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Review Article

Undescended testis: A roundtable discussion based on clinical scenarios – Part 1

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Summary
Undescended testis (UDT, cryptorchidism) is the most common congenital anomaly of the genital tract. Despite its high incidence, the management of UDT varies between specialties (urology, pediatric surgery, pediatric urology, pediatric endocrinology). Therefore, as the European Association of Urology – Young Academic Urologists Pediatric Urology Working Group, we requested experts around the world to express their own personal approaches against various case scenarios of UDT in order to explore their individual reasoning. We intended to broaden the perspectives of our colleagues who deal with the treatment of this frequent genital malformation.

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Introduction

Undescended testis (UDT, cryptorchidism) is a common clinical problem with an estimated prevalence ranging from 0.1 to 9% at birth and 1.1—2.1 % at 1 year of age [1]. Previous studies have indicated that incomplete testicular descensus is multifactorial (genetic, maternal and environmental) [2]. UDT has been shown to implicate short and long-term issues including testicular torsion/inguinal hernia, hypogonadism or testicular cancer [3]. Surgical treatment, namely as orchi(d)opexy, constitutes the basis of the treatment which is advised to be completed before 18 months of age latest [4,5] with a historical evolution of earlier intervention during the last 20 years. Well-implemented surgical techniques can achieve high rates of success, with the actual approach (inguinal, scrotal, laparoscopic, vessel dissecting) being routinely discussed in literature [6]. Hormonal stimulation, which had been a mainstay of treatment in the beginning of the century, has witnessed diminished use during the last decade, due to very low efficacy concerning testicular descent. There has been a resurgence recently however, as there is growing evidence relating to the use of hormonal treatment in selected patients to foster germ cell development, especially in bilateral disease [7,8]. Despite the high prevalence of the condition and the vast body of research, as well as fairly clear international guideline recommendations, clinical management varies significantly. Additionally, the entity of undescended testes encompasses a wide spectrum of clinical manifestations, ranging form apparently simple and uncomplicated cases to highly complex situations that surgical approaches involve vascular dissection, where hormonal as well as reproductive function is at risk.

The aims of this roundtable discussion series were to highlight global differences in clinical practice by presenting the views of renowned international experts and to put them into perspective by discussing the relevant literature. Correspondingly, we intended to include a spectrum of cases which would give a basis on clinical reasoning.

Experts were invited according to the personal opinions of the members of the YAU Group taking into account as well scientific as clinical expertise. Consequently, a total of 10 experts were asked to comment on 11 clinical scenarios that will be published in a series of two articles. The manuscript is split into two parts consisting of five scenarios for the Part 1 and six scenarios for the Part 2 for enhanced readability. We sincerely thank the international experts who contributed to this panel discussion. (Duncan T. Wilcox (USA): DTW, Josef Oswald (Austria): JO, Faruk Hadziselimovic (Switzerland): FH, Yutaro Hayashi (Japan): YH, Orhan Ziylan (Turkey): OZ, Jorgen Thorup (Denmark): JT, Klaus Kapelari (Austria): KK, Tarkan Soygür (Turkey): TS, Luciano A. Favorito (Brazil): LAF and Luis H. Braga (Canada): LHB))

Scenario 1

- Physical examination of a newborn reveals a right UDT at the level of the external/superficial inguinal ring. How would you inform and counsel the parents regarding the potential management algorithms, and future functional/developmental outcomes?
- How would you proceed with treating this patient?

All experts agreed on a chance of spontaneous testicular descensus and advice to treat surgically if the testis has not descended by 6—12 months. However, the role of hormonal therapy and information on risks of infertility and malignancy differed. JO stated that there is no connection with possible infertility or malignancy in this condition at this time of development. Also, if the testis has not descended by 6th month, discussion of Gonadotropin-releasing hormone (GnRH) therapy should also be considered. Subsequently, if the testis does not descend, this is an indication for surgery from 12 months of age. FH preferred monthly or bimonthly physical examination until 6th month. YH plans for a clinic visit at 3 months of age and does not discuss about infertility or malignancy at this time. He also advises to perform surgery no later than 2 years of age and to consider a Bianchi procedure [9] when testis is near the scrotum. DTW explained that after 6 months the testis is unlikely to spontaneously descend and therefore recommends to orchidopexy prior to one year of age because of the slight increased risk of cancer, and to allow for optimal endocrine function within the scrotum. Therefore, he arranges a visit at 6 months of age. OZ informs the family that scrotal position is crucial for the normal development of the testis and there is almost no risk of infertility if the testis is located in the scrotum at correct age. He discusses the increased malignancy risk if the treatment is delayed for years but does not stress the point in order not to cause unnecessary anxiety on parents. He would see the baby at 6 months of age and if there is progression in descent at the follow-up examination, he follows the baby until one year of age. However, if there is no movement in the position of the testis, he offers inguinal orchiopexy between 6 and 9 months of age. JT indicates that the risk of infertility in unilateral disease is low and the risk of increased future malignancy risk is almost eliminated with early surgery. KK recommended intranasal preoperative hormone therapy (neo-adjuvant with GnRH, not hCG). TS would not use hormonal therapy to facilitate descent but states that GnRH analogues may improve future fertility and should be discussed with parents. LAF specifies that he would talk about the anomalies associated to undescended testis (epididymal anomalies and patency of processus vaginalis) in about 30 % of the cases. LHB warns that patients should be appropriately called for examination at 3—6 months of age in order to arrange timely surgery. Most experts would choose inguinal approach for the given scenario whereas YH and DTW would proceed with a scrotal approach.

It is evident that the approaches of surgeons vary in clinical setting. Despite this common and seemingly simple case scenario, the array of statements displays the many nuances in the management, where clear literature is not available and also, how systemic (availability of appointments) factors might influence treatment. However, it is obvious that there is consensus on surgery within infancy as current evidence based knowledge prevails [10].

Scenario 2

- How would you treat a 1-year-old boy with a testis located at the internal inguinal ring?

DTW: 'If the testis is palpable, I would recommend that this is treated with surgical repair. I attempt to bring the testis down via a scrotal approach, which is usually successful'.

JO: 'In principle, surgical, if possible one-stage, therapy: if vessel transection is necessary, then the Koff procedure [11]. It would be ideal to see this child before the age of one and to recommend a hormonal pre-treatment, last but not least for spermatogonial maturation [12] and due to the (local) paracrine effect with GnRH nasal spray [13]'.

FH: 'First treatment; Luteinizing hormone-releasing hormone LH-RH followed by Human chorionic gonadotropin (HCG); one injection per week for three weeks, if necessary. If unsuccessful, surgery after 3 months of last HCG injection [8]'.

OZ: 'If I palpate the testis, I always perform open inguinal approach for an ideal preparation of hernia/processus vaginalis and dissection of the lateral transvers fascia connection of the cord. Thus, mobilization of the vessels and vas deferens would be superior. In case of a non-palpable testis, I proceed with laparoscopy and prefer two stage Fowler-Stephens (FS) laparoscopic orchiopexy'.

YH: 'When the testis does not reach the scrotum after inguinal incision, exposure of the spermatic cord and transection of the patent processus vaginalis is required. Also, I usually conduct the Prentiss procedure. I rarely choose the Fowler-Stephens procedure because the spermatogenesis after the Fowler-Stephens procedure was proved to be unacceptable by our experimental study [14]'.

KK: 'As a pediatrician, I would recommend a one-stage inguinal orchidopexy with preoperative intranasal neoadjuvant GnRH therapy, if there is not a compensatory hypertrophy of the contralateral testis'.

TS: 'If the testicle is palpable on the physical examination under general anesthesia, I would proceed with open orchidopexy with high inguinal incision above the ring. I would rather prefer one stage procedure with extensive retroperitoneal dissection and I might use Prentiss maneuver for re-routing the cord under the epigastric vessels if needed'.

LAF: 'If the testis is palpable, I treat with a surgery via inguinal approach in one stage'.

LHB: 'If the testicle was palpable at the internal inguinal ring, then I would proceed with a classic inguinal orchidopexy. If the testicle is palpable at the internal inguinal ring but the testicular pedicle is very short, i.e., it barely moves during physical exam manipulation (palpation), then a classic open Fowler-Stephens orchidopexy can be used with great success'.

JT: 'The testis is almost certainly non-palpable. Therefore, I would schedule for a one stage laparoscopic assisted orchidopexy. I would inform parents about an approximal 15 % risk of a non-satisfactory scrotal position indicating redo surgery and also inform about the risk of atrophy'.

There seems to be a clear trend to perform an open, inguinal approach whenever possible and foremost if the testis is palpable under anaesthesia [15]. Vessel dissecting methods are only to be used if no other option is available - all but one expert would advise for a staged approach in such cases. On the other hand, as recent data indicated hormonal therapy resulted in better sperm analysis results even in unilateral disease [8], which is backed by previous research showing the absence of mini-puberty as a possible factor in these patients [16], some clinicians might tend to give hormonal therapy even in single sided undescended testis.

Scenario 3

- What is your preferred approach for a 10-month-old infant with a right non-palpable testis, and an orthotopic contralateral scrotal testis within a normal size range?
- Do you use any imaging modality etc. in order to assess the presence of the testis, its location, or volume prior to surgery? If yes, what modality do you prefer?

In such a case, some authors would directly proceed with laparoscopy (LAF, JT) whereas most would repeat physical examination under general anesthesia prior to laparoscopy (OZ, KK, TS, LHB). DTW chooses another strategy: he would start scrotally to see if he can identify the testis via exploration or a testicular nubbin and if he cannot find the testis scrotally, he would switch to a laparoscopic approach. Regarding imaging, none of the authors except from JO, OZ and YH would request US to confirm or exclude a location in the groin or on the inner inguinal ring (peeping) while they use US as a part of their clinical approach and then proceed to laparoscopy while YH also uses MRI if no testis is found in the US [17,18]. Further, LAF would use US in obese patients. TS does not use US prior to surgery unless there is a suspicion of difference of sexual development so that Müllerian structures can be identified. In case of non-blind ending vessels that proceed through the internal inguinal ring JT would continue with an inguinal exploration in order to remove the possible nubbin and send for histological examination. A normal size contralateral testicle would not affect TS's approach. On the other hand, YH indicates that the size of contralateral scrotal testis provides valuable information for preoperative counseling and treatment planning. According to their clinical study, the optimal cut-off for contralateral testicular hypertrophy with calipers was 21 mm and 1.6 cm^3 [19]. Since the boy's contralateral scrotal testis is within a normal size range, he predicts that the right non-palpable testis must be an intraabdominal testis and he would do a laparoscopic orchiopexy. LHB suggests similarly on the use of contralateral hypertrophy as their study showed contralateral testicular cut-off length of 19—20 mm had the best accuracy in predicting monorchism in boys aged 11—30 months with unilateral non-palpable testis [20]. JO also assumes of an abdominal testis or high-scrotal testis in the case of a normal contralateral testis and due to the absence of contralateral hypertrophy (with high sensitivity when

testis diameter >16 mm in US), he considers preoperative GnRH therapy useful. FH would initially start with hormonal treatment and if the testis is still not palpable or descended after hormonal treatment he would proceed with surgery, preferably laparoscopic.

Three controversial aspects can be clearly delineated in this clinical scenario: 1. The use of US in the diagnosis 2. The use of contralateral hypertrophy to guide management and approach, as well 3. The indication for hormonal treatment in non-palpable testes. These will be discussed below.

Scenario 4

- A 5-year-old boy is brought to you with a complaint of an empty scrotum most of the time. He was diagnosed with retractile testes in a different clinic. How would you define retractile testis?
- Do you use any type of volumetric assessment in patients with retractile testis?

Although there seems to be a clear definition of retractile testis, we noticed several small details that differ amongst the experts. The overall agreement of retractile testis is that the testis must remain in the scrotum, even temporarily, after manipulation into the scrotum. All authors agree on a follow-up for retractile testes with the intervals changing from 6 to 12 months.

OZ would recommend a follow-up examination in 6—12 months and only if he has some suspicion about the size or consistency of the retractile testis, does he request volumetric assessment by scrotal ultrasonography. JO underlined that it appears to be mainly a functional (cremasteric) problem combined with a loose distal (gubernacular) fixation of the testis rather than a problem of testicular descent during development. YH prompted that 2 % of retractile testes can become ascending testes, thus annual examination is necessary [21]. On the other hand, DTW stated that if he can bring the testis down into the scrotum and if it can stay there, he recommends returning in 6 months to check again. LHB indicates that in case of retractile testis he would reassure the parents that surgery is not needed at that time and would continue to follow him until age of 9 years with annual appointments bearing in mind that adverse effects may not be obvious until the boy reaches this age. FH favors yearly assessment.

LAF pursues periodical examination until adolescence or the end of testicular migration to the scrotum. JO, KK and TS all suggested that up to 30 % of retractile testes can become ascended. TS is the only one who uses an orchidometer in the clinical assessment. JT underscored that if the testis is in a suprascrotal position and can be pulled down to the upper scrotum, but does not remain there after exhausting the cremasteric activity, it is defined as an undescended testis, and also requires orchidopexy. In addition, JT explained that if the testis remains in the upper or lower scrotal position after the traction is released, his recommendation is that the testis should not be subject to treatment.

Although retractile testes often might cause difficulties in clinical management with insecurity especially on the parents side, all experts agree that while no therapy is indicated, further follow-up is mandatory. It remains unclear as to the role of testicular size and on what embryophysiopathological basis the patients should be followed-up, as well as for how long.

Scenario 5

- In a 9-month-old boy with bilateral UDT, both located within the inguinal canal (canalicular), do you routinely consider/request genetic testing and/or an endocrinological evaluation?
- Do you prescribe any type of medication, for how long, and before or after surgery?

There are many different opinions on this topic, with regular ongoing debate. Endocrinological and genetic assessment before proceeding to surgery is supported by some of the experts (TS, JT, KK, LHB, JO) when signs for DSD are found, as well as in the presence of concomitant hypospadias, genital ambiguity or scrotal hyperpigmentation. Also, some (LHB, OZ, DTW, JO, LAF) would plan to refer to endocrinological evaluation if testis or penis sizes are abnormal.

Apart from that JT highlighted the importance of testicular biopsy as if hypogonadotropic hypogonadism is proven, he offers participation in a randomized double blind, placebo-controlled study on the effect of 4 months GnRH treatment on germ cell maturation.

Further, KK would prescribe intranasal GnRH-therapy preoperatively for 4 weeks (3 × 2 sprays daily) depending on the underlying diagnosis. TS advises GnRH analogues to improve future fertility, but not for testicular descent. FH endorses hormonal treatment and considers surgery with biopsy if treatment fails. He also recommends Buserelin (GnRH agonist) treatment (10 μg) on alternate days in the evening if the histology confirms high infertility risk.

Regarding hormonal assessment, YH stated that their group recently elucidated serum hormone levels could be useful for the prediction of germ cell number per seminiferous tubule in bilateral cryptorchid boys aged <24 months at surgery, although not covered by their health care system [22]. JO would primarily recommend GnRH (nasal spray) therapy for spermatogonial maturation, and orchidopexy on both sides around the first year of life.

It is impressive, how diverse the recommendations concerning further diagnostics (DSD) in this case are: some would do it routinely — sometimes even combining this with intra-operative testicular biopsy whereas others only undertake further diagnostics with additional signs of DSD or penile/testicular size abnormalities. Most of the experts would consider hormonal therapy with no clear consensus reached, reflecting the ambiguity of this frequent clinical situation.

Discussion

This roundtable discussion evidently confirmed that a high global diversity exists in the management of undescended testis. As the most common abnormality of the male genitalia, there is substantial data on this topic. However, it is

obvious that these data have not been solid enough to persuade clinicians in various continents to shape their practice accordingly.

Most clinicians would expect testicular descent within the first 6 months of life due to the well-established 'mini-puberty' in the form of a gonadotropin peak that takes place around 3—6 months of age. Surgical treatment is generally planned up to 2 years of age, at the latest [5,23]. With evidence highlighting the potential benefits of early treatment [24,25], aiming for orchidopexy at an earlier age may lead to a reduction in the use of assisted reproduction techniques, as demonstrated in a large, populations based study as well as decrease in testicular cancer risk (relative risk decrease from 5.4 to 2.2 when orchiopexy performed <13 years of age) [26,27].

Use of hormonal therapy (GnRH) for undescended testis has gained contemporary traction in some northern European countries, mostly for fertility concerns. This might be attributed to the data published by these groups [13,28]. Also, recent evidence suggests a far more complex picture regarding the benefits and risks of hormonal treatment in these patients, with an emphasis to try to identify those who might derive the greatest benefit [29—31]. The most recent meta-analysis on this subject came up with a conclusion that LHRH analogues may provide benefit in some children with undescended testis regarding fertility index [32]. However, this medication might be unavailable in some countries.

For a testis located at the internal inguinal ring, which can be assumed one of the most common clinical scenarios in the clinical setting, there is broad consent about a primary inguinal approach, whereas if the testis cannot be palpated under anesthesia, laparoscopy remains the approach of choice through either a single or staged procedure. One interesting question relates to the use of ultrasound, which seems to be determined mostly by systemic factors such as local availability. The literature suggests a number needed to treat of 4—5 ultrasound exams in order to spare one laparoscopic procedure, which needs to be taken into account [33].

Regarding a unilateral non-palpable testis, only some of the experts would request an ultrasound to detect a peeping or ectopic testis — which is clearly determined by geographical factors and the local guideline situation [5,23]. Moreover, some would request an MRI as they have shown some utility when used with fat-suppressed T2-weighted and diffusion weighted imaging [17,18]. The majority of clinicians would start with laparoscopy in this case while colleagues from western and northern Europe favor hormonal treatment. Most would consider a staged, vessel dissecting approach (Fowler-Stephens) if necessary, however, also a non-staged Koff procedure is discussed [11]. A point of contention in the literature also relates to the preservation of the gubernaculum, which might contribute to a better outcome [34,35]. Whether contralateral hypertrophy is important in clinical management appears to be controversial. Despite clear data about high specificity and sensitivity at between 16 and 18 mm to predict an ipsilateral nubbin, the practicality of excising a nubbin should be discussed [36,37]. Apparently, there is no clear recommendation for the three points mentioned earlier on this case scenario.

With regard to retractile testis there is a consensus that initially no treatment is necessary, however individual minor differences exist. As to the question of follow-up, there is no consensus, however the literature does suggests a considerable risk of secondary ascension with data about embryologic underlying causes as well as associated harm to the germ cells [38,39]. Also, it should be remembered that histological studies have shown abnormal muscular structures in retractile testes [40,41]. Volumetric assessment mostly depends on personal preference.

Finally, in the case of bilateral undescended testes, some would use GnRH analogues not to induce descent, but to improve fertility, whereas most of the authors indicated that genetic testing and hormonal work-up could be avoided if the testes are normal/near-normal sized with a normal penis. These have been in accordance with the published data available that also indicates mandatory endocrinological and genetic evaluation when bilateral undescended testes and signs of ambigus genitalia are encountered [28,42]. Moreover, there is no consensus on the initiation and duration of the treatment as well as the evaluation of the effectiveness of treatment according to testicular biopsy [43]. Last but not the least, a recent study showed the use of low-dose postoperative LHRH every-second-day improves fertility outcome in bilateral cryptorchidism [7].

Conclusion

Responses from experts around the world in the first part of this roundtable discussion support the notion that management of UDT involves considerable variability. The wide spectrum of approaches reflects the yet unclear data as well as the importance of individualized decision making. This should prompt further high quality experimental and clinical studies with the aim of the development of unequivocal guidelines that could help clinicians throughout the world provide better and more precise risk stratification models.

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Conflict of interest

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