International Surgery Journal
Agrawal SN. Int Surg J. 2018 Oct;5(10):3453-3459
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20184110

Review Article

Cryptorchidism: its influence on male fertility and the risk of the testicular tumor

Sujan Narayan Agrawal*

Department of Surgery, SBRKM Government Medical College, Jagdalpur (Bastar), Chhattisgarh, India

Received: 06 August 2018
Accepted: 08 September 2018

***Correspondence:**
Dr. Sujan Narayan Agrawal,
E-mail: drsujanagrawal@gmail.com

ABSTRACT

In the embryonic stage, the testes develop in the abdomen and descend to scrotum, just before or at birth. The undescended testis is the result of the arrest of descent of testis in some part along its path, to the scrotum. The bilateral undescended testis is called Cryptorchidism which means hidden testis. The factors that contribute to the descent of testis includes Gubernaculum testis, the differential growth of abdominal wall, intra-abdominal pressure and temperature, Calcitonin gene-related peptide (CGRP), male sex hormones, insulin-like hormone 3 (INSL3) and maternal gonadotrophins. The descent of testis may become erratic and gives rise to undescended testis, ectopic testis, congenital hernia, and hydrocoele etc. As a rough estimate approximately 2-4% of male infants are born with Cryptorchism, thus making it, one of the most common congenital anomalies, in the male genitalia. It was found that the incidence of azoospermia in unilateral cryptorchidism was 13%, but in untreated bilateral cryptorchidism, it reaches up to 89%. Cryptorchid boys have increased the risk of a testicular tumor, mainly seminoma. Persistent exposure to high temperature in cryptorchidism could allow maturation of the neonatal gonocytes that has failed to mature as spermatogonia or undergo apoptosis. These cells may persist in testes for years together and eventually become carcinoma in situ cells with a high risk of testicular malignancy later in life i.e., 20-40 years of age. This review addresses the cryptorchidism, its influence on fertility and the risk of developing testicular germ cell tumor. The hormonal factors involved in testicular descend or otherwise is also highlighted.

Keywords: Adult dark spermatogonia, Cryptorchidism, Gubernaculum testis, Mini-puberty, Testicular germ cell tumor

INTRODUCTION

The testes develop in the abdomen in the embryonic stage and descend to scrotum just before or at birth. The undescended testis is the result of the arrest of descent of testis in some part along its path to the scrotum. The bilateral undescended testis is called Cryptorchidism which means hidden testis. The Cryptorchidism may be associated with Klinefelter's syndrome, Hypogonadotrophic hypogonadism, Prune-belly syndrome, renal agenesis, bladder exstrophy, gastroschisis, horseshoe kidney, anorectal malformation etc.[1]

The primitive testis develops from the genital fold which is attached to the posterior abdominal wall by mesorchium. It lies below the developing kidney. The testis develops before birth on the dorsal abdominal wall. During the human fetal period, the testis migrates from the abdomen to scrotum traversing the abdominal cavity and the inguinal canal by 15th to 28th-week, post conception. During the ninth month of gestation, testis

reaches the deep inguinal ring. Later, just before or after delivery it descends into the scrotum.

The factors that contribute to the descent of testis includes Gubernaculum testis, the differential growth of abdominal wall, intra-abdominal pressure and temperature, Calcitonin gene-related peptide (CGRP), male sex hormones, insulin-like hormone 3 (INSL3) and maternal gonadotrophins. The descent of testis may become erratic and gives rise to undescended testis, ectopic testis, congenital hernia, and hydrocoele etc.[2]

As a rough estimate approximately 2-4% of male infants are born with Cryptorchism, thus making it, one of the most common congenital anomalies, in the male genitalia.[3] The rate of Cryptorchism decreases to 0.7-1% when the child reaches the age of one year.[4,5] It seems that the incidence varies with geographical location, social and environmental factors. For example; in Denmark, 9% of the newborn male was diagnosed with undescended testis as compare to 2.4% in Finland. There may be some influence of genetic factors also.[6,7] The incidence of UDT (Undescended testes) is higher in industrialized western societies.[5]

There is a strong co-relation of Cryptorchidism and low birth weight. In premature and low birth weight babies (<2500 g), the incidence may be 5-7 times higher. It may be because of the fact that the process of testicular descend completes around 36 weeks to just before/after the birth.[8-10] There may be an element of impaired placental function in premature and low birth weight babies since testicular descent is influenced by hCG from the placenta.[11]

Jensen et al hypothesized that both intrauterine environment and maternal inheritance can contribute to cryptorchidism; i.e., concordance rates of 24.1% UDT in dizygotic twin brothers, 27.3% in monozygotic twin brothers, and 3.4% in paternal half-brothers vs. 6.0% in maternal half-brothers.[12,10] The overall incidence of undescended testis in premature infants is 30%, in a full-term infant is 4%, and after one year is 2%. Right sided UDT alone in 50% cases, left-sided UDT in 30% and bilateral in 20% of cases.[1]

Before proceeding further it is imperative to revise the definitions of interrelated terms. The Cryptorchidism means undescended testis on one or both the sides. The ectopic testis is those where the testis has deviated from its usual path and found to lie at ectopic positions like the superficial inguinal pouch, the root of penis, perineum, or thigh/femoral triangle.

Here the testis function is normal, but the abnormal position is more prone to trauma and causes psychological problems. The retractile testis; in this case, the testis is normally descended, but gets retracted near external ring due to over-active cremesters. In such cases, the testis can be coaxed to bottom of scrotum manually (which is not possible with undescended testis or ectopic testis).[1]

THE FERTILITY RISK

Primitive germ cells are present in testis at the time of birth.[13] Gene activation specific to testis leads to regulated cell proliferation and differentiation of spermatogonia, meiosis, and haploid differentiation or spermatogenesis.[14]

The primordial germ cells (PGC) or gonocytes migrate towards the developing gonads by end of the fifth week. It goes on proliferating by mitosis. These gonocytes or PGC act as a fetal reservoir of stem cells.[15] Due to the maturation of the hypothalamic-pituitary-testicular axis the gonocytes are replaced by Adult Dark Spermatogonia (AD-S). This event gives rise to the substantial reduction in germ cells per tubule. The transformation starts at 2-3 months of age and is normally completed by six months. These AD-S exhibits a characteristic dark (electron-dense) cytoplasm and a bright nuclear spot. The early post-natal transformation of neonatal gonocytes into adult dark-spermatogonia (AD-S), plays a key role in subsequent fertility.[16] AD-S is considered to be committed for subsequent spermatogenesis.[17]

Shortly after birth, there is a brief surge in gonadotrophins, followed by a transient rise in testosterone and a sustained rise in MIS/AMH levels.[18,19] Inhibin B is also elevated in the first few months after birth. This hormonal surge around the third month is known as “mini-puberty”.[20] It is critical for normal germ cell development because the transformation of neonatal gonocytes into AD-S is proposed as a key function of mini-puberty. It may also be involved in the masculinising of the brain, as well as helps in the obliteration of Processus vaginalis after testicular descent is complete.[21] The AD-S is thought to be the stem cell for spermatogenesis and its appearance at 3-9 months of age is linked to the potentially optimal time for orchidopexy. In Cryptorchidism this step of gonocytes transformation into AD-S (the putative stem cells) is inhibited or is ineffective.

At 4-5 years of age, a second crucial event takes place. There is a transient appearance of primary spermatocytes and prophase of the first meiotic division. This is due to the maturation of the hypothalamic-pituitary-testicular axis. It is characterized by the transient onset of meiosis and histological appearance of primary spermatocytes. It is associated with a short-lived rise in both the germ cell count and AD spermatogonia (AD-S) count. Spermatogenesis arrests at this stage, and resumes, after the onset of puberty.

It is interesting to note that about half of the neonatal gonocytes only are transformed into AD-S, and rest of it undergo apoptosis. It is very likely that in cryptorchidism this apoptotic pathway, as well as transformation, is

disrupted. This leads to some gonocytes persisting in tubules. This persisting abnormal gonocytes may explain the origin of carcinoma-in-situ and eventual overt malignancy in cases of cryptorchidism. A surge in luteinizing hormone releasing hormone (LHRH) causes the release of LH which stimulates the release of testosterone. The testosterone, in turn, triggers the maturation of germ cells and establishment of an adequate size of adult stem cells. This normal surge in LH and testosterone at 2-3 months of age is significantly lower in patients remaining Cryptorchid (unilateral or bilaterally) than in infants with a delayed spontaneous descent of one or both testes.[22]

In the patients with unilateral or bilateral cryptorchidism, there is delayed onset or failure of meiosis and appearance of primary spermatocytes. In an analysis of testicular biopsies done at orchidopexy, of 529 unilaterally Cryptorchid boys, Huff et al found that there is an absence of transient onset of meiosis and appearance of primary spermatocytes in all but one boy. This patient was of nine years of age and it was likely that he might have already entered puberty.[23]

It has already been mentioned that the neonatal gonocytes undergo differentiation into AD-S which is thought to be the stem cells for spermatogenesis.[24,25] For this process to occur normally, the environmental temperature should be lower than the core body temperature i.e. around 330 within the scrotum. This process is significantly impaired in the undescended testis. Thus, in Cryptorchid, there is poor spermatogenesis, sub-optimal semen quality, and a higher risk of infertility. There is a reduced number of germ cells in the testis as compare to the normal population.[6] The germ cells may be lacking after 15 months of age.[26] It was found that the incidence of azoospermia in unilateral cryptorchidism was 13%, but in untreated bilateral cryptorchidism, it reaches up to 89% it may be related to impaired mini-puberty, the surge of gonadotrophins, and testosterone that occurs in early infancy.[27,28]

THE TESTICULAR TUMOR RISK

Cryptorchid boys have increased risk of a testicular tumor, mainly seminoma.[29-32] Persistent exposure to high temperature in cryptorchidism could allow maturation of the neonatal gonocytes that has failed to mature, as spermatogonia or undergo apoptosis.

These cells may persist in testes for years together and eventually become carcinoma in situ cells with a high risk of testicular malignancy later in life i.e., 20-40 years of age.[33] Testicular cancer affects 1% of the male population and is the most common solid tumor to affect young man between the ages of 15-34.

The following facts highlight the association of cryptorchidism and testicular germ cell tumor:

- Cryptorchidism is an accepted risk factor with a relative risk of 3.7-7.5 times higher than scrotal testis population.[34]
- 5-10% of men who develop testicular cancer was or is Cryptorchid.
- There is an increased risk of TCGT in bilateral as opposed to unilateral cryptorchidism.
- There is a direct correlation between how long the testis remains in the Cryptorchid position and TCGT incidence.[35]
- The relative position of the Cryptorchid testis also determines the occurrence of TGCT. The abdominal testis presents more risk as compared to inguinal testis because former is exposed to environmental insult to a greater degree as compared to the later one.[36]
- Corrective surgery does reduce the incidence of TGCT but the risk is still there. It is because permanent epigenetic changes in Cryptorchid testis.[37]
- Genome-wide studies have identified six susceptible loci for TGCT, and they are KITLG and ATF7IP on chromosome 12, SPRY4 on chromosome 5, BAK1 on chromosome 6, TERT- on chromosome 5, and DMRT1 on chromosome 9.[38,39]
- The mutation of p53, PTEN, PDGF is also implicated in the causation of TGCT.[40,41]
- The concept of testicular dysgenesis syndrome was first coined by Shakkebaek et al in 2001. It is suggested that there existed a developmental disorder resulting from disruption of embryonic programming and gonadal development during fetal life. It can be manifested as one or any combination of four developmental abnormalities viz. Cryptorchidism, Hypospadias, Testicular cancer and reduced semen quality.[42]

THE HORMONAL FACTORS AND CRYPTORCHIDISM

Insulin-like hormone 3 (INSL3)

Insulin-like hormone 3 is considered the key hormone influencing the trans-abdominal phase of testicular descends.[43-47] This is a secretary product of Leydig cells expressed in a differentiation-dependent manner. Recent studies in downstream signalling pathways activated by INSL3 in the Gubernaculum show roles for the NOTCH and Wnt/β-catenin pathways.[48]

The result from the studies of Bay et al has demonstrated that there are measurable levels of INSL3 in the amniotic fluid of human male fetus at 15 weeks of gestation, which were absent in female foetuses.[49]

The result from this study also suggests that INSL3 plays a significant role in the gubernacular swelling reaction that is essential for the trans-abdominal relocation of testes in the first stage of descent of mammals.

Mullerian-inhibiting substance/anti-Mullerian hormone (MIS/AMH)

Mullerian-inhibitory substance, also known as an anti-Mullerian hormone, is a member of the TGF-β multigene family of glycoprotein and is produced by Sertoli cells.[50] Failure of regression of embryonic Mullerian ducts in the male embryo during the transabdominal phase of testicular descent is supposed to be influenced by MIS/AMH (hormone).[51] Failure of this event results in persistent Mullerian duct syndrome (PMDS). In this syndrome, the affected male has a persisting uterus and fallopian tubes, and frequently intra-abdominal testis.

The MIS/AMH has a limited role in the process of testicular descent; it can be used as a marker of Sertoli cell function in the evaluation of children with cryptorchidism. The MIS/AMH levels are highest in normally descended testes, lower in Cryptorchid testes, and virtually absent in anorchia.[52,53] Hence, in prepubertal boys with nonpalpable gonads, detectable levels of serum MIS/AMH suggests that the testes are potentially present.[54]

Androgen

The androgens regulate the inguinoscrotal descent. Prenatal treatment (embryonic d 16-17) of rats with an antiandrogen (flutamide) resulted in deranged gubernacular migration during the postnatal inguinoscrotal period, with the failure of downward growth of the processus vaginalis, resulting in cryptorchidism in most rodents.[55,56]

The timing of flutamide administration is quite critical because it is only effective during a limited time window i.e. 15-19 day in rat fetus. The role of androgen is indirect by stimulating the genitor-femoral nerve, to release a specific neurotransmitter, Calcitonin Gene Related Peptide (CGRP).[57] The Genito-femoral nerve (GFN) is a sexually dimorphic nerve with its sensory nucleus found in the L1-L2 dorsal root ganglia of the spinal cord.[58]

CGRP released from the sensory nerve root terminals of the GFN induces rhythmic contractility of the developing cremesters muscles of the Gubernaculum. This rhythmic contraction is important to orient the gubernacular tip towards the scrotum and assist gubernacular migration in the appropriate direction.[59] The rhythmic contractions are important to orient the gubernacular tip towards the scrotum and assist gubernacular migration in the appropriate direction. In addition, CGRP released from sensory nerve terminals of GFN also provides a chemotactic gradient to stimulate the gubernacular migration towards the scrotum.

DISCUSSION

The testis develops before birth in the dorsal abdominal wall. During the human fetal period, the testis migrates from the abdomen to scrotum traversing the abdominal wall and the inguinal canal by 15th to 28th-week, post conception. During the ninth month of gestation, testis reaches the deep inguinal ring and just before or after delivery it descends into the scrotum. Approximately 2-4% of male infants are born with Cryptorchism, thus making it, one of the most common congenital anomalies, in the male genitalia. Pre-mature birth, low birth weight (<2.5 Kg) abnormally decreased maternal estrogens, and insufficiency of the placenta is considered to be the risk factor for developing cryptorchidism.[60] Cryptorchidism, even if treated early and successfully, it has long-term consequences such as reduced fertility and testicular cancer.

As far as fertility is concerned it is significantly compromised in cases of the bilateral undescended testis, with sub-fertility in unilateral UDT. The critical surge of gonadotrophins and testosterone in the third month of life, fundamental to the development of optimal fertility, later in life, is seriously impaired in boys with cryptorchidism.

In normally descended testis, germ cells transform into adult dark (AD) spermatocytes. It is considered to be the stem cells for spermatocytes. This process is seriously impaired in cryptorchidism. It is also found that the number of the Leydig cells is reduced and gonocytes take more time to disappear. This reduced number of Leydig cells may be related to sub-fertility through the failure of optimal maturation of germ cells.[61]

The incidence of azoospermia in unilateral UDT is 13%, but in untreated bilateral cryptorchidism it reaches up to 89%. The causes are attributed to impaired mini-puberty, the surge of gonadotrophins and testosterone, in early infancy. In 1975, Ludwig and Potempa found that the fertility rates are inversely proportional to the age of the patient at the time of surgery.[62] It is recommended that surgery for cryptorchidism should be done between the ages of the 6-12 month, in order to lower the sub-fertility.[63]

There is also a role of hormone treatment. It is suggested that hormone therapy with Luteinising Hormone-Releasing Hormone (LH-RH) creates a rise in testosterone levels; this effect is same as the postnatal mini-puberty surge.[64] Epidermal growth factor therapy, gene therapy, and stem cell therapy could be considered to play a role in the future management of cryptorchidism.[65]

Testicular cancers are accountable for 1% of all cancers in men and are the most common in men between the ages of 14 and 34. In the Cryptorchid testis, the risk of developing cancer is 5-10 times more than the general male population. It may be due to the aberrant testicular environment which has got a detriment effect on the Sertoli and Leydig cell population, and accumulation of mutant cells.

CONCLUSION

The anatomical and embryological step in the descent of the testis is a complex phenomenon. It is influenced not only by anatomical factors but hormonal factors also play an important role. The optimum time to do orchidopexy is six to twelve months of age. The role of hormone therapy is not well established and remains controversial.

The learning points:

- Cryptorchidism is one of the most common congenital anomalies in male genitalia
- Approximately 2-4% of male infants are born with Cryptorchism,
- Pre-mature birth, low birth weight (<2.5 Kg) abnormally decreased maternal estrogens, and insufficiency of the placenta is considered to be the risk factor for developing cryptorchidism
- The optimal age of correction of cryptorchidism is 6 to 12 months of age
- The role of hormone therapy is controversial
- The Cryptorchid male is more prone to testicular germ cell tumours
- The role of epidermal growth factor, gene therapy, and stem cell therapy may be investigated for the management of cryptorchidism.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Agrawal SN. Cryptorchidism: its influence on male fertility and the risk of the testicular tumor. Int Surg J 2018;5:3453-9.