Long-Term Effect of a Luteinizing-Hormone-Releasing Hormone Analogue (Buserelin) on Cryptorchid Testes (Extended Summary)

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Cryptorchidism is a disorder of the hypothalamic-pituitary-gonadal axis and is not a malformation. We advocate early treatment (10 months of age) to avoid pronounced secondary gonadal changes starting after 12 months of age. The lower the testes are situated the better their histology; the younger the children are the more normal their gonads. During the 1st important months of life, transformation of gonocytes into spermatogonia takes place. This transformation is gonadotropin- and testosterone-dependent and is impaired in cryptorchid boys. After the 2nd year of life, 38% of cryptorchid boys completely lack germ cells. This group of patients is therefore at risk of being sterile. Standard treatment with luteinizing-hormone-releasing hormone (LHRH) and human chorionic gonadotropin has proven successful in 74% of all boys treated [1]. An LHRH agonist analogue (Buserelin, Hoechst) is about 10 times more active than native LHRH and it has been shown to stimulate germ cell division if given after successful surgery for cryptorchidism [2].

The results of our study show for the first time that it is possible to increase the number of germ cells with hormonal therapy even when the testis is undescended [3]. This also provides additional support for the hypothesis that lack of germ cells in boys with cryptorchidism is due to impairment of the hypothalamic-pituitary-gonadal axis [4, 5] and not to high temperature or elevated pressure as generally believed. Furthermore, our previous studies have shown that buserelin treatment should be started early in life if an optimal response is to be achieved [2]. The lack of a good response in boys older than 7 years could be explained by the secondary changes that are already significant by the age of 2 years [6, 7]. Therefore, hormonal and surgical treatment should be initiated before the age of 12 months. No side effects and particularly no down-regulation of the hypothalamic-pituitary-gonadal axis occurred during treatment with buserelin.

In older boys low doses of buserelin given on alternate days induced a low but significant increase in testosterone, indicating a stimulatory effect of gonadotropins on the Leydig cells [3]. This effect was not observed in the urine of young boys with cryptorchidism despite the fact that Leydig cell number increased indicating an augmentation of intratesticular testosterone. However, until further controlled studies have confirmed our findings treatment with Buserelin should be given only after orchio-pxy in those boys whose germ cell number is lower than 0.1 germ cell per tubular cross section.

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Discussion

Sizonenko: Did you measure testosterone levels in the boys you treated with your GnRH agonist, as it is supposed to cause desensitization of the pituitary?

Hadziselimovic: Yes, in fact we did find an increase in plasma and urine testosterone levels after treatment in boys older than age 7. There was no down-regulation of the pituitary.

Ritzén: By using a GnRH agonist are you not inducing mild precocious puberty in your boys? Do you maintain improved spermatogenesis in these subjects?

Hadziselimovic: We have had neither clinical nor biochemical signs of precocious puberty in boys treated.

de Muinck Keizer-Schrama: Is the reason why you observe no change in spermatogonial numbers in cryptorchid testes during the 1st year of life related to the presence in your samples of normal testes which have descended later in the 1st year?

Hadziselimovic: Intraabdominal testes will never descend spontaneously. The histology of intraabdominal infant testes is the same as in all other (> 100) cryptorchid infants studied: normal number of germ cells but atrophy of Leydig cells and impaired transformation of gonocytes. Since the histology obtained was not normal and parallels that from intraabdominal testes, we have no reason to assume that the testes studied were retractile or even normal.

de Muinck Keizer-Schrama: Why do you treat your patients with a GnRH agonist at such a young age? Why do you not wait until puberty, allowing nature to take its course?

Hadziselimovic: Because of the irreversible secondary changes and importance to induce the priming effect of gonadotropin at optimal time of prepubertal development we consider and we have also experienced that delaying treatment until puberty would be ineffective.