Cryptorchidism and its implication on fertility

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Cryptorchidism and its implication on fertility

- Definition and general Incidence
- Is cryptorchidism a major risk in infertility?
- Cryptorchidism early therapy implication on fertility
- Orchidopexy techniques implication on fertility
- Cryptorchidism and its implication on infertility management
- Conclusion and future directions

Definition

- Cryptorchidism means “hidden testis”.
- It is used to describe an undescended testis (UT) and the diagnosis is defined as deviation or arrest of the testis at any point along the normal path of its descent from an origin below the kidneys down into the scrotal sac

(Rezvani, 1987).

Incidence of cryptorchidism in general population

- The undescended testis represents the single most common disorder of male sexual differentiation.
- It occurs in approximately 3% of human males at birth and decreasing to 1% during the neonatal period because of spontaneous descent.

(Berkowitz, 1993)

Is cryptorchidism a major risk in infertility ?

Is cryptorchidism a major risk in infertility?

- Incidence :
  - UT in fertile and infertile population
  - Incidence of infertility in cryptorchid population
- Cryptorchidism impact on testicular function
  - Cryptorchidism impact on semen analysis
  - Cryptorchidism impact on paternity
- Cryptorchidism impact on testicular histology

Incidence of cryptorchidism in fertile and infertile population

- **8.96%** of the cases in 212 infertile men (Carizza et al, 1990)
- Out of 85 fertile and 1014 infertile men, two (2.4%) and 95 (**9.4%**) respectively had a history of cryptorchidism (Mieusset et al., 1995).
- 20-27% in men with azoospermia (Lee and Coughlin, 2001; Fedder et al, 2004).
- 3–8% with oligo-terato-asthenospermia (Lee & Coughlin, 2001).

Incidence of infertility in cryptorchid population

- In unilateral cryptorchidism, the incidence of infertility may be as high as 32% and up to 59% of men with bilateral cryptorchidism may be infertile despite surgical correction by orchidopexy.

  (Mathews, 1997; Lee et al.,1996, 1997).

- 89% of untreated UT patients with bilateral maldescent develop azoospermia.

  (Hadziselimovic and Herzog , 2001).

Cryptorchidism
impact on testicular function

- In unilateral cryptorchidism, the volume of a former cryptorchid testis is smaller than the contralateral normally descended one and sperm analysis is less impaired than in bilateral cryptorchidism.

(Mieusset et al., 2005)

Cryptorchidism
impact on testicular function

- In Bilateral cryptorchidism, most of the patients have low orchidometry, abnormally soft testes and elevated serum FSH (Nistal and Paniagua, 1997), with altered semen parameters and low paternity rate (Lee and Coughlin, 2001).
- Severe impairment of semen quality in bilateral forms has also been reported by other authors (Gracia et al, 2000; Vinardi et al., 2001; Lee, 2005).

Cryptorchidism
impact on testicular function

- They represents the phenotypical expression of a severe anatomical and functional defect of the gonads (Hadziselimovic, 1996) and are usually associated with a secretory dysfunction (Ezeh et al., 1999; Sharif, 2000).

Cryptorchidism
impact on testicular function

- A retractile testis, defined as a testis reported by the patient to be spontaneously and regularly, i.e. at least once a week, ascending up into a supra-scrotal position, is more frequent in infertile men with a history of cryptorchidism than in fertile men.
  - (Mieusset et al., 2005)

Cryptorchidism
impact on testicular function

- Retractility is more frequent on the cryptorchid side, and is found more frequently after hormonal than after surgical treatment.
- Independently of all epidemiological and clinical parameters studied, retractility is associated with a lower sperm output.

(Mieusset et al., 2005)

Cryptorchidism
impact on semen analysis

- Chilvers et al. (1986) found rates of oligospermia and azoospermia 31% and 42%, among formerly bilaterally cryptorchid men and respectively, 31% and 14% among formerly unilateral cryptorchids.

Cryptorchidism
impact on semen analysis

- Adult men with persistent bilateral cryptorchidism have azoospermia, whereas 28% (24–32%) after operation have a normal sperm count.
- Approximately 49% (41–58%) of men with persistent unilateral cryptorchidism have a normal sperm concentration as compared to 71% (68–74%) after orchidopexy.

(Virtanen et al., 2007)

Cryptorchidism impact on paternity

- Compared with controls, Reduced paternity rates have been found after treatment for bilateral (Lee et al, 2001), but not unilateral cryptorchidism (Lee et al., 1996; 2002; Miller, 2001).
  - Lee (1995) postulated that paternity itself is a better index than sperm count since it is known that men with subnormal sperm counts may have normal paternity rates.

Cryptorchidism impact on paternity

- These finding were previously supported by two subsequent studies in which up to 90% men with unilateral undescended testis had fathered children, as opposed to only 33-65% with bilateral undescended testes (Cendron et al., 1989; Coughlin et al., 1989).
  - The “normal” paternity rate is believed to be about 85% (Elder, 1988).

Cryptorchidism
impact on testicular histology

- This group of patients represents a highly heterogeneous cohort when it comes to predicting the level of preserved spermatogenesis.
- These patients represent the entire histologic subtypes at the time of testicular biopsy.

(Nieschlag et al. 2000; Negri et al.,2003; Raman and Shlegel, 2003; Varneaeve et al, 2004)

Cryptorchidism
impact on testicular histology

- Variables to be considered include the degree of cryptorchidism (abdominal, inguinal, high scrotal, ectopic), laterality (unilateral or bilateral), age at orchidopexy, and age of the patient when he seeks evaluation.

(Nieschlag et al. 2000; Negri et al.,2003; Raman and Shlegel, 2003; Varneaeve et al, 2004)

Cryptorchidism
impact on testicular histology

- Glander et al. (2000) found that patients with a history of cryptorchidism show a significantly lower Johnsen score compared with the patients who had not had any testicular disease in the past.

Cryptorchidism
impact on testicular histology

- Vernaeve et al (2004) found on 79 patients Germ cell aplasia (54), Maturation arrest (20) Sclerosis and atrophy (5)
  - (after exclusion of patients with a history of orchidopexy with a testicular histopathology showing normal spermatogenesis)

Cryptorchidism
impact on testicular histology

- Nieschlag et al. (2000) report that two-thirds of 63 patients with a history of maldescended testes suffer from SCOS or from maturation arrest while 28% with hypospermatogenesis.
- Defective spermatogenesis has been documented to occur in the contralateral testis in men with unilateral cryptorchidism (Woodhead, 1973).

Normal spermatogenesis in undescended testes!

- Despite these data, high prevalence of obstructions referring to histological pictures(normal spermatogenesis or mild hypospermatogenesis) and TESE outcomes in orchidopexed azoospermic men (~40%) compared with NOA patients without maldescended testes is suggested.

Negri et al. (2003)

Normal spermatogenesis in undescended testes!

- It may be explained by the fact that some of these patients may have been misdiagnosed in their youth as having undescended testis when in fact they may have had a retractile testis (Hack et al., 2003).
  - Although generally regarded as not requiring any therapy (Schoorl, 1982), some authors describe retractile testes as a risk factor for subfertility and suggest orchidopexy (Caucci et al., 1997).

Normal spermatogenesis in undescended testes!

- The association between testicular maldescent and seminal duct anomalies (from rete testis to vas deferens) is a well-known fact. Prevalence of congenital epididymal or vasal anomalies is 36-43% in orchidopexed patients.

  (Gill et al.,1989; Cicigoi and Bianchi, 1991; Mollaeian et al., 1994; D'Agostino et al., 1996; Nistal and Paniagua, 1997; Nistal et al., 2002).

Cryptorchidism
impact on testicular histology

- Biopsy of the testes with severe anomalies of ductal fusion shows preservation of germ cells in 69% and diminished germ cells in 31% (Gill et al., 1989).
  - The prevalence and the severity of these anomalies appear to be strictly correlated to the level of undescended testis (Cicigoi and Bianchi, 1991) and with the degree of patency of the processus vaginalis (closed, partially closed or open) (Bartholdand Redman, 1996).

Normal spermatogenesis in undescended testes!

- Not to be underestimated is the risk of a iatrogenic obstruction, by transection of the vas deferens or by an excessive tension exerted on the spermatic cord (Adamsen and Borjesson, 1988; Redman, 2000).
- Therefore, these data suggest that some form of obstruction is the cause or an associated cause of azoospermia in many orchidopexed men.

Cryptorchidism early therapy and its implication on fertility

Cryptorchidism early therapy and its implication on fertility

- Testes of normal boys are located in the scrotum at birth and contain both the fetal stem cell pool (gonocytes) and the adult stem cell pool (adult dark spermatogonia). The total number of germ cells increases during the first 3 month of life, after which it decreases until 3 years of age.
- Transformation of spermatogonia to primary spermatocytes usually starts at around the age of 3 years, and the testes of most 4-year-old boys contain primary spermatocytes.

(Cortes *et al.*, 1995)

Cryptorchidism early therapy and its implication on fertility

- In contrast, boys with cryptorchidism are born with fewer gonocytes and spermatogonia, and the transformation of gonocytes to spermatogonia occurs less efficiently and the number of spermatogonia is reduced in almost all non-descended testes in 1-year-old boys.
- Further, formation of primary spermatocytes also seems to be impaired, already indicating at this stage future fertility problems.

(Cortes *et al.*, 1995)

Cryptorchidism early therapy and its implication on fertility

- The longer a testis remains undescended, the more severe the adverse effect.
- The higher the testicular position at the time of treatment, the fewer the number of germ cells compared with the matched controls.
- The degree of spermatogenic damage is higher in bilateral UT than unilateral UT.

(Gracia et al 2000, Vinardi et al 2001, Lee 1995)

Cryptorchidism early therapy and its implication on fertility

- Most studies of fertility in formerly cryptorchid men have occurred in populations of men where orchiopexy was performed without the realization that testicular damage occurs as early as six months of age.
- Nowadays, based upon that fact, and as few testes descend spontaneously after one year of age, earlier intervention at 1 year or soon therafter by surgical orchiopexy has been recommended.

American Academy of Pediatrics, (1996)

Cryptorchidism early therapy and its implication on fertility

- The European Association of Urology and the European Society for Paediatric Urology; in 3/2009 recommended orchidopexy at the latest by 12-18 months of age.

(Tekgül et al, 2009)

Cryptorchidism early therapy and its implication on fertility

- Judging from the publications available to date, the Nordic consensus group on treatment of undescended testes (2007) came to the unanimous conclusions that Orchiopexy should be done between 6 and 12 months of age, or upon diagnosis, if that occurs later.

Ritzén et al, 2007

Cryptorchidism early therapy and its implication on fertility

- Early surgery therefore seems more advantageous. However, It is yet unknown, whether current guidelines of earlier orchidopexy would further improve the outcome.
- So far, randomized studies designed to identify the precise optimal time for surgery before 3 years of age are needed.

Ritzén et al, 2007

Cryptorchidism early therapy and its implication on fertility

- The first results from a randomized controlled study, comparing the testicular growth after surgery at 9 months or 3 years of age, showed that orchiopexy at 9 months was followed by a partial catch-up growth, which was not seen after the late surgery.
  - This suggests that the testis at least partly loses its capacity for recovery if left in the scrotum beyond 1 year of age.

(Kollin et al., 2006; 2007).

Cryptorchidism early therapy and its implication on fertility

- Few studies have assessed semen quality in relation to age at orchidopexy. Due to different previous guidelines, the age range is usually higher than in current recommendations (Virtanen et al., 2007).
- In a study of orchidopexy for bilateral UT in patients less than 16 years of age, 35% reported fertility up to 12 years after surgery (Gilhooly et al, 1984).

Cryptorchidism early therapy and its implication on fertility

- Surgery between 10 months and 4 years of age in bilateral cryptorchidism led to a normal sperm count in 76% (50–93%), compared to 26% (9–51%) with surgery between 4 and 14 years.
- In unilateral cryptorchidism this impact of timing was not as obvious: 75% (68–81%) versus 71% (61–80%) if operated between 10 months and 6 years versus 9–12 years.

(Virtanen et al., 2007)

Adult orchidopexy implication on fertility

- Even when corrected peripubertally, sperm may be present in the ejaculate of men with bilateral undescended testes. Stuart et al., (2005).
- UT sometimes escapes detection until adulthood. Surgery for bilateral UT in late childhood or early adulthood was considered to be cosmetic and unlikely to have any effect on spermatogenesis.

(Chiba et al, 2009).

Adult orchidopexy implication on fertility

- Although, some reports have documented fertility after bilateral adult orchidopexy (Heaton, 1993; Shin et al, 1997), Chiba et al (2009) could not show the efficacy of orchidopexy as a treatment of infertility in adulthood (20 cases).
  - In this study, there was no patient with bilateral UT who achieved pregnancy. In one patient who underwent testicular biopsy 10 months after orchidopexy, no improvement of spermatogenesis was seen.

Cryptorchidism early GnRH therapy and its implication on fertility

- Hadziselimovic, (2006) reported that early successful orchidopexy did not prevent from developing azoospermia in 9% of a cohort of 231 patients who had a semen analysis when became adults.
- Importantly, Ad spermatogonia were absent in the azoospermic population.

Cryptorchidism early GnRH therapy and its implication on fertility

- Ad spermatogonia proved to be a discriminating factor for the fertility outcome in cryptorchidism (Hadziselimovic and Hoecht, 2008).
- Male fertility depends on the transformation of gonocytes into dark adult spermatogonia, during the first 3 months of postnatal life, and this is an androgen-dependent process (Biers et al., 2010).

Cryptorchidism early GnRH therapy and its implication on fertility

- This essential developmental step appears to be defective in undescended testes, and in many patients orchidopexy alone (at the age it is currently performed) does not improve fertility indices, either because it does not address the underlying pathophysiology or the surgery is performed too late.

(Biers and Malone, 2010)

Cryptorchidism early therapy and its implication on fertility

- Hormone therapy with gonadotrophin-releasing hormone creates a rise in testosterone levels, copying the postnatal gonadotrophin surge.
- This can improve germ cell numbers, with the implication of enhanced longer-term fertility.

(Biers and Malone, 2010)

Cryptorchidism early therapy and its implication on fertility

- The role of hormone therapy has been controversial, and although favored at the European Society of Paediatric Urologists' workshops in 2008 and 2009, it is not routine clinical practice in many countries.
- The evidence for improved fertility indices, semen analysis and paternity rates following hormone therapy in undescended testes is sufficiently strong to recommend a change in clinical practice.

(Biers and Malone, 2010)

Post orchidopexy GnRH therapy implication on fertility

- Prepubertal treatment of cryptorchidism with the GnRH analogue Buserelin in patients with a fertility index (which may act as a predictor for fertility later on in life) of less than 0.2 (fewer than 0.2 cells per tubular cross section) based on testis biopsy at orchiopexy has resulted in improved total germ cell counts and improved spermiograms.

(Hadziselimovic, 1983;1997).

Post orchidopexy GnRH therapy implication on fertility

- Huff et al (2001) showed that 75% of boys with significantly reduced germ cell counts who were treated with nafarelin after orchiopexy and bilateral testicular biopsy, showed a significant improvement in total germ cell counts on rebiopsy after 5 months.

Post orchidopexy GnRH therapy implication on fertility

- Although, data from the long-term follow-up of the impact of hormonal treatment on fertility potential was lacking, Hadziselimovic (2008), was able for the first time, to demonstrate that infertility in cryptorchidism can be successfully corrected when suitably treated with a LH-RHa.
  - Sperm parameters normalized following therapy in the majority of cryptorchid males (86%) who, untreated, would have remained infertile.

PRE- orchidopexy GnRH therapy implication on fertility

- Neoadjuvant GnRH in prepubescent boys before surgery may also positively affect future fertility, with the highest fertility indices reported with therapy before age 2 years (Schwentner , et al. 2005).

HCG Therapy
implication on fertility

- Reported side effects of HCG include germ cell apoptosis and, importantly, reduction in the number of germ cells and the size of the testes in adulthood (Dunkel et al., 1997).
- The adverse effects of hormonal treatment may be age-dependent, most harm being caused at 1–3 years of age (Cortes et al., 2000).

Orchidopexy techniques implication on fertility

Orchidopexy techniques implication on fertility

- Rosenmerkel in 1820 was the first to advocate placement of the undescended testis in the scrotum (Cabot and Nesbit, 1931).
- A variety of surgical techniques of orchiopexy have been reported since then, from the various forms of dartos pouch to the commonly performed transparenchymal suture fixation (Lotan et al 2004).

Orchidopexy techniques implication on fertility

- The deleterious effect of this latter technique on testicular histology and the phenomenon known as “sympathetic orchiopathy” (damage to the contralateral testis in cases of unilateral testicular injury or ischemia) raised questions concerning the ideal technique of orchiopexy (Lotan et al 2004).

Orchidopexy techniques implication on fertility

- Basic studies of intratesticular arterial anatomy have shown that placement of sutures in the testicle, or even into the tunica albuginea alone, may result in testicular parenchymal damage (Jarow, 1990; Smith, 1974).

Orchidopexy techniques implication on fertility

- Bellinger et al. (1989), studying the effects of surgical technique on testicular histology, emphasized the risk of testicular parenchymal injury after suture fixation, particularly with absorbable suture material. At the same time, they found complete circumferential adherence and normal spermatogenesis in 94% and minimal focal tubular atrophy in 23% using dartos-fixed testes.

Orchidopexy techniques implication on fertility

- Dixon et al. (1993) also evaluated the effect of transparenchymal suture fixation of the testis on testicular histology. Significant inflammatory reactions were observed in all groups of animals with suture fixation, regardless of suture size and material.
- However, only 5% of the animals in the “dartos pouch” control group had an inflammatory response.

Orchidopexy techniques implication on fertility

- These findings raise concerns about the effect of surgical technique on the future reproductive capabilities of the testis when the transfixation technique is used.
- Another argument against transfixation orchiopexy is the phenomenon known as “sympathetic orchiopathy,” which refers to damage to the contralateral testis in cases of unilateral testicular injury or ischemia.

Orchidopexy techniques implication on fertility

- The mechanism for this process is autoimmunization, which occurs when breakdown of the blood-testis barrier exposes tubular antigens to the immune system (Wallace et al., 1982).
- In addition to contralateral testicular damage, autoimmunization can produce antisperm antibodies (Peters et al, 1991).

Orchidopexy techniques implication on fertility

- Since autoimmunization occurs when breakdown of the blood-testis barrier allows for exposure of tubular antigens to the immune system, it does not occur with the True dartos pouch orchiopexy technique.

Orchidopexy techniques implication on fertility

- In an experimental study on mature golden hamsters Lotan et al. (2005), concluded that dartos pouch orchiopexy, is the method of choice for orchiopexy.
- Anatomically sound, technically simple, very effective, and avoiding the placement of traumatizing anchoring sutures through the testicle itself, it should replace Classic transfixation orchiopexy in the treatment of the undescended testis in children.

Cryptorchidism and its implication on infertility management

Cryptorchidism and its implication on infertility management

- For adult infertile patients with a history of Undescended Testes, currently no rational therapy is available; as symptomatic treatment, techniques of assisted fertilzation may be considered and applied (Nieschlag, et al, 2000).

Cryptorchidism and its implication on infertility management

- In infertile couples in whom unilateral cryptorchidism was the causal factor. The spontaneous conception rate was very low (1% per cycle). (IUI) and (IVF) resulted in similar success rates of 6.1 and 8.7% per cycle/attempt respectively.
- After ICSI, 46.7% pregnancies were obtained per attempt, and sperm requirements for the latter treatment to be successful were lower than for IUI.

(Mahmoud et al, 1996)

Cryptorchidism and its implication on infertility management

- In azoospermia associated with cryptorchidism Recovery of testicular spermatozoa (TESE) for ICSI is the only option (Schlegel etal, 1997).
- Several small-scale reports have described successful pregnancies after TESE for men with NOA associated with cryptorchidism

(Shin et al., 1997; Giwercman et al., 2000; Lin et al., 2001; Negri et al., 2003 ; Raman and Schlegel, 2003, Wiser et al., 2009) .

Cryptorchidism and its implication on TESE and ICSI outcomes

- A large patient population (79) with a history of orchidopexy with the exclusion of any other pathology that could explain testicular failure and histologically proven NOA was subjected for TESE with ICSI (Vernaeve et al., 2004).
  - Testicular spermatozoa were recovered in 41 patients (52%).
    - 21 of the 49 patients (43%) with bilateral and in nine out of the 16 (56.2%) with unilateral cryptorchidism (P = 0.4).

Cryptorchidism and its implication on TESE and ICSI outcomes

- This higher recovery rate (52%) in patients with a history of orchidopexy than that observed in unexplained NOA (71 out of the 213 patients (33.3%) may be explained by the fact that some of these patients may have been misdiagnosed in their youth as having undescended testis when in fact they may have had a retractile testis (Hack et al., 2003).

Cryptorchidism and its implication on TESE and ICSI outcomes

- Higher sperm recovery 73% versus 43% was also reported by Negri et al (2003), Raman and Schlegel reported 74% (2003) versus 58%.
- Differences in the populations studied may account for this (Normal and hypospermatogenesis) (Vernaeve et al., 2004).

Cryptorchid TESE positive predictive factors

- In the case of NOA, the history of cryptorchidism is a factor of better prognosis of testicular sperm extraction than in idiopathic NOA (Marcelli et al., 2008, Robin et al, 2010).
  - Marcelli et al (2008) found that the subgroup with normal fsh and testicular volume more than 10 ml has 75% positive retreival.

Cryptorchid TESE positive predictive factors

- Negri et al., (2003) reported patient age and FSH level as positive predictive variables.
- Raman and Schlegel (2003) reported patient age at orchidpexy time and testicular volume as positive predictive variables.

Cryptorchid TESE positive predictive factors

- Glander et al., (2000) found that that successful sperm retrieval can be expected in all azoospermic patients irrespective of the results of clinical examination.
- However, the probability of retrieval of spermatozoa decreased significantly in patients with a FSH level > 18 U/L, testicular volume < 5 mL, mean Johnsen score <5, and maximum Johnsen score <7.

Cryptorchid TESE positive predictive factors

- Vernaeve et al., (2004) didn't find any clinical parameters (i.e. age at testicular biopsy, age at orchidopexy, testicular volume, FSH, FSH/LH ratio and androgen sensitivity index) predicting successful sperm retrieval.
- A high recovery rate can only be expected when histology shows spermatids or spermatozoa (Vernaeve et al., 2004).

Cryptorchid TESE positive predictive factors

- Age at orchidopexy, either at 10 years of age or younger or above 10 years of age, was not a predictive factor for successful TESE. (Wiser et al., 2009).

Cryptorchidism and its implication on ICSI outcome

- The outcome is comparable with that in the population of men with non-obstructive azoospermia (Negri et al., Raman and Schlegel; Vernaeve et al., 2003; Haimov-Kochman et al, 2010).
- In both groups, a high rate of early pregnancy loss was observed. None of the children born had a cryptorchidism (Vernaeve et al., 2003).

Cryptorchidism and its implication on ICSI outcome

- The outcome of ICSI is not influenced by age at orchidopexy, either at 10 years of age or younger or above 10 years of age (Wiser et al., 2009).

Conclusion

- Cryptorchidism is a major risk for male infertility impacting on testicular anatomy, histology and reproductive function.
- Very early diagnoses and management of UT is worth trying.
- Choice of a non traumatizing surgical technique is advised.
- ART is the only therapeutic option available nowadays for infertility issues with satisfactory outcome.

Future directions

- It is now hoped but not proven, that timely therapy will reduce the incidence of infertility and malignancy.
  - Large scale studies investigations of patients subjected to early treatment and who have reached reproductive age to clarify the benefit of early treatment are needed.
  - Because of the multiple etiologies of the cryptorchid state, factors such as the relative size of the testis before treatment, and the position of the testis and the histology of the testis need to be considered.

Future directions

- Surgical and medical treatment technique optimization.
- identifying environmental and behavioral causes of cryptorchidism.
- Evaluating, in a larger series, the prevalence of cryptorchidism in boys born from fathers with an undescended testis.

Future directions

- Exploring new possibilities for fertility preservation in young boys with undescended testes for future fertility restoration options from frozen tissue, i.e. cell suspension transplantation, tissue grafting and IVM (Kvist et al, 2006; Wyns et al, 2010).

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