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The undescended testis: Clinical management and scientific advances

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ABSTRACT

Undescended testes (UDT), where one or both testes fail to migrate to the base of the scrotum, can be congenital (2–5% of newborn males) or acquired (1–2% of males). The testis may be found in any position along its usual line of descent. Cryptorchidism affects the developing testicular germ cells and increases the risk of infertility and malignancy. Clinical management aims to preserve spermatogenesis and prevent the increased risk of seminoma. Examination to document the testicular position will guide the need for imaging, medical management and the surgical approach to orchidopexy.

Introduction

An undescended or cryptorchid testis, by definition, does not lie at the base of the scrotum, and it occupies an alternative position either in the groin or within the abdominal cavity. Congenital undescended testis (UDT) affects 2–5% of newborn males, when one or both testes are not located in the scrotum at birth.[1] This figure decreases to 1–2% by 3 months of age, as about half will descend spontaneously shortly after birth.[2] However, by about 12 weeks post term, an UDT is very unlikely to spontaneously descend further, and medical management is required.[3] At present, the recommended age for orchidopexy is between 6 and 12 months, and there is reasonable consensus for this in North America,[4,5] Europe[6,7] and the UK.[8]

Foetal testicular hormones are vital for testicular descent, and the primary cause for most cases of UDT is thought to be insufficient pituitary or placental stimulation causing inadequate production of insulin-like hormone 3 (INSL3) and androgens in the developing testis. Androgens are thought to act via the two genitofemoral nerves, with minor deficiencies affecting one side more than the other, leading to unilateral pathology.[9] Risk factors for congenital UDT include intrauterine growth retardation, prematurity, excessive oestrogen exposure and smoking during pregnancy.[10]

Acquired or ascending UDT is another form of UDT, which presents later in childhood and has an incidence of 1–2%.[11] In these cases, the testis has been clearly documented to be within the scrotum in infancy but does not remain there over time. We have attributed the cause of the ascending testis to failure of the spermatic cord to elongate as the child grows, causing the testis to 'ascend' out of its previously occupied scrotal position,[12] as the distance from the inguinal canal to the scrotum doubles in childhood because the pelvis enlarges. A persistent fibrous remnant of the processus vaginalis has been shown at surgery,[12] which is thought to prevent normal elongation of the spermatic cord between birth and later childhood. Boys with delayed (or postnatal) testicular descent are at higher risk of acquired UDT,[13] and should be kept under annual review for surveillance of testicular ascent.

Normal testicular descent

While the complete mechanism of testicular descent remains elusive, it is generally accepted to occur in two distinct stages. The first, or trans-abdominal stage, occurs between 8 and 15 weeks of gestation and involves swelling and strengthening of the distal gubernaculum (genito-inguinal ligament) under the control of insulin-like hormone 3 (Insl3). This 'swelling reaction' holds the gubernaculum at a fixed length, so that it does not elongate with foetal growth as happens in a female. At the same time, the

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cranial-suspensory ligament regresses under the control of foetal testosterone. These processes anchor the developing testis close to the inguinal region while the foetal abdominal cavity enlarges. The second, or inguinal-scrotal stage, occurs between about 25 and 35 weeks of gestation when the gubernaculum (with the testis inside it) grows out from the inguinal region in a manner very similar to development of an embryonic limb bud, and then physically migrates over the pubic ramus into the scrotum (Figure 1).

The initial outgrowth of the gubernaculum is likely to be controlled by the overlying mammary line, which comes to lie directly over the future external inguinal ring in both animal models and humans.[14–16] The mammary line is a specialized area of skin that is originally formed on the lateral boundary between the dorsal and ventral surfaces of the early mammalian embryo, and is in continuity with specialized skin, known as the apical ectoderm ridge, which controls outgrowth of the limb buds. In marsupial embryos, the link between the mammary line and the gubernaculum is intimate, as the inguinal breasts (inside the marsupial pouch) are supplied by the genito-femoral nerve (GFN) and the cremaster muscle has been modified to form the ilio-marsupialis that is the suspensory muscle of the nipples.[17] Similarly, in rat embryos, the inguinal breast bud is adjacent to the future external inguinal ring, just beyond the end of the gubernaculum, and is also supplied by the GFN.

This inguinoscrotal phase of descent is believed to be controlled indirectly by the action of androgen on the inguinoscrotal fat pad that is thought to respond to androgens by release of neurotrophins that regulate the sensory branches of the genitofemoral nerve.[18] The subsequent putative action of neurotrophins and the neurotransmitter released by the nerve, calcitonin gene-related peptide (CGRP), provides a local chemotactic gradient to guide the gubernaculum. A diverticulum of specialized peritoneum develops within the gubernaculum, providing a connexion between the abdominal cavity and the scrotum.[9]

Recently, we have proposed the following two final steps that should occur at the end of the inguinoscrotal phase of descent in humans: (1) perinatal closure of the processus vaginalis (PV) and (2) involution of the gelatinous gubernacular bulb and its fibrous adherence to the inside of the scrotum.[3] Failure of the former process to proceed to completion would lead to inguinal hernia, hydrocele or acquired UDT, while delays in the latter process may predispose to perinatal torsion (Figure 2).

Failure of the first stage of testicular descent is uncommon and results in an intra-abdominal UDT. In all, 5% of operated undescended testes are intra-abdominal.[19–21] Failure of the second stage of testicular descent is more common, with the UDT located between the internal inguinal ring and the neck of the scrotum.

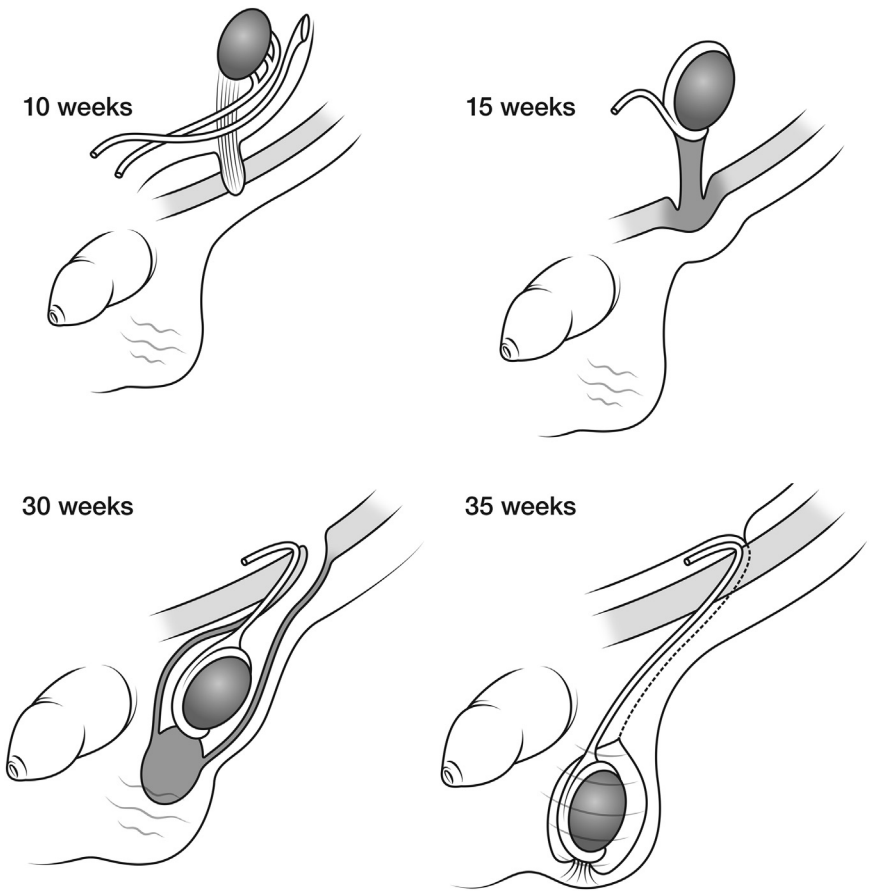

Fig. 1. The mechanical steps of testicular descent. Schema showing the testicular position and gubernaculum at different stages of fetal development. (A) At 10 weeks, the testis is in the urogenital ridge with both Wolffian and Müllerian ducts, and the gubernaculum (genito-inguinal ligament) attaches the testis to the abdominal wall. (B) By 15 weeks, the Müllerian duct, which holds the testis near the future inguinal canal, has regressed. The processus vaginalis is beginning to grow into the gubernaculum. (C) At 30 weeks, the gubernaculum is migrating to the scrotum with the testis inside the processus vaginalis, which is elongating within the gubernaculum so that the intra-abdominal testis can reach the scrotum while still inside the processus vaginalis. (D) By 35 weeks, migration is usually complete and the gelatinous gubernaculum has resorbed, leaving the processus vaginalis that becomes attached to the scrotal skin. The proximal processus vaginalis obliterates, leaving the testis in a satellite peritoneal cavity (tunica vaginalis) in the hemi-scrotum. (Reproduced from Hutson, Thorup and Beasley, *Descent of the Testis,* 2nd ed., Springer).