

NEGATIVE EFFECT OF HORMONAL TREATMENT ON PREPUBERTAL TESTIS



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(Not related to the production of GnRH (Kryptocur®))

EAU Guidelines on Paediatric Urology

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B. Burgu, M. Castagnetti, L.A. 't Hoen, F. O'Kelly,
N.A. Pakkasjärvi, J. Quaedackers, Y.F.H. Rawashdeh,
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ESPU/EAU-2025 guidelines recommend treatment with GnRH analogues adjuvant to surgery for boys with bilateral cryptorchidism in order to preserve fertility potential

“Identification of specific subgroups of boys with undescended testes who would benefit from using hormones is challenging.

Since these important data on specific groups as well as additional support on the long-term effects are still lacking, **the Nordic consensus does not recommend hormonal therapy** (Ritzén et al. Acta Paediatr. 2007;96:638-43) “

Evaluation and Treatment of Cryptorchidism (2018) 12. September 2025

Treatment

GUIDELINE STATEMENT 10

Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy. (Standard; Evidence Strength: Grade B) **DISCUSSION**

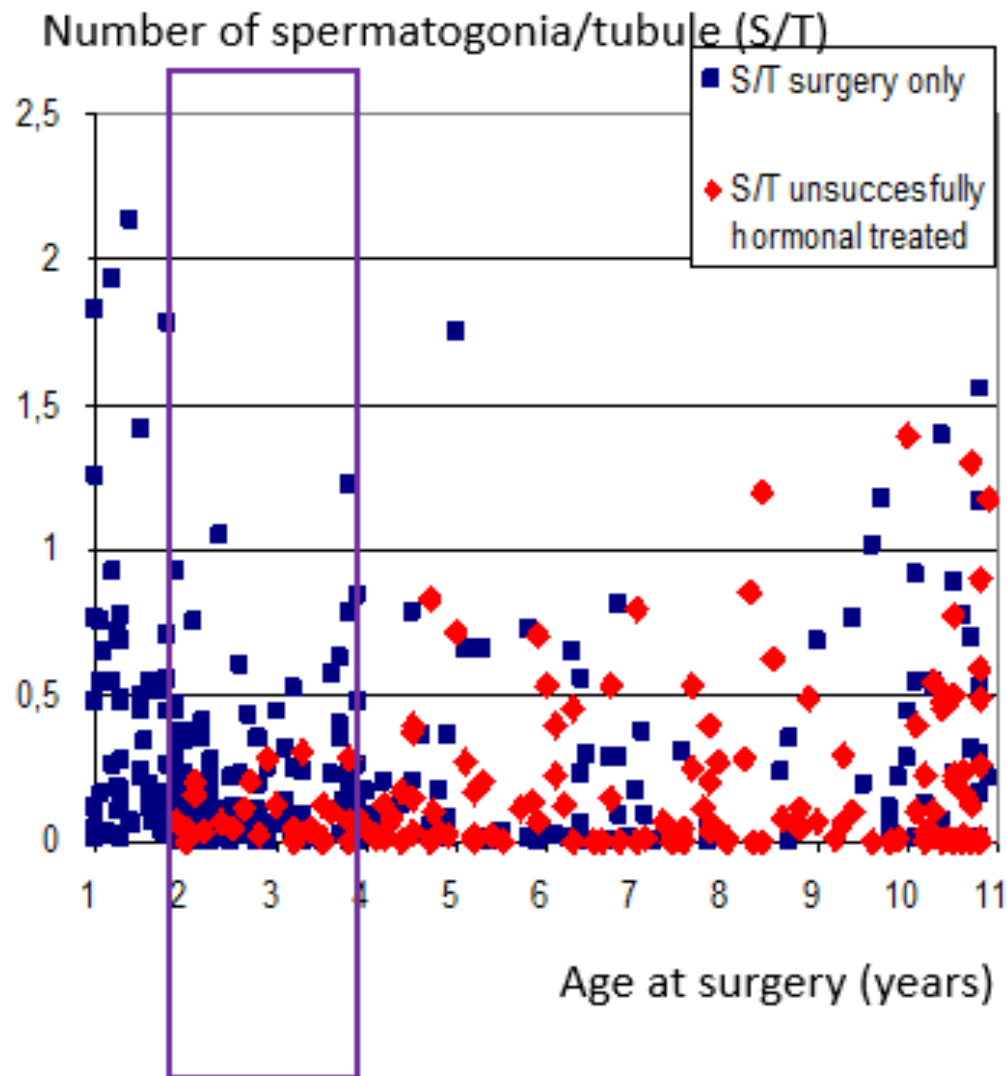
Overview of the Literature. Primary hormonal therapy with hCG or luteinizing hormone-releasing hormone (LHRH or gonadotropin-releasing hormone (GnRH)) has historically been used for many years, mostly in countries other than the United States. The action of hCG is virtually identical to that of pituitary LH although hCG appears to have a small degree of FSH activity as well. It stimulates production of androgens by the Leydig cells.....

Agonistic analogs of **LHRH**, such as Nafarelin or Buserelin, stimulate the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland and twice daily administration leads to decreased secretion of gonadal steroids by 4 weeks. This treatment is available as a nasal spray, but **is only approved to induce testicular descent outside of the United States.....**

HORMONAL TREATMENT MAY HARM THE GERM CELLS IN 1 TO 3-YEAR-OLD BOYS WITH CRYPTORCHIDISM

Vol. 163, 1290-1292, April 2000
Printed in U.S.A.

DINA CORTES, JØRGEN THORUP AND JAKOB VISFELDT



- 1985 -1990 we treated boys with cryptorchidism with GnRH 1.2 mg per day for 28 days, in 2 periods with a 3-month interval. GnRH did not induce testicular descensus in any boy younger than 4 years of age. After unsuccessful treatment, orchiopexy was performed.
- Other boys had unsuccessfully been treated with hCG
- Boys also underwent orchiopexy without previously hormonal treatment
- At time of orchiopexy the boys had a simultaneous testicular biopsy
- We measured number of spermatogonia/tubule at orchiopexy, S/T
- At 1 to 3 years of age, 72 consecutive patients
- In 19 unsuccessful treatment with GnRH, 1.2 mg per day in 2 series of 28-days treatment
- In 8 unsuccessful treatment with hCG, 6 injections, 100 IU/kg (max 1,500 UI) twice weekly for 3 weeks
- 45 had surgery only

HORMONAL TREATMENT MAY HARM THE GERM CELLS IN 1 TO 3-YEAR-OLD BOYS WITH CRYPTORCHIDISM

DINA CORTES, JØRGEN THORUP AND JAKOB VISFELDT

163, 1290–1292, April 2000
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Patient characteristics

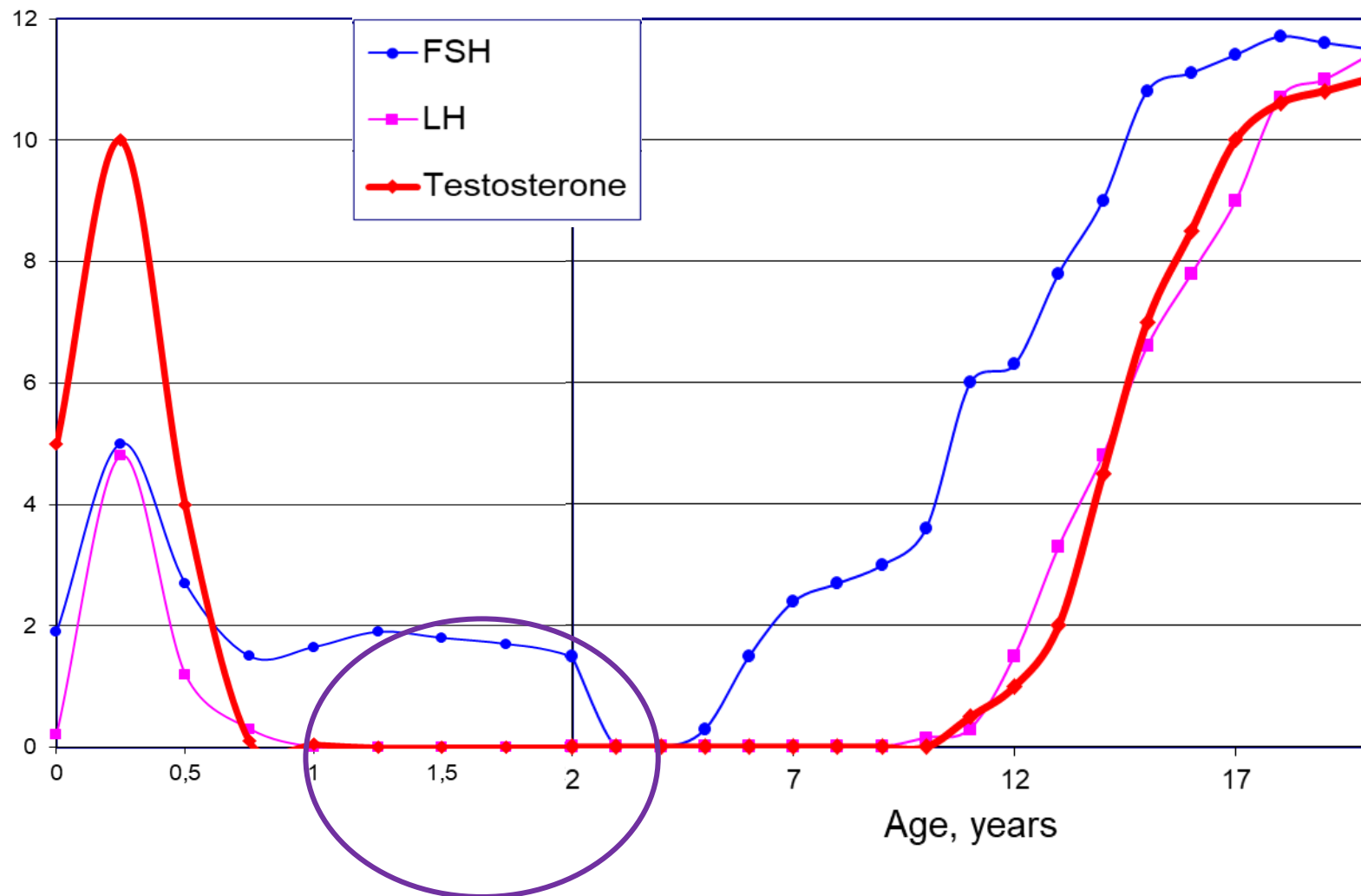
	Gonadotropin Releasing Hormone	HCG	Surgery Only
No. pts.	19	8	45
Median spermatogonia/tubule (range)*	0.07 (0–0.31)	0.06 (0.0025–0.21)	0.14 (0–0.86)
No. normal spermatogonia/tubule	0	0	7
No. biopsy without germ cells or with less than 1% normal value for age	3	1	4
Median age at orchiopexy (range)	2.9 (1.9–3.9)	3.2 (2.7–3.8)	2.6 (1.9–3.9)
No. intra-abdominal testis	0	2	5
No. bilat. surgery	3	2	5

* Hormonal treatment versus surgery only $p < 0.05$.

The patients with unsuccessful hormonal treatment had:

- lower S/T-values than those with surgery only (Mann-Whitney, $p < 0.05$)
- more patients with $S/T < 0.2$ than those with surgery only (Fisher's Exact Test, $p < 0.05$)
- equivalent risk of no germ cells 17% (4/23) like those with surgery only 9% (4/45) (Fisher's Exact test, $p = 0.69$)

Hormonal levels in boys, the minipuberty and the puberty

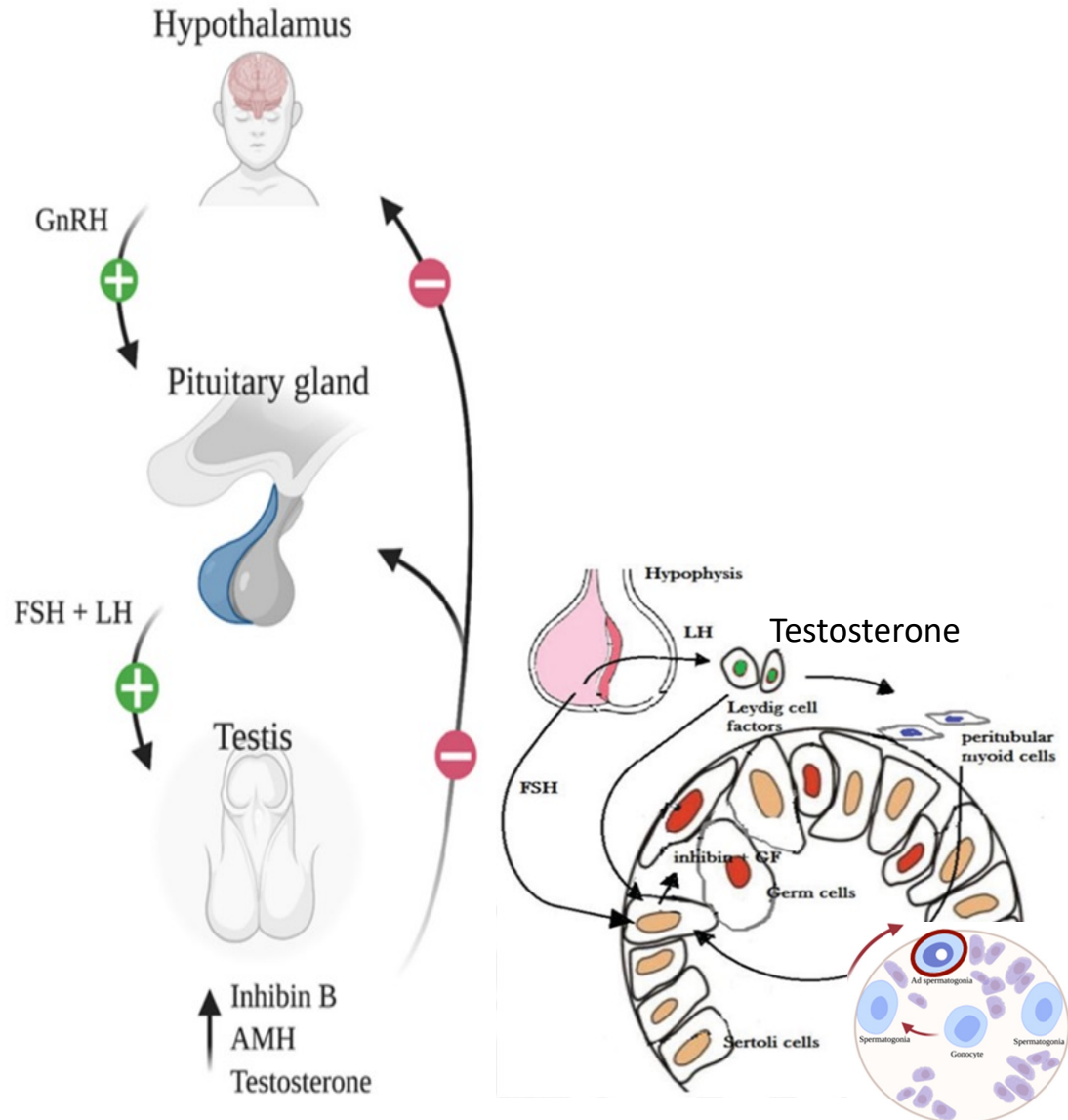


From 1 to 4 years of age the hormonal levels normally are very low

In prepubertal boys:

- HCG-treatment increases the level of testosterone to adult levels (Läeckgren & Ploën 1984, Dunkel et al. 1985)
- GnRH-treatment increases levels of FSH and LH (Bergada, Mancini et al. 1973, Garagorri et al. 1982)

Hypothalamus-pituitary-gonadal axis



Prostatic cancer

Gonadotropin-Releasing Hormone (GnRH) - chemical castration

- Men: an GnRH agonist for the first time may result in "testosterone flare" a temporary increase in testosterone because GnRH causes the pituitary gland to secrete extra luteinizing hormone
- The intense stimulation with GnRH leads to pituitary gland desensitizing and stopping release of FSH and LH

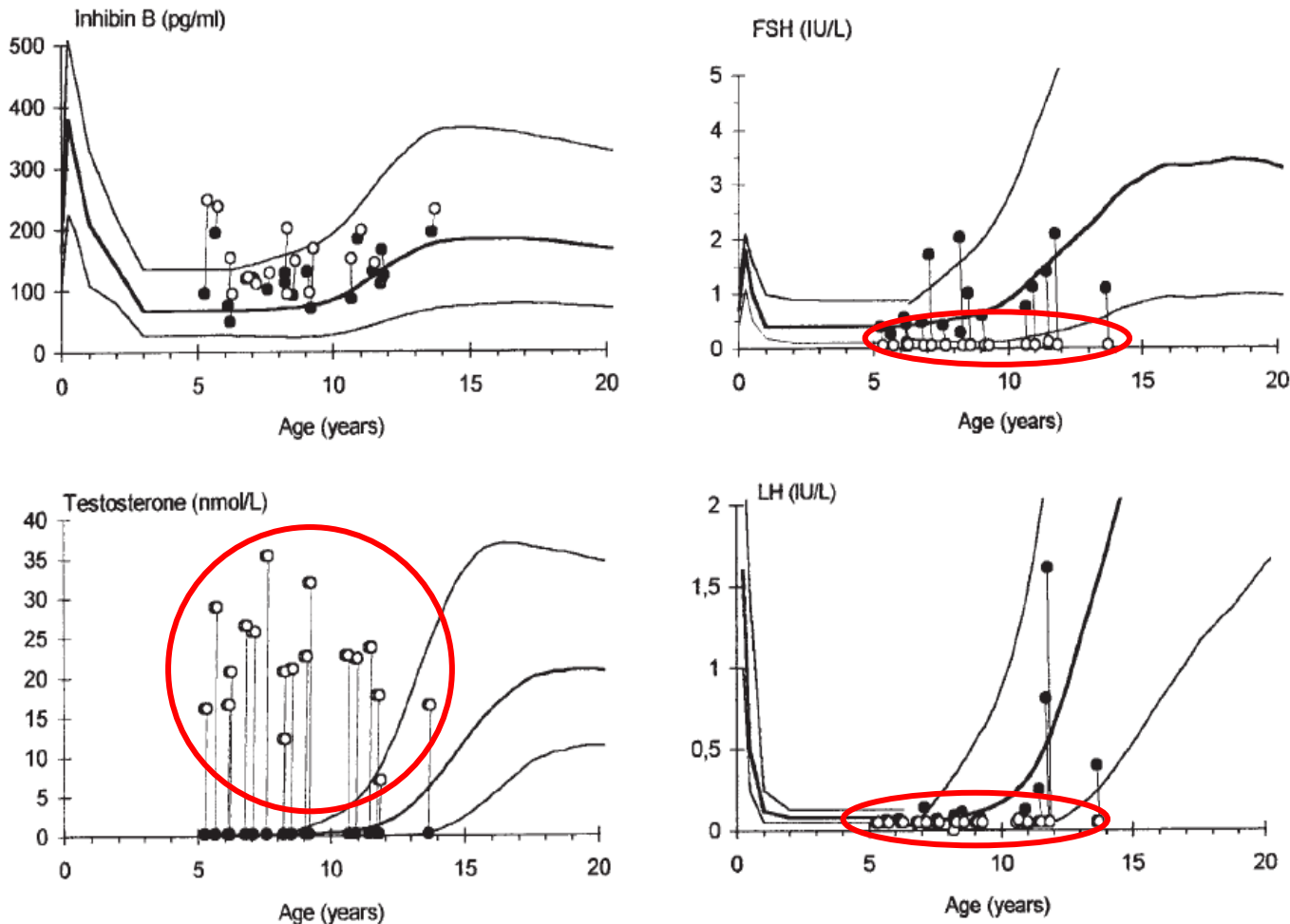
Central precocious puberty

GnRH - stops the sexual maturation

- GnRH overstimulates the pituitary gland, and leads it to desensitizing and stopping release of FSH and LH
- Once medication is stopped, children will progress through puberty normally, but faster than average
- No known long-term side effects
- Short-term side effects, pain or irritation at injection sites

Serum inhibin B, FSH, LH and testosterone levels before and after human chorionic gonadotropin stimulation in prepubertal boys with cryptorchidism

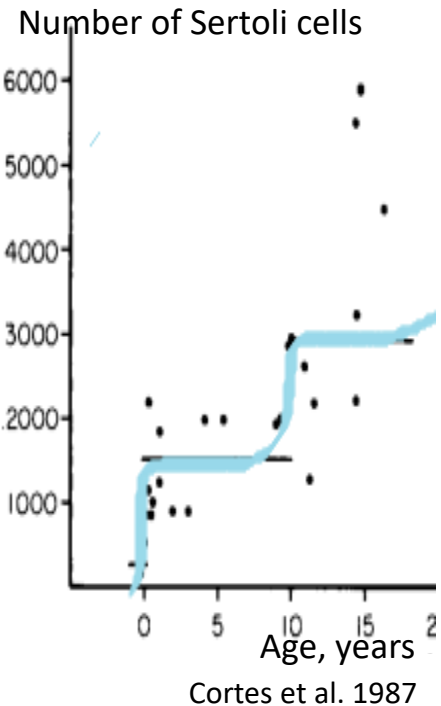
P Christiansen, A-M Andersson, N E Skakkebaek and A Juul European Journal of Endocrinology (2002)



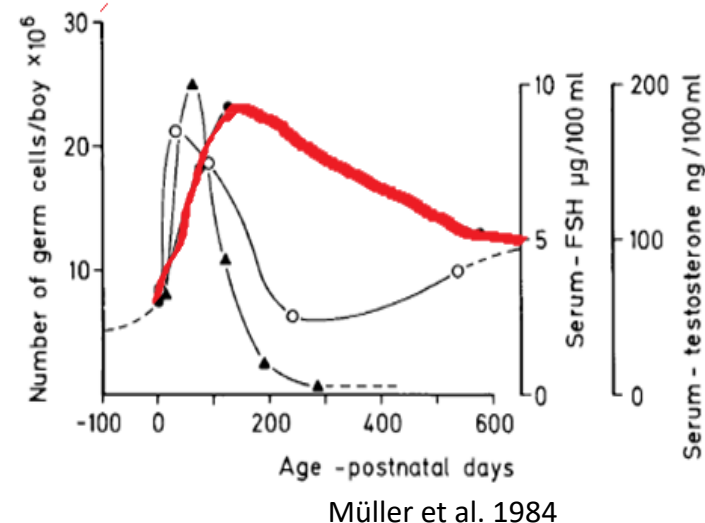
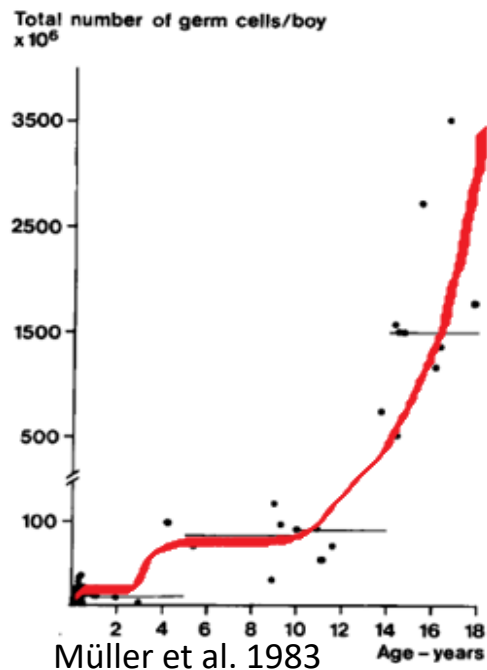
- 18 boys with cryptorchidism 5 to 14 years if age received hCG treatment, 1500 IU intramuscularly twice a week for 3 weeks
- HCG induced a marked increase in testosterone into the adult range and **complete suppression of FSH and LH levels**
- Totally 9 of 23 boys had testicular descensus after hCG treatment

Figure 2 Inhibin B, FSH, testosterone and LH before (●) and after (○) 3 weeks intramuscular hCG treatment in 18 prepubertal boys with cryptorchidism. Lines represent means and 95% confidence limits for healthy prepubertal boys as previously published (6).

The proliferation of germ cells in normal testes



- Normally, the total number of Sertoli cells primarily increases during the first 3 months of age, and during puberty
- Normally, the total number of germ cells increases up to 100 days of age, and then decreases, based on germ cell proliferation and transformation of gonocytes to spermatogonia and to spermatogonia A dark, primarily within the first year of age. Afterwards there is also germ cell proliferation and transformation, and at 4 years of age primarily spermatocytes appear
- Total suppression of FSH and LH, may harm the germ cell proliferation and transformation



Harmfull effects of GnRH/LHRH and hCG

Testicular Function in Men Treated in Childhood for Undescended Testes

By S. Vinardi, P. Magro, M. Manenti, R. Lala, S. Costantino, M.G. Cortese, and F. Canavese
Turin, Italy

2001

- 58 men were treated for cryptorchidism at mean age 5.4 years (2 to 12 years), evaluated in adulthood:
- 37 had unsuccessful hormonal treatment before orchiopexy GnRH 1.2 mg/d for 28 days followed by hCG, 9 injections, 500 IU 3 times a week for 3 weeks
- 21 had surgery only

Table 4. Semen Analysis in Relation to Hormonal Therapy

With Hormonal Therapy			Without Hormonal Therapy		
No. of spermatozoa			No. of spermatozoa		
Normal ($>20 \times 10^6/\text{ml}$)	23 cases	67.64%	Normal ($>20 \times 10^6/\text{ml}$)	19 cases	95%
$10-20 \times 10^6/\text{ml}$	5 case	14.70%	$10-20 \times 10^6/\text{ml}$	0 case	0%
$< 10 \times 10^6/\text{ml}$	6 cases	17.64%	$< 10 \times 10^6/\text{ml}$	1 cases	5%

(Fisher exact test, $p < 0.05$)

- But, **only the patients with bilateral cryptorchidism or non-palpable testes** were offered hormonal treatment before surgery

Inflammatory changes after hCG treatment

Hjertkvist et al. 1993

- HCG treatment before orchiopexy in 75 boys with cryptorchidism 4-12 years of age, 10 injections, twice a week for 5 weeks, < 6 years: 500 IU, otherwise: 1000 IU
- HCG induced:
 - enlargement of the testes,
 - appearance of Leydig cells,
 - Sertoli cells increased in size,
 - tubular diameter increased in size,
 - increased volume density of blood vessels
 - increased interstitial bleeding
 No signs of spermatogonial maturation or proliferation.
- After 6 months still increased volume density of blood vessels and interstitial bleeding

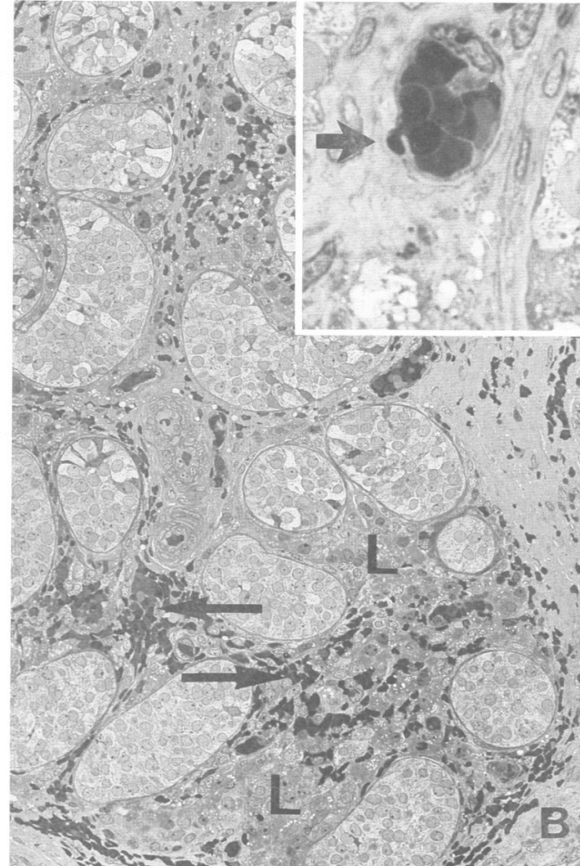


Table 1. Characteristics of and Results in the Control Group and the Groups Studied Within 4 Days or Within 6 to 12 Months After hCG Treatment

	Controls (n = 8)	Time Between Last hCG Injection and Biopsy	
		1 to 4 d (n = 13)	6 to 12 mo (n = 9)
Age range	4.3-10.2	4.7-12.4	4.1-11.8
Median age	6.7	8.4	7.4
Puberty stage (Tanner)	I	I (n = 11) II (n = 2)	I
Volume density of interstitial tissue (% of testis volume)	56 ± 3	58 ± 3	56 ± 3
Volume density of intravas- cular PMNs (% of total blood vessel lumina)	0.92 ± 0.08	2.95 ± 0.37*	1.00 ± 0.26
Volume density of blood vessel lumina (% of testis volume)	0.70 ± 0.12	2.57 ± 0.47*	2.45 ± 0.42*
Percentage of biopsies with interstitial bleeding	12.5	61.5†	55.6†

*Significantly different from control value ($P < .01$) according to Mann-Whitney U test.

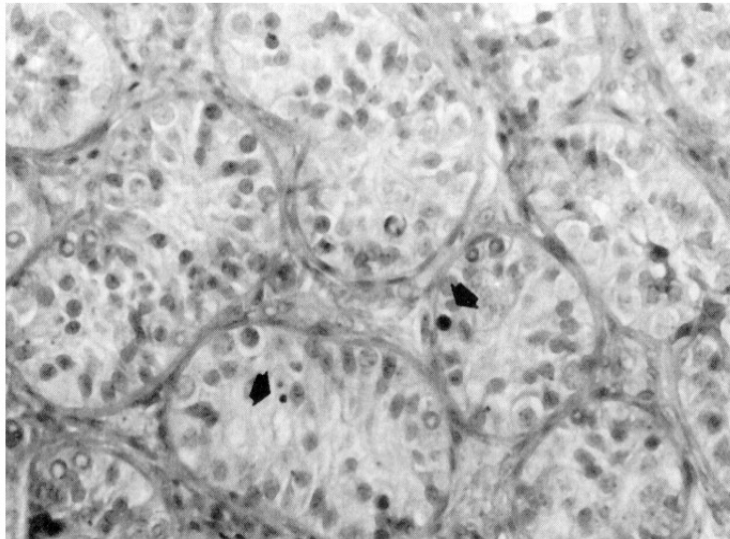
†Significantly different from control value ($P < .05$) according to χ^2 test.

Apoptosis after hCG treatment

Heiskanen et al. 1996

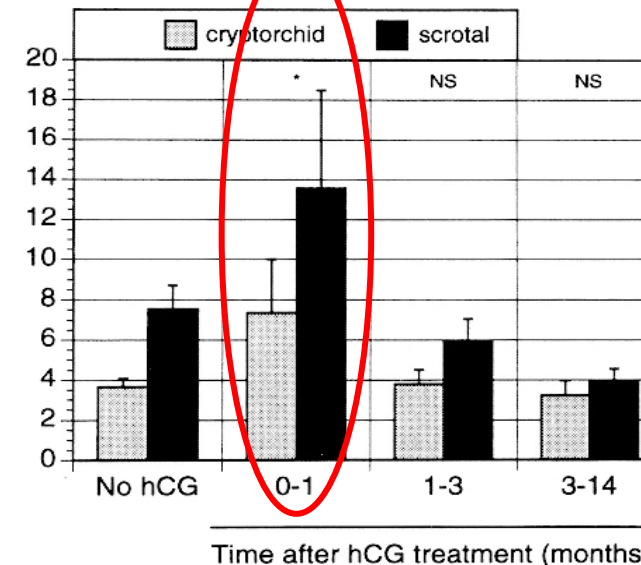
Unsuccessful treatment with hCG treatment before surgery in 43 prepubertal boys with cryptorchidism, aged 1.1 to 15.8 years

- During the 1st month after hCG treatment, the number of germ cell apoptosis increased in both scrotal and inguinal testes, not seen in those that underwent surgery only ($p < 0.001$)
- During 1-14 months after hCG treatment, the number of apoptotic germ cells was like those without hCG treatment, suggesting that hCG (and/or androgen) withdrawal results in germ cell apoptosis



Apoptotic cell death *in situ* in the germ cells of the human testis. A representative testicular biopsy from a scrotal testis is shown. The biopsy was taken from a 7-y-old boy less than 1 mo after hCG treatment. The histologic sections were stained with an *in situ* 3'-end labeling technique in which the

Number of apoptotic spermatogonia / mm² of tubular area



Germ Cell Apoptosis After Treatment of Cryptorchidism with Human Chorionic Gonadotropin is Associated with Impaired Reproductive Function in the Adult

1997

Leo Dunkel,* Seppo Taskinen,* Outi Hovatta,† Jonathan L. Tilly,§ and Sakari Wikström*

- Unsuccessful hCG treatment before orchiopexy in boys 10 months to 13 years of age, 10 injections over a period of 5 wk. For patients < 7 years old; 500 IU, otherwise 1000 IU
- In adulthood, after unsuccessful hCG treatment, in unilateral cryptorchidism, the previously undescended testis was smaller, but the sperm concentration was like those with surgery only

Table II. Various Parameters of Reproductive Function in Adult Patients Treated Operatively for Unilateral Cryptorchidism in Prepuberty

	hCG treatment			Relative level of low molecular weight DNA		
	No	Yes	P =	Normal*	Elevated‡	P =
Testis volume (mL)	20.6±2.3	10.8±1.4	0.0009	20.3±2.0	10.1±1.4	0.0002
Serum FSH (IU/liter)	3.1±0.3	6.2±1.0	0.05	3.0±0.3	6.5±1.1	0.008
Serum LH (IU/liter)	3.9±0.6	4.2±0.3	NS	4.0±0.5	4.1±0.4	NS
Serum testosterone (nmol/liter)	20.6±2.7	21.1±2.0	NS	20.6±2.3	21.1±2.3	NS
Sperm concentration (cells* 10 ⁶ /mL)	77.8±17.7	89.7±13.0	NS	84.1±16.6	84.3±13.7	NS
Normal sperm motility (A+B, %)	75.4±8.2	56.6±8.3	NS	73.0±7.5	56.6±9.8	NS
Normal sperm morphology (%)	44.0±6.1	30.6±6.3	NS	43.1±5.4	29.5±7.3	NS

Subjects were divided into two groups according to the treatment or the levels of low molecular weight DNA fragmentation in the undescended testis ($n = 21$). The biopsies were taken in prepuberty during orchidopexy. Values are mean±SEM. *Normal levels of low molecular DNA cleavage were based on results obtained from biopsies of control subjects (scrotal testes of nine prepubertal boys, no prior hCG treatment). In cryptorchid boys, values below the 95% confidence limit were considered normal. ‡Values above the 95% confidence limit were considered elevated.

A cross-sectional study of cryptorchidism in children: testicular volume and hormonal function at 18 years of age

2015

R. Varela-Cives¹, R. Méndez-Gallart¹, E. Estevez-Martínez¹, P. Rodríguez-Barca¹, A. Bautista-Casasnovas¹, M. Pombo-Arias², R. Tojo-Sierra²

- HCG treatment was offered to all patients, twice a week for 5 weeks, 10 injections: 250 IU for children <2 years, 500 IU for children 2-6 years and 1000 IU for those aged 6-11 years
- In unilateral cryptorchidism, surgery at 2-6 years of age, the previously undescended testis was smaller than those with surgery only, however, the contralateral testis seemed larger

Table 2 - Unilateral cryptorchidism (n=103) Features based on age and therapy (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone; TEST-Testosterone).

	< 2 years			2-6 years			> 6 years		
	Hormonal therapy		CX	Hormonal therapy		CX	Hormonal therapy		CX
	A	B		A	B		A	B	
FSH (UI/L)	4.0 (*)	3.5	5.3 (*)	2.3	4.1	3.5	4.0	3.8	3.8
Range		(2.5-5.4)		(1.1-7.0)	(2.5-5.7)	(2.2-8.0)	(2.0-9.5)	(3.2-6.3)	(2.5-7.6)
LH (UI/L)	2.8 (*)	4.2	2.7 (*)	3.2	4.8	3.1	5.1	3.8	3.5
Range		(3.3-5.6)		(3.2-3.5)	(2.9-5.9)	(2.9-3.3)	(3.2-6.1)	(2.7-5.1)	(3.3-5.8)
TEST (Ng/mL)	4.9 (*)	7.5	5.6 (*)	6.7	5.9	4.6	5.2	5.9	6.0
Range		(5.5-16.6)		(5.3-9.9)	(4.4-8.2)	(3.8-6.6)	(4.8-10.1)	(4.8-7.8)	(4.5-9.1)
Age at treatment (months)	11.9	18.3	17.8	37.2	50.1	36.0	96.2	80.9	128.7*
	(8.6-15.7)	(14.5-21.3)	(17.3-20.1)	(27.5-60)	(34.2-54)	(28.5-59)	(80.5-121)	(46.3-126)	(87.6-142)
Testic. Volume									
Affected testis	17.2	11.2	11.9	15.4	8.3***	11.2	11.5	10.9***	9.0***
	(11.4-23.0)	(9.3-13.5)	(0.1-15.0)	(11.8-18)	(6.5-11.1)	(7.1-12.4)	(8.9-15.8)	(7.7-13.8)	(4.8-11.4)
Non-affected testis	18.5	15.0	17.9	15.3	16.7	14.0	12.1	14.6	15.8
	(18.0-19.0)	(12.1-17.5)	(12.3-33.2)	(10.3-18)	(13.4-20)	(11.2-18)	(10.6-21.6)	(11-19.9)	(10-22.9)
Patients	2	5	3	4	20	4	16	30	19

(*) Only 1 case with data

* p < 0.05; ** p < 0.01; *** p < 0.005; **** p < 0.001

Table 4 - Bilateral cryptorchidism (n=80) Features based on age and therapy (A-only hormonal treatment; B-hormonal first and surgery later; CX – surgery alone; TEST- testosterone).

AGE	< 2 years	2 - 6 years			> 6 years		
	Treatment	Treatment		CX	Treatment		CX
Groups	B	A	B		A	B	
FSH (UI/L)	3.7	2.8	9.5	-	10.6	6.6	15.5
Range	(1.9-6.3)	(2.5-3.2)	(5.0-15.6)		(9.2-11.3)	(3.5-11.3)	(9.1-21.0)
LH (UI/L)	5.1	10.4	4.6	-	3.3	3.8	5.3
Range	(4.3-5.7)	(4.2-16.7)	(2.7-7.2)		(2.4-7.2)	(2.8-7.9)	(4.2-8.1)
TEST. (Ng/mL)	6.5	6.1	5.4	5.9 (*)	7.5	5.6	5.8
Range	(4.0-6.6)	(4.4-7.9)	(4.1-6.3)		(6.6-9.8)	(5.3-5.9)	(2.5-8.5)
Age at Treat.	20.4	43.7	47.4	37.0	100.5	119.5	101.6
(Months)	(16.1-23.4)	(29.6-71.8)	(33.6-61.0)	(36.9-37.2)	(95.3-111.3)	(92.4-139.8)	(91.5-112.2)
Testic Volume	10.3	15.0	10.3	6.6	13.9	12.1	14.5
Range	(7.4-18.9)	(12.4-16.1)	(6.6-19.6)	(1.2-12.1)	(10.0-17.2)	(8.8-15.4)	(6.7-12.8)
Patients	7	6	15	2	8	34	8

(*) Only 1 case with data

EFFECT OF AGE AT OPERATION, LOCATION OF TESTIS AND PREOPERATIVE HORMONAL TREATMENT ON TESTICULAR GROWTH AFTER CRYPTORCHIDISM

SEPPO TASKINEN AND SAKARI WIKSTRÖM 1997

- All 149 patients with orchiopexy aged 10 months to 13 years, mean age 4-5 years, in 1966 -1977, were offered follow-up examination. The patients were otherwise healthy
- 83 accepted: 26 have had unsuccessful hCG treatment twice a week for 5 weeks, 10 injections:
500 IU for children < 7 years old, otherwise 1000 IU
57 had surgery only
- The patients who had unsuccessful hCG treatment had smaller testes than those with surgery only (9 +/- 5 ml versus 12 +/- 6 ml ($p < 0.05$))

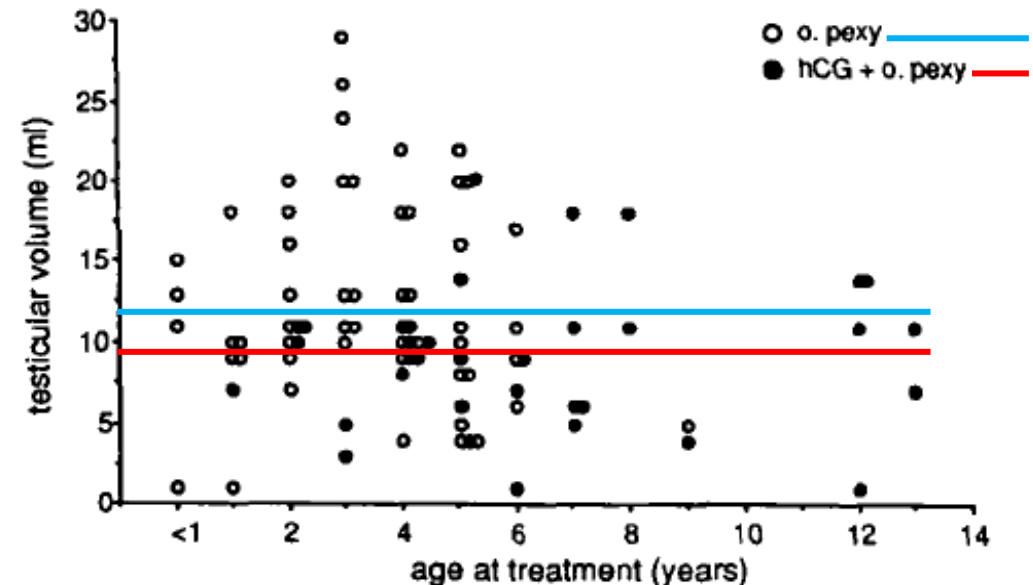


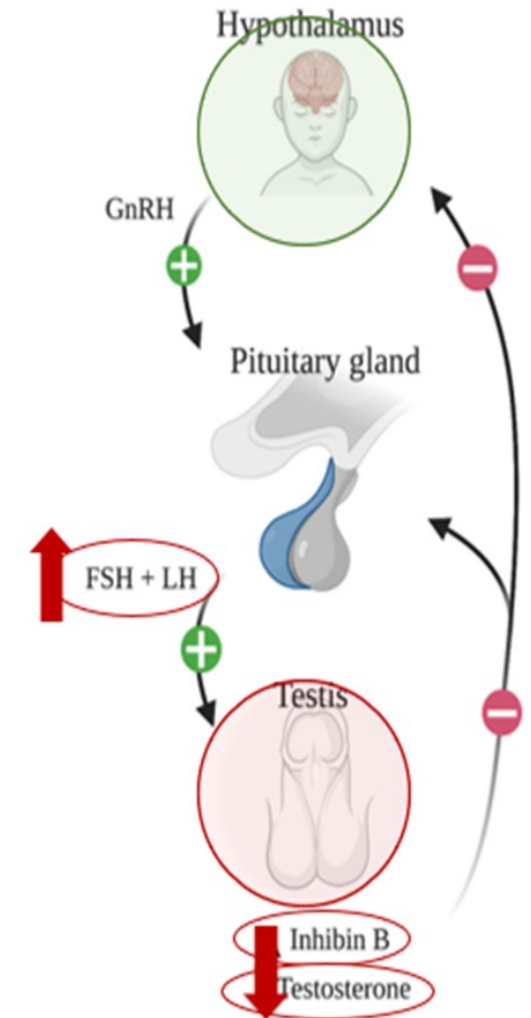
FIG. 2. Size of 88 cryptorchid testes at examination by patient age at time treatment. hCG, human chorionic gonadotropin. o.pexy, orchiopexy.

- For boys 10-11 years of age with unilateral cryptorchidism, the testicular volume in adulthood was similar for 26 with unsuccessful hGC or GnRH treatment and 30 with surgery only (Cortes et al. 1996)

Examination for infertility in 70 men (out of 91 men) with previous surgery for bilateral cryptorchidism. Cortes et al. 2003

Patients and methods

- 70 boys with surgery for bilateral cryptorchidism and a simultaneous testicular biopsy at median age 12.8 years (10.6-15.4 years)
 - In adulthood, at median age 29.0 years (19.9-34.7 years)
 - 2 samples of semen,
 - Blood-sample for FSH
 - Volume of testes
 - Repeat bilateral testicular biopsies
-
- Infertility was expected in men with sperm count < 5 million/ml
 - Males with an intact hypothalamic-pituitary-gonadal axis react on an impaired germ cell status with an increased FSH



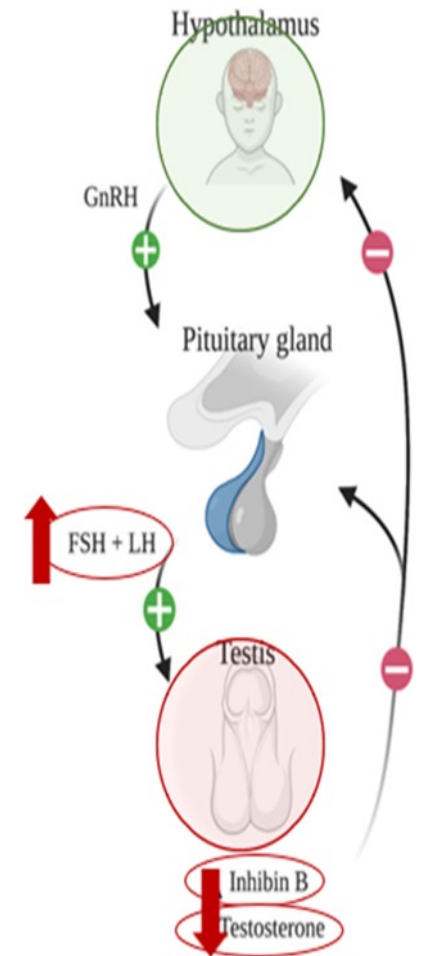
Infertility was suspected in 54% (38/70) men with previous surgery for bilateral cryptorchidism

Infertility despite surgery for cryptorchidism in childhood can be classified by patients with normal or elevated follicle-stimulating hormone and identified at orchidopexy

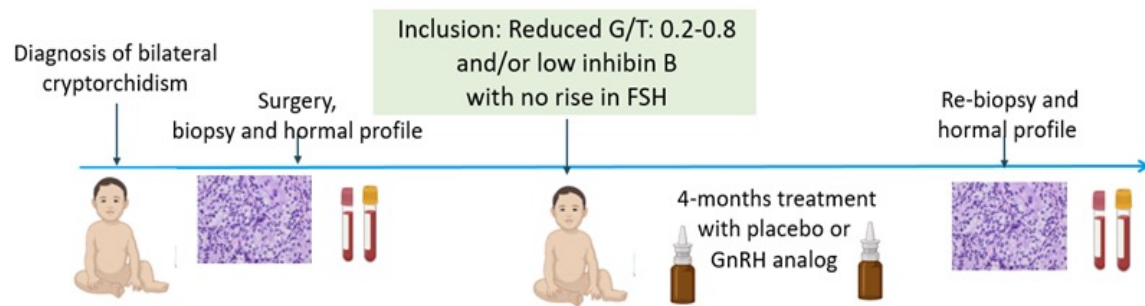
D. CORTES, J. THORUP, S. LINDENBERG* and J. VISFELDT 2003

	PRIMARY TESTICULAR DAMAGE - HYPER GONADOTROPIC HYPOGONADISM	DEFICIENCY OF FSH AND LH? HYPO GONADOTROPIC HYPOGONADISM
% (Number)	33% (23/70) patients	21% (15/70) patients
FSH IU/L*	16.0 (8.4-20.4) elevated	5.3 (2.6-7.4) normal
Sperm concentration million/mL*	0.0 (0 – 2.0)	1.5 (0 – 4.5)
Total testicular volume, mL*	22 (12-45)	30 (25-45)
Spermatogenic arrest, and % tubules spermatogenic arrest*	77% (10/13) 6% (5-80%)	100% (10/10) 29% (4-92%)
Sertoli-cell-only, and % tubules with Sertoli-cell-only*	100% (13/13) 77% (1-100%)	70% (7/10) 20% (3-96%)
Age at surgery *	12.9 (10.6-15.1)	12.8 (11.5-15.4)
Average S/T*	0.0015 (0-1.2)	0.31 (0-2.9)
Germ cells present, but S/T<30% of lowest normal value (<0.54)	0% (0/23)	60% (9/15)

* Median (range)



Evaluate efficacy and safety of postoperative GnRH treatment for boys suspected for **hypogonadotropic** hypogonadism after bilateral orchidopexy



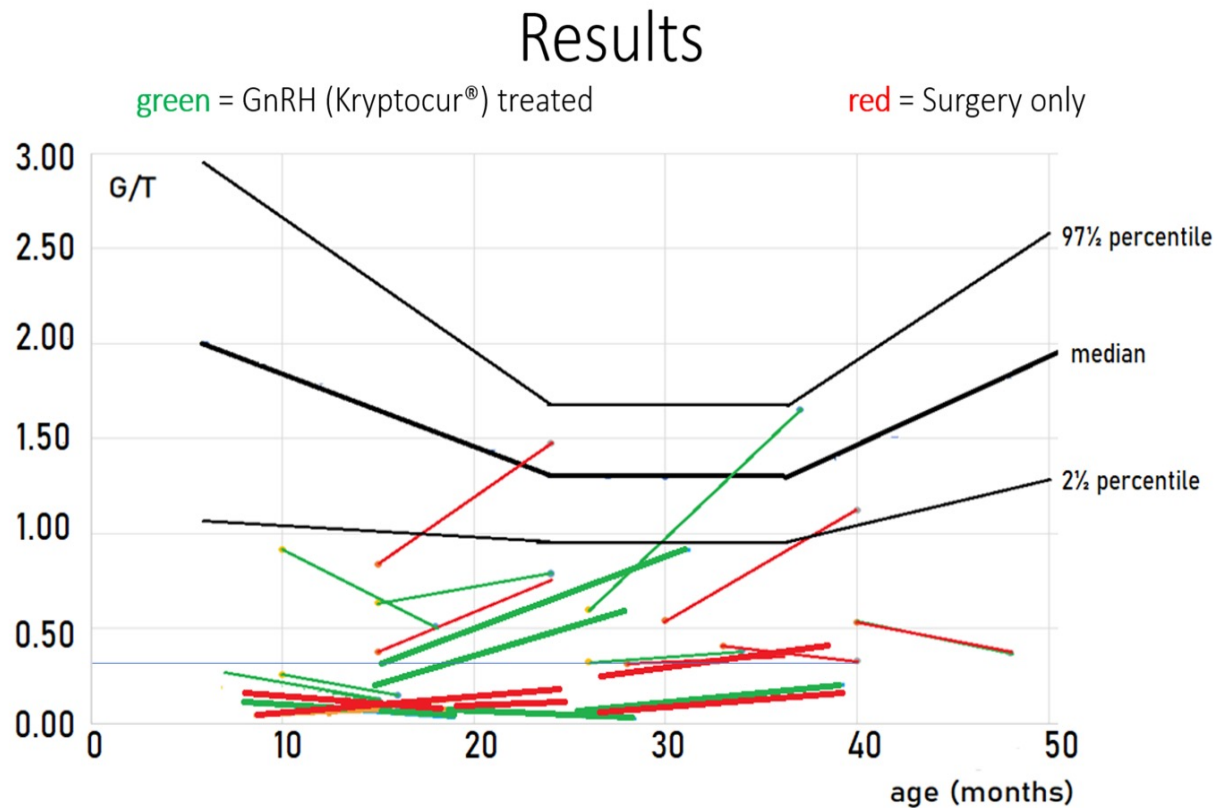
Prospective randomized clinical trial of adjuvant low dose GnRH (**Kryptocur®**), 4 months postoperatively (one spray in both nostril, 200 microgram every other day) or placebo

Data from the pilot study and the first part of the RCT-study, which was stopped...

22 boys with bilateral cryptorchidism, median 16 months old (8-46 months), suspected **hypogonadotropic** hypogonadism based on hormone-profile (FSH, LH and inhibin-B), and testicular biopsies with estimation of A dark spermatogonia (AdS/T) and total germ cell number per tubule (G/T) at orchidopexy

- 11 boys had adjuvant low dose GnRH (Kryptocur®), 4 months postoperatively (200 microgram every other day)
- 6 boys had double-blinded placebo
- 5 boys had no adjuvant treatment, pilot study
- All had repeat hormone-profile and testicular biopsies with G/T- and AdS/T-estimation, median 10 months after orchidopexy
- Hormonal values, G/T- and AdS/T were related to age dependent normal values

Results on germ cells



Drop in G/T, negative effect after GnRH treatment?

- At surgery 10 months old
Average G/T 0.83, SAd/T 0.004
Germ cells positive for PLAP, OCT3/4 and CD117+
- At follow-up 18 months old
Average G/T 0.47, SAd/T 0.019
Germ cells positive for PLAP only

Positive effects, increase in G/T

- Two patients with surgery only: 15 months of age and 30 months of age, respectively.
- One patient with GnRH treatment
- At surgery 25 months old
Average G/T 0.60, SAd/T 0.009
No germ cells positive for PLAP, OCT3/4 or CD117
- At follow-up 36 months old
Average G/T 1.68, SAd/T 0.06
Still germ cells not positive

	GnRH	Dose boys <6 years	HCG	Dose boys < 6 years
Cortes et al. 2000	Harmful effect for 1-4 years old boys can not be excluded	1.2 mg per day in 28 days, twice with a 3 months pause	Harmful effect for 1-4 years old boys can not be excluded	6 injections of 100 IE/kg (max 1,500). A 3 years old boy weights about 15 kg
Vinardi et al. 2001	Different inclusions, conclusion impossible	1.2 mg/d for 28 days followed by	Different inclusions, conclusion impossible	 9 injections of 500 IU
Hjertkvist et al. 1993	-		Increased density of blood vessels	10 injections of 500 IU
Dunkel et al. 1997	-		Apoptosis of spermatogonia In adulthood, previously undescended testis smaller, but sperm concentration not reduced	10 injections of 500 IU
Varela-Cievas et al. 2015	-		In adulthood, for boys 2-6 years of age, the previously undescended testis was smaller but the contralateral possible was larger	10 injections of 500 IU
Taskinen et al. 1997	-		In adulthood, smaller testes than those who had surgery only. The boys were 10 months to 13 years, mean age 4-5 years	10 injections of 500 IU
Thorup et al. 2025	No harmful effect	0.2 mg every other day for 4 months	-	

For boys younger than 6 years of age harmful effects can not be excluded, primarily in cases of high hormonal doses

Conclusion

A negative impact of hormonal treatment may depend on the doses used and boys younger than 6 years of age may be most sensitive

Thank you!

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- Extra slides