

Histopathological Changes in Cryptorchidism of Infertile Patients Undergoing Intracytoplasmic Sperm Injection

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Abstract: Cryptorchidism may cause histological changes such as testicular atrophy or fibrosis, or even carcinoma in situ of the testis or testicular malignancy. Early diagnosis of such changes can enable proper management, such as performing orchidectomy or localized irradiation, which can save the life of the patient. The present study included a retrospective evaluation of the biopsies of patients with cryptorchidism who underwent Intracytoplasmic sperm injection (ICSI) to evaluate the prevalence of such changes in the testis. The testicular biopsies of 20 patients with a history of cryptorchidism were stained with H&E specimens. It was concluded that cryptorchidism leads to severe changes that predispose to infertility, and delays in orchidopexy cause more severe changes.

Keywords: Histopathological changes, Cryptorchidism, Infertile Patients, Intracytoplasmic Sperm Injection, Carcinoma in situ (CIS), Testicular sperm extraction (TESE).

INTRODUCTION

It is widely accepted that most testicular tumors originate from a common precursor, carcinoma in situ (CIS), a premalignant condition believed to arise early in fetal life [1]. CIS of the testis is diagnosed by conventional surgical biopsy, based on the assumption that testicular intraepithelial neoplasia is randomly distributed throughout the testis [2]. High-risk groups for the development of CIS include individuals with infertility, cryptorchidism, contralateral tumors, extragonadal germ cell tumors, and familial tumors [3]. A study in Germany involving 766 sub-fertile men who underwent intra-cytoplasmic sperm injection (ICSI) and testicular biopsies followed by sperm extraction (TESE) found that five men had early-stage testicular tumors (CIS), with two cases being bilateral. This reflects a prevalence of 0.7% testicular malignancy [4].

Toppari (2022) supports the view that the incidence of malignancy in cryptorchidism is 20 to 46 times greater than in a normally located testis [5]. In adult men with a history of cryptorchidism, the prevalence of CIS is about 2% to 4% [6-8]. A much lower incidence is found in childhood, with testicular biopsies performed in young boys during surgical correction of cryptorchidism showing CIS in about 0.36% of cases [9]. The low prevalence of CIS in childhood is not surprising, as CIS is thought to replicate only after the endocrinological

stimulus of puberty. Thus, even in known risk groups of testicular GCT, infantile testicles are expected to harbor very few CIS cells [10]. The increased risk of CIS with cryptorchidism is recognized, but it is still unclear what additional factors render certain men with cryptorchidism and infertility more prone to testicular cancer. Studies have identified testicular atrophy and infertility as contributors to the increased risk of testicular cancer in the contralateral testis of men with this disease [11, 12].

At birth, cryptorchidism contains germ cells, but after one year, a reduced number of germ cells is generally found. Microlithiasis and CIS occur in cryptorchid boys. Multinucleated spermatogonia, investigated for their presence in cryptorchidism and their association with clinical features, were found in 13 of 163 consecutive cryptorchid boys. Multinucleated spermatogonia were present in cases of CIS in two cryptorchid boys [13]. This feature may be associated with an increased risk of testicular malignancy later in life. Surgery for cryptorchidism (orchiopexy) is recommended before 15-18 months of age because the lack of germ cells is rare before this age and is associated with subsequent risk of infertility. At primary surgery for cryptorchidism, examination for testicular neoplasia is important in cases of intra-abdominal testis, abnormal external genitalia, or a known abnormal karyotype [14]. A study by Cortes *et al.* (2004) on the incidence of testicular neoplasia after orchiopexy with simultaneous testicular biopsy in childhood recommended that a testicular biopsy be

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taken during surgery for cryptorchidism in cases of intra-abdominal testis, abnormal external genitalia, or a known abnormal karyotype, and that surgery be performed before 10 years of age with clinical follow-up [15].

Surgical biopsy is the only way to safely diagnose CIS [16]. The specimen should be passed directly into the fixative solution to prevent damage [17].

To effectively screen for CIS of the testis, it is essential to ensure that CIS cells are not missed and that other cell types are not incorrectly identified as CIS cells. CIS cells can sometimes be overlooked in routine histological sections stained with hematoxylin and eosin (H&E) [18]. Periodic acid–Schiff (PAS) staining can also be used to diagnose CIS, as CIS cells contain large amounts of glycogen, distinguishing them from non-malignant spermatogenic cells [19]. PAS staining is highly effective for diagnosing CIS and is used as the primary stain in some institutions [19]. The specimen examined under the microscope shows a characteristic staining pattern for glycogen, produced in large amounts by malignant *in situ* cells [20].

This study included a retrospective search through the electronic records of 20 patients who underwent ICSI at The Egyptian IVF-ET Center to evaluate the prevalence of histological changes or CIS of the testis. Testicular biopsies of patients with a history of cryptorchidism were reviewed using H&E and PAS staining to identify possible CIS. This group included patients with conditions such as azoospermia, intermittent azoospermia (cryptozoospermia), inability to collect semen, or cases where no viable sperm for injection was available on the day of ICSI. It also included individuals with teratozoospermia and necrospermia, where testicular sperm biopsy is routinely recommended because testicular sperm typically has better viability and motility than ejaculated sperm. The routine andrological work-up of patients undergoing surgical retrieval of spermatozoa included patient characteristics (age at diagnosis, presentation, history of cryptorchidism, and type of infertility), conventional semen analysis, endocrine profile, urine analysis, and examination of the expressed prostatic secretion. Additional investigations, such as transrectal ultrasound and preoperative diagnostic testis biopsy, were done when indicated. Karyotyping to exclude chromosomal abnormalities was offered to all patients, though some declined due to financial constraints.

Testicular biopsy was performed under local infiltration anesthesia and cord block using a mixture of

1:1 Bupivacaine and Lidocaine. Sedation was achieved using midazolam 5 mg IM 15 minutes prior to surgery, and general anesthesia was performed when requested. Surgical loops (4X or 6.5X magnification) were used for the procedure.

Cryptorchidism causes atrophy, fibrosis, CIS, and malignancy. This study of 20 ICSI patients highlights its link to infertility and worse outcomes with delayed treatment.

The aim of the study was to investigate changes associated with cryptorchidism and the incidence of CIS in infertile patients undergoing ICSI at an Egyptian IVF-ET center using histological examination of their testicular biopsies.

This study addresses gaps in understanding the histological impacts of cryptorchidism in patients undergoing ICSI, specifically its role in infertility and the effects of delayed orchidopexy on testicular health. By evaluating biopsy data, it provides critical insights into the prevalence of severe changes like CIS and malignancy, highlighting the need for timely intervention.

MATERIALS AND METHODS

This study involved a retrospective review of electronic records from 20 patients who underwent intra-cytoplasmic sperm injection (ICSI) at The Egyptian IVF-ET Center. The objective was to assess the prevalence of histological changes, including carcinoma *in situ* (CIS), in testicular biopsies of patients with a history of cryptorchidism. Histological evaluation of the biopsies was performed using Hematoxylin and Eosin (H&E) and Periodic Acid–Schiff (PAS) staining to identify potential CIS.

The patient cohort included individuals with azoospermia, intermittent azoospermia (cryptozoospermia), inability to collect semen, or absence of viable sperm for injection on the day of ICSI. Additionally, cases of teratozoospermia and necrospermia, where testicular biopsy is often recommended due to the superior motility and viability of testicular sperm compared to ejaculated sperm, were also included.

A detailed andrological evaluation was conducted for all patients undergoing surgical sperm retrieval. This included recording patient characteristics such as age at diagnosis, clinical presentation, history of cryptorchidism, and infertility type. Standard diagnostic

tests included conventional semen analysis, endocrine profiling, urine analysis, and examination of expressed prostatic secretions. Additional investigations, including transrectal ultrasound and preoperative diagnostic testicular biopsy, were performed as needed. Karyotyping was offered to all patients to rule out chromosomal abnormalities; however, some patients declined due to financial limitations.

Testicular Sperm Extraction (TESE)

Testicular biopsies were carried out under local anesthesia using a cord block with a 1:1 mixture of Bupivacaine and Lidocaine. Sedation was administered with an intramuscular injection of 5 mg midazolam 15 minutes before the procedure, and general anesthesia was used upon request. Surgical loops with 4X or 6.5X magnification were employed to ensure precision during the biopsy.

H&E staining was used to detect pathological changes and to screen for CIS, ensuring accurate identification without misinterpretation of other cell types as CIS. PAS staining, which highlights glycogen-rich CIS cells, was used to confirm findings and prevent oversight of malignant cells in routine histological sections. Both techniques were utilized to enhance diagnostic reliability and minimize missed cases of CIS [18].

RESULTS

The 20 patients who underwent ICSI/TESE, all of whom had a history of cryptorchidism, were evaluated for the possibility of carcinoma in situ (CIS). Histopathology of the eosin specimens was examined as shown in Table 1. The table outlines the histopathological findings from testicular biopsies of patients with cryptorchidism. Among the patients, 3

showed total hyalinization, and another 3 exhibited total hyalinization with focal spermatogenesis. The Sertoli cell-only pattern, observed in 9 patients, with an additional 11 showing incomplete Sertoli cell-only patterns. Spermatogenic arrest was noted in 5 patients, while incomplete spermatogenic arrest (hypospermatogenesis) was seen in 11 patients. These histological findings underscore the severe changes observed, as 11 patients had normal histology, and 7 displayed a mixed unclassified pattern. These results highlight the variety of histological changes associated with cryptorchidism.

This histopathological Sertoli cell-only pattern, seen in 9 patients is significant in the context of both infertility and malignancy risk. Clinically, the Sertoli cell-only syndrome suggests a severe disruption of spermatogenesis, where only Sertoli cells (which support germ cells) are present, but no germ cells or sperm production occur. This condition is often associated with infertility, as the absence of spermatogenesis means that the affected individuals are unable to produce viable sperm for reproduction.

Additionally, individuals with the Sertoli cell-only pattern, particularly in the context of a history of cryptorchidism, may have an increased risk of testicular malignancy, especially germ cell tumors. The long-term presence of such a histological pattern in cryptorchidism has been linked to a higher incidence of testicular cancer, necessitating careful monitoring and early detection strategies for malignancy in these patients.

The mean age of patients at the time of presentation was 38 years. Of the 20 patients, 16 had a history of bilateral cryptorchidism, while the remaining 4 had unilateral cryptorchidism. Some specimens showed seminiferous tubules with spermatogenic arrest at the spermatogonial stage. The suspected CIS

Table 1: Histopathology of Patients with History of Cryptorchidism

Histopathology	No. of patients
Total hyalinization	3
Total hyalinization with focal spermatogenesis	3
Sertoli cell only	9
Sertoli cell only (incomplete)	11
Spermatogenic arrest	5
Incomplete spermatogenic arrest (hypospermatogenesis)	11
Normal	11
Mixed unclassified pattern	7

cells appeared as polymorphic atypical cells, deeply stained, with large paranuclear halos and vacuolated cytoplasm. Histological examination of the testis showing thickening of basement membrane, tubular atrophy, spermatocytic arrest, fibrosed tubules, basement membrane thickened, hypercellularity at different stages, occluded lumen of seminiferous tubules (Figure 1).

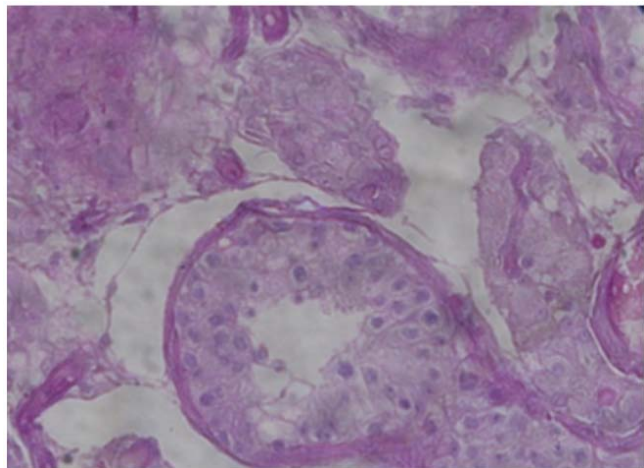


Figure 1: Thickening of basement membrane, tubular atrophy, 1 spermatocytic arrest, fibrosed tubules, basement membrane thickened, hypercellularity at different stages, occluded lumen of seminiferous tubules (H&E, x400).

Figures 2 through 5 illustrate various histological changes observed in testicular biopsies stained with hematoxylin and eosin (H&E) at x400 magnification. Figure 2 shows a thickened basement membrane, total tubular atrophy, stromal edema (bubbles of water), stromal fibrosis (hyalinosis), Sertoli cells only, empty tubules, and groups of Leydig cells appearing eosinophilic. Figure 3 highlights spermatocytic arrest with a thickened basement membrane. Figure 4 depicts

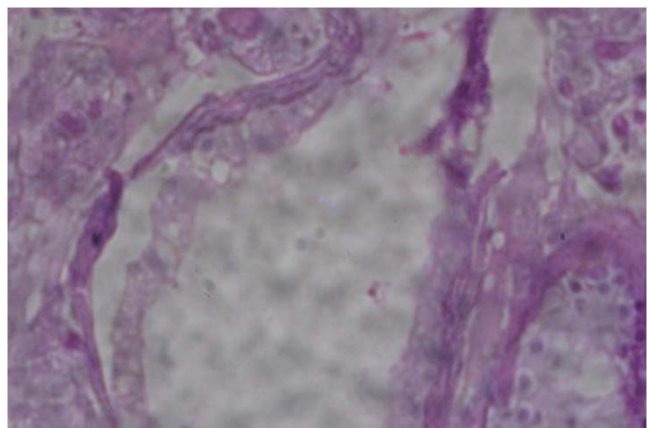


Figure 2: Thickened basement membrane, total tubular atrophy, stromal oedema (bubelles of water), stromal fibrosis (hyalinosis), sertoli cells only, empty tubules, groups of leydig cells appear eosinophilic (H&E, x400).

stromal vascular hyalinosis, Sertoli cell hyperplasia, tubular atrophy, and spermatocytic arrest. Finally, Figure 5 demonstrates sections with tubular hyalinosis, tubular atrophy, and spermatocytic arrest.

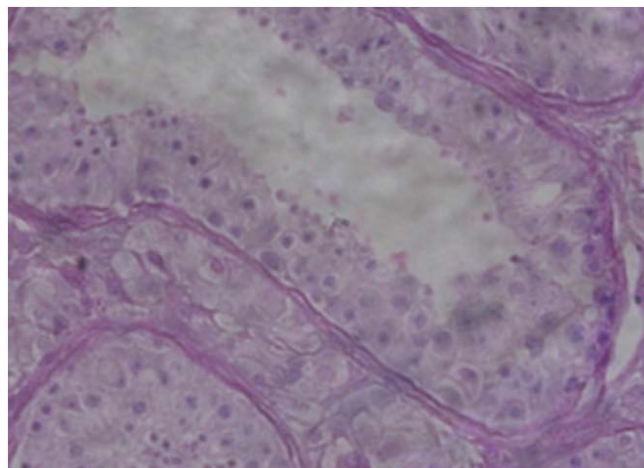


Figure 3: Spermatocytic arrest with thickened basement membrane (H&E, x400).

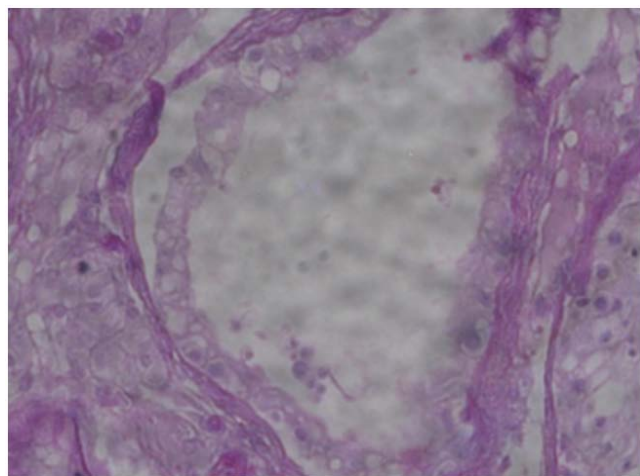


Figure 4: Stromal vascular hyalinosis, sertoli cells only (hyperplasia), tubular atrophy, spermatocytic arrest (H&E, x400).

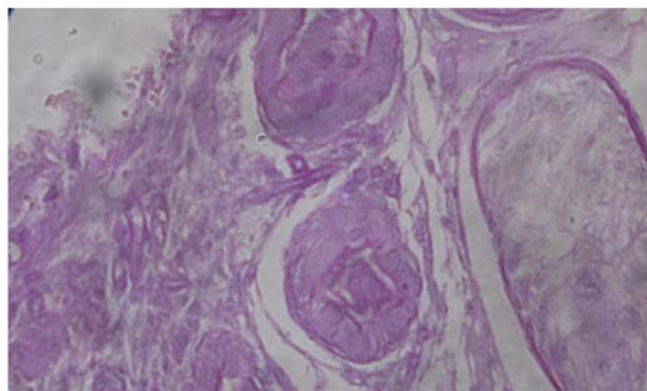


Figure 5: Some sections show tubular hyalinosis, tubular atrophy, spermatocytic arrest. (H&E, x400).

These histological findings underscore the severe changes associated with cryptorchidism, which can predispose individuals to infertility and increase the risk of testicular malignancy. The presence of thickened basement membranes, tubular atrophy, stromal fibrosis, and spermatocytic arrest indicates significant disruption in normal testicular architecture and function. Early diagnosis and timely surgical intervention, such as orchidopexy, are crucial to mitigate these adverse effects and improve patient outcomes.

Stained sections strongly suggested the presence of CIS Figure 6, in one patient with bilateral cryptorchidism who had undergone bilateral orchiopexy at the age of 8 years. The general clinical examination revealed no abnormalities, and the patient exhibited normal secondary sexual characteristics. A local examination of the scrotum revealed moderate testicular size, with no other abnormalities in the epididymis or the spermatic cord. Hormonal profiles showed an elevated FSH level of 37.2 (normal range: 1.4–18.2), while LH, testosterone, and prolactin levels were within normal limits.

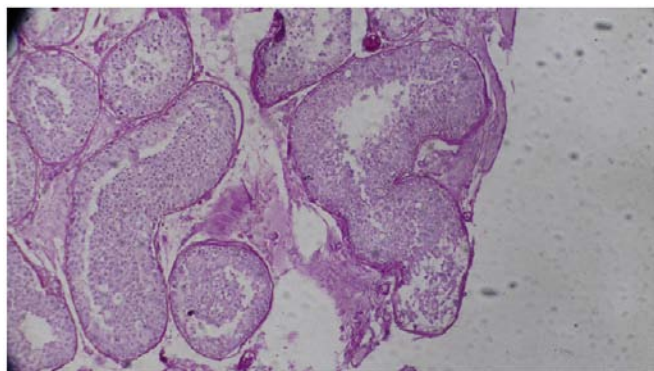


Figure 6: Testicular carcinoma in Situ (H&E, x400).

The table presents the histopathological findings of patients with a history of cryptorchidism. In total, 3 patients exhibited total hyalinization, a condition where the testicular tissue has completely degenerated without spermatogenesis. Another 3 patients showed total hyalinization with focal spermatogenesis, where some areas displayed spermatogenesis amidst degeneration. Nine patients had a Sertoli cell-only pattern, indicating the presence of only Sertoli cells, with no spermatogenesis occurring. Eleven patients were found to have an incomplete Sertoli cell-only pattern, suggesting partial spermatogenesis. Spermatogenic arrest, where spermatogenesis is halted at some stage, was observed in 5 patients, while 11 patients had incomplete spermatogenic arrest (hypospermatogenesis), reflecting a reduced but not

entirely halted spermatogenic process. Eleven patients showed normal testicular histopathology, indicating no abnormalities. Finally, 7 patients presented with a mixed unclassified pattern, showing a varied and unclear histological pattern. These findings highlight the diverse histopathological outcomes in individuals with cryptorchidism, ranging from normal tissue to various degrees of spermatogenic dysfunction.

DISCUSSION

Male infertility evaluations, in addition to identifying the cause of infertility, may uncover significant medical pathologies. A study reported a 6% incidence of significant medical conditions, including testicular cancer, found during infertility evaluations [22]. A large population-based study showed that men seeking infertility treatment had a 1.6-fold increased risk for testicular cancer compared to the general population [23]. A recent retrospective cohort study involving over 30,000 men revealed a strong association between male subfertility and subsequent risk of testicular cancer [24]. This association suggests an as yet undefined etiological factor. A higher incidence of testicular cancer has been observed among azoospermic men and those with abnormal semen characteristics, such as oligozoospermia, asthenozoospermia, and teratozoospermia.

The aim of our study was to detect histological changes and the incidence of CIS in the testis of infertile patients undergoing intra-cytoplasmic sperm injection (ICSI) and testicular sperm extraction (TESE). The testicular biopsies of these patients were examined retrospectively, and stained slides were prepared using paraffin blocks of the testicular biopsies.

The incidence of carcinoma in situ (CIS) in this study was 5%. This figure is higher than those reported in other countries, including: 0.6% in Switzerland [25], 0.77% in Germany [26], 0.4% in London [27], 1.1% in Denmark [28], and 1.8% in the USA [29].

The variation in these figures may reflect differences in patient selection for biopsy. For instance, the lower incidence in London may be due to a higher proportion of patients having testicular biopsies for obstructive azoospermia or vasectomy reversal. The incidence of CIS is also lower in Sertoli cell-only syndrome or Klinefelter syndrome [30]. The higher incidence in Denmark may be due to an increase in malignant testicular tumors in Scandinavian countries [31]. The surprisingly elevated incidence in our study

may be attributed to delayed surgery for cryptorchidism.

Over the past 30 years, research on testicular germ cell cancer prevalence has increased [32]. For all countries, the incidence showed a substantial upward trend during the observation period, with the annual increase varying from 2.3% in Sweden to 5.2% in former East Germany. If this trend continues, the overall incidence of testicular cancer may double every 15-25 years.

The strong association between male subfertility and subsequent risk of testicular cancer supports the hypothesis of a common prenatal origin [33]. Both testicular cancer and male subfertility may be caused by exposure to agents disrupting normal hormonal balance during embryogenesis [34]. CIS cells are believed to originate from primordial germ cells early in embryogenesis, possibly due to an endocrinological imbalance. An excess of estrogen during early embryonic life could stimulate primordial germ cells, causing them to acquire the tumorigenic potential of CIS cells [35].

It is estimated that invasive growth will develop in 50% of patients within 5 years of diagnosis [36, 37]. In a study of 7 infertile patients, testicular cancer was found over a 15-year period [38]. Additionally, two cases of CIS were found in infertile men with sperm counts below 2.5 million/ml and severe testicular atrophy [39]. However, the true prevalence of CIS in infertile men has been questioned, as no cases of CIS were found in a prospective series of 207 infertile men [40]. This discrepancy may be due to the small sample size or technical issues.

Although CIS was generally presumed to be dispersed throughout the testis, it was found that in about 60% of CIS-bearing tissues close to testicular tumors, the distribution was not homogeneously diffuse but may be focal [41], potentially leading to false-negative biopsies. In a previous study of 1,954 patients with testicular tumors, despite negative biopsies, five patients developed a second tumor, yielding a false-negative biopsy rate of 0.3%. The main reasons for diagnostic failure included non-random distribution of testicular intraepithelial neoplasia and technical issues with immunohistochemical staining. Despite this, surgical biopsy remains the gold standard for diagnosing testicular intraepithelial neoplasia [42].

It has been suggested that the increase in testicular cancer incidence is linked to a general decline in male

reproductive health [32]. In a study of 175 patients undergoing ICSI/TESE, histopathological evaluation revealed CIS in 5 patients (prevalence of 2.9%) [43]. Another study involving 766 subfertile men undergoing ICSI/TESE found CIS in 7 men (prevalence of 0.7%) [44].

In the present study, which involved 800 subfertile men undergoing ICSI/TESE, CIS was detected in one patient, resulting in a prevalence of 0.8%. The increased risk of CIS associated with cryptorchidism has been recognized, but the additional factors that make certain men with cryptorchidism and infertility more prone to testicular cancer remain unclear [45].

In adult men with a history of cryptorchidism, the prevalence of CIS has been reported as 2% to 4% [46]. However, the prevalence in children with cryptorchidism is much lower (0.36%) [47]. The lower incidence in children may be because CIS only begins to replicate after the endocrinological stimulus of puberty [48].

Multinucleated spermatogonia, which may be associated with an increased risk of testicular malignancy, were found in 13 of 136 cryptorchid boys. In cases of CIS testis, multinucleated spermatogonia were identified in two cryptorchid boys [49].

In this study, CIS was suspected in 6 patients with a history of cryptorchidism. One case was diagnosed as positive for CIS, with a history of bilateral cryptorchidism and bilateral orchiopexy performed at age 8. This is considered too late for optimal management. Early surgery for cryptorchidism, ideally between 15–18 months of age, is recommended to reduce the risk of infertility and the development of CIS or testicular tumors later in life [50]. Additionally, testicular biopsy during primary cryptorchidism surgery is recommended to examine for testicular neoplasia, particularly in cases of intra-abdominal testis, abnormal external genitalia, or known abnormal karyotype [51].

CONCLUSION

In conclusion, male infertility evaluations not only identify infertility causes but can also detect significant conditions, such as testicular cancer. Our study found a relatively high incidence of carcinoma in situ (CIS) among infertile patients undergoing ICSI and TESE, with variation in rates possibly due to differences in patient selection and biopsy practices. The association between subfertility and testicular cancer suggests a shared prenatal origin, potentially linked to hormonal

imbalances during embryogenesis. Early surgical intervention for cryptorchidism, ideally before puberty, is crucial to reduce infertility risk and prevent CIS. Histopathological evaluation, including testicular biopsies, is essential for accurate CIS diagnosis. These findings highlight the need for careful monitoring and early intervention in infertile men, particularly those with cryptorchidism, to reduce the risk of testicular cancer and related conditions [50].

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