



Cryptorchidism and Infertility

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ABSTRACT

Cryptorchidism is an anomaly of testicular migration. It is a congenital pathology that is the subject of many controversies. Its major risks are represented by malignant degeneration and male infertility. The purpose of this manuscript is to better understand the physiopathological implications of the undescended testicle in infertility through a review of the literature.

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Introduction

Cryptorchidism is defined as a testicle spontaneously and permanently located outside the scrotum at any point on its normal migration path. Thus, the cryptorchid testicle can be in the intra-abdominal position, inside the inguinal canal, at its external opening or at the root of the bursa. Cryptorchidism is the most common genital abnormality in boys.

It results from a migration stop of one or both testicles at a given point in its normal path and leads clinically either to an absence of palpable testicle in the bursae or to a palpable testicle but highly located and not lowerable during a physical examination.

Hormonal, genetic and environmental factors are implicated in the genesis of cryptorchidism and contribute to the recent increase in its incidence in industrialized countries. Cryptorchidism is considered a complex pathology because it is probably multifactorial.

It affects 3 to 4% of children born at term. It can be unilateral or bilateral. (1)

The diagnosis must be made early to avoid the risk of infertility, torsion and malignant degeneration (2) (3).

Cryptorchidism is one of the most common etiologies of male infertility. In the extreme, it can even lead to azoospermia since a history of cryptorchidism is found in 15 to 20% of azoosperm patients.

Cryptorchidism leads to impaired fertility. A reduced number of testicular germ cells can be shown histologically during the first years of life.

In the general population, the bilaterality of cryptorchidism is associated with more frequent fertility problems.

Indeed, 9% of men with a history of unilateral cryptorchidism may present fertility problems, while this phenomenon is observed in about half of men with a history of bilateral cryptorchidism. (4)

Cryptorchidism and Infertility

Cryptorchidism is a very common anomaly of testicular migration, different from ectopia, anorchidism or the retractile testicle. The pathophysiology of cryptorchidism is now well known. Recent epidemiological studies show a significant increase due to toxic environmental factors, in particular pesticides. Cryptorchidism is most often isolated but polymalformative entities must be eliminated, sometimes requiring hormonal or genetic investigations. The diagnosis is primarily clinical, but laparoscopy adds precision and reliability. Infertility and cancer are the two major risks of cryptorchidism, but their pathophysiological mechanisms are still debated. Regarding the risk of infertility, the primitive or acquired nature of testicular damage is still doubtful. Medical and surgical treatments are now fairly well codified. If, until now, there is no consensus on the age of treatment for cryptorchidism, numerous data in the literature lead pediatric urologists to treat these boys as quickly as possible, even at the age of 1 year. (3)

There are many mechanisms leading to male infertility in cryptorchidism:

1. Gonadal hyperthermia
2. Congenital anomalies of the seminal tract
3. Iatrogenic lesions of the testicle and / or the seminal tract
4. Immunological phenomena
5. Histological testicular lesions
6. Intrinsic sperm anomalies

I. Gonadal hyperthermia

Migration of the intra-scrotal testis is associated with a drop in the temperature surrounding the testicle, which is ideally at 33-35° C

In fact, according to Peltol et al, an increase in the metabolic needs of the gonad can lead to tissue hypoxia which is responsible of a decrease in the activity of enzymatic cell protection systems causing irreversible tissue damage, according to a study carried out on rats. (5)

In case of unilateral cryptorchidism, the analysis of the contralateral testis also finds stigmas of oxidative stress; which led Mieusset et al to think of the presence of structural and functional alterations of many intra testicular proteins, thus explaining the presence of alteration of spermatogenesis in patients with a history of unilateral cryptorchidism.

The use of thermal contraception like the heating panties are also in favor of the implication of gonadal hyperthermia in the infertility of the cryptorchid man. (6) (7)

II. Congenital anomalies of the seminal tract

Congenital anomalies of the seminal pathways associated with cryptorchidism are represented by segmental atresia of the epididymis and/or vas deferens, epididymo-testicular dissociation phenomena, or even other morphological abnormalities of the epididymis and / or vas deferens.

According to several studies, it has been noticed that cryptorchidism can be associated with several abnormalities of the spermatic conduits.

De Miguel MP, in fact, found in an immune histochemical and morphometric study a reduced development of epididymis of cryptorchid testes.

Cryptorchidism is therefore a primary congenital disease of the testis and spermatic ducts with obvious lesions from the first year of life, which suggests that surgical treatment would be unable to completely reverse the situation. (8)

D'Agostino et al in their study of 517 cryptorchid patients, worked on the epididymo-testicular anatomy with an incidence of 16.5% in the case of unilateral cryptorchidism and 26% in the case of bilateral cryptorchidism and suggest that azoospermia in adults could be related to bilateral occlusion or interruption of the spermatic ducts.

JOHANSEN et al in their study of 150 consecutive orchidopexies noted that epididymo-testicular dissociation is the most frequently encountered anomaly.

A 1996 Taskinen study found 36% of epididymal abnormalities in a group of adults treated for cryptorchidism in childhood. (9) (10)

III. Iatrogenic lesions of the testicle and / or seminal tract

In 1995, Docimo et al published a review of the literature in order to assess the success rate of orchidopexies in the surgical treatment of cryptorchidism and note that the success rate is inversely proportional to the level of the testicle which leads us to believe that dissections on testicular vessels during lowering gestures can cause testicular ischemia. (11)

Taskinen, on the other hand, evaluated 76 adults treated in childhood by an ultrasound coupled with a color doppler, finding 20% of arterial anomalies versus 3% for intra scrotal testes and concluded that intraoperative trauma could be more involved in infertility of cryptorchid subjects. (9)

In case of too early surgical intervention it is necessary to be wary of the presence of iatrogenic lesions especially due to the difficulty of visualization of the vas deferens hence the need for multidisciplinary management.

Some authors question the medical treatment with HCG, indeed the process causing the loss of germ cells in prepubertal cryptorchid boys remains unknown, but could result from a form of programmed cell death known as apoptosis.

Dunkel et al conducted a study of 25 adult men with a history of surgically treated cryptorchidism, 15 of whom had received unsuccessful human chorionic gonadotropin (HCG) therapy before orchidopexy.

Fragmentation of apoptotic DNA was assayed in testicular biopsies taken during orchidopexy by final labeling,

both in the DNA extracted and histochemically in situ. Only a few dispersed apoptotic spermatogonies were observed by the final labeling of biopsies of patients not treated with HCG, while more extensive labeling of spermatogonies was observed after treatment with HCG. About 20 years after the biopsy, low molecular weight DNA fragmentation is negatively correlated with testis volume and positively with serum FSH levels

The apoptotic loss of spermatogonia after treatment with HCG of cryptorchidism justifies a reassessment of the safety of this treatment.(12)

IV. Immunological phenomena

Immunological phenomena are characterized by a process of self-immunization and therefore the presence of anti-sperm antibodies in the seminal fluid.

URRY RL et al found in a comparative study 66% of patients with a history of cryptorchidism against 2.6% in a control group of infertile patients.

Progressive mobility is significantly lower in patients with positive antibodies.

It then appears that the presence of anti-sperm antibodies would also decrease fertility in patients with a history of cryptorchidism (13)

Antibodies against sperm surface antigens may be responsible for 3 to 20% of cases of male idiopathic infertility. Antisperm immunization may be suspected due to signs such as a history of orchidopexy, spontaneous agglutination of sperm or an inability of sperm to enter normal cervical mucus. The responsibility of anti-sperm antibodies in the state of infertility could be demonstrated in vitro by their effects on several functions of sperm. An inverse correlation between antibody titers and conception rates has been demonstrated and justifies a therapeutic approach in the presence of high antibody levels.

These antibodies could come from the exposure of sperm to the immune system following a rupture of the blood-testicular barrier during orchidopexy. (14)

V. Histological testicular lesions

They appear from the age of two and are marked by a progressive decrease in the number of germ cells and in particular of Ad spermatogonia in the pre-pubertal period (increased apoptosis), a decrease in the diameter of the seminiferous tubes (phenomenon of degeneration of Sertoli cells), thickening of the peri-tubular sheath and fibrosis of the interstitial tissue.

Gaudio observed the structural and ultra-structural changes in the testes of a cryptorchid patient.

Biopsies were performed on 15 patients aged 2 to 39 years, including 7 treated with hormone therapy without success.

The most important observations were:

- The precocity of lesions of the germinal epithelium and of the peri tubular connective tissue.
- The presence of frequent bilateral lesions in the event of unilateral cryptorchidism.
- The ineffectiveness of hormone therapy with HCG on the delayed maturation of the tubular epithelium.

These results provide additional information on the optimal time for surgical treatment which they believe should be done before the age of 2 years.

This was confirmed by HUFF et al who calculated the number of germ cells per tubule during 115 biopsies in cryptorchid patients noting that this number was normal

between 0 and 12 months and fell below the lower limits of normal between 1 and 2 years. (15) (16)

HUFF DS et al performed histo-morphometric analyzes including germ cell count as well as Leydig cells on biopsy sections of 459 undescended testicles and 356 of their contralateral descending partners in order to deepen the understanding of the histological lesions caused by uni or bilateral cryptorchidism.

Results Demonstrate Reduced Leydig Cells, Delayed Disappearance Of Gonocytes, Delayed Onset Of Dark Adult Spermatogonia, Failed Onset Of Primary Sperm, And Decreased Total Germ Cells In Undescended Testicles . These results support the hypothesis that under-stimulation of the testis leads to a reduction in the number of Leydig cells which leads to a delayed and defective germ cell maturation and a reduced number of total germ cells explaining the increased risk of under- fertility in cryptorchidism.

The appearance of dark adult spermatogonia in the first year of life and the onset of meiosis at three years of life in the descending contralateral testicles contradict the view that the prepubescent testicle is at rest. They support the theory that the complete assessment of prepubescent testicular biopsies should include the total and differential number of germ cells and the number of Leydig cells.

"Sertoli cell only syndrome" or, Sertoli cell only syndrome is an extreme form with a very poor prognosis for infertility corresponding to aplastic germ line aplasia and has been found by HUFF in one third of azoosperm patients reporting a history cryptorchidism. (17)

Endocrine testicular function may also be compromised in the case of cryptorchidism since an analysis by electron microscopy of the testicular parenchyma of cryptorchidism patients has revealed anomalies in the ultrastructure of Leydig cells. (18)

VI. Intrinsic sperm anomalies

Even in the presence of a "normal" spermogram, the presence of intrinsic sperm abnormalities may partly explain a decrease in fertility in patients with a history of cryptorchidism

Bacetti in his work applied Hoechst 33258 DNA staining, the TUNEL procedure and conventional electron microscopy to study the ejaculation of fertile and infertile men, in order to detect apoptosis in human sperm.

He observed that apoptosis is abnormally common in the ejaculate sperm of infertile men.

The percentage of apoptotic sperm was about 0.1% in fertile controls, and increased to about 10% in varicoceles 20% in cryptorchid males and 50% in seminoma carriers. (19)

Moretti et al in 2007 carried out a study whose aim was to analyze the quality of the sperm of men who underwent orchidopexy for unilateral or bilateral cryptorchidism during childhood. The quality of the sperm was studied by light microscopy to assess the concentration and motility of the sperm. Sperm morphology was assessed by transmission electron microscopy (TEM), and the data was developed mathematically. The presence of micro-deletions Y was observed by polymerase chain reaction. The effect of cryptorchidism on meiosis was studied by fluorescence in situ hybridization (FISH). The incidence of azoospermia was higher in the group with bilateral cryptorchidism than in the group with unilateral cryptorchidism, and semen parameters were better in the first group. The semen pathologies detected by electron microscopy indicated a serious deterioration in the quality of sperm in both groups. Necrosis and apoptosis

appeared to be the most frequent pathologies, and their values reached statistical significance compared to those of fertile controls. The presence of micro-deletions of the Y chromosome in patients with cryptorchidism and severe genetic sperm abnormalities is controversial. No micro deletion was found in this study. FISH values indicated that the average percentage of gonosome disomies and diploids was generally outside normal limits, indicating a serious disturbance of meiotic segregation. Conclusion of this study: the effects induced by resolved cryptorchidism during childhood seem to include a spermatogenetic alteration leading to the recommendation of ultra structural and spermatogenic chromosomal analyzes in detail before undertaking assisted procreation techniques. (20)

Nguyen carried out a study comparing 10 control subjects to 12 cryptorchids, 8 unilateral and 4 bilateral.

The ejaculates were collected and the mobile sperm were isolated by centrifugation, the total RNA was extracted and checked using a sperm-specific reverse transcriptase polymerase chain reaction (RT-PCR). The amplified biotin-labeled RNA has been hybridized to the Affymetrix Human Genome Focus networks. The genes expressed differentially were identified using the T permutation test.

The mean sperm volume was no different between the control and the patients with cryptorchidism. The mean sperm density was significantly reduced in the control, unilateral and bilateral cryptorchidism samples. From microarray expression data, we identified 43 differentially expressed genes between the two groups. Thirty-eight genes were significantly under-expressed in cryptorchidism samples including many transcriptional factors (cul3, prml1, hspcd35) and a specific cell adhesion gene to the testis (tpx-1) involved in the maturation of germ cells and tail formation.

The Gene Expression Profiles provide an overview of the various alterations that occur in cryptorchidism. The observed changes in sperm expression of transcriptional and anti-apoptotic genes can cause poor seminal parameters in males formerly cryptorchids. (21)

Conclusion

Cryptorchidism is a complex and multifactorial pathology with two major consequences:

#Infertility

Malignant degeneration

In fact, the risk of developing testicular cancer in a patient with a history of cryptorchidism is 10 times higher than that of the general population, hence the need for close radiological and andrological urological monitoring.

The pathophysiological mechanisms of the involvement of cryptorchidism in infertility are beginning to be elucidated; they are numerous and variable, going as far as the presence of intrinsic testicular and spermatogenic abnormalities.

Marcelli et al carried out a study on 142 azosperm patients with a history of cryptorchidism and a reduction before the age of ten with an extraction rate of 65%, while specifying the existence of predictive factors of good prognosis such as patients with a normal FSH levels and a testicular volume greater than 10ml in whom the extraction rate has reached 75%.

The evolution of medically assisted procreation has greatly improved the prognosis of fertility in patients with a history of cryptorchidism. (22)

Conflicts of interest: the authors do not declare any conflicts of interest.

What is known on this subject:

Cryptorchidism is one of the most common etiologies of male infertility. In the extreme, it can even lead to azoospermia. It is a complex and multifactorial pathology can even lead to malignant degeneration.

The diagnosis must be early to avoid its major consequences.

Our study brings again

Our goal through this writing is to be able to understand the mechanisms of implication of cryptorchidism in male infertility through a PUBMED review.

Author contributions

All the authors contributed to the writing of this work. The authors also declare having read and approved the final version of this work

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