Ministry of higher Education and Scientific Research/
University of Diyala /
College of Medicine

Hormone therapy in undescend testes

Done by
Layla Ahmed Salih
Supervised by
Dr. Waleed Khalid

الاهداء

اهداء اولاً الى الله تعالى

في جميع مراحل الحياة أناس يستحقون الشكر والتقدير وأولى الناس بالشكر

والدي العزيز الذي جرع الكأس فارغاً ليسقيني قطرة الحب

و والدتي العزيزة التي وضعتني على طريق الحياة و لها الفضل في كل نجاح

و الى أصدقائي و جميع اساتذتي بشكل عام و دكتور وليد خالد مشرف بحثي بشكل خاص الذي كان له دور في اعطائي المعلومة

اهدي لكم بحث تخرجي المتواضع و أتمنى ان ينال اعجابكم .

Abstract

Cryptorchidism or undescended testis is an evolutionary defect where one or both testes fail to descend into the scrotum. HCG causes the testes to fail, possibly due to weight gain, an increase in testicular vasculature, and stimulating the testosterone and di-hydro-testosterone. The present study has been conducted to evaluate the therapeutic effects of hormones on patients with undescended testis.

Contents:_

Purpose:

The goal of any intervention for cryptorchidism is to move the undescended testicle to a normal position in the scrotum, in as safe and least invasive way possible.

-

Introduction

Cryptochidism represents the most common disorder of sexual differentiation. The testes lie dormant within the abdomen until about the 23rd week of gestation, transinguinal migration occurred between 21 and 25 weeks after conception .Most undescended testicles are present at birth. Up to one third of premature male newborns are born with an undescended testicle, and 3-5% of term male infants are affected. By three months of age, the incidence is reduced to 0.8 percent. [1,2]

In clinical practice, the choice of initial therapy is often selected on the basis of age at presentation and the location of the cryptorchid testicle. Watchful waiting may be used in boys <1 year of age with lower-lying testis in whom spontaneous descent is still a realistic possibility. Hormonal and surgical options are primarily selected on the basis of location and appearance of the undescended testicle. Hormonal treatment with luteinizing hormone releasing hormone (LHRH) analogs and/or human chorionic gonadotropin (hCG) could theoretically increase circulating androgens that may, in turn, promote testicular descent Surgical options include various forms of orchiopexy or orchiectomy. Primary orchiopexy (surgical mobilization of the testicle with placement and fixation in the scrotum) is usually performed for palpable cryptorchid testicles that are of relatively normal size and appearance that are located in the inguinal canal. For nonpalpable testicles located just inside the internal inguinal ring or in the abdomen, surgical management is more complicated and is dependent on location in the abdomen and the length of the gonadal vessels. If the testicle is of normal size and appearance and if the vessels are of adequate length, primary orchiopexy is usually performed If the

vessels are so short as to prohibit tension-free placement of the testicle in the scrotum, a Fowler-Stephens (FS) orchiopexy is performed. This procedure entails ligating the testicular vessels. The testicular blood supply then depends on collateral circulation from the deferential artery and the cremasteric system. This procedure can be performed as a single-stage operation, in which the vessels are ligated and the testicle is then placed into the proper position in the scrotum, or as a 2-stage procedure. In a 2-stage procedure, the vessels are ligated in the first operation, the testicle is allowed to develop presumably better collateral circulation in its abdominal position and is then moved to the proper position in the scrotum during a second procedure, usually 3 to 6 months later. Both primary orchiopexy and the FS procedure can be performed using laparoscopic or open surgical technique. [3,4]

Classification

Testicular position is classified as intraabdominal, inguinal, suprascrotal, high scrotal, and scrotal according to the process of testicular descent. [5,6] Intra-abdominal testis is not palpable. Inguinal testis is sometimes palpable. Supra-scrotal and high scrotal testes are palpable. Scrotal testis is considered normal, as it lies in the bottom of the scrotum (Fig. 1).

Undescended testis is classified according to its location and presence. In palpable undescended testis, the testis may be palpable in the inguinal canal or ectopic area such as the inner thigh, femoral, pubic, and perineal regions. In impalpable undescended testis, the testis may be located in the abdomen, inguinal canal, or internal inguinal ring. It may also be absent. When the testis is found in the scrotum, sometimes in a supra
scrotal position, it is called retractile testis and has finished its descent. It can be pulled gently to the bottom of the scrotum and may stay there for a while, which is often considered normal.[7],However,up to one-third of retractile testis can reascend and become undescended, which is not considered normal. [8]

Reascended testis, which a previously descended testis ascends to a higher position, comprises some proportion of cases of undescended testis. An abnormally persistent fibrotic remnant of the processus vaginalis, [9] patent processus vaginalis, and nonorthotopic gubernacular insertion (higher insertion) [10] are suggested causes of reascended testis.

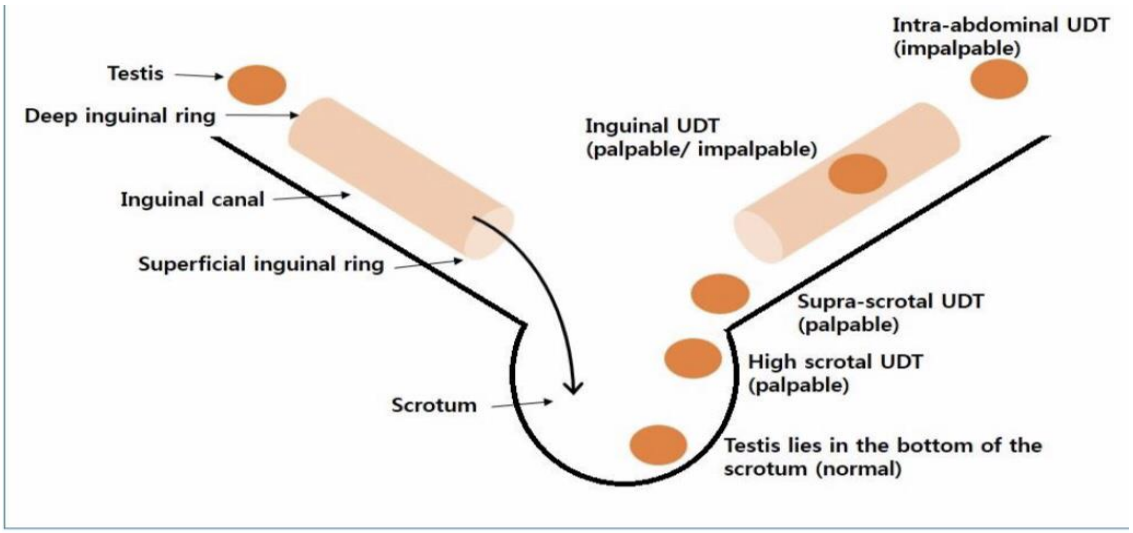

Fig. 1. Testicular position. Testicular position is classified as intra-abdominal, inguinal, suprascrotal, high scrotal, and scrotal according to the process of testicular descent. Intra-abdominal testes are not palpable. Inguinal testes are sometimes palpable. Suprascrotal and high scrotal testis is palpable. Scrotal testis is considered normal as it lies in the bottom of scrotum. UDT, undescended testis

Risk factors

Important risk factors of undescended testis are preterm birth (<37week gestation), low birth weight (<2.5 kg), and intrauterine growth restriction. [11].
A family history of undescend ed testis, associated hormonal disorders (such as congenital adrenal hyperplasia), associated penile abnormalities (such as hypospadias), slow fetal growth (such as Down syndrome), and disorders of sex development can increase the risk of un descended testis. A young maternal age is protective against the development of undescended testis. [12] Older maternal age is related to undescended testis. [13] The relative risk is 1.8 with a maternal age ≥30 years and 2.5 with a maternal age ≥40 years. However, controversy persists regarding the role of maternal old age and the development of undescended testis.
Maternal smoking during pregnancy is associated with an increased risk of undescended testis. [14,15] A history of previous surgery for inguinal hernia or orchiopexy can also increase the risk of undescended testis. [16]

The investigations

In addition to careful clinical examinations, ultrasound, CT scan and MRI are helpful for localization. CT scan is noninvasive but carries a radiation risk. MRI is very sensitive in obese children but require general anesthesia. However, the main two tools commonly used now for localization in routine practice are ultrasound and laparoscopy [17].

Imaging studies

In a systemic review, ultrasonography could not determine whether a testis is present or localize impalpable testes. It also could not rule out an intra-abdominal testis. [18] Similarly, in cases of impalpable undescended testis, diagnostic accuracy of ultrasonography or magnetic resonance imaging is low to determine the presence of the testis or the absence of intraabdominal testis. [19,20]

The AUA,[21] BAPS/BAUS,[22] CUA,[23]) and EAU [24] guidelines do not recommend ultrasonography or other diagnostic imaging, although the former is not invasive, because it cannot add diagnostic accuracy or change treatment Some practitioners perform ultrasonography to evaluate undescended testis before and after orchiopexy. [25]
Practically, ultrasonography is used because of uncertainty of the diagnosis. most urologists performed diagnostic imaging studies for unilateral impalpable undescended testis. [26] Fifty-two percent performed ultrasonography alone, while 40% performed ultrasonography and other imaging studies such as magnetic resonance imaging or computed tomography.

The complications

Cryptorchidism can cause several complications, including hernia and torsion, infertility, testicular tumor, low self-confidence, and disorders of sex development if it is not treated. People with cryptorchidism are at a higher risk of testicular cancer (5%) compared to the general population. [27]

Hormonal therapy

Human chorionic gonadotrophin (hCG) stimulates testicular hormone synthesis and enables the testes to descend into the scrotum. Intramuscular hCG therapy was first introduced in 1930 to treat undescended testis. However, hCG therapy can cause germ cell apoptosis, penile growth, pubic hair, frequent erection, behavior problems, and injection site pain in up to 75% of patients.[28,29] There is a lack of documentation to prove the longterm efficacy of hCG therapy. A significant reascending rate after descending has been reported.[30] Thus, hCG therapy is not justified anymore for undescended testis.[31]

Intranasal gonadotrophin releasing hormone (GnRH) analog was introduced in 1974. The success rate of testicular descent with intranasal luteinizing hormonereleasing hormone (LHRH) therapy was as low as about 20% in prescrotal or inguinal palpable undescended testis, but not in impalpable testis. However, LHRH therapy can cause hydrocele requiring surgery, penile growth, pubic hair, frequent erection, and behavioral problems. [32]

GnRH/LHRH therapy can also harm germ cells and suppress their numbers.[33]Longterm followup of GnRH/LHRH therapy has not been reported yet. Besides, the success rate of testicular descent with hormonal therapy is low and the risk of testicular reascending is high, although the testes descend with hormone therapy. On the other hand, in a small study of 10 boys, GnRH agonist therapy with orchiopexy improved impaired minipuberty and spermatogonia in patients with bilateral undescended testes. [34]

According to international guidelines, routine hormonal therapy with hCG or GnRH/LHRH for undescended testes. is not recommended due to the lack of evidence. [35,36,37]

Consensus is developing that orchi opexy but not hormonal therapy is required in the first year of life. [35,38,39] In an identified hormonal defect in congenital hypogonadotropic hypogonadism or partial androgen insensitivity, hormonal therapy can be considered by a pediatric endo- crinologist. However, debate persists over whether hormonal therapy is useful as an adjunct to orchiopexy

to stimulate germ cell development, although hormonal therapy for undescended testes is ineffective.

Harms of Treatments

Eleven studies of hormonal and surgical interventions included harms; two studies were of good quality, [40,41] two studies [42,43] were of fair quality, and seven studies were of poor quality. (Eight of 14 hormonal studies reported harms. The most common outcomes were virilizing effects (eg, hair, increase in penis size, and erections), and behavioral changes (e.g. aggression). reporting harms, 2 did not segregate data by study arm, and thus harms could have presented in either a treatment or placebo arm. One study reported that 74% of 116 boys receiving hCG had virilizing effects, compared with 5.1% of boys receiving only LHRH, but 1 of the hCG arms also included LHRH and another included human menopausal gonadotropin. All side effects had receded by the 6-month follow-up. No other study reported side effects to be as common as virilization. Reported harms of hormonal treatments were mild and transient and had receded by 6 months.

Three studies reported harms associated with laparoscopic surgery. [44] Rare cases of intestinal injury due to Veress needle puncture (1 case). [45] postoperative laparoscopic port site reducible (3 cases), and incarcerated (2 cases) hernia [44] were noted with laparoscopy. They are not specific to cryptorchidism repair and can occur with any type of laparoscopy. Overall, adverse effects specifically associated with surgical repair for cryptorchidism were rare.

Conclusions

Hormonal treatment is marginally effective relative to placebo, with moderate SOE, but is successful in some children and with minimal side effects, suggesting that it may be an appropriate trial of care for some patients. If successful, these patients should continue to be monitored for late re-ascent, as most of the studies on this issue did not include long-term followup. we found in other study about single undecended testis that more than 50% of the cases in all the groups responded to HCG therapy and the testes descended from the initial positions to lower levels. Consequently, the need for performing surgical procedures, laparoscopy and orchiopexy, on children with unilateral cryptorchidism decreased and they could be treated through a cost-effective and less invasive method. Considering the fact that recurrent undescended testes occurred in 20-25% of the patients, at least one-year follow-up of the patients is required to ensure outcomes of the treatment. Moreover, according to the results, HCG therapy would be more successful in patients with

cryptorchidism if the testes are located at the lower levels. One of the most important results of this study is that 20% of abdominal undescended testes descended into the inguinal canal, which eliminated the need for invasive laparoscopy and two-stage surgery.

References

1. Berkowitz GS , Lapinski RH, Dolgin SE, et al. Prevalence and natural history of cryptorchidism. Pediatrics. 1993 Jul; 92(1):44-9.
2. Barthold JS, Goonzalez R. The epidemiology of congenital cryptorchism, testicular ascent and orchiopexy, J Urol 2004;
3. Campbell MF, Wein AJ, Kavoussi LR. Campbell-Walsh Urology. 9th ed. Philadelphia, PA: W.B. Saunders; 2007
4. White S. Undescended testes (cryptorchidism). In: Gomella LG, ed. The 5-Minute Urology Consult. Philadelphia, PA: Wolters Kluwer Health; 2010:464–465
5. Cho A, Thomas J, Perera R, Cherian A. Undescended testis. BMJ 2019; 364:l926.
6. Cryptorchidism: a prospective study of 7500 consecutive male births, 1984-8. John Radcliffe Hospital Cryptorchidism Study Group. Arch Dis Child 1992;67:892. Keys C, Heloury Y. Retractile testes: a review of the current literature. J Pediatr Urol 2012;8:2**6.**
7. Keys C, Heloury Y. Retractile testes: a review of the current literature. J Pediatr Urol 2012;8:2–6.
8. yeap E, Nataraja RM, Pacilli M. Undescended testes: what general practitioners need to know. Aust J Gen Pract 2019;48:336.
9. Haid B, Silay MS, Radford A, Rein P, Banuelos B, Oswald J, et al. Late ascended testes: is nonorthotopic gubernacular insertion a confirmation of an alternative embryological etiology? J Pediatr Urol 2019;15:71.e16. :388-94.
10. RadmayrC,DoganHS,HoebekeP,KocvaraR,NijmanR,SilayS,etal. Management of undescended testes: European Association of Urology/ European Society for Paediatric Urology Guidelines. J Pediatr Urol 2016;2010;39:160518.
11. Mavrogenis S, Urban R, Czeizel AE. Characteristics of boys with the so called true undescended testis diagnosed at the third postnatal month a populationbased casecontrol study. J Matern Fetal Neonatal Med 2015;28:11527.

12. Gurney JK, McGlynn KA, Stanley J, Merriman T, Signal V, Shaw C, et al. Risk factors for cryptorchidism. Nat Rev Urol 2017;14:53448.
13. McGlynn KA, Graubard BI, Klebanoff MA, Longnecker MP. Risk factors for cryptorchism among populations at differing risks of testicular cancer. Int J Epidemiol 2006;35:78795.
14. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Hum Reprod Update 2011;17:589604.
15. Zhang L, Wang XH, Zheng XM, Liu TZ, Zhang WB, Zheng H, et al. Maternal gestational smoking, diabetes, alcohol drinking, prepregnancy obesity and the risk of cryptorchidism: a systematic review and meta analysis of observational studies. PLoS One 2015;10:e0119006.
16. Cho A, Thomas J, Perera R, Cherian A. Undescended testis. BMJ 2019; 364:l926.
17. Weiss RM, Carter AR, Rosenfield AT. High resolution real-time ultrasonography in the localization of the undescended testis. J Urol 1986 135:936–93.Andrologia. 1974;6(3):197-201.
18. Tasian GE, Copp HL. Diagnostic performance of ultrasound in non palpable cryptorchidism: a systematic review and metaanalysis. Pediatrics 2011;127:11928
19. Tasian GE, Yiee JH, Copp HL. Imaging use and cryptorchidism: deter minants of practice patterns. J Urol 2011;185:18827.
20. Esposito C, Escolino M, Savanelli A, Alicchio F, Roberti A, Settimi A. Ultrasonography is unnecessary and misleading in evaluating boys with a nonpalpable testis and can be a cause of a legal process. Med Sci Law 2013
21. Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY, et al. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014;192:33745.
22. British Association of Pediatric Surgeons. Commissioning guide: pae diatric orchidopexy for undescended testis. London: Royal College of Surgeons of England (RCS); British Association of Urological Surgeons (BAUS), 2015.
23. Braga LH, Lorenzo AJ, Romao RLP. Canadian Urological Association Pediatric Urologists of Canada (CUAPUC) guideline for the diagnosis, management, and followup of cryptorchidism. Can Urol Assoc J 2017; 11:E25160.

24. Radmayr C, Bogaert G, Dogan HS, Kočvara R, Nijman JM, Stein R, et al. EAU Guidelines on Paediatric Urology 2018. Arnhem (The Netherlands): European Association of Urology; European Society for Paediatric Urology, 2018.
25. Jedrzejewski G, Wieczorek AP, Osemlak P, Nachulewicz P. The role of ultrasound in the management of undescended testes before and after orchidopexy an update. Medicine (Baltimore) 2016;95:e5731.
26. Lee SW, Kim KS, Chang HS, Ryu DS. Comprehension and practice patterns toward cryptorchidism in Korean Urologists. Korean J Urol 2009;50:16978 J
27. Francis X. Schneck MD and Mark F bellinger MD: Abnormalies of the testes and and scrotum and their Surgical Management-walsh, patrik C et al:" Campbells urology 8th ed. 2002;
28. Chua ME, Mendoza JS, Gaston MJ, Luna SL Jr., Morales ML Jr. Hormonal therapy using gonadotropin releasing hormone for impro vement of fertility index among children with cryptorchidism: a meta analysis and systematic review. J Pediatr Surg 2014;49:165967..
29. Hjertkvist M, Lackgren G, Ploen L, Bergh A. Does HCG treatment induce inflammationlike changes in undescended testes in boys? J Pediatr Surg 1993;28:2548.
30. Waldschmidt J, elDessouky M, Priefer A. Therapeutic results in cryptorchidism after combination therapy with LHRH nasal spray and hCG. Eur J Pediatr 1987;146 Suppl 2:S314.
31. Ong C, Hasthorpe S, Hutson JM. Germ cell development in the descend ed and cryptorchid testis and the effects of hormonal manipulation. Pediatr Surg Int 2005;21:24054
32. Li T, Gao L, Chen P, Bu S, Cao D, Yang L, et al. A systematic review and metaanalysis of comparative studies assessing the efficacy of luteinizing hormonereleasing hormone therapy for children with cryptorchidism. Int Urol Nephrol 2016;48:63544.
33. Cortes D, Thorup J, Visfeldt J. Hormonal treatment may harm the germ cells in 1 to 3yearold boys with cryptorchidism. J Urol 2000;
34. Vincel B, Verkauskas G, Bilius V, Dasevicius D, Malcius D, Jones B, et al. Gonadotropinreleasing hormone agonist corrects defective minipuberty in boys with cryptorchidism: a prospective randomized study. Biomed Res Int 2018;

35. Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY, et al. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014;192:33745.
36. Braga LH, Lorenzo AJ, Romao RLP. Canadian Urological Association Pediatric Urologists of Canada (CUAPUC) guideline for the diagnosis, management, and followup of cryptorchidism. Can Urol Assoc J 2017; 11:E25160.
37. Radmayr C, Bogaert G, Dogan HS, Kočvara R, Nijman JM, Stein R, et al. EAU Guidelines on Paediatric Urology 2018. Arnhem (The Netherlands): European Association of Urology; European Society for Paediatric Urology, 2018.
38. Hutson JM, Thorup J. Evaluation and management of the infant with cryptorchidism. Curr Opin Pediatr 2015;27:5204.
39. Steinbrecher H. The undescended testis: working towards a unified care pathway for 2014. Arch Dis Child 2014;99:3978
40. Rajfer J, Handelsman DJ, Swerdloff RS, et al. . Hormonal therapy of cryptorchidism. A randomized, double-blind study comparing human chorionic gonadotropin and gonadotropin-releasing hormone. N Engl J Med. 1986;314(8):466–470
41. Al-Mandil M, Khoury AE, El-Hout Y, Kogon M, Dave S, Farhat WA. Potential complications with the prescrotal approach for the palpable undescended testis? A comparison of single prescrotal incision to the traditional inguinal approach. J Urol.
42. Christiansen P, Müller J, Buhl S, et al. . Treatment of cryptorchidism with human chorionic gonadotropin or gonadotropin releasing hormone. A double-blind controlled study of 243 boys. Horm Res. 1988;30(4-5):187–192] Androl. 1992;15(2):135–143
43. Olsen LH, Genster HG, Mosegaard A, et al. . Management of the non-descended testis: doubtful value of luteinizing-hormone-releasing-hormone (LHRH). A double-blind, placebo-controlled multicentre study. Int 44_moursy EE, Gamal W, Hussein MM. Laparoscopic orchiopexy for non-palpable testes: outcome of two techniques. J Pediatr Urol. 2011;7(2):178–181
44. Baker LA, Docimo SG, Surer I, et al. . A multi-institutional analysis of laparoscopic orchidopexy. BJU Int. 2001;87(6):484–489 []