

Hypothalamus-pituitary-gonadal axis in cryptorchid boys

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Disclosures

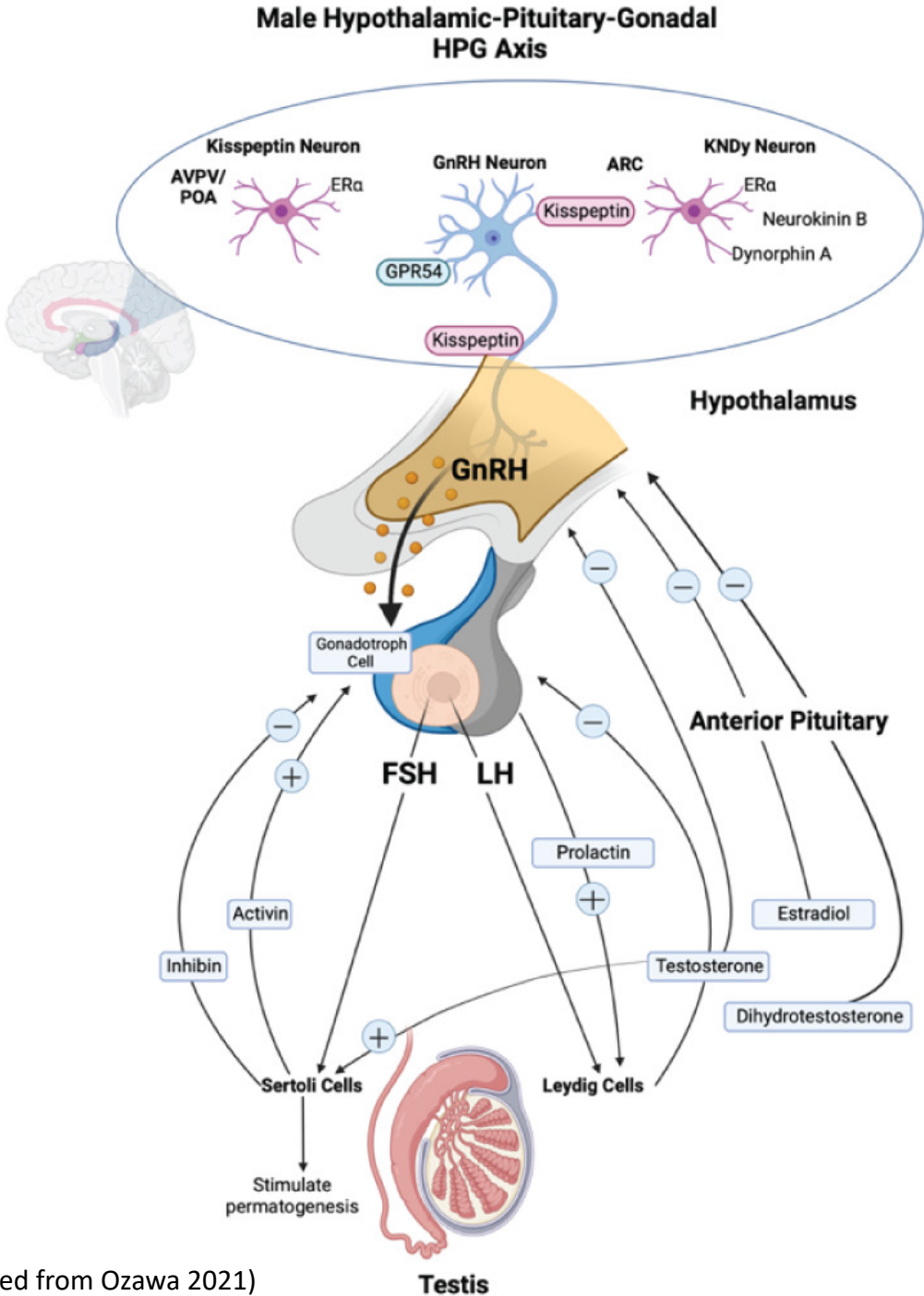


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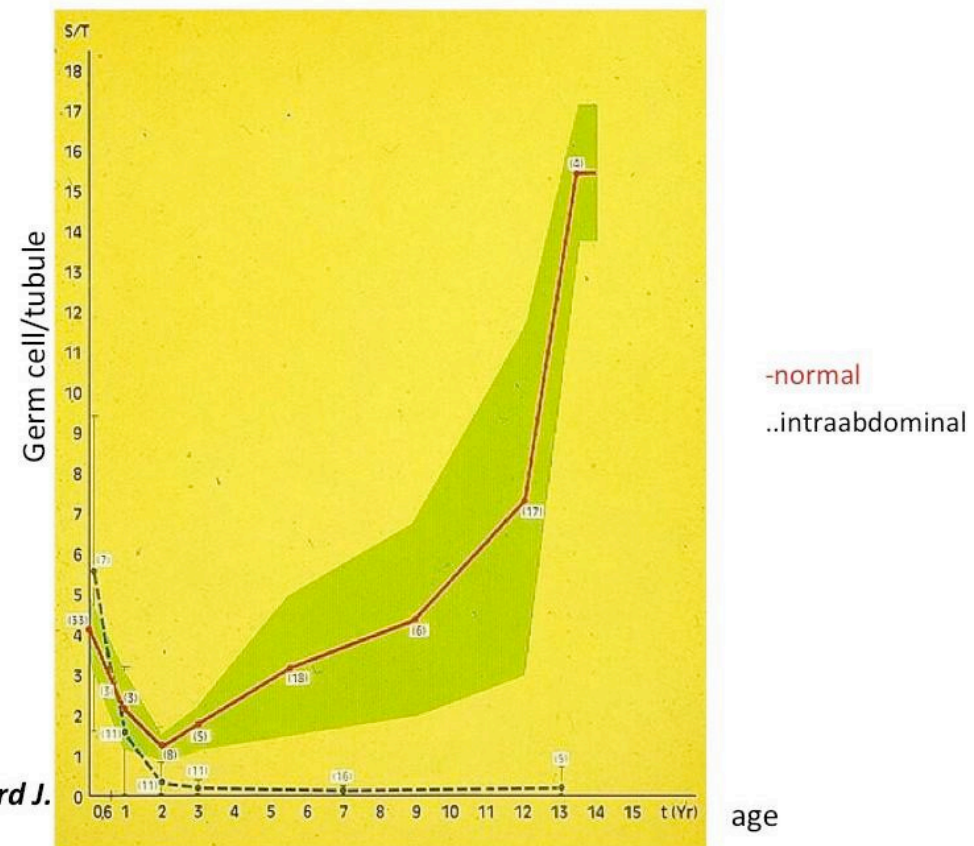
Hypothalamus- pituitary-gonadal axis



(Image created with [Biorender.com](https://biorender.com), adapted from Ozawa 2021)

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

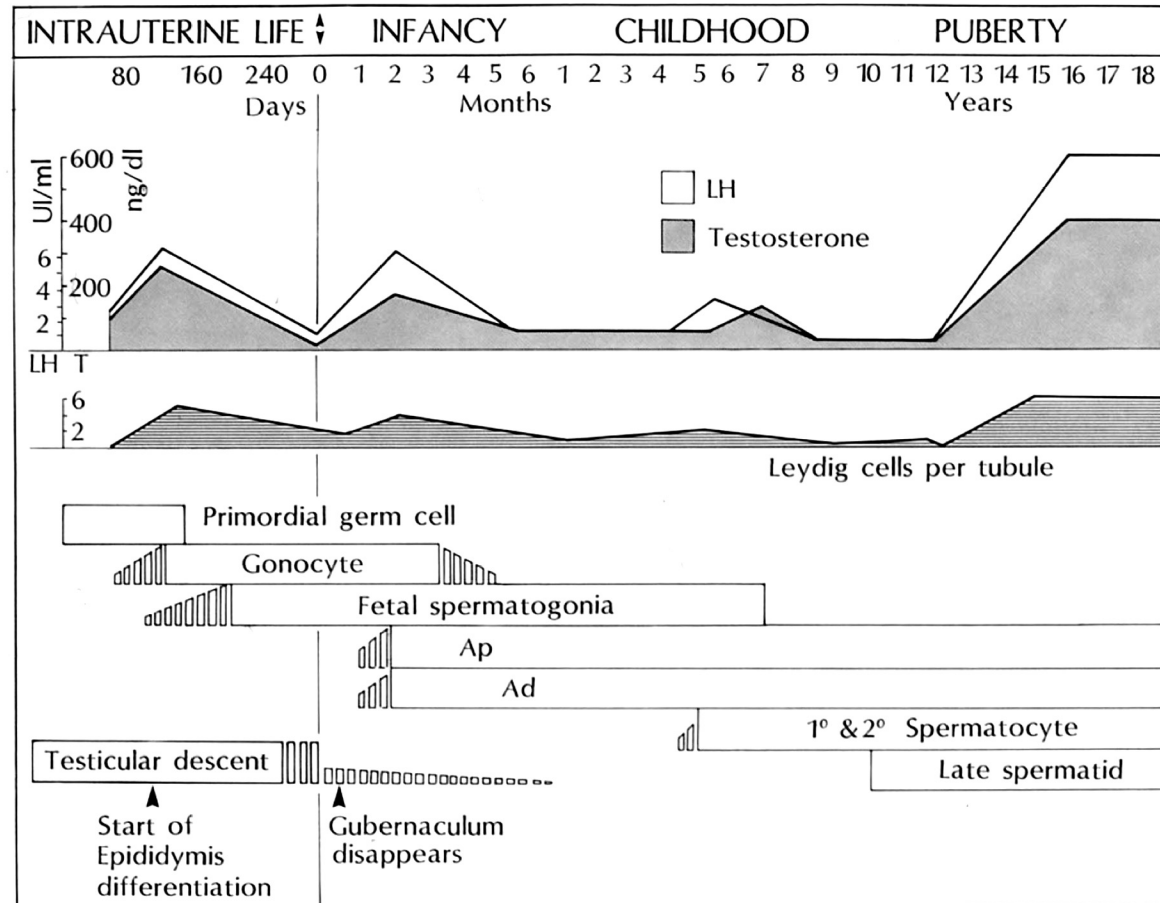
Hadziselimovic F, Girard J.
Horm Res. 1977;8(2):76-83



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

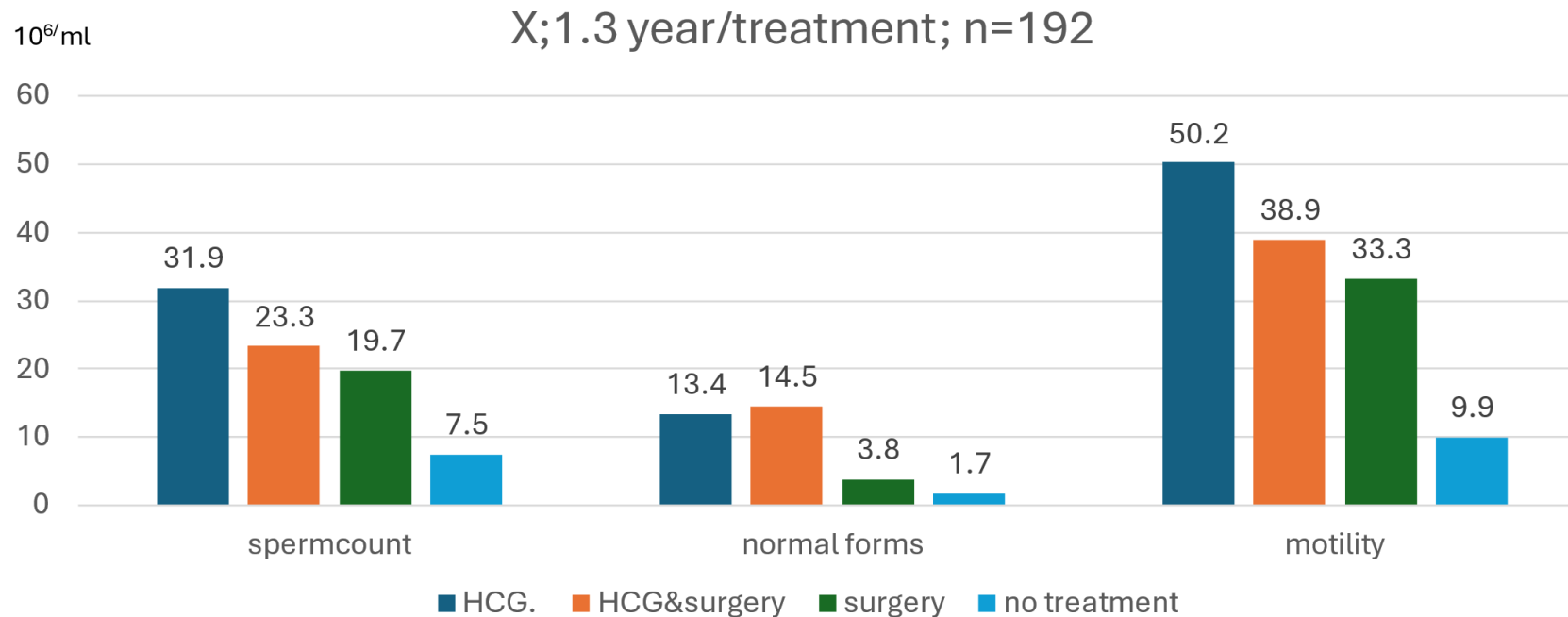
- High prevalence of obstruction histological pictures Negri et al. (2003). Prevalence of congenital epididymal or vasal anomalies is 36-43% Nistal et al., 2002
- Biopsies several months or years after orchidopexy (Schindler AM 1987)
 - Orchidopexy does not improve the number of germ cells
- Our data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

Early surgery improves fertility?

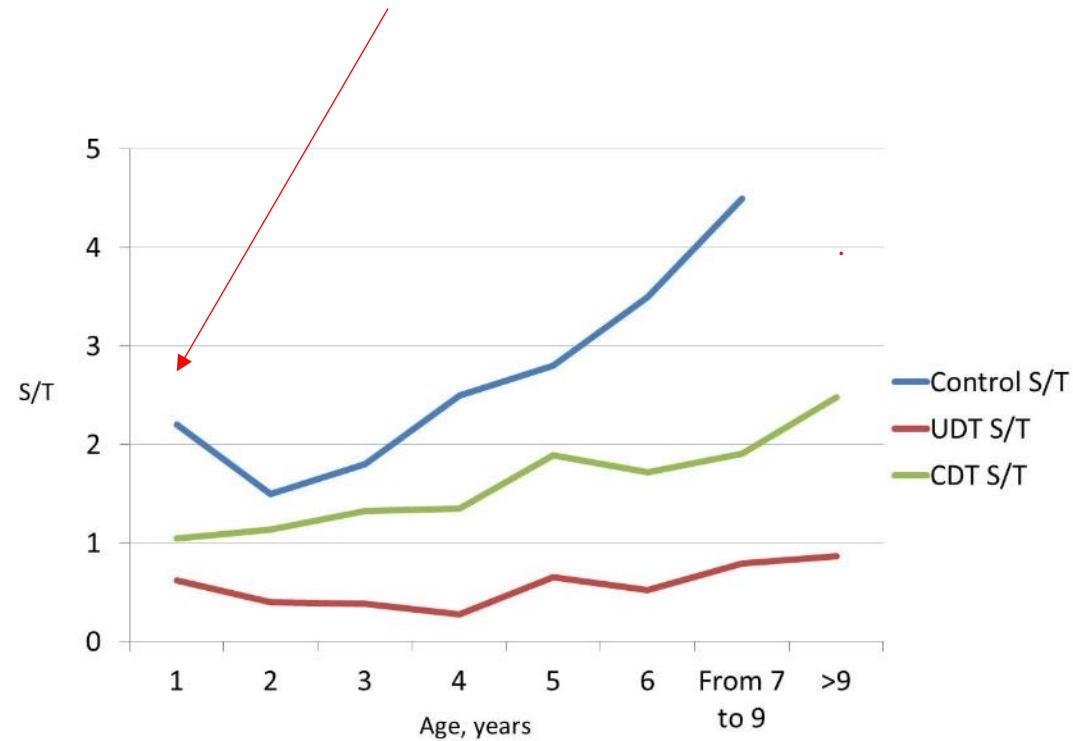
- <1 year: better sperm count and motility than <2 years. But most of <1 year hormonally treated and no difference in oligoazoospermic proportions (Feyles F et al 2014)
- <1 year: improves Inhibin B, later not. 25 % remain unimproved (Hildorf S 2021)
- Early orchiopexy improves subsequent testicular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



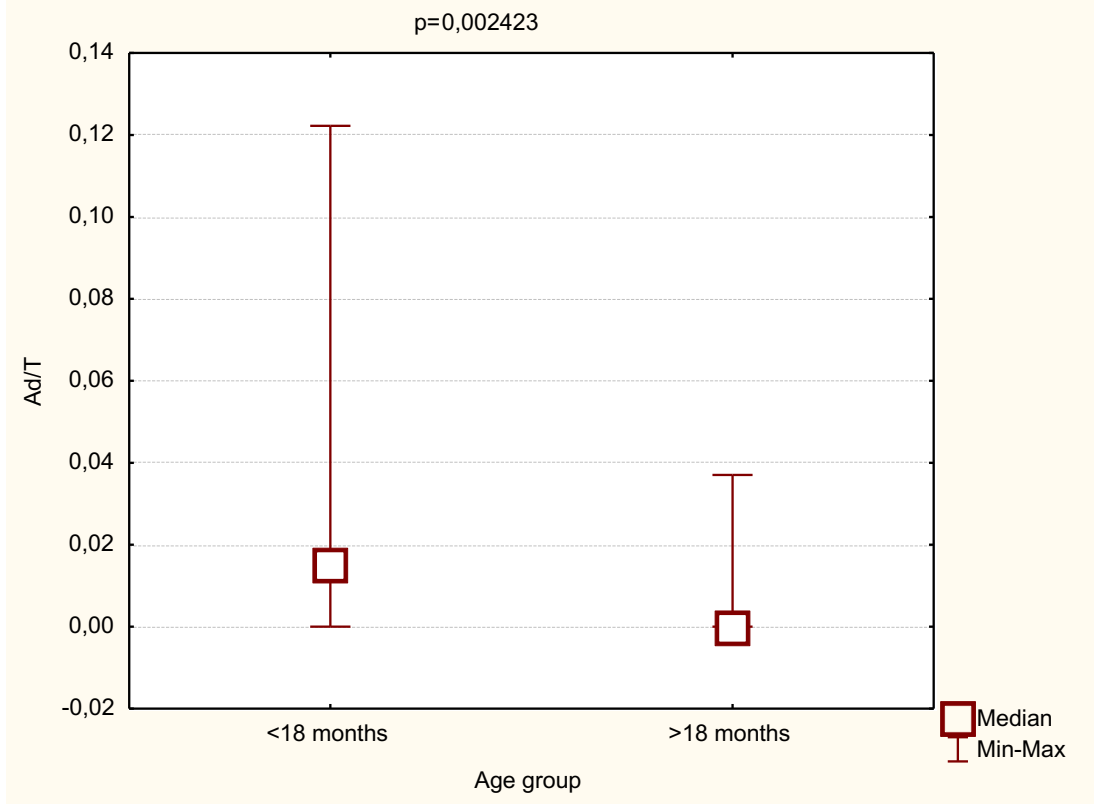
Early surgery helps, but does not restore the damage made by the earlier consequences of HPG axis dysfunction?



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**)

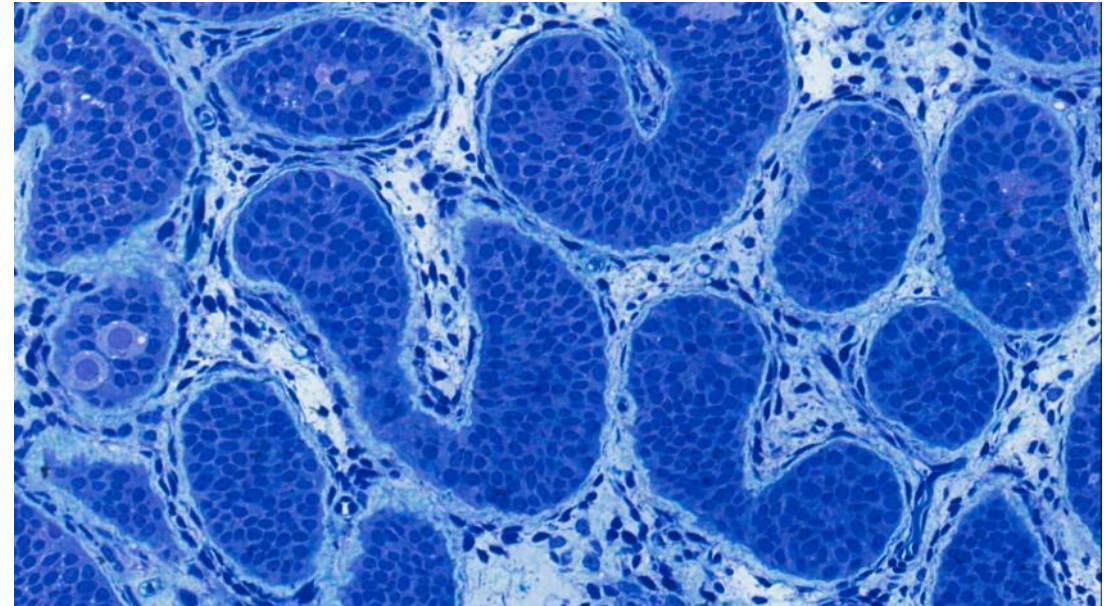
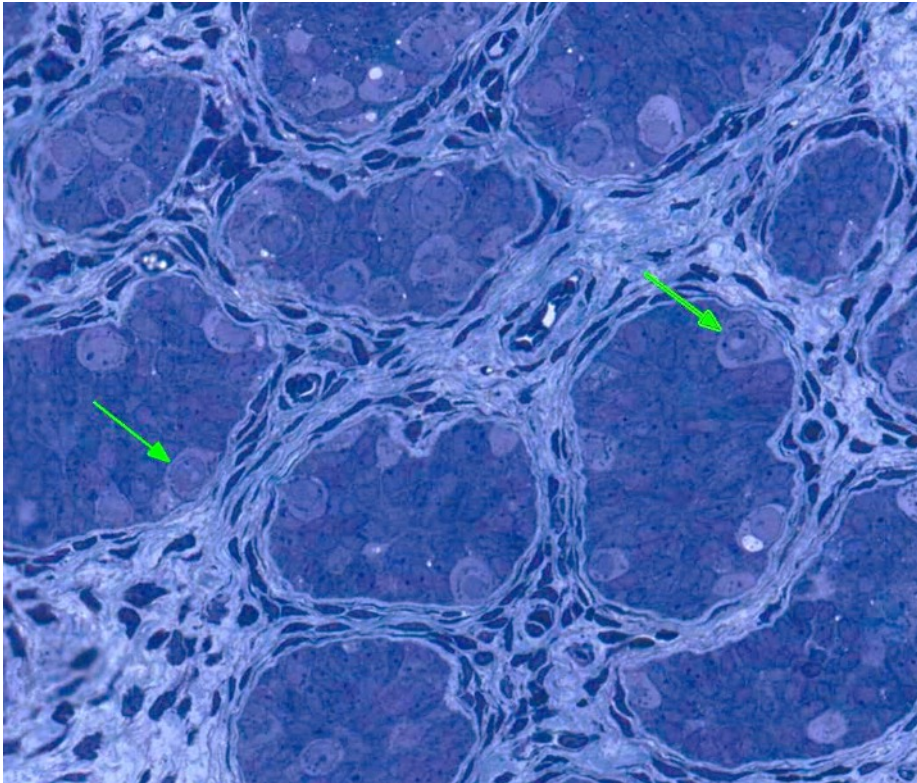
Aim of prospective study

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

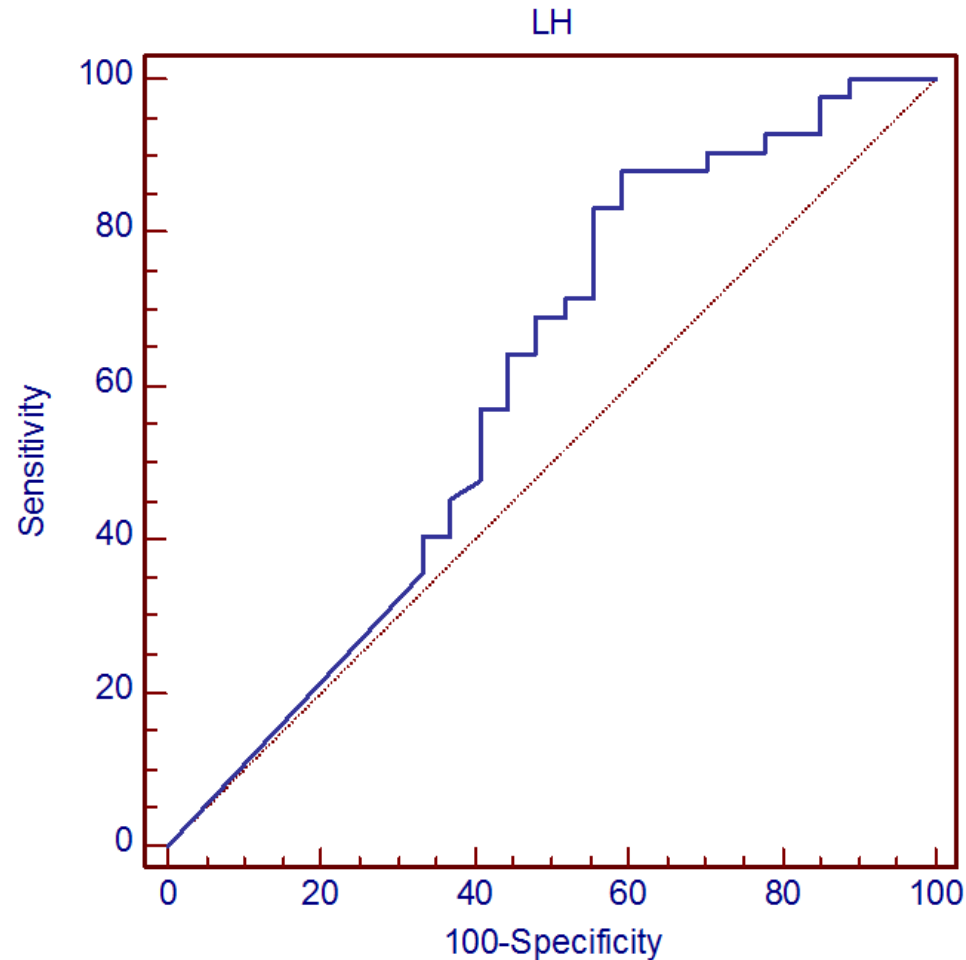
Materials and Methods

- 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).



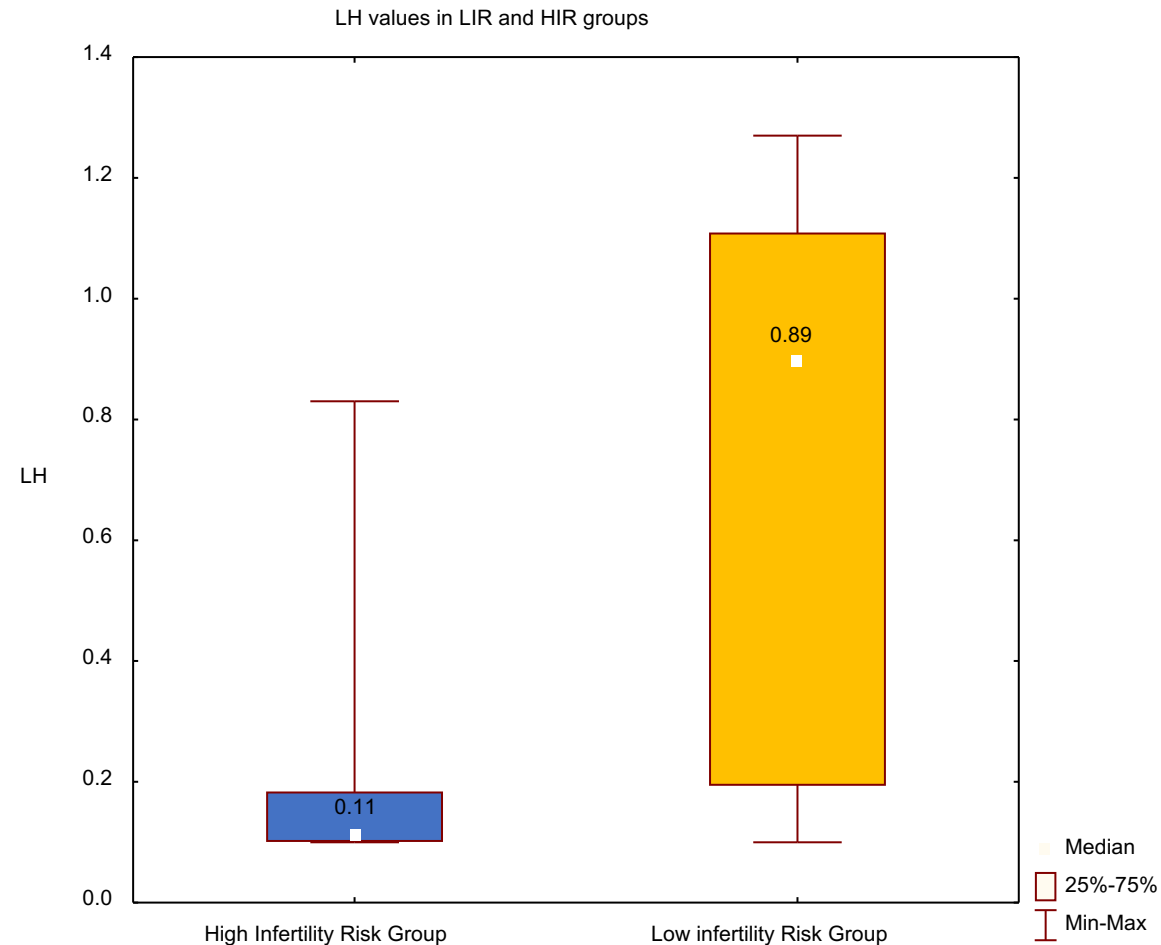
Sensitivity 88.1%

Specificity 40.7%

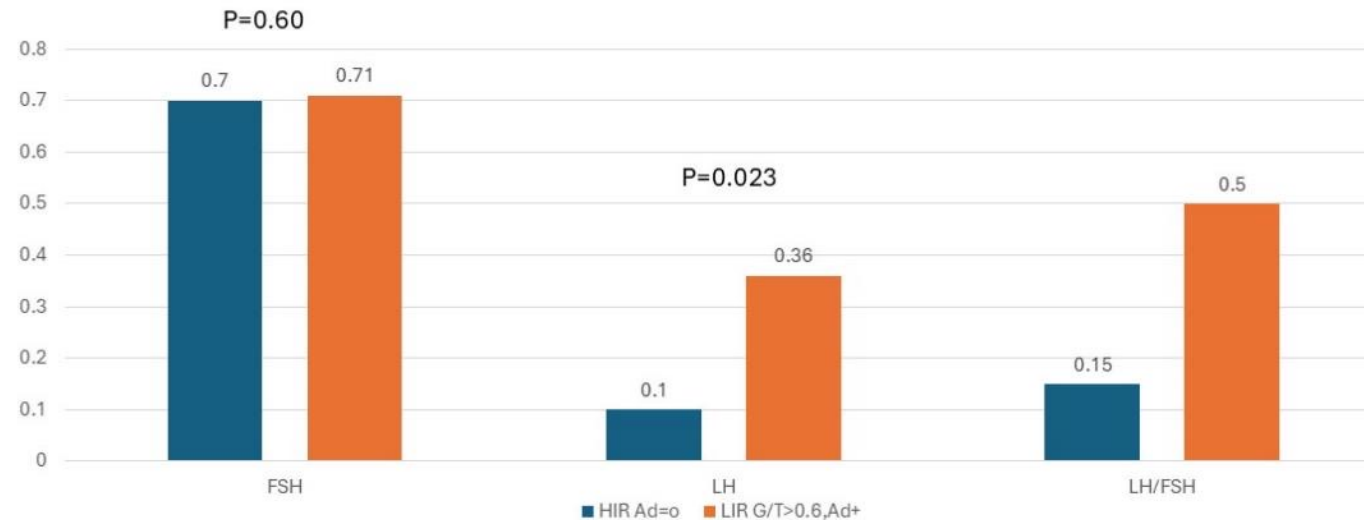
Criterion (cut-of value) ≤ 0.815

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-Jedrejowska 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

