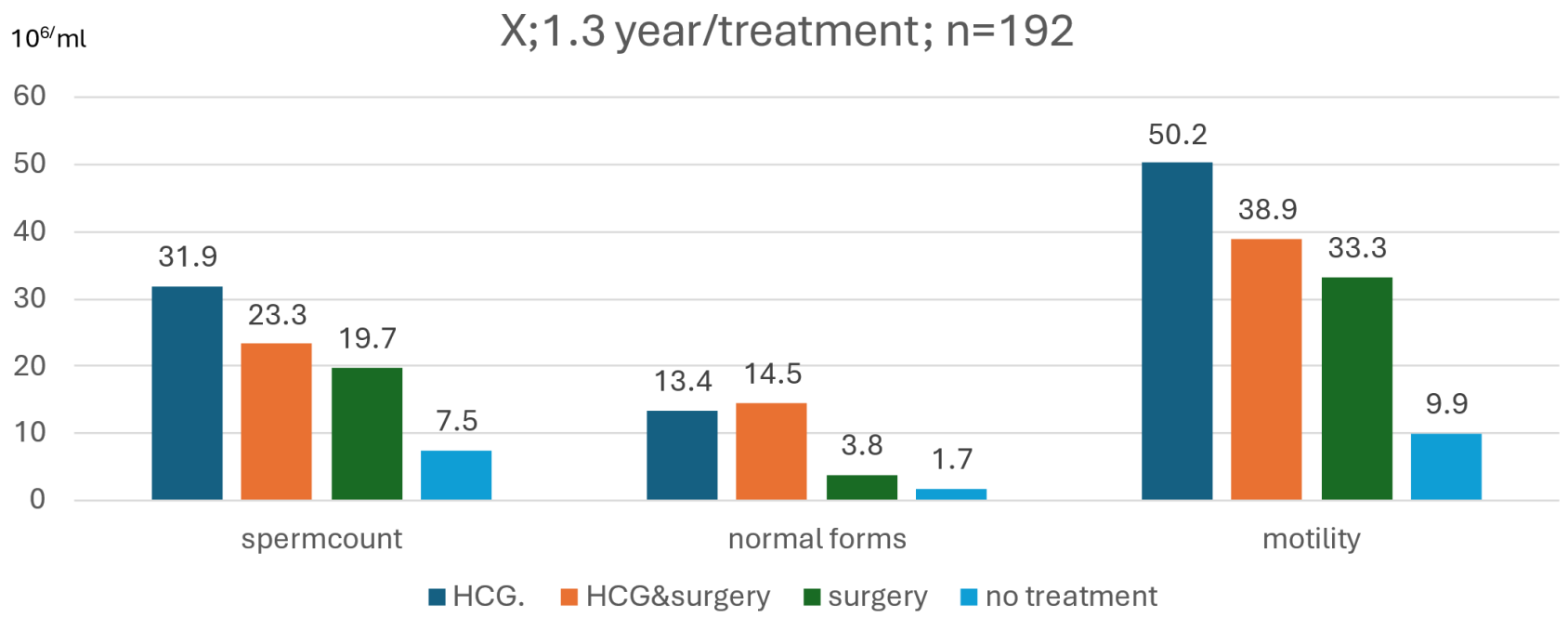
- High prevalence of obstruction histological pictures Negri et al. (2003). Prevalence of congenital epididymal or vasal anomalies is 36-43% Nistal et al., 2002
- Biopsies several months or years after orchidopexy (Schindler AM 1987)
  - Orchidopexy does not improve the number of germ cells
- Our data on long term bilaterals:
  - Sperm count was 0.42×10^6 (SD ± 0.64×10^6) ml^{-1} (Vincel B). No normal count
- Normal testosterone; LH and FSH higher but in the normal range

Early surgery improves fertility?

- <1 year: better sperm count and motility than <2 years. But most of <1 year hormonally treated and no difference in oligoazoospermic proportions (Feyles F et al 2014)
- <1 year: improves Inhibin B, later not. 25 % remain unimproved (Hildorf S 2021)
- Early orchiopexy improves subsequent testicular development and spermatogenesis in the experimental cryptorchid rat model (Mizuno K)

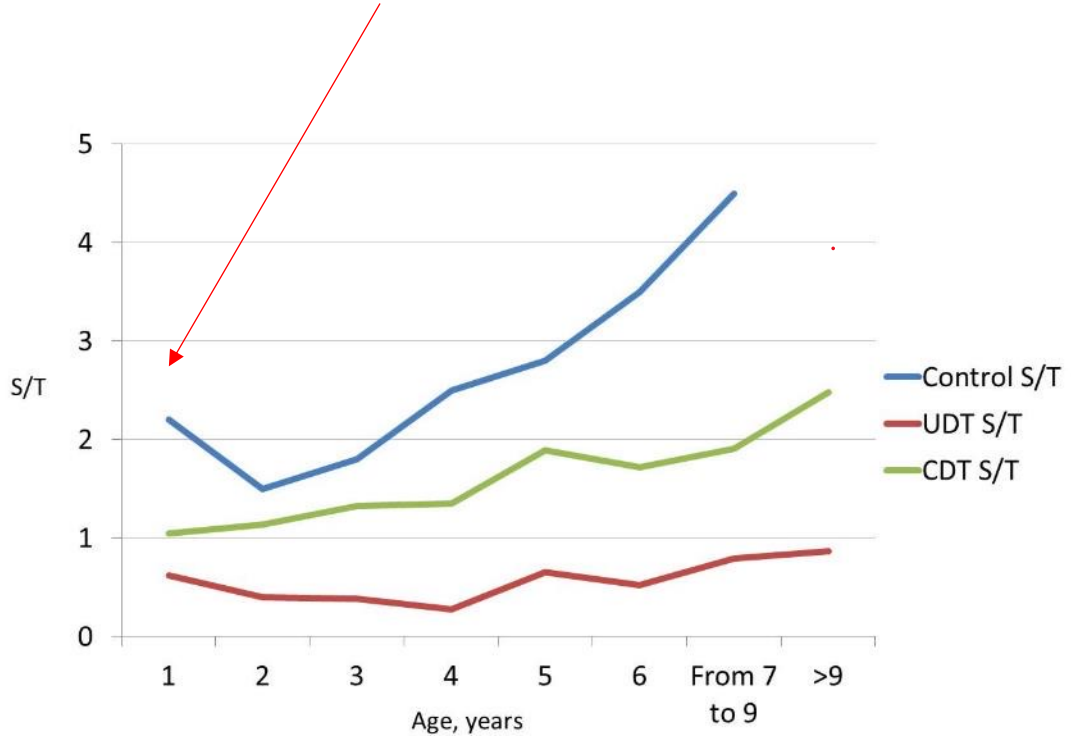
Response to treatment

A 16-year follow-up evaluation of the fertility of cryptorchid patients after immediate vs delayed vs. combined hormonal therapies



Bartoletti R et al. Reprod Biol Endocrinol. 2022 Jul 14;20(1):102

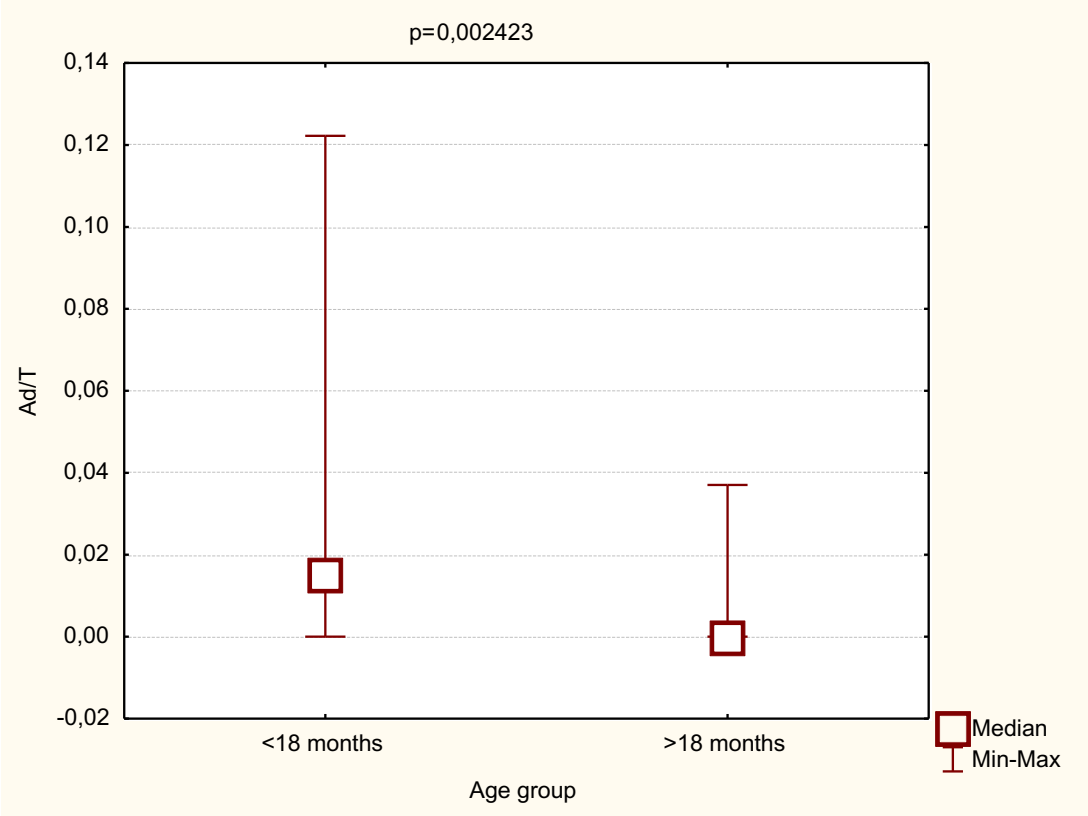
Early surgery helps, but does not restore the damage made by the earlier consequences of HPG axis dysfunction?



Changing S/T (median) in the undescended testis (UDT), contralateral descended testis (CDT), and control group with age. (Hadziselimovic and Herzog 1990)

Timely start of infertility prevention

- Significantly higher median Ad/T in the group under 18 months of age.
- Postpubertal treatment of infertility is possible but less effective because of reduced germ cell pool. Pubertal activation of hypothalamo-pituitary axis is not enough



Rationale for treatment during mini-puberty

- Serum testosterone concentration at 3 months of age is a positive predictor of adult total sperm count (Scheutz Henriksen L et al. 2022)
- Start of treatment at the time of minipuberty in CHH is effective in treating cryptorchidism and micropenis (Papadimitriou et al. 2019; Lambert and Bougnères 2016)
- Systematic review provides robust evidence to support the efficacy of gonadotropin therapy in stimulating clinical and biochemical outcomes of mini-puberty in male infants with CHH (Rhys-Evans S et al. 2024, **European Consensus Statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment**)

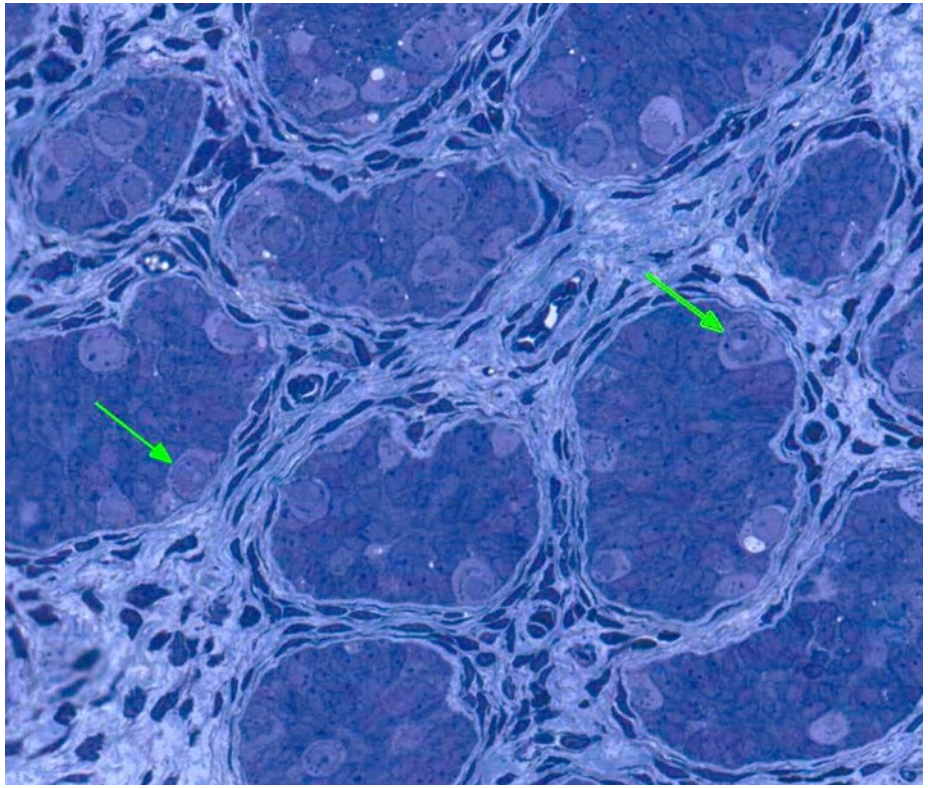
Aim of prospective study

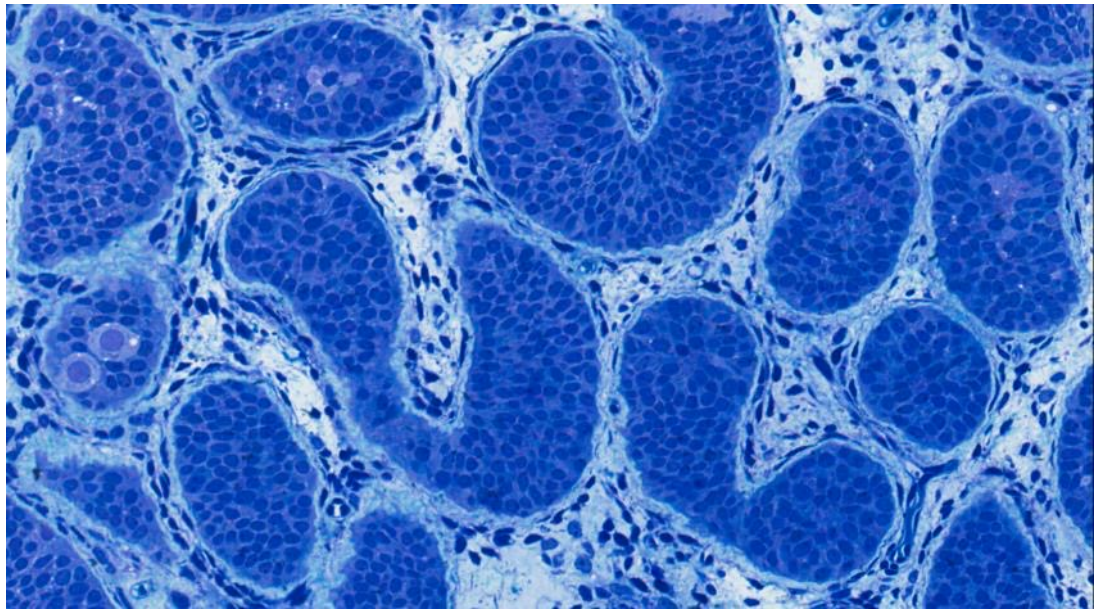
- Histological and hormonal evaluation of our cryptorchid patients before the start of the treatment
- Randomised treatment...

Materials and Methods

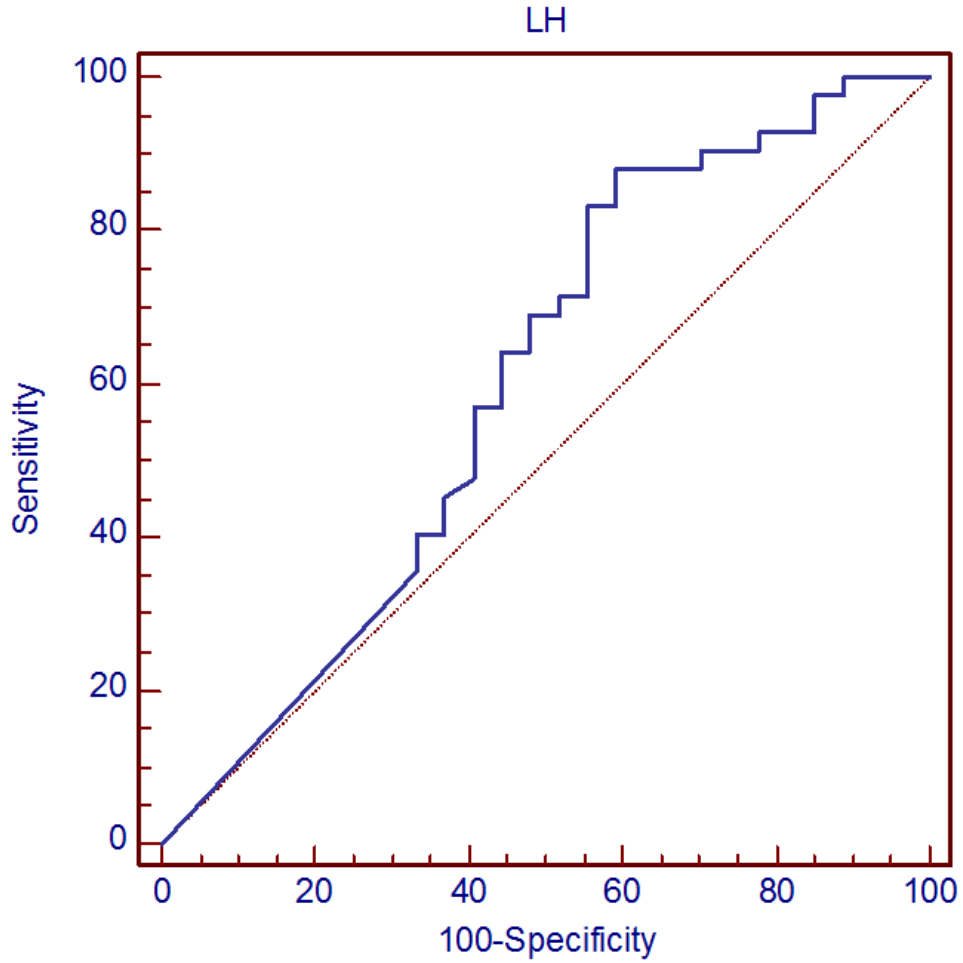
- 71 boy operated for cryptorchidism at the median age 15 mo included prospectively
- At the start of anesthesia - LH, FSH, testosterone and Inhibin B
- Biopsy of the ipsilateral testis during orchidopexy
  - TFI, Ad/T

2 subgroups of cryptorchidism- LIR, HIR



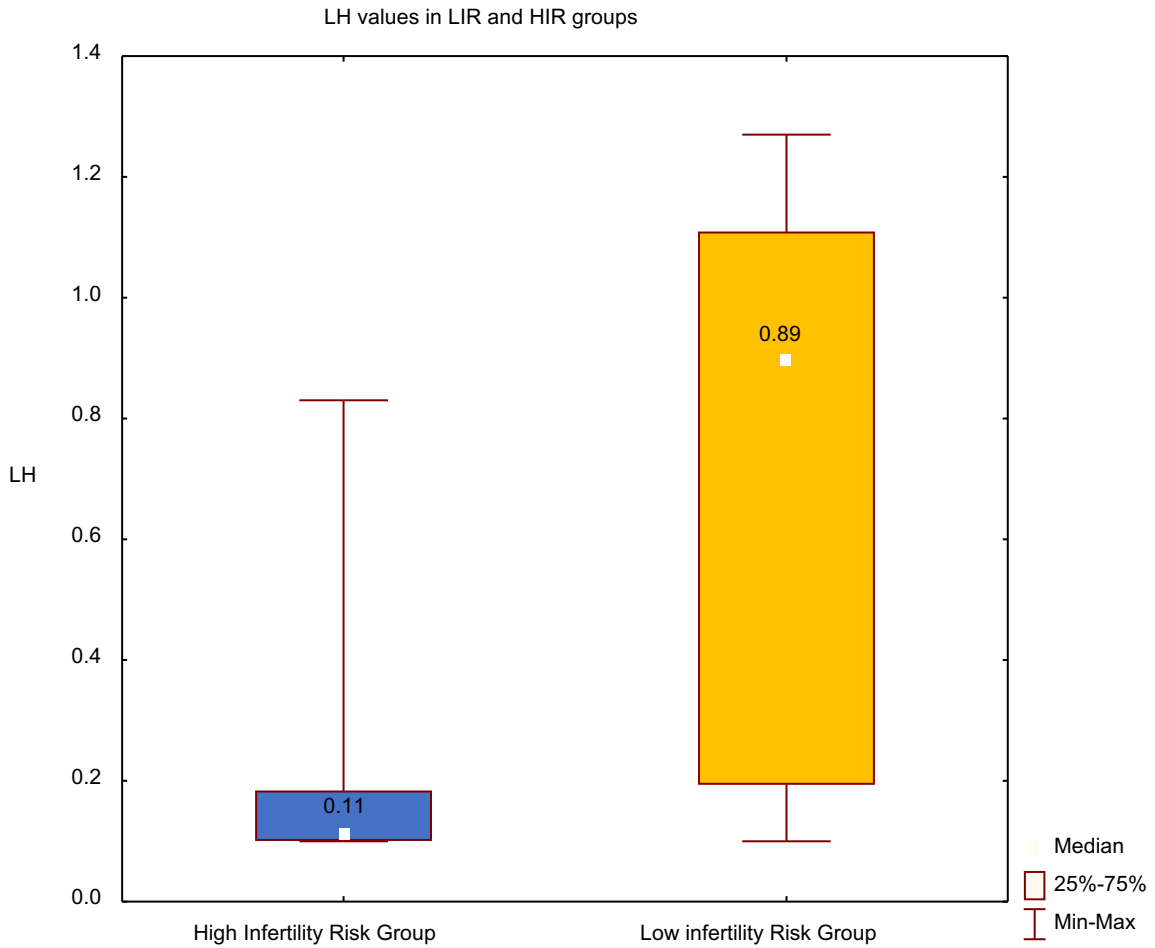


Analyzing ROC curves we found low diagnostic value of FSH, LH, testosterone and Inhibin B concentrations for predicting high infertility risk (no Ad spermatogonia).

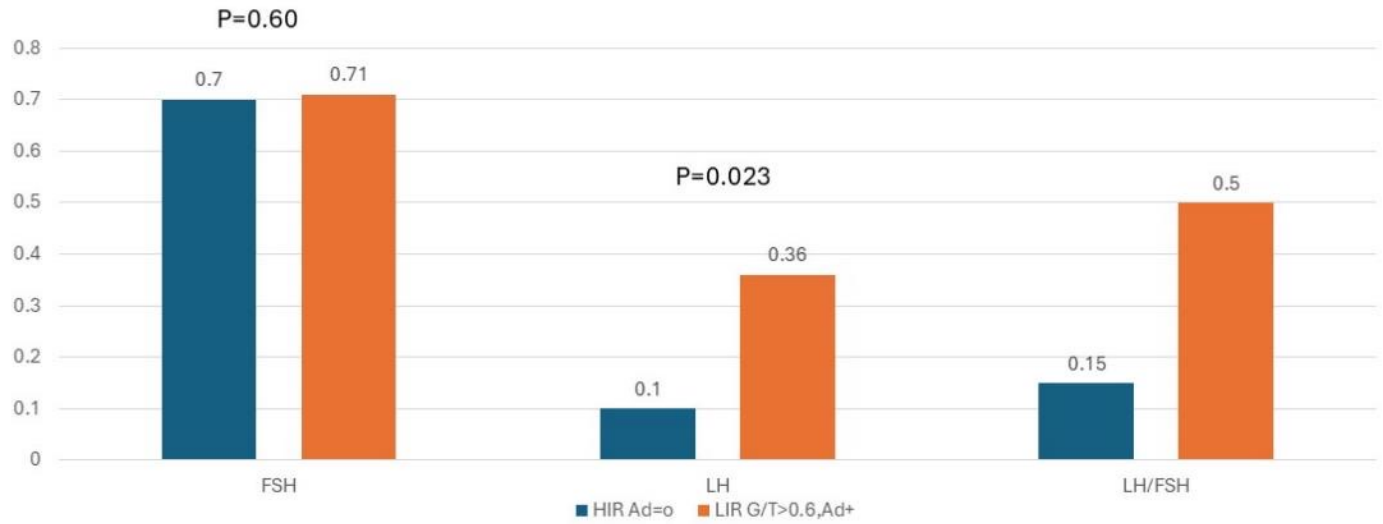


Sensitivity 88.1%
Specificity 40.7%
Criterion (cut-of value) ≤0.815
Area under ROC curve – 0.601

Two extreme groups were compared:
high infertility risk group (HIR) with TFI <0.15 and Ad/T=0 and low infertility risk group (LIR) with TFI >0.9 and Ad/T>0.02



Similar results in Danish study (Mamsen LS et al, 2024)



Gonadotropin insufficiency in cryptorchid patient

- Our hormonal data at a median age 15 mo let us suspect gonadotropin insufficiency in 42%
- Thorup J et al. recently presented a study on a series of 453 consecutive boys with **bilateral** nonsyndromic cryptorchidism: 45% of the boys were classified as having gonadotropin insufficiency

Median FSH levels were significantly higher in the older group (1.258 IU/L) than in the younger group (0.711 IU/L)

- Low inhibin B/FSH and AMH/ FSH may indicate risk of infertility. (Kato T et al. 2021; Walczak-Jedrzejowska R et al. 2025; Thorup J et al. 2024)
- Blunted LH and T responses after GnRH, but not FSH (Job 1977)
- Results are variable between studies as hormonal levels- with pulsatile/circadian secretion

Conclusions

- High infertility risk group had significantly lower basal LH values indicating a hypogonadotropic hypogonadism
- Routine hormonal levels in the serum of cryptorchid boys at the age of 15 mo were not reliable in predicting the histological findings of a single **biopsy**
- High prevalence of gonadotropin insufficiency features in cryptorchid boys

Suggestions?

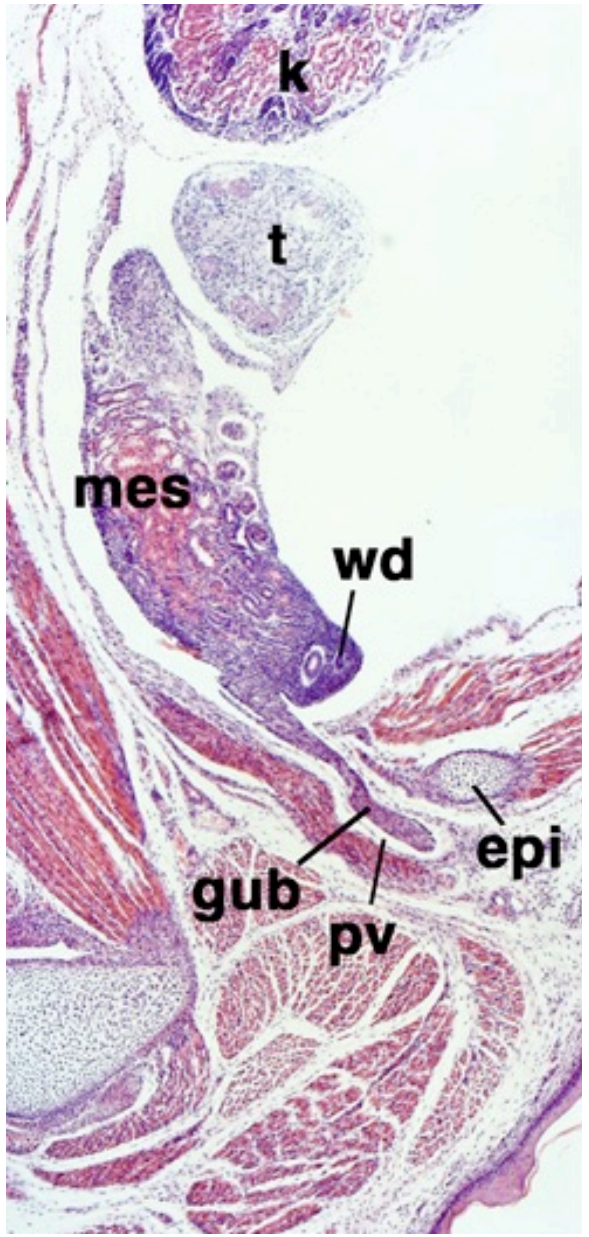
- See our patients at 2 mo of age and make decision on treatment (hormonal studies, liquid biopsy, research...)
- Do surgery (and biopsy) at around 1 year of age, at convenience



Epididymis first







Wakamatsu et al.