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Screening for cryptorchid boys risking sterility and results of long-term buserelin treatment after successful orchiopexy

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Abstract. This long-term prospective follow-up study showed that in cryptorchid patients a significant correlation exists between the number of germ cells at the time of orchiopexy (prepuberty) and the spermiogram, and thus a biopsy has a prognostic value. Fifty percent of our patients had a germ cell count of < 0.1 per tubule and belong to the risk group for sterility. Successful surgery could not induce a significant increase of germ cells in the risk group, although it does prevent secondary testicular damage. Patients with cryptorchidism developed after birth have significantly better chances of fertility than those with primary cryptorchidism. The priming effect of testosterone in the first months of life is important for male fertility. In patients belonging to the risk group treated with buserelin, a significant age-dependent increase in germ cell count occurred.

Key words: Cryptorchidism – Biopsy – Risk group – Fertility – Buserelin treatment

Introduction

In the 1960s, it was believed that surgical techniques for orchiopexy were insufficient, and consequently the vast majority of cryptorchid adults suffered from sterility [3]. Several observers had found no increase in the germ cell population after successful surgery and therefore postulated the theory that a cryptorchid testis is dysgenetic and functionally imperfect [2, 3, 12].

This study extends previously published observations of a prospective follow-up of adult patients who underwent orchiopexy as children [7] and of cryptorchid boys with severely impaired germ cell count having subsequent stimulation with low doses of buserelin [8].

Patients and methods

Fifty now adult patients (aged 18–24 years) had their spermiograms analysed after 4 days of sexual abstinence. Forty-one of the patients had been cryptorchid since birth. Seven had secondary cryptorchidism: two of these had iatrogenic cryptorchidism which developed after hernia repair in the first year of life, while in the remaining five, testicular ascent was noted one or several years after having conclusively determined on previous hospitalization that the testes were in the scrotal position. Finally, two patients with retractile testes had been operated on at the insistence of their parents and against our advice.

Thirty-five prepubertal boys (P1 stage according to Tanner criteria) aged 2–11 years were treated with 10 µg buserelin nasal solution on alternate days for a period of 5–6 months. Since no biochemical or hormonal studies were available to determine the degree of effectiveness of buserelin treatment, a repeat biopsy under general anaesthesia was performed after treatment cessation. This was approved by the parents and the local ethical committees in Basel and Würzburg. In eight other boys with a germ cell count of their cryptorchid gonads of < 0.1 per tubule, the testes were successfully surgically brought down and stayed in the scrotum for at least a year but subsequently became gliding at the second operation a repeat biopsy was performed. The biopsy investigation was undertaken according to the method previously published [4].

Results

If germ cell count obtained at surgery (prepuberty) is compared to the number of the sperms of each patient analysed, than a significant positive correlation is obtained irrespective of uni- or bilateral testicular maldescent. The greater the number of germ cells at the time of surgery, the better was the spermiogram (Fig. 1). This was independent of the age at which surgery was performed (the youngest patient was 1 year old, $\bar{x}$: 9.3 ± 3.6 years). Surgery had no beneficial effect on the fertility chances of those boys whose germ cell count was < 0.1 per tubule (Fig. 1). However, it succeeded in preventing secondary damage to the testes due to the undescended position.

A further conclusion from this study was that biopsy had no adverse effect on the testis and its function.

The group of patients examined encompassed 50 of the first 58 patients from our prospective study group who had now reached adulthood. Only 14 of 48 patients (if two patients with retractile testes are excluded) had a normal spermiogram – volume ≥ 1.5 ml, $\geq 20 = 10^6$ sperms/ml, $\geq 50\%$ normal sperm forms, normal motility (Fig. 2).

When secondary cryptorchid boys are compared to those having cryptorchidism since birth (primary), a significant difference with regard to the spermiogram is found (Table 1). Despite the observation that three of seven boys with second-

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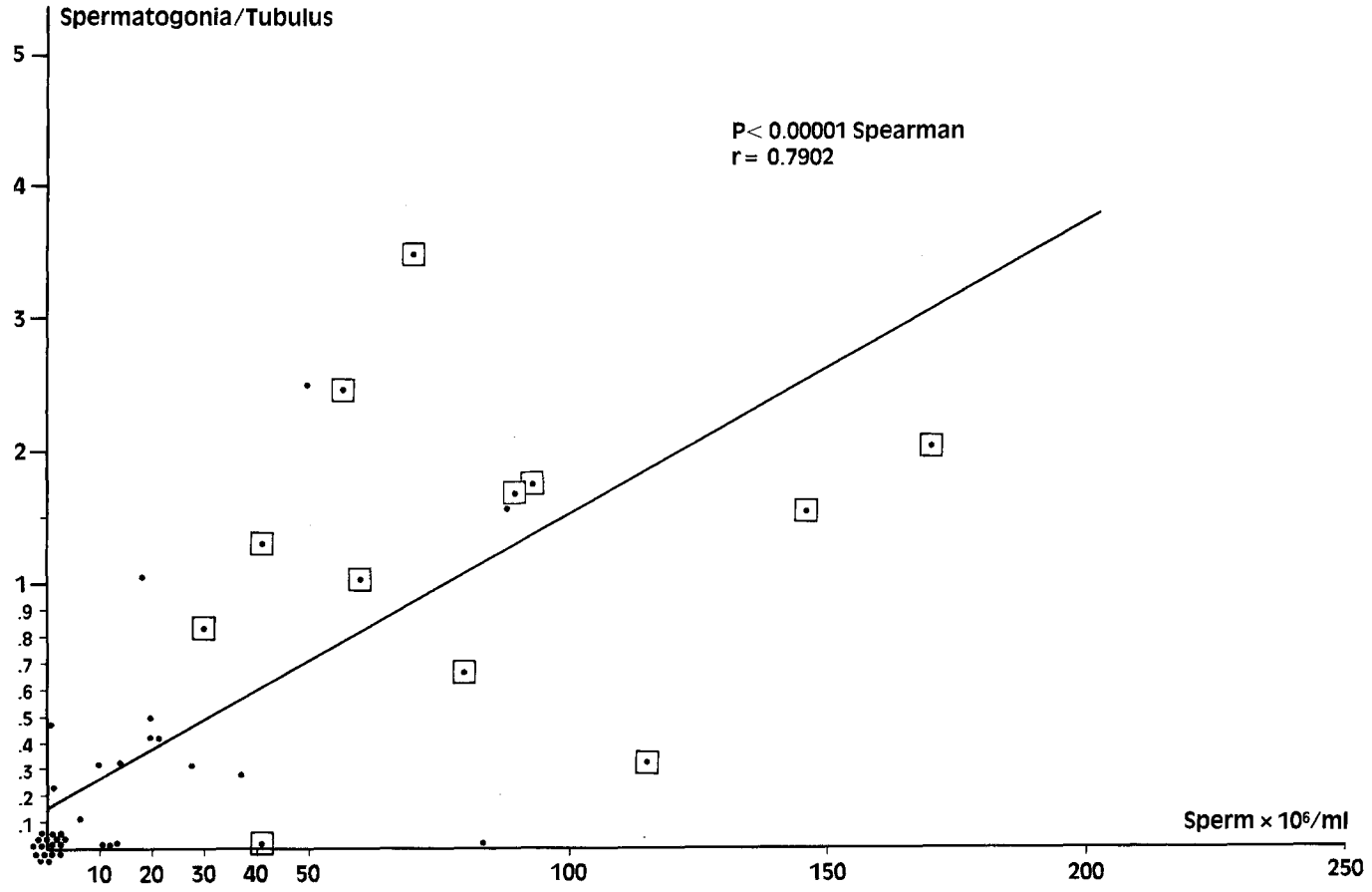

Fig. 1. Correlation between spermatogonia count per tubule at time of orchiopexy (prepuberty) and the recent sperm count in 46 cryptorchid patients

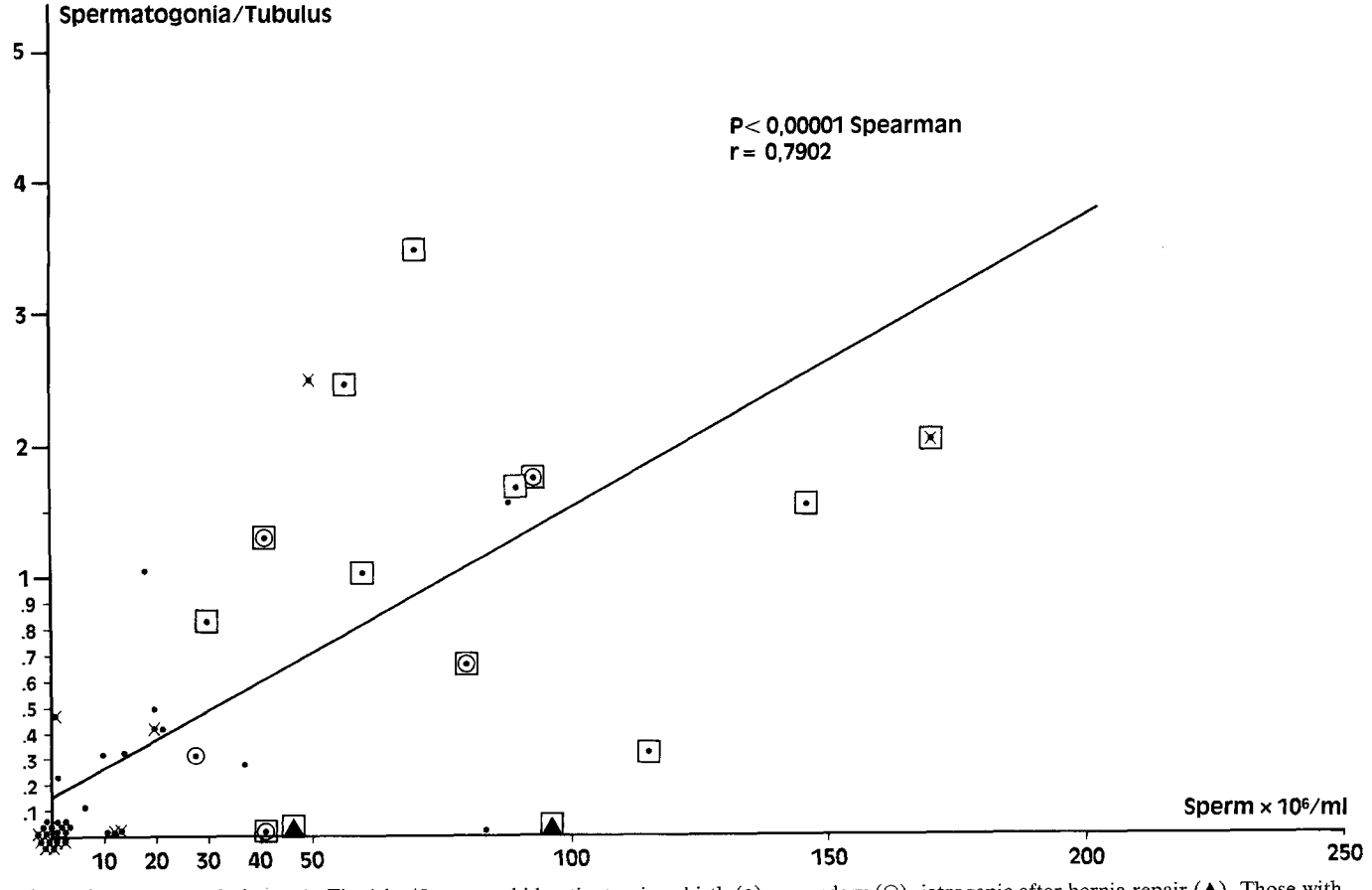

Fig. 2. the same correlation as in Fig. 1 in 48 cryptorchid patients: since birth (•), secondary (⊙), iatrogenic after hernia repair (▲). Those with completely normal spermiograms according to the WHO guidelines are within the squares (□). Bilateral (✖), unilateral (•)

Table 1. Comparison between secondary and primary cryptorchid patients with regard to their spermiograms

	Spermiogram	
	Normal	Pathologic
Secondary cryptorchid	6	1
Primary cryptorchid	8	33
Fischer-test $P < 0.0014$		

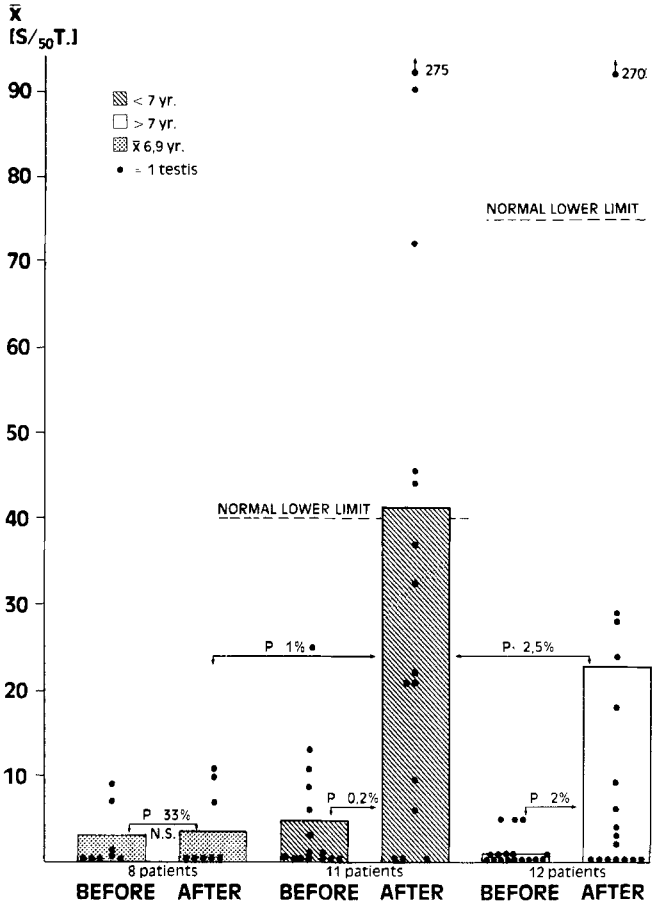

Fig. 3. Effect of surgery *(first two bars)* and buserelin treatment on germ cell count

ary unilateral cryptorchidism had no germ cells in their cryptorchid gonads, these patients had a completely normal spermiogram, thus there was no adverse effect on the contralateral descended partner, although there was severe atrophy of the undescended testis.

Two boys with retractile testes and orchiopexy had normal spermiograms. In our non-selected cryptorchid population, 22 of 41 primary cryptorchid patients had a germ cell count of ≤ 0.1 per tubule. Not a single one of these patients had a completely normal spermiogram (Fig. 1, 2), and 17/41 (41%) were azoospermic or severely oligospermic. Ten of these 17 had bilateral cryptorchidism and the remaining seven had unilateral cryptorchidism.

The inability of successful surgery to improve the germ cell population was additionally shown in eight boys who had a repeat biopsy one or several years after orchiopexy. No change in the number of germ occurred, although they were intrascrotally located for at least a year after surgery. It is obvious, therefore, that there is a group of cryptorchid patients (50% of our cases) with germ cell counts < 0.1 per tubule, who will not benefit from successful surgery with respect to fertility.

In 35 patients with uni- or bilateral cryptorchidism belonging to the group at risk of developing sterility (< 0.1 germ cells per tubule), a significant increase in the number of germ cells was found after 5–6 months of buserelin treatment (Fig. 3). In patients under 7 years, two-thirds improved their germ cell count considerably (Fig. 3). In older boys, the stimulatory effect of buserelin was significant, although not so effective as in the younger boys.

No side effects of buserelin treatment were observed. First void morning urine and values for LH and FSH remained unchanged throughout the whole treatment. This corresponds to the values previously reported in our pilot study [8].

Discussion

Fifty of 58 patients (86%) accepted our invitation to participate in the follow-up prospective study. This underlines how important information about fertility is for young adults. Completely normal spermiograms, according to WHO recommendations, were found in only 19% of these cryptorchid patients known to have undescended testes since birth but in 85% of those with secondary cryptorchidism. The difference is highly significant and indicates that the postnatal priming effect of testosterone at the male gonad is an important step for achieving fertility [10]. Surprising to us was the fact that 11% (5/46) of our cryptorchid patients had one or both testes descended at birth; secondary cryptorchidism as described by Privat [11] and Atwell [1] seems to be a reality.

According to our histological findings, 50% of our patients had germ cell counts of < 0.1 per tubule [9]. This corresponds with the spermiogram findings, where 17/41 patients were severely oligozoospermic or aspermic. In addition, a positive correlation between germ cell count and sperm count, as well as normal number of sperm forms [7], confirms that biopsy

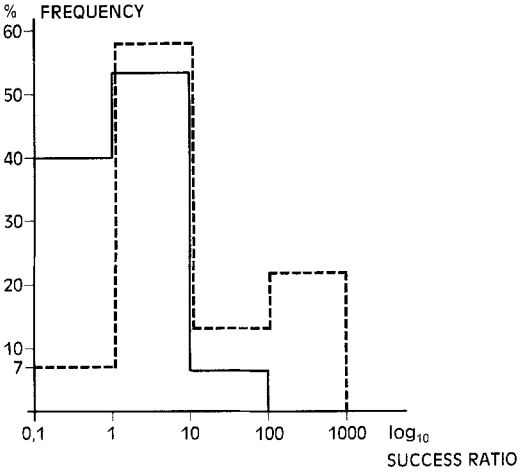

Fig. 4. Increase in germ cell count of cryptorchid boys treated with buserelin while in undescended position (——, $n = 45$) or after successful surgery (– – –, $n = 33$). The mean increase of the in situ treated group was 2.3-fold, while that after surgery was 141.1-fold. The Y axis gives frequency, the X axis the amount of increase in $\log_{10}$ fashion. Fischer test, $P < 0.01$; Wilcoxon-Mann-Whitney-U-test, $P < 0.01$

has a prognostic value and should be mandatory during orchiopexy. Furthermore, the biopsy technique utilized during surgery had no adverse effect on the fertility outcome of our patients. Therefore, there is no scientific background for not performing the biopsies in cryptorchid patients, particularly since the biopsy, analysed preferably by semithin sections, represents the only possibility today to find those patients at risk of sterility and admit them to subsequent buserelin treatment.

This extended study has confirmed our pilot study findings on the effect of buserelin in the risk group of patients with maldescended testes [8]. Buserelin treatment produces its best results when started early in life. In boys older than 7 years of age, the failure to achieve a good response may be due to progressive secondary and additional effects produced by development in the cryptorchid position. These secondary changes are already significant during the 3rd year of life [4–6]. Thus, hormonal and surgical treatment should be completed whenever possible not later than during the 2nd year of life. The germ cell increase in the undescended position, however, was significantly less than in those cases where the testis was treated intrascrotally following successful surgery (Fig. 4).

It does appear that, despite stimulation, an optimal position has to be realized in order to achieve maximum stimulation of the germ cell division.

In this study, patients with iatrogenic or secondary cryptorchidism had normal spermiograms despite severe unilateral testicular atrophy. Thus, the hypothesized sympathetic orchiopathy or "contralateral effect" seems very unlikely to exist.

If this increase in germ cells after buserelin treatment proves to be permanent (preliminary data support this for the first 6 months), buserelin could represent a powerful and effective new treatment of cryptorchid boys who are at risk of sterility.

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