

Benefits and Drawbacks of Hormonal Treatment in Cryptorchidism



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Cryptorchidism = symptom

- Not “normal”
- Doctors want to mimick “normal” – “nature”
- What we know =
Orchidopexy = standard;
hormonal treatment remains controversial

Summary: **multifactorial etiology**

**Endocrine +
mechanical +
“production” error**

Impossible to find out the exact cause(s) in your patient

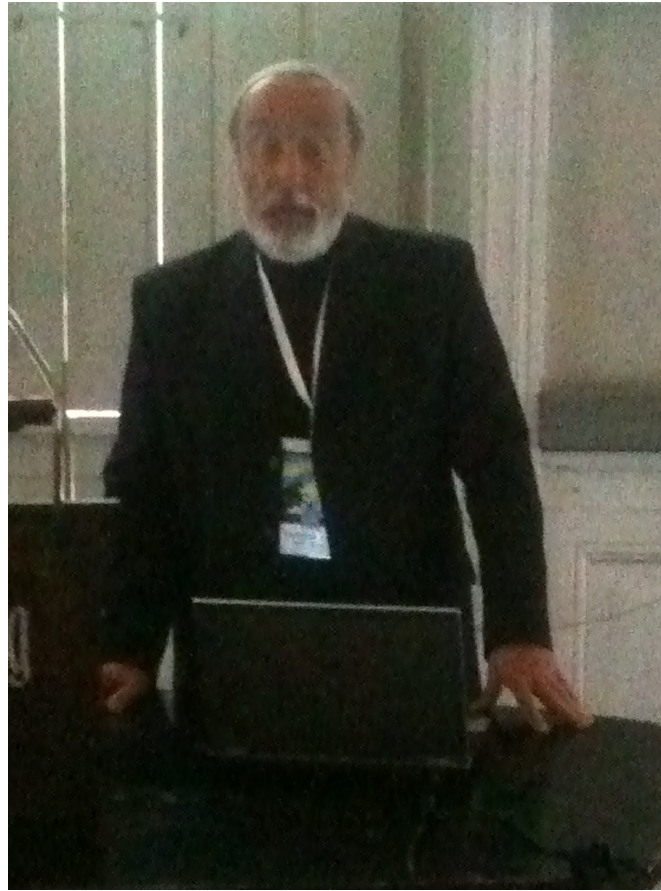
Multifactorial treatment



THE IMPORTANCE OF MINI-PUBERTY FOR FERTILITY IN CRYPTORCHIDISM

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Rationale for Hormonal Therapy

- Mimics postnatal “mini-puberty” (hCG or GnRH/LHRH)
- Intended effects:
 - Promote germ cell maturation
 - Potential fertility preservation

Hormones as primary treatment for (real) undescended testes

- It does NOT work!

Evaluation and Treatment of Cryptorchidism: AUA Guideline

Thomas F. Kolon, C. D. Anthony Herndon, Linda A. Baker, Laurence S. Baskin, Cheryl G. Baxter, Earl Y. Cheng, Mireya Diaz, Peter A. Lee, Carl J. Seashore, Gregory E. Tasian and Julia S. Barthold

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

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Treatment

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*)



Guidelines

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Science & Publications

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Paediatric Urology

3.2.4.1.1. Medical therapy for testicular descent

Hormonal therapy using hCG or gonadotropin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent, but has a limited success rate of only 20% [94]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [95]. In general, success rates depend on testicular location. The higher the testis is located prior to therapy, the lower the success rate, suggesting that testicular position is an important determinant of success [90]. Some authors recommend combined hCG-GnRH treatment. Unfortunately, it is poorly documented and the treatment groups were diverse. Some studies reported successful descent in up to 38% of non-responders to monotherapy [96]. A recent meta-analysis concludes that there is no consistent evidence to support hormone treatment alone in the management of undescended testes [65].

3.2.4.1.2. Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [97,98] and therefore serve as an additional tool to orchidopexy. A longitudinal study on boys undergoing hormone therapy (hCG) with or without surgery showed that patients with hormone therapy had better sperm quality compared to patients undergoing surgery alone or no treatment at all [99]. There is no difference in treatment with GnRH before (neo-adjuvant) or after (adjuvant) orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life [100].

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 [101].

As endocrine treatment may improve fertility index, the consensus of this Panel is to recommend endocrine treatment with GnRH analogues for boys with bilateral undescended testes in an attempt to preserve fertility potential (LE: 4).



TREATMENT WITH A LUTEINIZING HORMONE-RELEASING HORMONE ANALOGUE AFTER SUCCESSFUL ORCHIOPEXY MARKEDLY IMPROVES THE CHANCE OF FERTILITY LATER IN LIFE

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Pediatric Urology

International Braz J Urol

Vol. 34 (3): 319-328, May - June, 2008

Successful Treatment of Unilateral Cryptorchid Boys Risking Infertility with LH-RH Analogue

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CONCLUSIONS

The testes must be in a scrotal position (surgically corrected as indicated) before treatment with a low dose of luteinizing hormone-releasing hormone. Buserelin induced a significantly increased number of germ cells in testes located in a scrotal position compared to those in an undescended position. The earliest possible initiation of treatment greatly improves the chance of later fertility and 10 µg. of the luteinizing hormone-releasing hormone analogue buserelin administered as a nasal spray every other day for 6 months post-operatively seem to be effective for enhancing the chance of fertility later in life.



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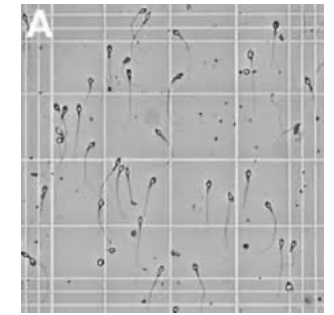
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Fertility. Formerly bilateral cryptorchid men have greatly reduced fertility compared with men with a history of unilateral cryptorchidism and the general male population.⁴⁸ One retrospective study showed a paternity rate of 62% (38% infertile) in formerly bilaterally cryptorchid men compared with a matched control group of 94% (6% infertile), indicating a six fold increased risk.⁴⁹ In contrast, unilaterally cryptorchid men had a paternity rate of 89.5%, which is similar to the level of fertility found in other studies of the general population (94%).

PATERNITY

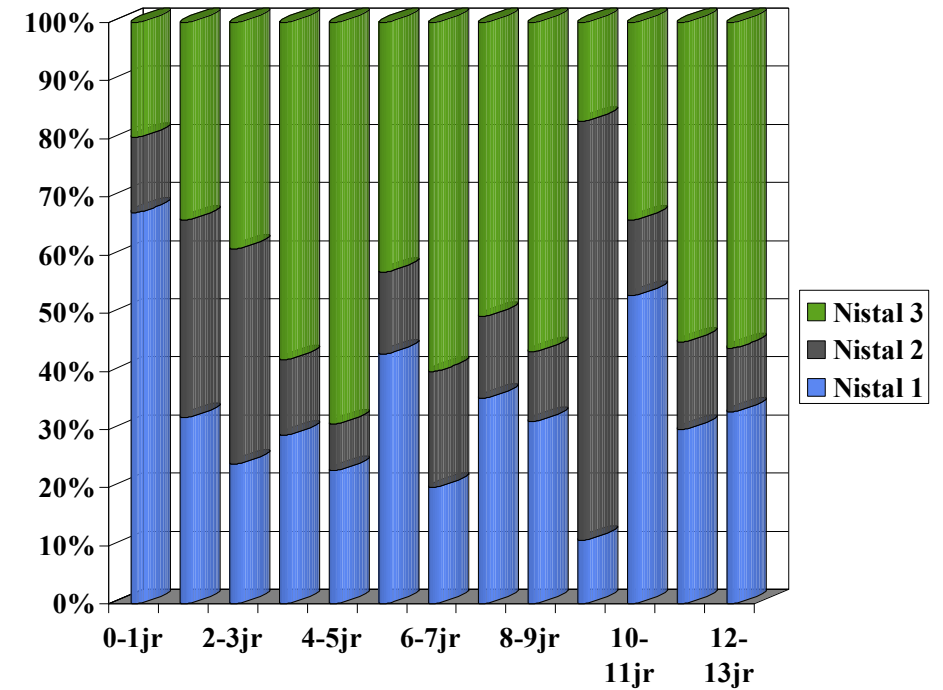


Guideline Position (EAU/ESPU 2024)

- **Do not recommend hormonal therapy as routine**
- Orchidopexy before 12–18 months = standard of care
- Hormonal therapy may be considered:
 - Bilateral non-palpable testes
 - Research protocols on fertility outcomes

Material and Methods

- January 2000 and December 2005
- 212 prepubertal boys
- age 7 months - 12 yr 11 months
- Mean age 4 yr 3 months
- 262 inguinal explorations
- 50 bilateral (24%)
- 162 unilateral (76%): 43% left vs 57% right





-
- Ideal = neonatal or perinatal
(high LHRH from mother)
 - Looking (no touch)
 - Cross legged (frog) position + WAIT
(cremasteric smooth muscle fibers = tired)



Categorize undescended testes

- Palpable

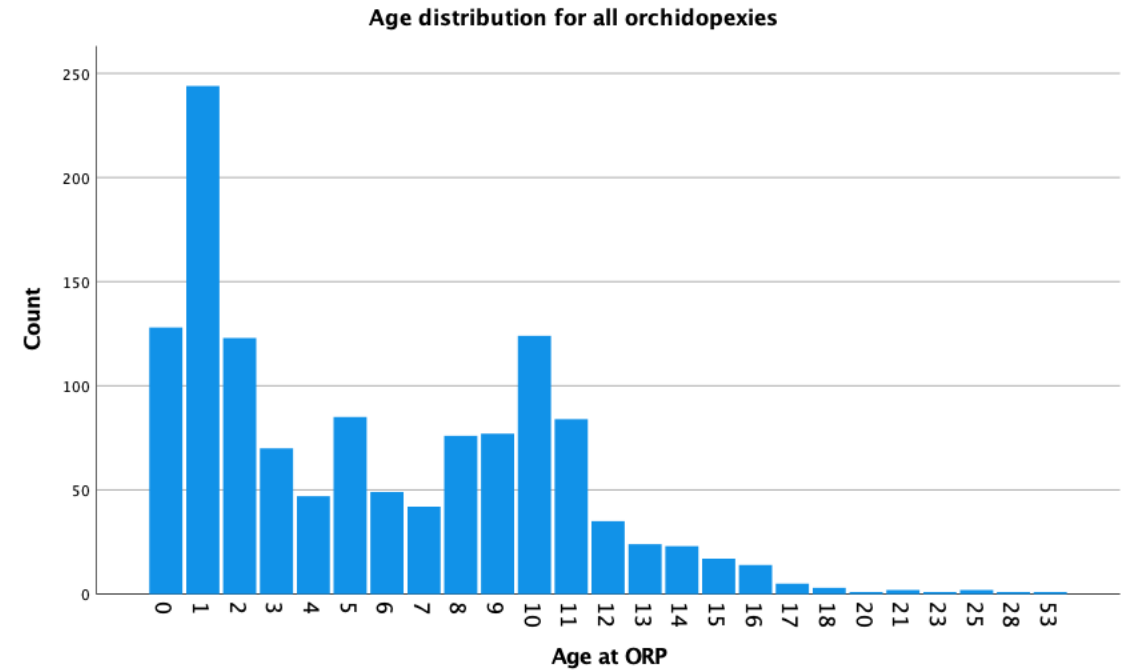
undescended
ectopic
retractile

- Non palpable

intraabdominal
absent
vanishing (torsion)

Cryptorchidism – undescended testis

- Congenital
- Ascending



Ascending testis: does it exist?

Figure : Age distribution among all orchidopexies performed at UZ Leuven between February 6th 1997 and November 21st 2019.

Ascending testis

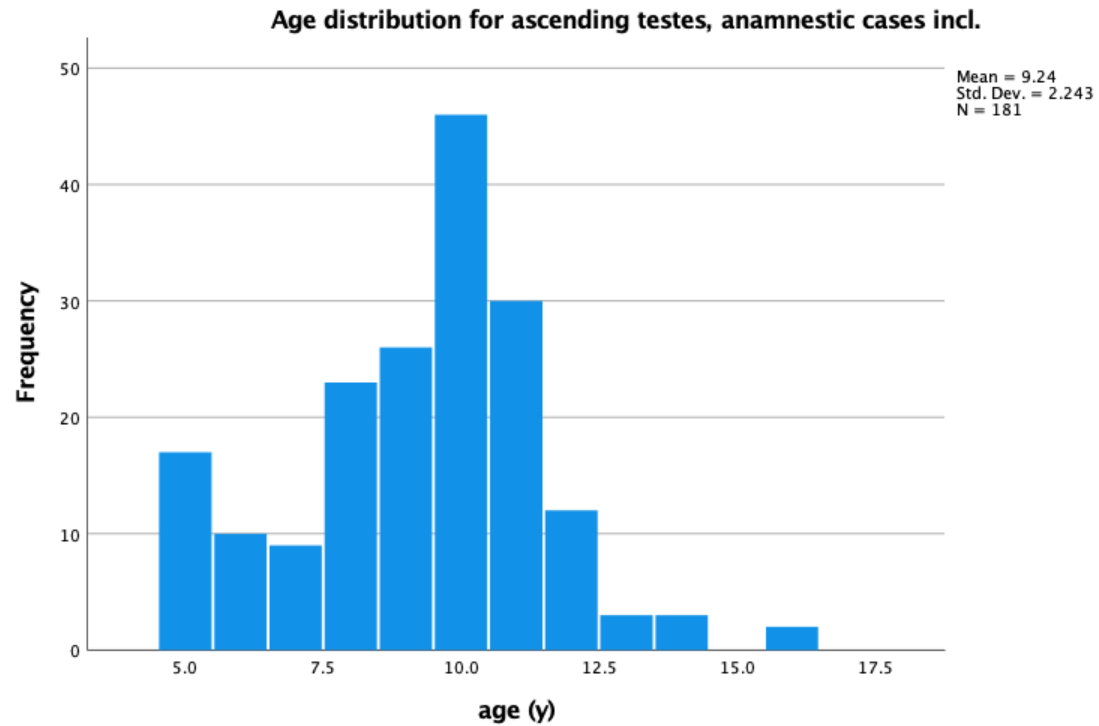
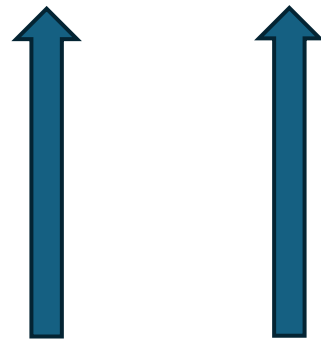


Figure 4: Age distribution within the subgroup of ascending testes, anamnestic cases included.



Quality

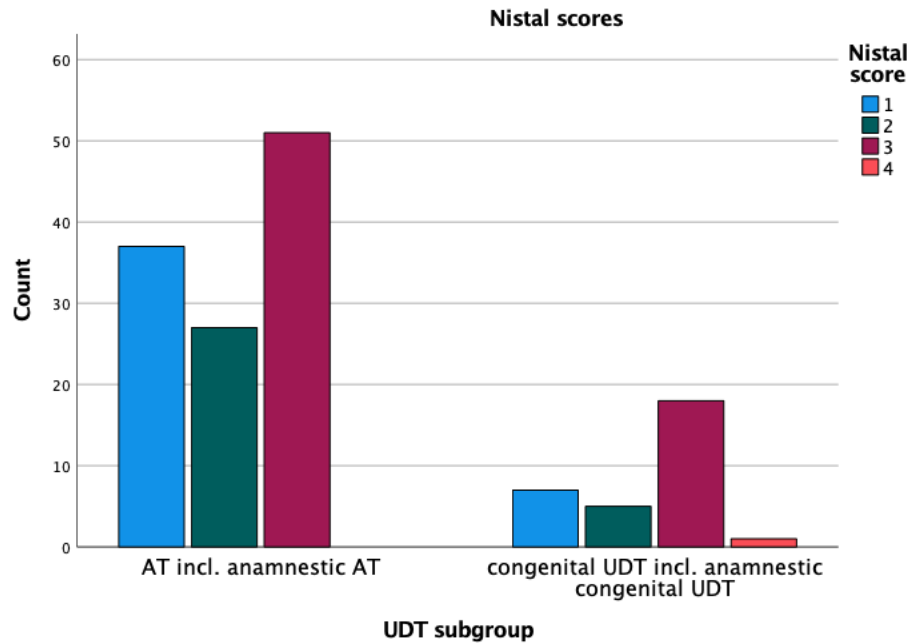


Figure 8: Nistal scores compared between ascending testes and congenital undescended testes, anamnestic cases included. Abbreviations: AT, ascending testes; UDT, undescended testes.

Nistal et al, Human pathology, nov 1980

- Mean tubular diameter (MTD)
age dependent - mean value
- Tubular fertility index (TFI)
50 cross section tubules,
1 spermatogonia/tubule = ok
if 60% = ok
- Sertoli cell index
number of Sertoli cells per tubular section

Nistal classification

- **Type I**
MTD <10% TFI 40-60% SCI nl
- **Type II**
MTD 10-30% TFI 20-40% SCI nl
- **Type III**
MTD >30% TFI < 20% SCI nl/low
- **Type IV**
MTD (nl) TFI < 10% SCI 30% high



men with a history of bilateral cryptorchidism: >20 years after their surgery +/- LHRH

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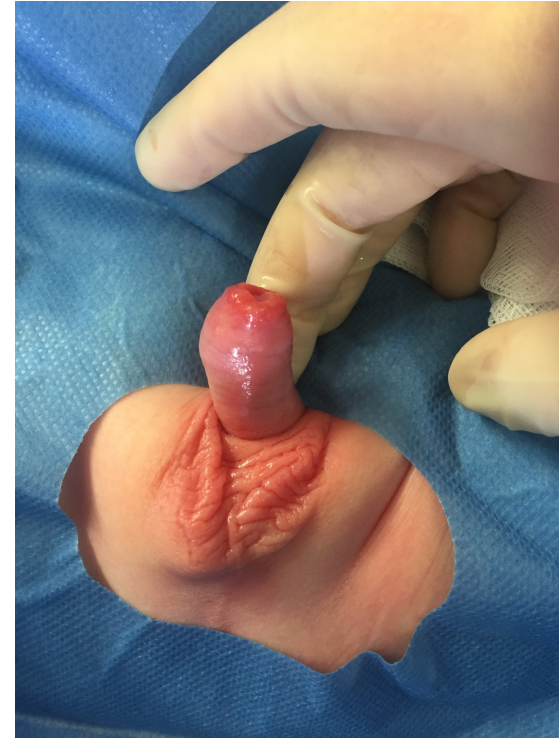
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TREATMENT WITH A LUTEINIZING HORMONE-RELEASING HORMONE ANALOGUE AFTER SUCCESSFUL ORCHIOPEXY MARKEDLY IMPROVES THE CHANCE OF FERTILITY LATER IN LIFE

F. HADŽISELIMOVIĆ AND B. HERZOG

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Bilateral Cryptorchidism

All had surgery + offered intermittent low-dose
LHRH intranasal therapy for at least 6 months



Table 1 Testicular histology and hormonal levels of LH, FSH, inhibin B and testosterone grouped by severity of sperm analysis abnormalities.

Sperm analysis	LH-RH administration	Age at surgery (years)	Histology (Nistal grade)	Sperm concentration (x10 ⁶ /mL)	Normal sperm morphology (%)	Sperm motility (%)	LH (IU/L)	FSH (IU/L)	Inhibin B (ng/L)	Testosterone (ng/dL)
Normal (N = 3)	☒	4.8	1 ^(1,1)	57.6	6	84	5.8	11.9 ^a	117.9	661.9
	☐	9.3	1 ^(1,1)	40.1	4	86	5.5	4.5	160.1	340.0
	☒ ^A	9.5	3 ^(3,3)	31.4	3 ^a	52	N/A	N/A	N/A	N/A
Oligospermia (N = 9) Mild	☒	1.6	3 ^(3,3)	14.2 ^a	6	68	6.2	4.0	103.8 ^a	493.3
	☒	4.1	3 ^(3,3)	10.2 ^a	5	84	7.5	9.3 ^a	50.6 ^a	600.2
	☒	2.1	2 ^(2,N/A)	8.5 ^a	1 ^a	74	3.8	4.2	286.3	469.3
	☒ ^B	2.0	1 ^(2,1)	8.0 ^a	1 ^a	34	N/A	N/A	N/A	N/A
	☒	11.3	2 ^(2,2)	5.2 ^a	1 ^a	51	6.5	8.4	107.7	683.3
	☒	2.2	2 ^(2,2)	1.8 ^a	5	16 ^a	8.7 ^a	7.1	88.6 ^a	583.0
Moderate	☒ ^C	10.4	2 ^(2,3)	1.2 ^a	3 ^a	21 ^a	5.7	3.7	239.5	570.5
Severe	☐	11.4	3 ^(3,3)	0.5 ^a	7	54	4.4	4.8	203.1	295.5 ^a
	☐	7.3	1 ^(1,1)	0.4 ^a	N/A	52	5.4	14.5 ^a	38.2 ^a	420.6
Azoospermia (N = 4)	☒	10.8	SO ^(SO,SO)	<0.3 ^a	N/A	N/A	5.5	7.0	39.6 ^a	289.2 ^a
	☒	5.3	2 ^(2,3)	<0.3 ^a	N/A	N/A	8.4	15.7 ^a	114.2	555.3
	☐ ^D	9.2	2 ^(2,2)	<0.3 ^a	N/A	N/A	4.1	6.1	149.9	559.1
	☐ ^E	11.2	3 ^(3,3)	0 ^a	N/A	N/A	11.2 ^a	16.6 ^a	<10.0 ^a	147.0 ^a
No sperm analysis (N = 6)	☒	1.6	3 ^(3,N/A)	N/A	N/A	N/A	5.9	19.5 ^a	60.9 ^a	382.9
	☒	9.1	2 ^(2,2)	N/A	N/A	N/A	4.1	6.0	115.4	491.2
	☒	8.7	1 ^(1,2)	N/A	N/A	N/A	7.0	4.5	160.6	399.4
	☒	11.2	SO ^(SO,SO)	N/A	N/A	N/A	5.4	5.0	102.4 ^a	627.7
	☒	10.7	3 ^(3,3)	N/A	N/A	N/A	5.0	3.4	118.6	528.4
	☒ ^F	3.2	3 ^(3,3)	N/A	N/A	N/A	6.6	22.2 ^a	<10 ^a	536.7

☒ LH-RH administered ☐ No LH-RH administered ☒ HCG administered.

Superscript in histology column indicates bilateral Nistal score.

A) Sperm analysis already done because patient knew the risks of cryptorchidism and wanted a "check-up".

B) Sperm analysis already done because of erection problems.

C) Sperm analysis already done because of prolonged period of trying to conceive a pregnancy without success. Eventually fathered a child without medical assistance. Sample was produced out of the hospital and we therefore excluded motility percentage from our analyses.

D) No CFTR mutation, no Y-chromosome microdeletions and normal karyotyping.

E) Paternity attempt failed. Negative Testicular/Epididymal Sperm Extraction (TESE).

F) Excluded from comparisons between LH-RH and non-LH-RH treated groups due to administration of HCG (Pregnyl).

^a Value out of normal range

- Search for the patients...
>150 patients
(44 were found)
22 agreed

Low-dose every-second-day LHRH treatment following bilateral orchidopexy in children with bilateral cryptorchidism may improve their fertility outcome

}, Guy Bogaert ^{a,*}, Michael Vanhoyland ^b, Faruk Hadziselimovic ^c



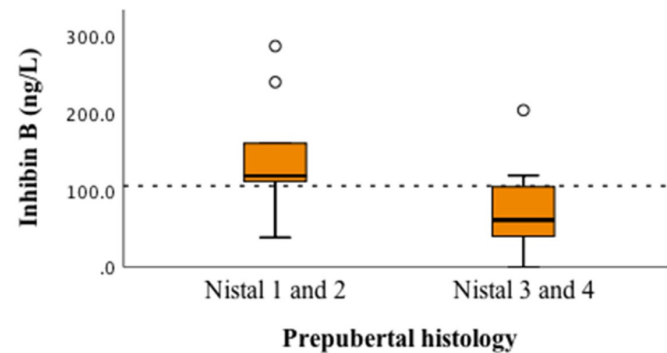
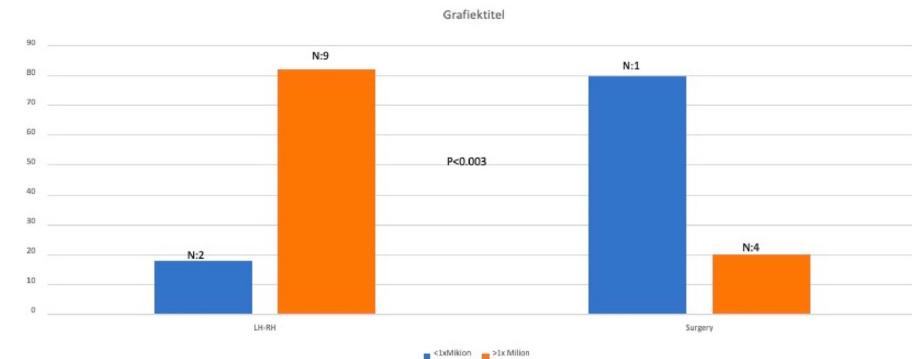


Fig. 1 Post-pubertal Inhibin B levels grouped according to prepubertal histology. Nistal grades 3 and 4 (N = 9) are associated with higher rates of inhibin B levels below the lower normal limit ($P \leq 0.022$, Fisher's exact test) and lower mean inhibin B levels ($75.44 \text{ ng/L} \pm 64.41$; N = 9) compared with Nistal grades 1 and 2 ($143.49 \text{ ng/L} \pm 69.21$; N = 11) ($P \leq 0.037$). Dots indicate outliers. Dotted line indicates lower limit of normal (105.0 ng/L).

This study confirms the already known correlations between FSH, LH, inhibin B, and testicular volume [23,24]. Inhibin B was not correlated with sperm concentration or total sperm count, which is contrary to the literature [24,25]. Since testicular volume during orchidopexy was correlated to patient age at surgery, it was not possible to correlate this volume to any data gathered in adulthood because of confounding. Furthermore, 94% of treated and 75% of untreated men had LH values in the normal range despite moderate to severe infertility, indicating a relatively hypogonadotropic hypogonadism. Identical results were obtained in a large prospective study [11].

Adult spermogram results in men with history of bilateral cryptorchidism and comparison if they received postoperative low-dose intermittent long-term LHRH treatment



Summary figure Administration of a postoperative low-dose every-second-day LHRH (Kryptokur®) treatment in boys with bilateral undescended testes can rescue their fertility potential to a considerable degree and reduce the development of azoospermia. The main study limitations are the non-random administration of LHRH and heterogeneity among LHRH regimens.

None of the patients and their parents reported any side effects or problems during or after the LHRH treatment.

Our data show that Nistal grading of testicular biopsies, albeit correlated with inhibin B levels, however, is not accurate enough to predict later fertility and therefore should not be used to decide who should receive LHRH post surgery.

It's all
about
PATERNITY



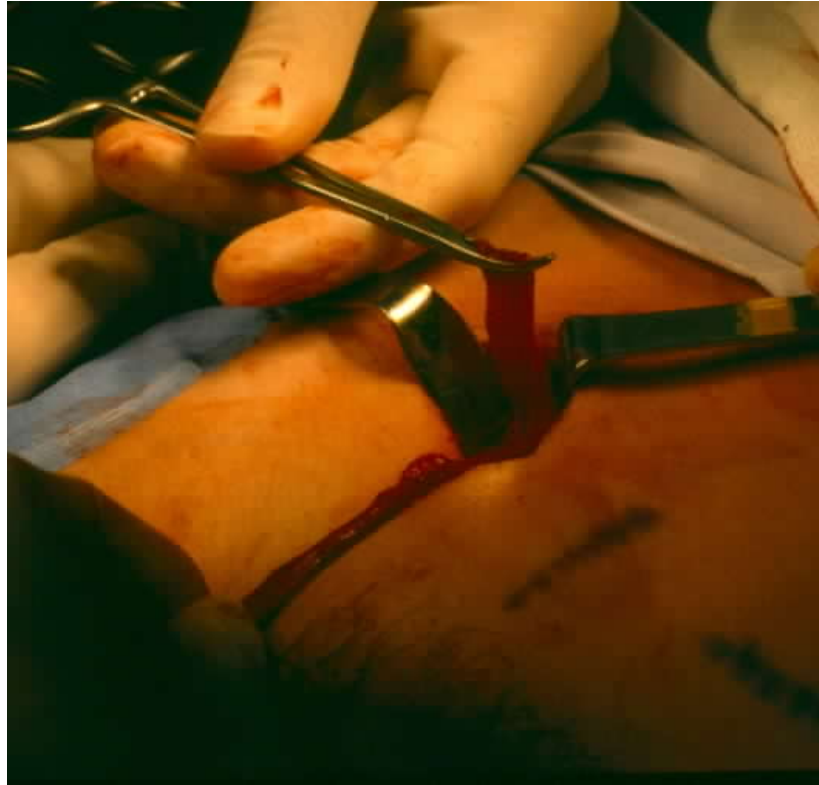


Benefits and Drawbacks of Hormonal Treatment in Cryptorchidism



Choose an excellent
pediatric urologist

- **complete cremaster dissection
(smooth muscles)**
- **section of the processus vaginalis
(peritoneum)**
- **Subdartos pouch
(between skin and scrotum muscle)**



Conclusion: hormones in/for cryptorchidism

- Unilateral = > 90% paternity within 1yr (= 2 descended testes): don't
- Surgery (good) remains gold standard
- Reserve LHRH chronic low dose intermittent for bilateral (real) undescended testes
- Safety profile low dose intermittent LHRH treatment = good
(if you can buy it in Europe...?)



M&S
-FOOD-



BELGIAN

- CHOCOLATIER -

MILK, DARK & WHITE
FLAKED TRUFFLES



M&S
-FOOD-



SWISS

- CHOCOLATIER -

TRUFFLE ASSORTMENT

INDIVIDUALLY WRAPPED MILK, DARK, HAZELNUT
AND GOLDEN BLOND CHOCOLATE TRUFFLES

