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Review papers

Gubernaculum and Epididymo-Testicular Descent: Review of the Literature

Gubernaculum, antsėklidžio ir sėklidės nusileidimas: literatūros apžvalga

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Abstract: Cryptorchidism is a common disorder in boys that has been widely studied both experimentally and clinically. The role of the gubernaculum, a mesenchymal tissue extending from the fetal testis and epididymis to the developing scrotum, is still unclear. Even the name is debated: 'gubernaculum epididymis' or 'gubernaculum testis'. This review does not aim to provide a global overview of competing theories on testicular descent, but focuses on the role of the gubernaculum in epididymo-testicular descent. We identified four major pitfalls of gubernaculum research: the role of the gubernaculum, of insulin-like peptide 3, anti-Müllerian hormone, and androgens. The major critical issues were that the gubernaculum plays a guiding role for the epididymis, descending prior to the testis and expanding the inguinal canal; insulin-like peptide 3 is not as important for the process of descent in humans as the rate of insulin-like peptide 3 mutations is low; anti-Müllerian hormone plays no significant role in epididymo-testicular descent; androgens and gonadotropins play a crucial role in epididymo-testicular descent. The role of the epididymis in the complex process of gubernaculum, epididymis, and testis migration is underestimated and should be included in future research.

Keywords: cryptorchidism, epididymo-testicular descent, gubernaculum, Insl3.

Summary: Nunusileidusios sėklidės (kriptorchizmas) yra dažna vyriškų lytinių organų patologija. Sėklidės pavadis (lot. gubernaculum testis) – mezenchiminis audinys tarp vaisiaus sėklidės ir prielipo bei besiformuojančio kapšelio. Jo reikšmė sėklidei ir prielipui nusileisti nėra aiški. Šios apžvalgos tikslas nėra įvertinti vienų kitoms prieštaraujančių sėklidės nusileidimo teorijų, o susitelkiama ties sėklidės pavadžio (ar dar kitaip vadinamo prielipo pavadžio) svarba sėklidei nusileisti. Mes kėlėme šiuos pagrindinius klausimus apie sėklidės pavadį: sėklidės pavadžio svarba, į insuliną panašaus hormono 3, antimiulerinio hormono ir androgenų reikšmė. Sėklidės pavadis atlieka tik orientacinį vaidmenį prielipui ir leidžiasi prieš sėklidę plėsdamas kirkšnies kanalą. Į insuliną panašus hormonas nėra svarbus sėklidei nusileisti, nes žmonių populiacijos šio geno mutacijos yra retos. Antimiulerinis hormonas neatlieka reikšmingo vaidmens, kad sėklidė ir prielipas nusileistų. Androgenai ir gonadotropinai yra svarbiausi, kad įvyktų sėklidės ir prielipo nusileidimas. Prielipo reikšmė sudėtingame pavadžio, prielipo ir sėklidės migracijos procese yra nepakankamai įvertinta.

Keywords: kriptorchizmas, sėklidės pavadis, sėklidės ir prielipo nusileidimas, Insl3.

Introduction

Cryptorchidism, one of the most common disorders in boys, has been widely studied both experimentally and clinically. Many review articles have been published, but the main conclusions remain debatable. In trying to understand testicular descent, one of the most controversial issues is the gubernaculum. Though it may seem that this topic is all sorted out, upon a closer look, even the name 'gubernaculum testis' or 'gubernaculum epididymis' needs to be decided [1]. Of course, in the heads of many people, testis and epididymis are no more than a 'testicle', but for a surgeon operating on an undescended testis it is more complex (shown in Figs. 1, 2).

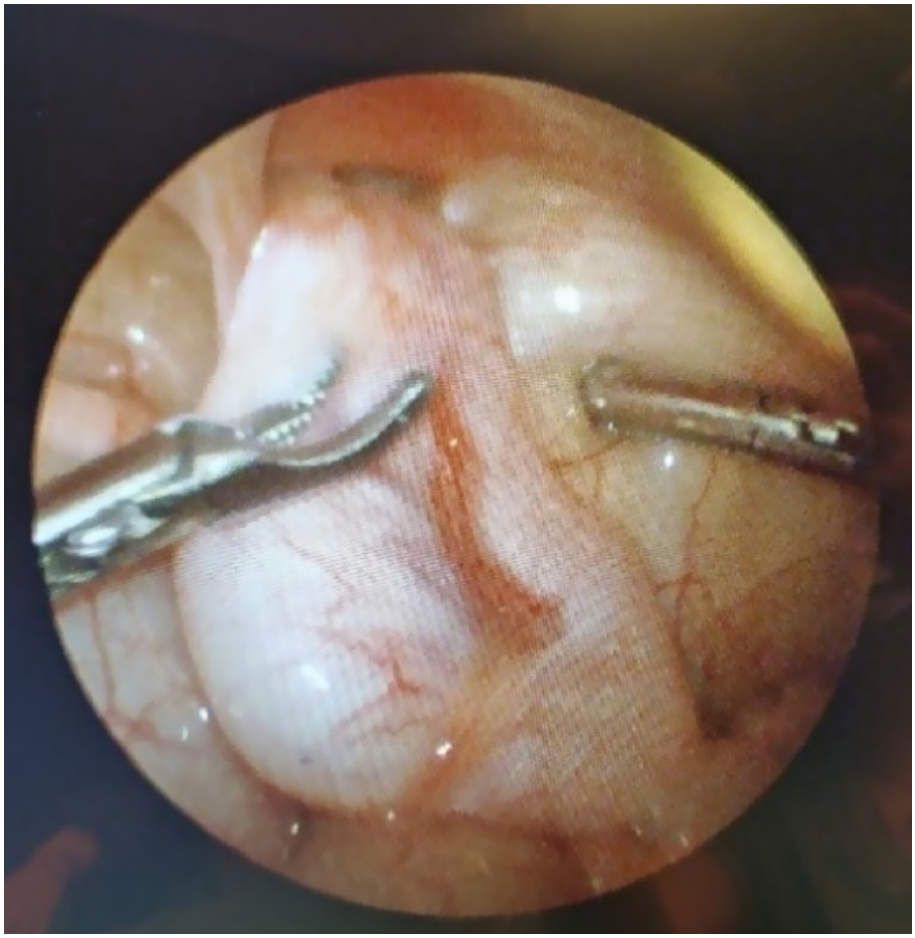

Figure 1.
Laparascopic view of an intra-abdominal testis showing prior descent of the body and tail of the epididymi

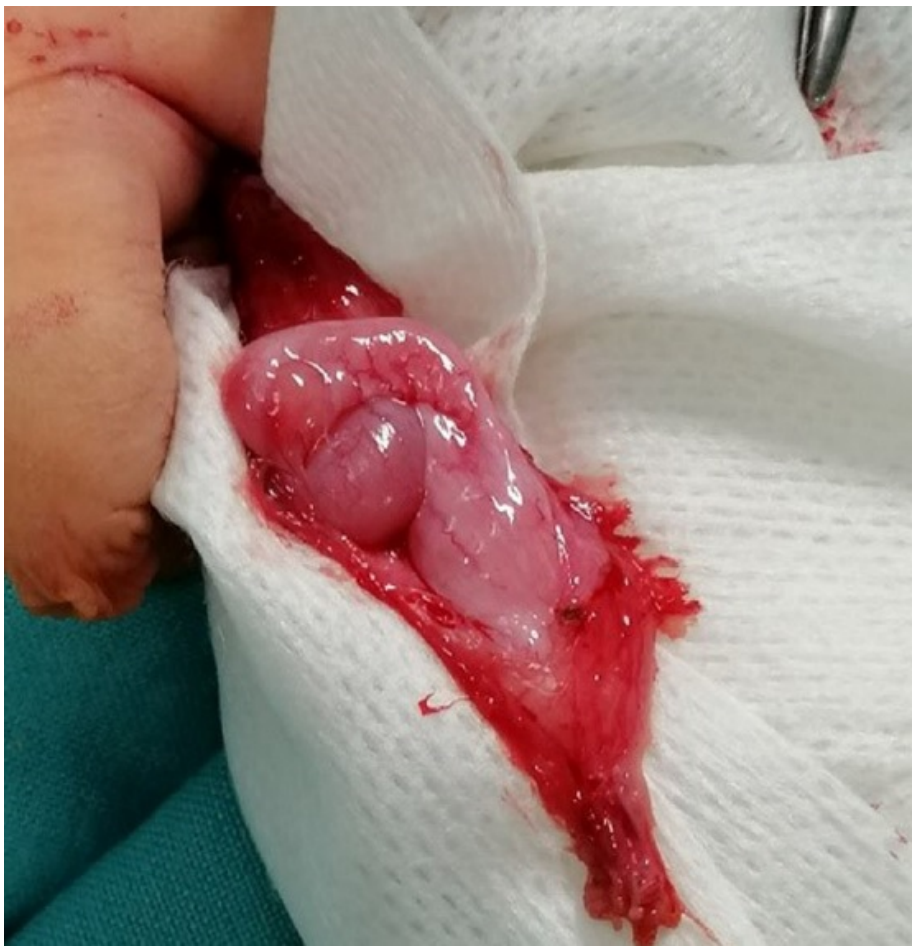

Figure 2.
Prescrotal testis showing prior descent of the body and tail of the epididymis

The gubernaculum, the mesenchymal tissue extending from the fetal epididymis and testis to the developing scrotum, was originally named by John Hunter [2]. Later, many theories emerged that assigned the gubernaculum different active and passive roles. Seiler characterized the gubernaculum as a muscle-like structure, whereas Cleland described it without such tissue [3,4]. However, the gubernaculum was given an active role of pulling the testis down to the scrotum by both investigators. The passive role of gubernaculum was advocated by Weil's intra-abdominal pressure hypothesis [5].

Gubernaculum research is mostly conducted in rodents. The rodent gubernaculum differs from human gubernaculum in terms of structure, migration time, and last step of descent. A major difference is that the rodent gubernaculum is fibrous with a circumferential cremaster muscle, but the human gubernaculum is jelly mesenchymatous [6]. In addition, testicular descent in humans is complete at birth (approximately 35th week of gestation), whereas complete testicular descent in rodents occurs at puberty. Moreover, in humans, the descent ends with closure of the *processus vaginalis* and in rodents it remains open with a fat pad on the epididymis, which helps prevent inguinal hernias [7,8].

Main Text

In this review, we discuss the four major pitfalls met earlier and still potentially misleading the research on this common congenital disorder in boys:

- The role of the gubernaculum;
- The link between hypogonadism and epididymo-testicular descent;
- The role of insulin-like peptide 3 (Insl3) in epididymo-testicular descent;
- The role of anti-Müllerian hormone (AMH) in epididymo-testicular descent.

Literature to review was found in the PubMed database excluding case reports, editorials, and opinions.

Pitfall No. 1 – The role of the gubernaculum

The human gubernaculum consists of a fibrous structure rich in collagen and elastic fibers without contractile potential and extracellular matrix [9]. It undergoes remodeling during descent with a trend towards fibrous tissue [10]. The most important question about the function of the gubernaculum remains is whether it holds the testis near the inguinal region and migrates towards the scrotum, clearing the space ahead, or the epididymis holds the testis while descending with the gubernaculum [8,11].

In 1978, Bergh et al. reported that testis descent can occur with a severed proximal gubernaculum, whereas testicular descent is prevented when the distal gubernaculum is cut. In addition, descent of the epididymis can occur in the absence of a testis [12]. These findings highlight the importance of the epididymis in epididymo-testicular descent. However, many of the later studies continued research in which gubernaculum was given the key role, disregarding the findings by Bergh et al. For example, Favorito et al. stated that differentiation of the muscular gubernacular bulb results in traction through the inguinal region [13]. Other ideas derived from schematic (hypothetical) presentations of epididymo-testicular descent led to the conclusion that the gubernaculum retains the testis close to the inguinal canal, whereas the rest of the abdominal contents grow dorsally [14]. Even recent papers exclude the epididymis from schematic presentations [15].

Going back to the findings reported by Bergh et al. and taking a closer look at the epididymis reveals interesting discoveries. In 2012, Rachmani et al. showed that the degree of nonfusion between the testis and epididymis is associated with a higher position of the testis. Total nonfusion reliably interferes with descent [16]. In 2014, Caterino et al. reported a large series of 1002 cryptorchid patients and 230 controls, examining the surgical data for evidence of anomalies in epididymal/

testicular fusion. The cryptorchid group had a significant number of epididymal/testicular fusion anomalies compared to the control group. This finding correlated with persistence of the *processus vaginalis* and more proximal location of the testis [17]. In general, epididymal anomalies are common in cryptorchid boys, and testicular-epididymal fusion anomalies are associated with intra-abdominal cryptorchidism [18,19]. An improper connection between the epididymis and testis may lead to cryptorchidism. The true morphogenesis of this junction is not yet clear, but several genes have been implicated, including paired-Box 2/8 (*Pax2/8. and* fibroblast growth factor [20]. In 1984, Hadziselimovic reported that August-Copenhagen-Irish cryptorchid rats lacking an epididymis had no transabdominal descent and, in 2017, presented histological sections that showed the epididymis precedes the testis throughout descent by the gelatinous gubernaculum dilating the inguinal canal [11,1]. In 1986, Heyns dissected 178 male human fetuses and found that 'the gubernaculum, epididymis, and testis appear to move through the inguinal canal as a unit, covered on its anterior aspect by the open *processus vaginalis*'. Furthermore, no extension of the gubernaculum into the bottom of the scrotum exists [21,22]. In 2020, a three-dimensional (3D) histological reconstruction of testicular descent in mice showed the tail of the epididymis being pulled down to the inner ring by the gubernaculum, and then the tail and body of the epididymis expanding the inner ring and inguinal canal through their morphological changes. The epididymis then continued to go down into the scrotum and expand it. Finally, the testis and the head of the epididymis followed the body of the epididymis and entered the scrotum through the enlarged inner ring and inguinal canal. This shows that the epididymis descends prior to the testis. In regards to the role of the gubernaculum, according to the 3D model, it is not directly anchored to the testis itself and plays a guiding role for the epididymal tail and testis [23]. This supports the idea that the gubernaculum should be called 'gubernaculum epididymis' rather than 'gubernaculum testis'.

Genetic studies on the etiology of cryptorchidism also support the importance of the epididymis for testicular descent. Recent research by Jorgez et al. showed that E2F transcription factor-1 (E2F1) regulates genes required for testicular descent, such as *Wnt4, Insl3, Ar, Lgr8, Hoxa10, Amh, Dmrt1*, and *Fst*. In addition to spermatogenic failure and gubernacular defects, *E2F1*-null cryptorchid mice have a significant decrease in epididymal size compared to wild-type individuals [15].

Both gubernaculum and cremaster muscle are a derivative of mesenchyme and have a distinct myosinic pattern [24]. The epididymis exhibits spontaneous contractions along the epididymal duct through cAMP-mediated smooth muscle contractions [25]. Histological investigation has also shown the presence of smooth muscle around the epididymal duct [26]. This suggests a common molecular mechanism for mesenchymal-epithelial transition involved in the process of epididymo-testicular descent.

Pitfall No. 2 – Hypogonadism and epididymo-testicular descent

The next topic of debate is the role of hypogonadism and androgens in epididymo-testicular descent and whether it is staged. Clarnette et al. stated that, 'in conditions of androgen insensitivity, the testis is located in the inguinal region, indicating that the first phase of descent is normal, but the inguinoscrotal descent has failed to occur' [27]. Antiandrogen treatment with flutamide has been shown to induce cryptorchidism, epididymal anomalies, and failure of gubernacular regression in pigs, affecting both transabdominal and transinguinal descent of the testes [28]. In subjects with complete and partial androgen insensitivity syndrome, the complete female phenotype with abdominal testes was found in 86% of patients, and this incidence decreased significantly with increasing masculinization [29].

Mutations in Wilms' tumor gene (*WT1*) may be associated with testicular maldescent and genital abnormalities consistent with defects in the androgen pathway of testis descent [30]. Studies on *WT1* have shown that androgens are important for both intra-abdominal and inguinoscrotal descent, but multiple other factors may modulate this process [31]. An inverse relationship between *androgen receptor* and *WT1* expression has been found in prostate cancer cell lines, together with WT1 repression of the androgen receptor promoter [32]. The early growth transcription factor family response to gonadotropin-releasing hormone (GnRH) treatment indicates involvement of gonadotropins, androgens, and WT1 in the process of testicular descent [33,34].

Measuring testosterone production in testes from 18-day-old fetal mice showed that active gonadotropin material is present in the pituitary gland and exerts significant actions on the production of testosterone in the fetal testis [35]. The importance of gonadotropins in the development of fertility is highlighted when investigating luteinizing hormone receptor knockout (LuRKO) mice. These mice exhibit dramatically reduced Leydig cell counts and arrested spermatogenesis [36]. Further research on LuRKO mice has shown that testosterone replacement therapy corrects the cryptorchidism. This confirms that testosterone facilitates the completion of testicular descent [37]. Migratory arrest of GnRH neurons to the hypothalamus in transgenic mice has been shown to be the cause of hypogonadotropic hypogonadism, resulting in crypto-epididymis, severe gonadal hypoplasia and, consequently, infertility [38].

Androgens and estrogens are involved in multiple processes in both males and females. Male offspring of estrogen-treated mice present with low levels of pituitary luteinizing hormone, Leydig cell atrophy, and low testicular testosterone, resulting in abnormal epididymal development and cryptorchidism [39]. Control mice clearly exhibited a sharp increase in testicular testosterone around embryonic days 17 and 18. This was completely missing in estrogen-treated cryptorchid mice [40]. When pregnant female mice were given injections of estradiol, all of their male offspring lacked gubernacula and the testes were freely mobile within the abdomen [41,42].

At least partial reversal of estrogen action by human chorionic gonadotropin administration suggested that the leading cause of epididymo-testicular maldescent is induced by an insufficiency of the hypothalamo-pituitary-gonadal axis [39]. In summary, the data provided above confirms the crucial role of androgens for epididymo-testicular descent, both abdominal and inguinoscrotal. It also supports the hypothesis of hypogonadotropic hypogonadism as the cause of cryptorchidism.

Pitfall No. 3 – Role of Insl3 in epididymo-testicular descent

Over the last 30 years, many theories have been proposed to explain epididymo-testicular descent. The most important factor responsible for this step was considered to be Insl3, a major product of fetal and adult Leydig cells [14]. The role of Insl3 in the descent of the testes was evoked after two studies found that Insl3 knockout mice have intra-abdominal undescended testes and impaired development of the gubernacula [43,44]. Later studies in mice revealed the importance of both Insl3 and androgens for transabdominal testicular descent [45]. When LuRKO mice received testosterone replacement therapy, that had no impact on Insl3 expression but restored Insl3 receptor expression in the gubernaculum. This suggests that testosterone maintains normal receptor levels and even low INSL3 levels can activate them [37].

Analyzing pictures of Insl3-null mice, one should notice not only a gubernacular abnormality, but abnormal cauda epididymis, though this was not acknowledged in the paper [44]. In a similar study by Kubota et al., the epididymides of $Insl3^{-/-}$ mice look abnormal [46]. Overlooking these observations may underestimate the role of the epididymis in the descent of the epididymo-testicular unit. Abnormal epididymides in Insl3-deficient mice suggest an impact of Insl3 on the development of the epididymis rather than the testis [26].

With all of the evidence on the significance of Insl3 in rodent testicular descent, the question remains: how important is the INSL3-LGR8/G-protein-coupled receptor (GREAT) for cryptorchidism in humans? When trying to replicate the motivating results, many studies were looking for INSL3 gene mutations in former cryptorchid boys and men; surprisingly, it appeared at extremely low rates. The cumulative incidence of INSL3 gene mutations in eight studies with a total of 859 patients was 2.3% (Table 1). Similar results were obtained when searching for GREAT gene mutations; the cumulative incidence from six studies with a total of 990 patients was 3.1% (shown in Table 1). It is also worth mentioning that GREAT mutations were present in patients with retractile testes or spontaneous testicular descent (i.e., not really cryptorchid). This may indicate that GREAT mutation does not have a direct effect on testicular descent in this group [47–49]. Based on the data provided in the 12 studies, INSL3/GREAT mutations are not as important in the development of cryptorchidism in humans as previously thought.

Pitfall No. 4 – Role of anti-Müllerian hormone in epididymo-testicular descent

AMH is another factor commonly discussed in the process of testicular descent. It is produced by Sertoli cells and causes the regression of Müllerian ducts [59]. Clarnette et al. performed a literature review and came to the conclusion that, in conditions in which AMH is absent, the gubernaculum is 'feminized', resulting in a testis position normally occupied by an ovary [27]. Moreover, the review supported the hypothesis of the biphasic hormone-dependent model for testicular descent proposed by Hutson [60]. Based on the aforementioned review, Clarnette et al. agreed that the 'transabdominal'

Table 1
Cumulative incidence of INSL3GREAT gene mutations in 12 studies

Author	INSL3 incidence	GREAT incidence	Remarks
Incidence of mutations found, research groups were not uniform/homogeneous			
Ferlin et al. 2003 [47]	4.6% (4/87)	4.6% (4/87)	Study included five patients with retractile testes. One of the GREAT mutations was present in a patient with retractile testis.
Foresta et al. 2004 [48]	4.4% (6/135)	3% (4/135)	Study included eight patients with retractile testes. One of the GREAT mutations was present in a patient with retractile testis.
Bogatcheva et al. 2007 [49]	–	3.3% (20/598)	T222P mutation. Study included 94 patients with spontaneous testicular descent. One of the GREAT mutations was present in one of these patients.
El Houate et al. 2007 [50]	2.75% (3/109)	–	Study included 19 patients with cryptorchidism and hypospadias, and 1 patient with bilateral cryptorchidism and micropenis. One of the INSL3 mutations was detected in a patient with bilateral cryptorchidism and micropenis.
Incidence of mutations found, uniform research groups			
Canto et al. 2003 [51]	2.7% (4/150)	–	DNA obtained from patients with cryptorchidism. Two of the mutations did not alter the encoded amino acid and one was also found in the controls.
Tomboc et al. 2000 [52]	1.4% (2/145)	–	Patients who underwent surgical correction for cryptorchidism, no histological diagnosis.
Gorlov et al. 2002 [53]	–	1.6% (1/61)	Unilateral and bilateral cryptorchidism, no histological diagnosis.
Research groups with 0% incidence of mutations or mutations with no clinical significance			
Baker et al. 2002 [54]	0% (0/118)	–	Unilateral and bilateral cryptorchidism.
Koskimies et al. 2000 [55]	0% (0/30)	–	Seven patients had possible familial form.
Lim et al. 2001 [56]	1.2% (1/85)	–	Study included patients with undermasculinized genitalia. The only mutation was found in the patient with completely female genitalia, bilateral intra-abdominal testes.
El Houate et al. 2008 [57]	–	2.75% (3/109)	T222P mutation. No association with cryptorchidism found (incidence in control group, 4/250).
Nuti et al. 2008 [58]	–	3.6% (13/359)	T222P mutation found to not be causative. Difference with incidence in controls not significant (1.7%, 8/463).
Total	2.3% (20/859)	3.4% (45/1349)	

INSL3, insulin-like peptide 3; GREAT, G-protein-coupled receptor affecting testis descent.

phase of testicular descent is AMH-dependent and controls the swelling reaction in the male gubernaculum [27]. However, several studies published before and after have shown that these ideas about AMH were not correct. Lyet et al. analyzed transgenic mice expressing human AMH throughout prenatal life and found that this hormone had no effect on the growth and development of the gubernaculum [61]. Another study performed on AMH-deficient mice found that they have normal epididymo-testicular descent [62]. This result was confirmed by another study on disruption of AMH receptor genes [63]. Moreover, a Emmen et al. showed that AMH has no effect on the gubernaculum [45]. Thus, it seems that AMH alone has no significant role in epididymo-testicular descent.

Conclusion

Most experimental evidence supports the leading role of gonadotropins and androgens in epididymo-testicular descent. However, the role of the epididymis is underestimated. Future research should not omit the role of the epididymis in the complex process of gubernaculum, epididymis, and testis migration.

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