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Therapeutic results in cryptorchidism after combination therapy with LH-RH nasal spray and HCG

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Summary

72 boys with 81 cryptorchidisms were treated with combined therapy of LHRH nasal spray and HCG in the period between 1984 and 1986. Kryptocur (LHRH) was applied as nasal spray at a dose of 1,2 µg daily over a period of 14 days. Half a HCG treatment was carried out subsequently according to the guidelines set up by the WHO with administration of 5 injections at 2-day intervals. Primary treatment results were considerably improved using this regime. The rate of complete descent was 86.4 % at the end of therapy and later dropped to 70.6 % after two years of follow-up. These results support those obtained by HADZISELIMOVIC with the combined treatment.

Key words: Cryptorchidism, hormonal treatment, combined LH-RH/HCG therapy

Introduction

Hormonal treatment of cryptorchidism has been applied for more than 55 years. The first therapeutic attempts with HCG detected in pregnancy urine by ASCHEIM and ZONDEK were made by the Berlin urologist Dr. Schapiro in 1930 by which it was possible to imitate the LH effect on Leydig cells and to obtain descent [3,16]. In 1960 McCann was able to prove that hypothalamus extract produced an increase in LH, thus confirming the assumption of HARRIS (1937) that the hypothalamus is controlled by releasing factors. In 1971 GUILLEMIN and SCHALLY succeeded in isolating the LH-RH and demonstrating it in its pure form. In 1974 BARTSCH and FRICK reported on the treatment of cryptorchidism using LHRH applied by intramuscular injections [1,5]. In the same years DAHLEN was capable of confirming intranasale absorption of the LHRH syray, and intranasal application of this has been routinely performed since the recommendation of HAPP in 1975 [4,11,12] (Fig. I).

Figür I. History

1930	Schapiro	HCG-Therapy
1937	Harris	Releasing Factor
1960	McCann	Hypotholomus-Extract
1971	Guillemin, Schally	Isolation of LH-RH
1974	Dahlen	Intranasal Resorption
1975	Happ	Spray-Treatment
1979	Hadziselimovic	LH-RH/HCG Combined Therapy

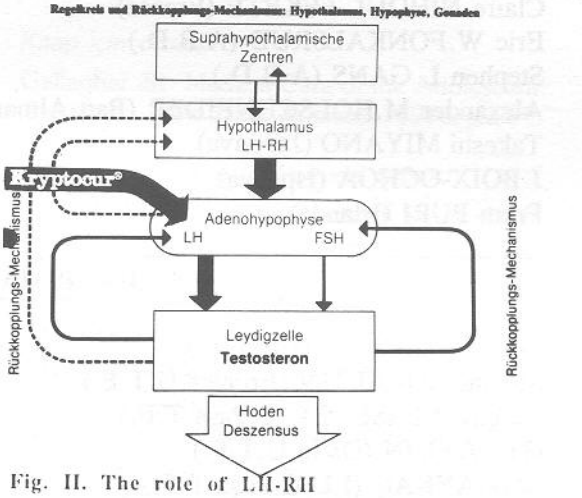

Fig. II. The role of LH-RH

LH-RH-therapy

LH-RH applied in prepubertal boys stimulates the pituitary to release LH and FSH as well as the Leydig cells. LH-RH is produced by the eminentia mediana and acts as chemotransmitter. Through the pituitary-portal system it is delivered to the gonadotropin-producing cells within the pituitary [6] (Fig. II). Maximum plasma values of LH and FSH were achieved 30-45 minutes

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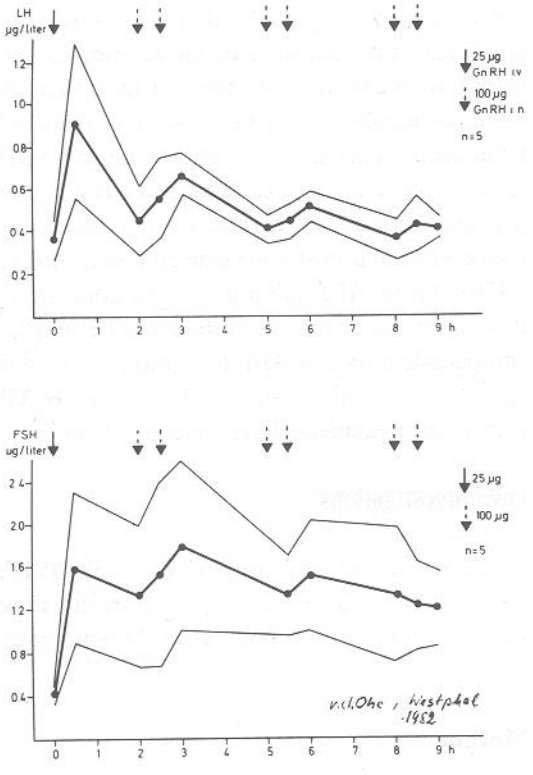


Fig. III. LH- and FSH-profile after repeated LH-RH-stimulation (6x1µg intranasally) [6]

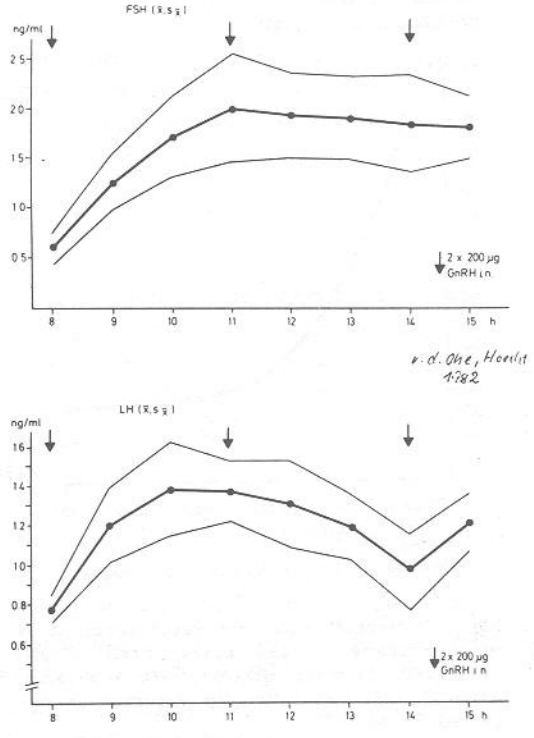


Fig. IV. Gonadotropin profile after administration of 400 µg LH-RH thrice [6]

after application repeated LH-RH-stimulation (6 x 100 µg intranasally) leads to a downregulation of the pituitary receptors as shown by Westphal [6] (Fig. III). This does not occur when the periods between stimulations are prolonged, as you can see in this picture by Hoecht [6,13]. LH-RH-application did not alter basal testosrerone serum levels [6] (Fig. IV).

Results of LH-RH therapy

Publications of controlled studies on the therapeutic results obtained with LH-RH were very rare in the beginning. The results of our own investigations performed within the scope of one of the most comprehensive controlled treatment series, in 161 cryptorchid boys, were presented in 1980. Succesful therapeutic results were achieved in about 53 % of the children (Fig. V). This corresponded to the results obtained by other authors [2,3,4,8,9,10,12,13,14,15,17,18,19]. The same therapeutic results were also reported for HCG therapy [4,28].

Fig. V. Primary success rate of Kryptocur therapy in 161 cases

age	No. of cases	success n	%
1- 3 years	84	41 =	48.8
4- 7 years	36	20 =	55.5
8-14 years	41	24 =	58.5
total	161	85 =	52.79 %

Recurrences after LH-RH therapy

Control examinations following both HCG and LHRH treatment showed that a high relapse rate must be expected [3,7,8]. Our own patient collective, which had been treated with LH-RH nasal spray in the years 1978 to 1980, was followed-up over a period of 7 years. The results are seen in table 2 (Fig. VI). At termination of the 28-day treatment with nasal spray 53.4 % of the testes showed complete descent. The recurrence rate was 44.2 % after one year. Thus, only 48 testes had descended, that is 29.8 %. Secondary retention was found in 10 further testes after 3 years, that

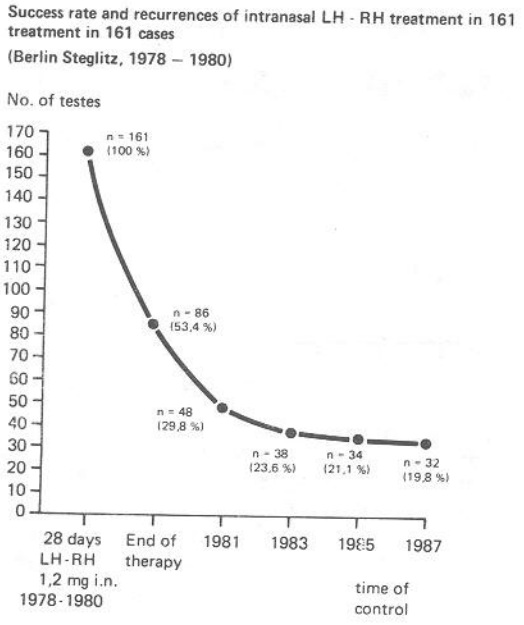


Fig. VI. Success rate and recurrences of Kryptocur therapy in 161 cases, Berlin-Steglitz 1978-1980. Primary descent rate was 53.4 %. After 7 years of follow-up recurrences occurred in 62.7 %.

is a total descensus rate of 23.6 %, and 34 boys still had their testes descended after 5 years. This means that recurrences were found in a further 4.6 % of the children. Two further recurrences were reported in the following 2 years, so that the total descensus rate was 19.8 % after 7 years. This corresponds to the observations reported in the literature for HCG therapy.

Combined therapy of LH-RH and HCG

The theoretical basis for an improvement of these results, which were on the whole disappointing because of the high relapse rate, was the fact that secretion of testosterone via FSH can only be stimulated in the presence of an equivalent amount of LH. In this connection, the FSH may play the role of a mediator which increases the sensitivity of Leydig cells to LH. KETELSLEGRS assumed an increase of gonadal receptors, and HANSSON an increase in the formation rate of androgen binding protein (ABP). This led to the attempt to continue treatment with HCG following unsuccessful LH-RH treatment. HADZISELIMOVIC was thus able to raise the success rate to approximately 80 % [9]. The recurrence rate was only 12 % after 6 months. This significant improvement in the therapeutic results can be explained by the fact that, first, an increased number of Leydig cells can be recruited from fibroblasts due to LHRH-induced FSH stimulation, leading to an increased LH receptor density; second, that there is a simultaneous increase in local testosterone concentrations due to FSH-induced ABP stimulation. In contrast to this, treatment with testosterone and LH has no comparable effect on ABP formation. Combined application of both substances (LHRH and HCG) is therefore assumed to have a greater effect.

Own investigations

Based on the conception of HADZISELIMOVIC, we started a controlled combination treatment of LHRH and HCG in 72 boys with 81 cryptorchidisms.

Method

Our therapeutic prodedure included LHRH treatment with nasal spray in combination with HCG treatment for equal periods of time. First, 400 µg (1,2 mg/day) weye applied there times daily over a period of 2 weeks; immediately there after, 5 injections of 250, 500, or 1000 IU HCG were administered intramuscularly at 2-day intervals depending on the age of the patient and according to the gudelines set up by WHO (Fig. VII). Treatment thus lasted for 4 weeks; the side effects of HCG application were considerably less pronounced than during application of 10 x the full dosis. Only in a few cases has occurred a slight penile unlargement following the HCG-application in combined treatment. However, testicular growth was observed in all cases. No other side effects were seen.

A LH-RH nasalspray for 2 weeks	3 x 400 µg daily
B HCG	
< 2 years	5x250 IE
3-5 years	5x500 IE
> 6 years	5x1000 IE

Fig. VII. Therapeutic procedure

	No. of testes
1- 3 years	23
4- 7 years	30
8-14 years	28
total	81

Fig. VIII. Age of children

position	No. of testes
abdominal	2
inguinal	49
perscrotal	30
scrotal	--
total	81
Pretreatment: without	43
LH-RH	31
HCG	7

Fig. IX. Anatomical findings

Age

For comparison with other studies, we establisled 3 different age groups: 23 boys belonged to the age group of 1 to 3 years, 30 boys to that of 4 to 7 years, and 28 boys were between 8 and 15 years (Fig. VIII).

Initial anatomical findings

These testes were not palpable in 2 cases. Inguinal palpations were possible in 49 cases, and prescrotal positioning of the testes was found in 30 children. Boys with retractile testes were excluded from the study (Fig. IX).

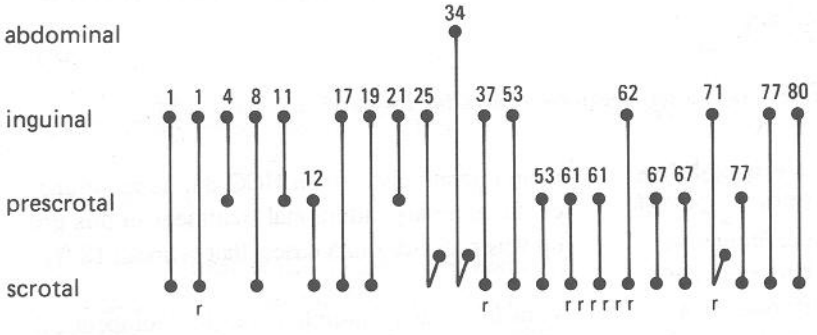
Pretreatment

43 of these 81 children presented for the first time, while previous treatment with HCG (n=7) or LHRH nasal spray (n=31) had proved unsuccessful in the remaining 38 boys.

Results

I. In 23 children of the lowest age-group from 1 to 3 years, complete descent occurred in 20 cases, 17 with final position and 3 with recurrences after 6-12 months (Fig. X). Five of them, however, had retractile testes. In this connection, the success was satisfactory in prescrotaly and inguinally positioned testes. Primary surgery became necessary in only three cases following hormonal treatment. Recurrences were found in 3 cases so that surgery had to be performed in a total of 6 testes, that is about 26 %.

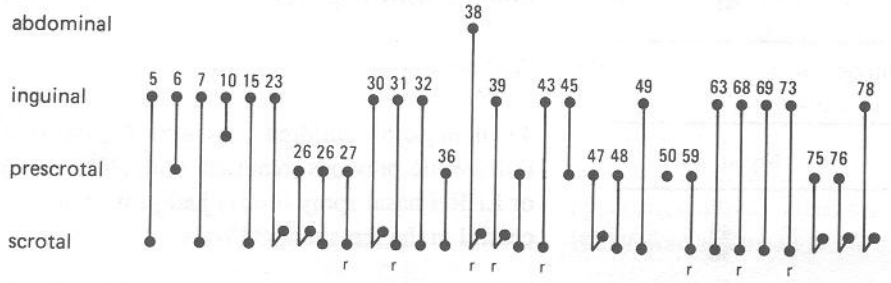
Success rate and position of testes before and after treatment.
Age group 1 – 3 years (n = 23)



total n = 23	success	surgery	
scrotal position	12	prim.surg.	3
scrotal-retractile	5	replase-surg.	3
total	17		6

Fig. X. Position of testes before and after treatment in 1-to 7-year-old boys (n=23).

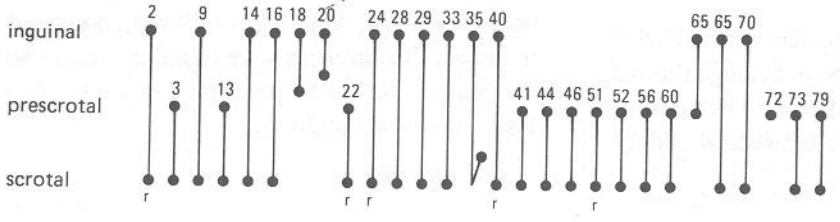
Success rate and position of testes before and after treatment. Age group 4 – 7 years (n = 30)



total n = 30	success	surgery	
scrotal position	11	prim. surg.	4
scrotal-retractile	6	replase-surg.	9
total	17		13

Fig. XI. Position of testes before and after treatment in 4-to 7-year-old boys (n=30).

Succsess rate and position of testes before and after treatment.
Age group 8 – 14 years (n = 28)



total n = 28	success	surgery	
scrotal position	18	prim. surg.	3
scrotal-retractile	5	HCG	1
		relapse-surg.	1
total	23		5

Fig. XII. Position of testes before and after treatment in 8-to 14-year-old boys (n=28).

2. Simalar results are found in the group of 4-to 7-year-old children (Fig. XI). 26 of 30 testes had descended: 8 of them were retractile. Primary surgery was required in four cases. There were recurrences in 9 cases. Surgery was performed in a total of 13 cases in this group, that is about 43 %.

3. We were able to find similarly good results in the group of 8- to 14-year-old boys, who almost exclusively had secondary retentions following retractile testes (Fig. XII). 23 of 28 testes had descended; 4 cases had to be treated primarily, 3 of them operatively, 1 with HCG due to recurrences. In summary, additional treatment in this gro up was necessary in 5 cases, that is about 18 %.

4. In bilateral cryptorchidism, the therapeutical results were different (Fig. XIII). After discontinuation of treatment with nasal spray, 14 testes of 9 boys with 18 testes had descended, 7 of them being located inguinally and 7 of 10 prescrotally. In 3 cases, the result was unsatisfactory, and surgery was mandatory. In 1 boy, in whom neither

Success rate and positon of testes before and after treatment in bilateral cryptorchidism (n = 18)

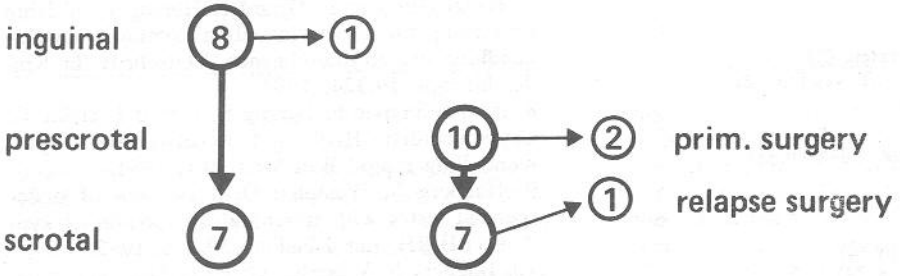


Fig. XIII. Position of testes in bilateral cryptorchidism

Fig. XIV. Primary results of LH-RH / HCG-(combined) therapy in 72 boys with 81 undescended testes

age	No. of cases	descent	surgery
1- 3 years	23	20	3
4- 7 years	30	26	4
8-14 years	28	24	4
total	81	70	11
		= 86.4 %	13.6 %

of the testes descended, was submitted to surgery. Furthermore, secondary retention occurred in 1 case. 6 children had their testes descended bilaterally; 2 boys exhibited descent on one side and a retractile testis on the other. 5. Thus, the rate of descent for a total number of 81 testes in 72 children was 86.4 % at termination of the combined LHRH-HCG treatment. Retractile testes were seen in 19 cases. Primary surgery was necessary in only 13.6 % of all cases (Fig. XIV).

Recurrences

At the end of treatment, 10 boys were submitted to surgery, and subsequent HCG treatment was successful in another case (Fig. XV). There were recurrences in 5 cases after 6 months, in 3 after 12 months, in 3 more after 18 months and in 2 after 24 months. That correspands to 70.3 % in contrast to 23 % of those treated by a single therapy only. We therefore considered the difference between combined therapy and single therapy to be highly significant (Fig. XVI).

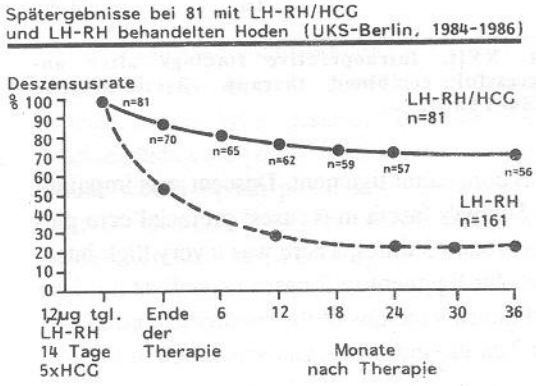


Fig. XV. Late results and relapses in 81 cases treated with LH-RH/HCG. The difference between LH-RH therapy and combined therapy is highly signgficant.

The surgical findings of unsuccessful primary treatment were similar to the findings obtained for recurrences (Fig. XVII). There were anatomical irregularities in all cases: inguinal hernias were present 8 times, hydroceles in 2 cases, 1 of them

Final results of LH-RH/HCG treatment in 72 boys with 81 undescended testes (Berlin Steglitz, 1984-1986)

age	No. of cases	descent	prim. surg.	relapses
1- 3 years	23	20	3	3
4- 7 years	30	26	4	9
8-14 years	28	24	3	1
total	81	70	10	13
successful treatment		primary 86.4 %		after 2 years 70.3 %

Fig. XVI. Final results

Intraoperative findings in 24 testes after unsuccessful LH-RH/HCG-treatment

Cause of maldescensus	number of cases
1. Hernia inguinalis	8
. Hernia, Scarpa-fascia (2)	
. Hernia, Scarpa-F.,T. vag.fun. (2)	
2. Hydrocele	2
. Hydrocele, cong. ligament (1)	
3. Prefascial ectopy	3
4. Scarpa Fascia	6
. Scarpa F., ectopy (2)	
. Scarpa F., hernia (2)	
5. Lig. interfoveolare	2
6. Tunica vag. funiculi	2
7. testicular separation	1
total	24

Fig. XVII. Intraoperative findings after unsuccessful combined therapy (Berlin-Steglitz 1984-1986).

with congenital ligament. Descent was impaired by Scarpa's fascia in 6 cases; prefacial ecto pies were found 3 times. There was a very high interfoveolar ligament in 2 cases as well as a thicke ned tunica vaginalis of the spermatic cord in anot her 2 cases, and a testicular separation in 1 case.

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