

Luteinising hormone releasing hormone for incomplete descent of the testis

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SUMMARY Forty boys with 54 incompletely descended testes took part in a double blind, controlled trial of intranasal luteinising hormone releasing hormone. In the control (placebo) group of 18 boys there was no significant change in testicular descent and all required orchidopexy; in the 22 treated boys, however, 12 of 29 testes (42%) were found in a lower position.

This study supports the idea that a trial of intranasal luteinising hormone releasing hormone (1200 µg/day for 28 days) will help clarify the need for orchidopexy in at least 30% of boys with incomplete descent of the testis, particularly those in whom the testes have emerged from the inguinal canal.

It is more than 50 years since Shapiro used hormone treatment for the undescended testis.¹ The place of this treatment remained unclear because controlled studies were not performed and retractile testes may well have been included.² For these reasons success rates after hormone treatment have ranged from 0% to 90%. In one of the largest uncontrolled studies of intramuscular human chorionic gonadotrophin, however, 23% of 350 undescended testes were found to descend,³ and when luteinising hormone releasing hormone (LHRH) became available similar claims for success followed its use in injectable form.^{4,5} More recently, intranasal LHRH has been available and several studies have again shown variable success rates.⁶⁻⁹

The first controlled study of intranasal LHRH, based at four separate centres in Europe, showed success rates varying between the centres from 15% to 60%.⁷ Despite continuing confusion intranasal LHRH is being widely used,^{10,11} although it is expensive.¹² For these reasons we have performed a single centre, controlled trial to determine the efficacy of the drug.

Patients and methods

This study was carried out in two stages. The first trial recruited 20 boys with incomplete testicular descent. Initially each child underwent a full clinical examination, questions were asked specifically about orchitis, trauma, and torsions; body weight and height were measured; and the position and size

of the testes were recorded. The boys were divided by random, double blind allocation into two groups; eight controls who received a spray containing placebo and 12 who received active LHRH intranasal spray at a dose of 300 µg twice daily.

Results of this trial were inconclusive and a second trial was organised using a higher dosage regimen. For this another 20 boys were recruited and allocated in a similar manner into a control group of boys and an active treatment group of 10 who received LHRH spray at a dose of 400 µg three times per day (200 µg before and after meals).

In both trials children were re-examined after four weeks; side effects noted, body height and weight measured, and position of testes recorded. Testicular position was assessed independently by two observers. The furthest point along the normal line of descent to which the testis could be comfortably manipulated was recorded and for this study we have defined five positions of testicular descent (Table 1). An inguinal testis lies within the inguinal canal and a prepubic testis lies between the external

Table 1 *Clinical assessment of testicular position*

Position	Description
1	Inguinal
2	Prepubic (at external ring)
3	High scrotal or neck of scrotum
4	Mid-scrotal
5	Low scrotal (normal)

ring and the neck of the scrotum. Where there was doubt, the testis was judged to be at the lower of the two positions. Testicular size was assessed by comparison with artificial testes of known volume.

Statistical significance was determined using a χ^2 test with Yates's correction.

Results

In expressing the results we have combined the control groups and shown the results of the two treatment groups separately. Twenty five incompletely descended testes were found in the 18 boys in the control group (mean age 6.5 years). There were 16 in the first study (low dose) group and 13 in the second study (high dose) group (mean ages 8.3 and 6.3 years respectively) (Table 2). Positions of these incompletely descended testes before and after four weeks' treatment are shown in the Figure.

In the control group three testes were found at a lower position after four weeks and three at a higher position. Of the 16 testes of boys receiving low dose

LHRH, five improved position—four from position 3 to 4 (high to mid-scrotal) and one from position 4 to 5 (mid-scrotal to normal). In the high dose group, seven of 13 testes improved—four from position 3 to 4 (high to mid-scrotal), one from position 3 to 5 (high to normal), and two from position 4 to 5 (mid-scrotal to normal). Two testes were found in a higher position after receiving LHRH treatment.

Orchidopexy was performed if the testis could not be brought lower than position 3 (high scrotal) or could only be manipulated into position 4 (mid-scrotal) with difficulty after four weeks' observation. All controls and 17 of 29 treated testes underwent orchidopexy. In those who have undergone orchidopexy the position of the testis corresponded to the preoperative clinical evaluation.

Nasal spray LHRH was well tolerated by all children. Treatment sheets completed by parents indicated excellent compliance with all therapeutic schedules. After treatment changes in weight and height were minimal and similar for both groups. No side effects were reported.

Discussion

This study has confirmed that treatment with intranasal LHRH in boys with incomplete descent of the testis is associated with a therapeutic response that may enable avoidance of orchidopexy. This result was obtained after use of LHRH during two successive trial periods. In the first part of the trial we used the lower dose of LHRH as described by Pirazzoli *et al.*⁸ Because these initial results seemed inconclusive we decided to repeat the study using the higher dose regimen suggested by Illig *et al.*⁷ Boys receiving lower dose LHRH showed an improvement in testicular position in five out of 16

Table 2 Results of luteinising hormone releasing hormone (LHRH) treatment in low dose (300 µg/day) and high dose (400 µg/day) groups and a control group

Group	No boys	Age range (mean) (yrs)	No IDT	Position improved	No operated
Control	18	2.5-11.1 (6.5)	25	3	25
Low dose LHRH	12	4.5-12.3 (8.3)	16	5	11
High dose LHRH	10	4.3-9.9 (6.3)	13	7	6

IDT=incompletely descended testis.

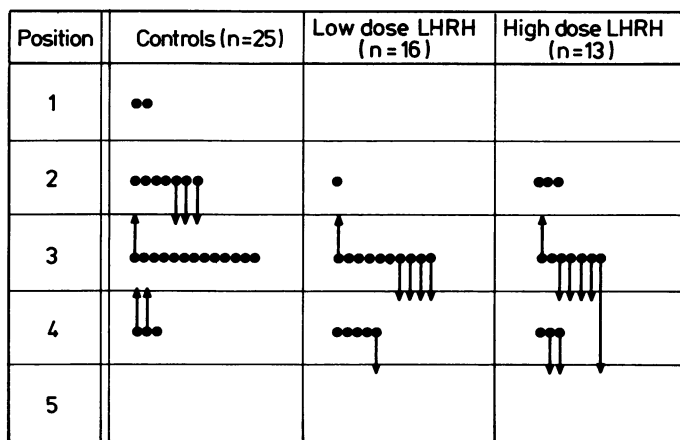


Figure Change in position in 54 incompletely descended testes in patients treated with luteinising hormone releasing hormone (LHRH) and controls.

↑=higher position; ↓=lower (improved) position. For definition of position, see Table 1.

testes (31%); using the higher dose seven out of 13 improved (54%).

Comparisons with previous studies are made difficult because of variations in methods of clinical assessment and classification. When we started our trial only one double blind, controlled study had been reported (Illig *et al*),⁷ which showed complete descent of 23 of 61 testes (37%). More recently two other controlled clinical studies have been published. Bertelsen *et al*¹³ reported that eight testes out of 34 (24%) descended and Hagberg *et al*¹⁴ showed descent in eight of 29 (28%). Thus results of four double blind, controlled trials indicate that between 24 and 41% of testes may descend under the influence of LHRH. This conclusion is similar to that drawn from one of the earliest studies of hormonal treatment performed by Spence and Scowen in 1938.¹⁵ They used painful injections of gonadotrophic hormone and found improvement in 27 of 65 testes (42%). Some of these older regimens of human chorionic gonadotrophin treatment also caused secondary sexual changes, thus the advent of painless intranasal LHRH spray without side effects affords treatment that is more acceptable to patient and doctor.

A review of previous uncontrolled trials of hormone treatment for undescended testes is confused by different definitions and the inclusion of retractile testes in some studies. We believe that careful definition and assessment of these boys is of vital importance before conclusions can be accepted. The term 'incomplete descent' has been used in this study to describe a testis that has become arrested along a normal line of descent—as opposed to an ectopic testis. The incompletely descended testis must be distinguished from the retractile testis which is a variant of normal.¹⁶ A retractile testis is often initially located above the scrotal neck, it can be manipulated, when the child is lying supine, into the middle or lower third of the scrotum and remains at least temporarily in that position after the examining finger has been removed. Diagnosis is confirmed with the child in the crouching position when the cremasteric reflex is inhibited and the testis descends into the scrotum.¹⁷ In assessing changes induced by treatment we have found it valuable to record testicular position as the furthest point to which the gonad can be manipulated and have expressed this numerically (Table 1). The accuracy of this technique was reflected in the considerable measure of agreement between the two independent observers.

Many surgeons would not operate on testes which reach the mid-scrotum (position 4) and it is our policy not to treat testes which can comfortably be brought to the mid-scrotum. The 10 testes in

position 4 which we have included in the study could only be manipulated into the mid-scrotum with difficulty and rested in a higher position; we would usually operate on these testes. In the control group two of three testes in position 4 were found in the high scrotal position (position 3) on review, whereas improvement was seen in three of eight treated mid-scrotal testes (the remaining five underwent orchidopexy). In the study group, eight testes improved position to end up at the mid-scrotum (position 4) and these did not undergo orchidopexy.

At the initial assessment most (56%) of the 54 testes were localised in position 3 (high scrotal) as shown in the Figure. It is this group of patients which is often difficult to assess and who are usually subjected to orchidopexy. After treatment nine of the 17 testes (53%) initially in position 3 were located one position lower in the mid-scrotum. The study by Hagberg *et al*¹⁴ also suggested that LHRH treatment may be most successful when the initial testicular position is upper scrotal.

Including testes from all positions, 12 of the 29 actively treated testes did not undergo orchidopexy compared with none in the control group ($P < 0.001$). Excluding those which started in position 4, nine of 21 actively treated avoided orchidopexy whereas all 22 controls underwent surgery ($P < 0.001$).

It may be that total dose and frequency of administration of LHRH has some effect. The frequent priming of the six dose daily regimen of Illig *et al*⁷ may stimulate more gonadotrophin actively than the twice daily regimen of Pirazzoli *et al*,⁸ which had not been subjected to controlled trial until this study. As compliance was good, however, we would suggest that the higher dose is used until further studies indicate that it is not necessary. Our numbers are too small to confirm the suggestion that boys of less than 6 years of age respond more readily than older boys.¹³ The small numbers of inguinal or prepubic testes we have studied have not shown a response and testes in these positions require early operative treatment¹⁸ unless further studies show greater efficacy for LHRH.

We have shown that there may be a place for LHRH nasal spray in treating patients whose testes have emerged from the inguinal canal but have not descended sufficiently to avoid surgical treatment. A four week course of LHRH would be expected to improve the position of at least 30% of these testes and help determine which patients need orchidopexy.

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