

“CRYPTORCHIDISM”

EMBRYOLOGICAL BASIS AND ITS CLINICAL IMPORTANCE

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ARTICLE INFO**Article history:**

Received: 9 December 2016;

Received in revised form:

13 January 2017;

Accepted: 26 January 2017;

Keywords

Nephrogenic cord,
Mullerian duct,
Cryptorchidism,
Orchiopexy,
Mesonephros,
Anorchia.

ABSTRACT

Cryptorchidism is the most common defect of the male urogenital tract at birth. It signifies a risk factor for primitive testiculopathy associated with long-term complications (infertility, testicular neoplasia, and hormonal changes). It may appear as an isolated disorder or can be a consequence of genetic and endocrine abnormalities connected with somatic anomalies. Its genetic relation still seems to be indistinct although a choice of genes can be answerable for the growth of this syndrome. Cryptorchidism can be related with serum testosterone level though the co-existing hypogonadotropic hypogonadism may also designate the association of pituitary hormones.

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Introduction

Cryptorchidism (from Greek KRYPTO meaning “hidden,” and ORCHIS meaning “testis”) refers absence of a testis from the scrotum. During embryonic life, the testes form by the mesonephric kidneys and incline via the inguinal canal to the scrotum [1-8]. If this process is damaged, a cryptorchid testis may break beside the normal path of descent (undescended or retractile testis), might travel off the normal path of decent (ectopic testis), or might die or do not develop (absent testis). Therefore, the terms “cryptorchid” and “undescended” are not identical. Cryptorchidism is the disorder of non-descent of the testes, and the diagnosis is defined as deviation or stop of the testis at any point along the regular path of its descent from an origin below the kidneys down into the scrotal sac [10-14]. An undescended testis is the most common genital anomaly known at birth among human males. Cryptorchidism happens in about 3% of human males at birth and declining to 1% through the neonatal period because of spontaneous descent. The most common treatment for this illness over the last 50 years has been the surgical correction by orchiopexy. The undescended testis signifies the single most common illness of male sexual variation [9-11].

There are two potential negative outcomes of cryptorchidism they are, infertility and testicular cancer. In spite of the widespread occurrence of undescended testis, there is a determined absence of knowledge about many aspects of its etiology, treatment, and outcomes [15].

The complete aim of this work will be to better understand the impact of cryptorchidism on fertility. Regardless of the knowledge that male fertility problems account for 30-50% of infertility between couples there are very few data talking specific potential reasons of male infertility when linked to the abundance of research on reasons of infertility in women [15].

Incidence

About 3% of full-term and 30% of early infant boys are born with at least one undescended testis. However, about 80% of cryptorchid testes descend by the first year of life (the majority in three months), creating the true occurrence of cryptorchidism about 1% overall [16].

Ontogenesis of normal development of Testis

If the embryo is genetically male, the primordial germ cells have an XY sex chromosome compound. Under the influence of SRY (sex-determining region Y) gene on the Y chromosome, which encrypts the testis determining factor (TDF), the primitive sex cords continue to multiply and pierce deep into the medulla to form the testis or medullary cords. Near the hilum of the gland, the cords breakdown into a network of minute cell strands that later give rise to tubules of the rete testis [17]. Throughout the development, a thick layer of fibrous connective tissue, the tunica albuginea, divides the testis cords from the surface epithelium [18]. In the fourth month, the testis cords become horseshoe-shaped, and their extremities are continuous with those of the rete testis. Testis cords are now composed of primitive germ cells and sustentacular cells of Sertoli resulting from the surface epithelium of the gland. Interstitial cells of Leydig are derived from original mesenchyme of the Gonadal ridge, which lies between testis cords [19-22]. They initiate the development soon after the beginning of differentiation of these cords. By eighth week of gestation, the Leydig cell begins production of testosterone and the testis is able to effect sexual differentiation of the genital ducts and external genitalia. Testis cords persist solid until puberty, when they acquire a lumen, forms the seminiferous tubules. As soon as the seminiferous tubules are directed, they join rete testis tubules, which in turn pass in the efferent ductules [22-28]. These efferent ductules are the remaining of the excretory tubules of mesonephric system.

They link the rete testis and the mesonephric or wolffian duct, which becomes the ductus deferens [28].

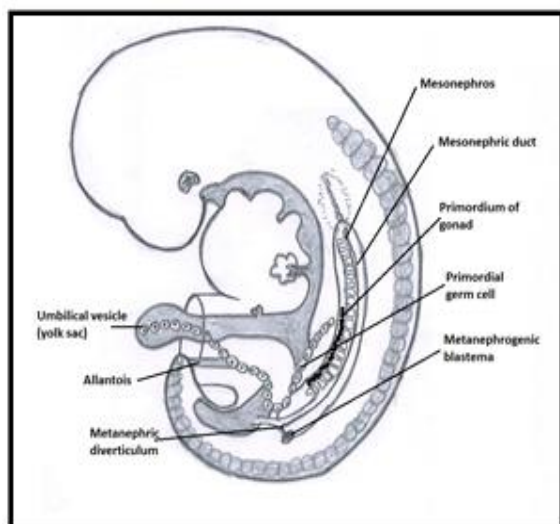


Fig1. Schematic representation of 5-week embryo illustrating migration of primordial germ cells from yolk sac into embryo.

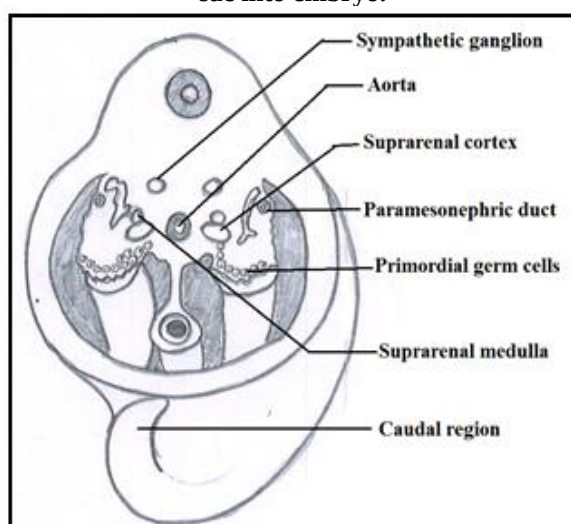


Fig 2. Schematic representation shows location and extent of the Gonadal ridges of caudal region of 5-week embryo.

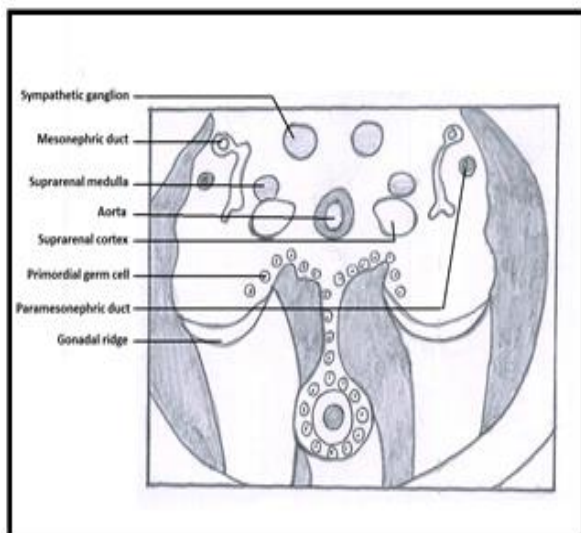


Fig 3. Transverse section showing primordium of Gonadal ridges and migration of primordial germ cells into developing gonads.

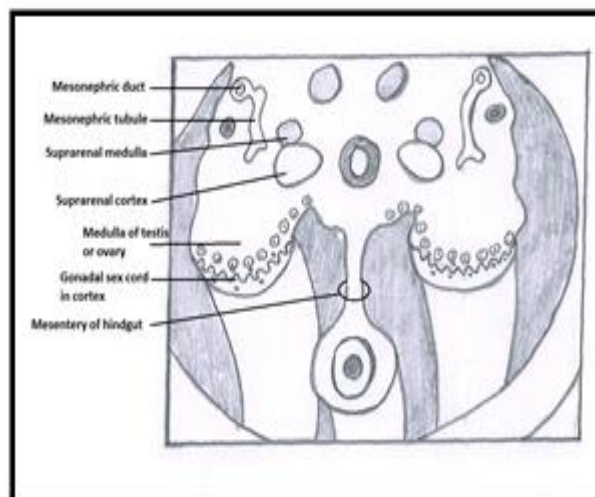


Fig 4. Transverse section showing 6-week Gonadal cords.

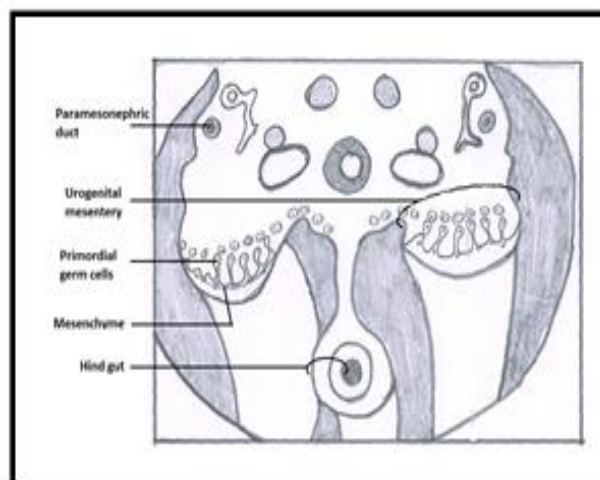


Fig 5. Transverse section showing indifferent gonads and paramesonephric ducts.

Descent of the Testes

The testes do not remain in their original site of development; they migrate from their intra-abdominal location into the scrotum. Similar to the kidneys, the testes are retroperitoneal structures, and their descent occurs behind the peritoneal epithelium. Before their descent, the testes are anchored cranially to the cranial suspensory ligament, derived from the diaphragmatic ligament of the mesonephros, and caudally to the inguinal (caudal) ligament of the mesonephros, which in later development is called the gubernaculum [30-40]. Control of testicular descent, which occurs between the 10th and 14th week of pregnancy, occurs in three phases. The first is associated with the enlargement of the testes and the concomitant regression of the mesonephric kidneys. Under the influence of androgens, acting through androgen receptors in the cranial suspensory ligament, the ligament regresses, releasing the testis from its location near the diaphragm. This regression causes some caudal displacement of the testes [45]. The second phase, commonly called trans-abdominal descent, brings the testes down to the level of the inguinal ring, but not into the scrotum. This phase depends on the activity of *Insl-3*, produced by the Leydig cells, without which the testes remain high in the abdomen [40-48]. The third phase, called transinguinal descent, brings the testes into the scrotum, usually just a few weeks before birth. This phase involves the action of testosterone and the guidance of the inguinal ligament of the mesonephros, which in later development is called the gubernaculum.

Whether the gubernaculum actively pulls the testes into the scrotum or just acts as a fixed point while the other tissues grow has not been resolved. Testicular descent begins during the seventh month and may not be completed until birth. As it descends into the scrotum, the testis slides behind with an extension of the peritoneal cavity called the vaginal processes [49-55]. Although this cavity largely closes off with maturation of the testis, it remains as a potential mechanical weak point. With straining, it can open and permit the herniation of intestine into the scrotum.

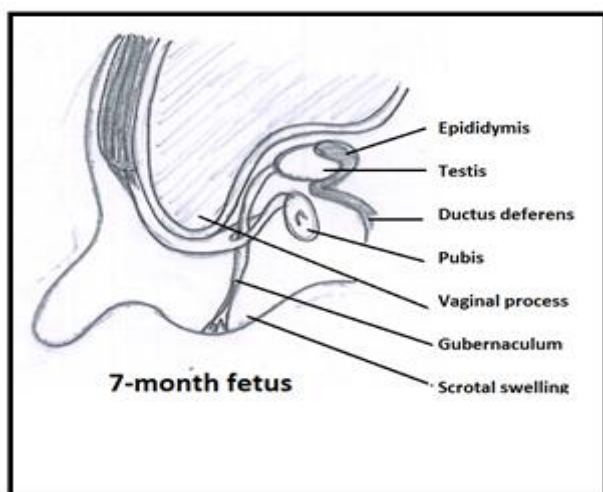


Fig 6. This schematic representation shows the stage of descending of the testis in 7-month fetus.

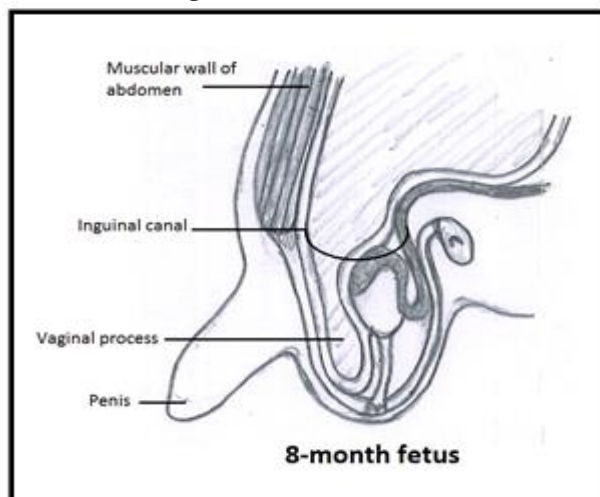


Fig 7: This schematic representation shows the stage of descending of the testis in 8-month fetus.

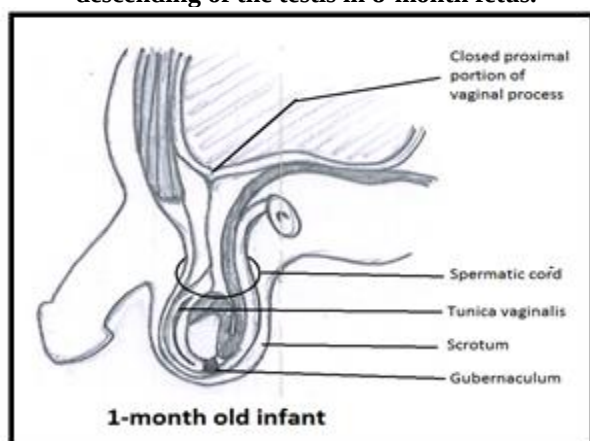


Fig 8. This schematic representation shows the stage of descending of the testis in 1-month old infant.

Ontogenesis of Cryptorchidism

The embryology of testis development is dangerous to understand the most common theories that explain cryptorchidism. Shortly after 6 weeks' gestation, the testis-determining SRY gene on chromosome Y directly disturbs the differentiation of the indifferent gonad into a testis [55-60]. Germ cells are situated in the germinal ridge near the kidney in the retroperitoneum. Around 6-7 weeks' gestation, Sertoli cells grow and secrete müllerian inhibitory substance (MIS; also known as antimüllerian hormone [AMH]), which leads to the reversion of the female genital organs. Around 9 weeks' gestation, Leydig cells start generating testosterone, which stimulates development of the wolffian duct into portions of the male genital tract [61]. Concurrently, the testis categorizes as a distinctive organ with its distinct seminiferous tubules bounded by vessels and compressed by the tunica albuginea [62]. Remaining to the differential growth of the fetus, the testicles transfer into the pelvis, close to the internal ring. The testis resides in a retroperitoneal position until the 28 weeks' of gestation, after which from the inguinal, the descent of the testicle starts. Most testes have completed their descent into the scrotum by 40 weeks' gestation [64-70].

Discussion

Cryptorchidism is a congenital condition in which one or both testicles are not properly positioned in the scrotum at birth and cannot be moved into the proper position manually [66]. The term "cryptorchidism" factually means "hidden testicle" and is frequently used interchangeable with the term "undescended testicle." It affects an estimated 3 percent of full-term male neonates and up to 30 percentage of early male infants, creating it the most common male genital anomaly identified at birth. The etiology of cryptorchidism is not well assumed, and the undescended testicles could be palpable or nonpalpable. The undescended testicles may be existing in the abdomen, in the groin area, or misdirected in the scrotum. In some cases they are viable testicles, however in others they have atrophied and are no longer viable. Lastly, in some individuals no testicle occurs at all (anorchia) [68-70].

Cryptorchidism is often apparent to parents, and examination for the disorder is portion of general pediatric care. Therefore, boys with cryptorchidism are generally identified early in life, often within the first year. Clinical decision-making about treatment is inclined by many factors, containing whether or not the testicle is palpable, whether the situation is present unilaterally or bilaterally, the age at demonstration, and coexisting medical conditions [70]. In boys below 1 year of age whose testicle is palpable and is close to, but not pretty inside, the scrotum, it may be hard to differentiate between "true" cryptorchidism and a retractile testicle. In this case, health care workers often selected to observe the patient's condition until he is 1-year-old. While about 70 percent of cryptorchid testicles instinctively descend within the first year of life, the number of boys with persistent undescended testicles rests constant at approximately 1 percent. Between 1992 and 2000, there were more than 600,000 physician office appointments among males below age 18 for which cryptorchidism was the principal diagnosis (96 per 100,000 visits) [70-73]. Once cryptorchidism is diagnosed, treatment selections may include watchful waiting, hormonal treatment, or surgery. Conclusions about which clinical pathway to trail may be directed by results of hormonal stimulation testing and/or imaging, mainly when the testicle is nonpalpable. The purpose of hormonal stimulation testing for bilateral nonpalpable cryptorchidism is to regulate

if viable testicular tissue is existent [75]. Precisely, if a boy has nonpalpable testicles, hormones such as human chorionic gonadotropin (hCG) are directed to motivate the testicles. Increased levels of testosterone later direction of hCG propose that there is at least one viable testicle somewhere in the body, while no hormone response suggests anorchia. The theoretical origin for using hormone stimulus to monitor treatment is that, if there is no testicle present at all, then surgery is pointless and a child may be able to be secure the risks of examining surgery to find a missing testicle [76].

Imaging also is used to regulate whether there is in fact a testicle and, if there is, to localize it in order to guide the optimum treatment method. Imaging methods comprise ultrasonography (US), computerized tomography (CT) scanning, routine magnetic resonance imaging (MRI), and magnetic resonance (MR) angiography and venography, some of which need sedation or anesthesia and are thus not deprived of risks. Medical choices in the treatment of cryptorchidism comprise of hormones projected to rise circulating androgens [77]. This increase in circulating androgens, in turn, is supposed to potentially endorse testicular descent. The two hormones that are most frequently used for the treatment of cryptorchidism are luteinizing hormone-releasing hormone (abbreviated as LHRH and also ES-2 sometimes referred to as gonadotropin-releasing hormone [GnRH]) and hCG. Though used much less commonly, human menopausal gonadotropin (hMG) similarly is used irregularly and is supposed to function in a method similar to hCG. LHRH and its correspondents and agonists can be administered intra-nasally, while hCG and hMG must be injected intra-muscularly [78].

There are three primary surgical possibilities for orchiopexy (surgery to move an undescended testicle into the scrotum), dependent on the position and presence of the undescended testicle. Primary orchiopexy is conceivable if the testicle is of regular size and presence and if the testicular vessels are of sufficient length. In this technique, the testicle is surgically relocated to the scrotum and fixed in place. Primary orchiopexy needs that the vessels be long ample to grasp into the scrotum. If the vessels are so short that tension-free placement of the testicle in the scrotum is not thinkable, a Fowler-Stephens (FS) orchiopexy is performed [79]. This process involves ligating the testicular vessels. The testicular blood supply then be determined by collateral circulation from the deferential artery and the cremasteric system. The FS technique can take place in one of two ways: either (1) as a single-stage operation, in which the vessels are ligated and the testicle is then located into the correct position in the scrotum, or (2) as a two-stage process, in which the vessels are ligated in the first operation, the testicle is permitted to mature presumably better collateral circulation in its abdominal location, and it is then moved to the correct position in the scrotum during a second procedure, usually 3–6 months later [75]. Both primary orchiopexy and the FS procedure can be achieved using laparoscopic or open surgical procedure. Finally, surgical orchiectomy (removal of the testicle) also can be accomplished, although this is usually earmarked for cases where the testicle is not felt to be viable, as the primary goal of treatment is replacement of a viable testicle to a reliant location in the scrotum. Orchiectomy is not reviewed in this account, which emphasizes only on procedures to continue testicular tissue and possibility. Clinical hesitation and lack of guidance occur on the applicable clinical pathway for treatment of cryptorchidism [78]. Areas of uncertainty comprise selecting the optimal methodology to treatment

planning (imaging vs. no imaging, hormonal stimulation testing or not) and intervention (surgical vs. hormonal, one-stage vs. two-stage FS, various alterations of each of the surgical techniques, and open vs. laparoscopic approach) [72-78]. The instantaneous goal of utmost interventions for cryptorchidism is to relocate the undescended gonad in a “normal” location in the scrotum. Intermediate consequences comprise psychological assistances in terms of body image, and long-term goals comprise protection of fertility and inhibition of testicular malignancy. All of these outcomes are important to patients [79].

Conclusion

The concept of ‘early orchidopexy’ has recognized itself with a scientific experience. However, orchidopexy alone is not adequate to completely reinstate spermatogenesis and there is possibility for a germinal epithelial defensive matter. Improved germ cell maturation has a part to play in examine for the misplaced link between orchidopexy and subsequent fertility [15,22,57]. Hormonal treatment may have some favorable consequence to attain normal transformation to adult dark spermatogonia[55]. Although there is increasing indication supporting the use of hormone therapy with hCG or GnRH correspondents as an adjunct to orchidopexy to advance the fertility projections of cryptorchid patients, the possibility of the harmful effects of hormones on future spermatogenesis is always there. The exact role of pre- or post-orchidopexy hormone treatment is yet to be distinct conclusively. The key role of intra-testicular heat and ROS needs additional research and has the potential to modify the management of cryptorchidism in a optimistic way.

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