Cryptorchidism and Fertility

Fatma Fawzy[1], Amr Hussein[2], Mostafa Mahmoud Eid[3], Ahmed Mahmoud El Kashash[2] and Hosni Khairy Salem[4]

[1]Resident, Faculty of Medicine, Zagazig University, Zagazig, Egypt. [2]Student, Faculty of Medicine, Cairo University, Cairo, Egypt. [3]Resident, Faculty of Medicine, October 6 University, Giza, Egypt. [4]Professor of Urology, Faculty of Medicine, Cairo University, Cairo, Egypt.

ABSTRACT: Cryptorchidism, the failure of one or both testes to descend into the scrotum prenatally, occurs in 2.4%–5% of newborns. Many of these testes will descend spontaneously shortly after birth, but ~23% will remain undescended unless surgery is performed. Bilaterally cryptorchid men have a six times greater risk of being infertile when compared with unilaterally cryptorchid men and the general male population. Approximately 10% of infertile men have a history of cryptorchidism and orchidopexy. The main reasons for infertility in men with a history of cryptorchidism treated by orchidopexy are maldevelopment of the testes and an improper environment for the normal development of the testes, hyperthermia, and antisperm antibodies.

KEYWORDS: fertility, undescended testis, cryptorchidism, orchidopexy

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CORRESPONDENCE: dr_hosni@yahoo.com

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Introduction

Cryptorchidism is simply defined as the absence of one or both testes from the scrotum. It is the most common birth defect of the male genitalia.[1,2] Cryptorchidism is considered to be part of testicular dysgenesis syndrome (hypospadias, germ cell tumor, cryptorchidism, and subfertility).[3–5] It occurs in ~1% of infants aged more than three months,[6] and despite being such a common event, the exact cause of cryptorchidism is still unknown.[7] Cryptorchidism could be considered to be a bilateral disease even if only one testis fails to descend properly in the light of claiming certain endocrinal disturbances to cause such maldevelopment, to which both testes will be exposed, which is supported by the finding of the malfunction of the primary scrotal testis in 70% of unilateral cryptorchidism.[8]

Prevalence of Cryptorchidism

The prevalence in full term is ~2%–5%,[9] decreased to 1%–2% within three months, while after six months, spontaneous descent become less likely to occur. This particular observation paves way to watchful waiting strategy for spontaneous descent till the age of six months.[10,11] The prevalence was found to be more in the premature neonates (up to 30%).[9] It seems to occur so frequently that 27,000 boys undergo surgery because of cryptorchidism each year in United States of America.[12] It is noticed that the incidence of cryptorchidism is increasing. This increase may be only due to advances in screening tools with the detection of potential cases that normally could be missed in the past.[6] Environmental factors, which are considered to contribute to the development of the cryptorchidism, might be implemented as a potential cause of increased incidence of cryptorchidism recently. This reason is supported by the finding that the increased incidence of cryptorchidism has been mainly noticed in industrial countries where exposure to harmful environmental materials is expected to be more.[13]

Factors Normally Controlling Testicular Descent

Many hormones such as the Leydig cell-derived hormones, testosterone, and insulin-like factor 3 (INSL3) are suggested to have a role in testicular descent. Also, genetic evidence regarding role of INSL3 in human beings is still recently introduced or investigated, but in animals, there are many evidences about it.[13]

Etiology of Cryptorchidism

Although the definitive etiology of the cryptorchidism is still unknown,[7,13] such anomaly is considered to be multifactorial regarding its etiology as many factors (including endocrinal, environmental, genetic, anatomical, and mechanical factors) may be implemented in the development of such abnormality;[14,15] hence, it is generally considered a complex disease.[13,14]

Endocrinal factors. Many endocrinal factors are suggested to play a role in the development of cryptorchidism. Due to these endocrinal factors, undescended testis may be considered as the most common endocrine disease to affect boys.[16] Some degree of endogenous hormonal abnormality

is suspected in some patients. According to the endocrine disruptor hypothesis theory, the compounds like pesticides with its estrogenic or antiandrogenic effect may cause endocrine disruption and lead to the increased risk of cryptorchidism. This has been observed in the sons of mothers who are exposed to such compounds like diethylstilbestrol, for instance, during pregnancy.[6] It is interesting to mention that, normally, there is a period of hypogonadism in mid-childhood, where previously normal descended testes could raise, which may point to the role of endocrinal environment in maintaining scrotal testicular position.[17]

Environmental factors. Environmental factors might also contribute to the etiology of cryptorchidism and its increased incidence in recent years. Mutations in the gene for INSL3 and its receptor and mutation in the androgen receptor gene could explain a minority of cases of cryptorchidism, but research on genetic polymorphisms that may also influence susceptibility to endocrine disruptors is shedding light on this field.[13]

INSL3 is a peptide-structured secretory product of the Leydig cells that could be considered as a reliable indicator for Leydig cell function and differentiation.[18,19] This peptide is suggested to play a paracrine role in germ cell survival and an endocrine role in bone metabolism.[19] The importance of INSL3 is that it is not affected by negative feedback from pituitary unlike testosterone and so it is an accurate parameter for Leydig cells' dysfunction with an early postnatal peak.[20]

INSL3 is not acutely regulated by the hypothalamic–pituitary–gonadal axis (HPG axis), but it is a constitutive product of Leydig cells, which reflects their number and/or differentiation status and therefore their ability to produce various factors including steroids (Leydig cell functional capacity). Because INSL3 is not subject to the acute episodic fluctuations inherent in the HPG axis itself, it serves as an excellent marker for Leydig cell differentiation and functional capacity, as in puberty, or in monitoring the treatment of hypogonadal patients.[20]

Surprisingly, it was found that in animal fetus, INSL3 is affected by estrogenic compounds. This supports the theory that exposure of pregnant women to endocrinal disruptors could result in the development of cryptorchidism.[20]

Genetic aspect. Genetic aspect of cryptorchidism has been proved in animals; however, in human beings, there is still no evidence or study confirming the genetic relationship.[6] It was found that damaging of INSL3 encoding gene in mice leads to impairment of transabdominal descent of mice testes with subsequent cryptorchidism.[20]

Risk Factors for Cryptorchidism

Birth-related factors. Birth-related factors such as premature birth, low birth weight (<2.5 kg), abnormally decreased maternal estrogen, and insufficiency of the placenta are considered to be risk factors for developing cryptorchidism.[21] In a case–control study, it was found that male children born to obese mothers and those who were born through cesarean section were related to high risk of cryptorchidism.[22]

Environmental factors. Many environmental factors that are chemical in nature are considered to have toxic effects that have the capability to disturb normal endocrinal environment needed for normal testicular descent.[21] Organic chlorines, one of the known popular pesticides,[21] are considered to be one of these toxic compounds. It has been found to be related to testicular dysgensis syndrome. Chemically, these compounds have a very long half-life,[23–25] and it is suggested that toxic effects of these compounds are related to its structure.[21] These compounds are insoluble in water and so accumulate in adipose tissue for a long time.[3]

Complication of Cryptorchidism

Cryptorchidism, even if treated early and successfully, is expected to have long-term consequences[7] such as reduced fertility, depression, and testicular cancer.[6,12]

Testicular carcinoma. Testicular carcinoma mostly seminoma may be considered as one of the most warring expected sequels of cryptorchidism, especially if intervention was done after the age of 12 years.[2] Study in 2005 has documented two hypotheses regarding possible relation between cryptorchidism early in life and potential risk for having testicular cancer diagnosis later on. One of them stated that developing cancer in patients with cryptorchid is related to maternal life style, which includes the exposure to certain pollutants, and it was confirmed by the influence of these factors on fertility. The other one stated that abnormal anatomical position of the testis may predispose to malignant transformation and develop testicular cancer. This was supported by the finding that orchiopexy as early as possible is related to decreased cancer risk.[26] Four other studies found that if orchiopexy was delayed after the age of 10 years, the risk of testicular cancer will be six times higher when compared with surgically corrected cases, so researcher concluded that prepubertal correction possibly could decrease cancer risk.[27] It seems that treatment cannot affect incidence of expected malignancy even if it is successful and not delayed, but it can affect the course by help early detection through facilitating local examination.[7]

A case–control study was carried out on a sample of cryptorchid males aged between 6 and 16 years after surgical intervention. Their research question was about incidence of depression after surgery, which revealed to be higher in patients than in healthy controls. The researcher suggested that warring about natural fertility is one of the factors that expose this category to the risk of depression.[28]

Cryptorchidism and Infertility

Bilateral cryptorchidism versus unilateral cryptorchidism regarding effect on fertility. The study was carried out on a sample of unilateral and bilateral cases of cryptorchidism with a control group and concluded that paternity was

significantly compromised in men with previous bilateral, but not unilateral, cryptorchidism.[29] Also, it was suggested that no difference was noticed between unilateral cases and normal population regarding fertility.[17] However, infertility is more noticed in cases of bilateral undescended testis, with subfertility logically to be with unilateral.[16] This may be explained in the light of evidence that bilateral cryptorchidism causes a significant decrease in spermatogenesis in comparison with unilateral cryptorchidism. However, unilateral cryptorchidism usually has much less impact.[30] A study stated that densities of sperm were noticed to decrease in ~30% of men, with unilateral cryptorchidism,[30] which turned to be only 17% in another two studies.[31] However, in cases of bilateral undescended testis, ~50% of patients show decreased sperm densities.[30] Follow-up of a sample of unilateral and bilateral cases revealed that unilateral cases showed normal rates of paternity and normal concentration of sperms versus only two out of 15 bilateral cryptorchidism cases who finally succeed to have children.[32]

Cryptorchidism, normal spermatogenesis, and early histological changes. Normally, gonadotropin and testosterones must possess a critical surge in the third month of life. This is considered to be so fundamental in development of optimal fertility later, and this seems to be impaired in boys with cryptorchidism.[15,33] It is well stated that three months postnatal, transformation of spermatogonia to adult dark (AD) cells is a very important critical hormone-dependent step, which is closely related to future fertility.[34] In normally descended testis, germ cell must transform to dark spermatocyte, which is considered to be stem cell for spermatocyte, but in nonscrotal testes, this is less likely to occur. In addition, retaining of these cells and not transforming to the dark cells was linked to intratubular carcinoma in situ, which also has enzymatic markers that mimic markers of these primitive calls.[16] In cryptorchidism, it was found that the number of the Leydig cells is reduced and gonocytes take more time to disappear; on the other hand, the appearance of AD cells will be delayed with consequence of delayed appearance of primary spermatocytes with generally reduced total number of germ cells. The authors concluded that the reduced number of these Leydig cells may be related to the detected subfertility through failure of optimal maturation of germ cells.[35] Also tubular and interstitial damage could be detected in early months of life in patients with cryptorchidism.[15]

Risk of azoospermia. It was found that the incidence of azoospermia in unilateral cryptorchidism was 13%, but in untreated bilateral cryptorchidism, it reached up to 89%.[30] It may be related to impaired minipuberty, the surge of gonadotropins, and testosterone that occurs in early infancy.[32]

A study was carried out in which histological changes of early fixed testis were compared with the number of sperms, and it was found that abnormal sperm parameters are expected if adult dark spermatogonia (AD spermatogonia cells) were absent despite early fixation.[36] A study that investigated the presence of antisperm antibody indicates that cryptorchidism may induce formation of autoimmune antibodies against sperms and that it is no more related to site of testis or surgical orchiopexy. However, it could be correlated to age as it was found more commonly in puerperal boys.[37] However, subfertility could be compensated later in life by assisted reproductive techniques, but that at least need testes that still contain living spermatozoa and so development of azoospermia in patients of cryptochidism would cancel that hopeful treatment alternative strategy.[29]

Management of cryptorchidism and how it could affect the fertility. It is well stated that the correction of cryptorchidism is a must;[6] however, some conflicts may be suggested regarding the role of surgery versus medical treatment or dual treatment and also regarding optimal timing of operation.

Timing of surgery in cryptorchidism and its effect on postoperative fertility outcome. In 1975, Ludwig and Potempa found that the fertility rate is inversely proportional to the age of the patient at the time of surgery,[38] and it is recommended to be done between 6 and 12 months of age in order to lower subfertility.[39] This suggestion for early as possible intervention, before 1 year of age, is recommended for the hope of improving fertility; however, there is no sure proof that such a strategy can reduce the risk of testicular cancer.[6] Also undescended testes with no correction till puberty are mostly not expected to function in a way that maintain fertility even after repair.[40,41] A study suggested that some of the patients with elevated level of gonadotropin could benefit from early surgery as elevated gonadotropins indicate testicular dysgenisis.[42]

Surgery alone versus dual approach in management of cryptorchidism. Cryptorchidism is strongly suggested to be related to endocrinal causes to the extent that it is defined as being the most prevalent pediatric endocrine abnormality in boys, and so, the role of hormonal treatment could not simply be omitted.[43] In 2008, a study was carried out in which the sperm parameters of a sample of unilateral cryptorchid males who received Lutenising Hormone Releasing Hormone Analogue (LH-RHa) analog after apparently successful surgery were compared with that of those who underwent surgery alone.[38] It was found that in surgery-only group, all patient have oligospermia and 20% have azoospermia, while in dual treatment, only one have oligospermia and only one noticed to have a diminished sperm concentration.[38] Also LH-RHa treatment for six months was found to increase the number of germ cells in cryptorchid testis[44,45] and also raise the number of germ cells when administrated to boys with cryptorchid after successful surgical interventions.[39] Hormone therapy with GnRH was suggested to create a rise in testosterone levels; this effect suitably matches with the so-called postnatal mini-puberty surge.[34] A study was performed in which 55 patients of unilateral cryptochidism were included to compare the results of dual hormonal and surgical treatment versus surgical treatment alone. Researchers concluded that cases that have an optimal functioning Leydig cells were expected to possess normal testicular histological

structure, especially the count of AD cells, after receiving dual treatment, while defective Leydig function was associated with suboptimal findings.[46] On the other hand, some studies suggested that hormonal therapy is still controversial and seems to be ineffective as a single treatment; however, it may be beneficial as an add-on therapy with surgery.[47]

It could be stated that the role of hormone therapy seems to be still controversial. Even in UK where many workshops recommended dual treatment strategy, hormonal therapy is still not considered as practice to be routinely done.[34] On the other hand, it is suggested that optimal fertility may not be achieved through surgery alone in cryptorchid males.[34]

Who could benefit from postinterventional gonadotropin? A study suggested that hormonal treatment is better to be considered when the biopsy of the undescended testis had no AD cells,[8,42] and this does not contradict with the management of cryptorchidism with both surgery and hormonal therapy together as they have a complementary role.[7] However, it is interesting to mention that hormone replacement could be considered to be the first-line treatment in the management of most cases, but if that strategy fails, it is better to consider early surgery to be performed as soon as possible.[7] Also hormonal treatment performed during the first year of life seems preferable since it can at the same time induce scrotal descent of cryptorchid testes and substitute postnatal gonadotropin insufficiency.[5]

Success of orchiopexy. Success of the surgery to restore normal scrotal anatomy depends on the location of the maldescended testis. In abdominal cases, 85% success occur, but if the testis is low enough to be palpable, the rate will increase up to 90%.[26]

Prognosis of fertility. It is suggested that poor fertility prognosis is possibly linked with decreased germ cell number with still normal level of gonadotropin, which mostly means hypofunction in the hypothalamo-pituitary testicular axis.[42] This will be more evident in patients with bilateral untreated undescended testes, for whom fertility would be greatly affected.[48] Also, it was found that boys with diagnosis of cryptorchidism who lack AD spermatogonia will be infertile despite a seemingly successful orchiopexy at an early age.[36] It is found that intra-abdominal testis that occurs in ~10%–20% of cases[49] has bad histological changes after one year of age, and so, it has a bad prognosis when compared with non-intra-abdominal cryptorchid testis.[50,51]

Parameters that could predict the potential future fertility after orchiopexy. It is so important to be able to decide the fertility potentials in the future, and actually, it may be measured before the surgical intervention. Thorup et al suggested that the number of AD spermatogonia and placental-like phosphatase positive gonocyte, which was measured after testicular biopsy at the time of orchiopexy, could have a significant predictive value of postorchiopexy fertility potentials.[8,52] Also the normal level of gonadotropins and inhibin B and the normal number of germ cells could indicate good future fertility.[42]

Paternity (the proven parameter). Although too many authors found that testicular biopsy at the time of orchiopexy seems to be a good parameter for predicting and assessing future fertility,[38] it is suggested that other more reliable parameters like semen analysis in later life or having a baby are better proofs for actual fertility.[43] However, when comparing paternity to sperm count as an indicator of fertility, it was suggested that paternity is considered more indicative.[17] Actually it is considered to be a retrospective confirmatory parameter, not a predictor, that helps to exclude infertility despite subnormal sperm count.[17,43] And so it is considered a better index for verification than sperm counts since it is known that men with subnormal sperm counts may have normal paternity rates.[17] Long-term follow-up of those cases is considered to be so challenging mission hindered by many factors, for instance in a study which was aiming to follow-up cases during postsurgical state to adulthood to explore fertility potentials was only able to have semen analysis from 20 cases of the total number of 200 cases,[32] that is at least follow-up for one year after hormonal treatment is recommended.[48]

Other treatment potentials. Epidermal growth factor therapy, gene therapy, and stem-cell therapy could be considered to play a role in future management of cryptorchidism.[29] Laparoscopy is considered to be an accurate diagnosing and beneficial therapeutic tool.[49] Actually, it allows both the therapies to be performed in the same setting,[53] so it may be suggested that future research must focus on whether laparoscopy has an advantage than traditional surgery in improving interventional outcome.

Conclusion

We could conclude that condition as cryptorchidism, however, seems to be common but still have no definite etiology. Much evidence relate it to infertility, which seems to be more with bilateral cases. Many management strategies have been suggested; however, different but all focus mainly on preservation of fertility and achieving paternity.

Author Contributions

Conceived and designed the experiments: HKS. Analyzed the data: HKS. Wrote the first draft of the manuscript: FF, AH, MME, AMEK. Contributed to the writing of the manuscript: HKS. Agree with manuscript results and conclusions: HKS. Jointly developed the structure and arguments for the paper: HKS. Made critical revisions and approved final version: HKS. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Serrano T, Chevrier C, Multigner L, Cordier S, Jégou B. International geographic correlation study of the prevalence of disorders of male reproductive health. *Hum Reprod*. 2013;28(7):1974–1986.
2. Wood HM, Elder JS. Cryptorchidism and testicular cancer: separating fact from fiction. *J Urol*. 2009;181(2):452–461.
3. Cook MB, Trabert B, Katherine A. Organochlorine compounds and testicular dysgenesis syndrome: human data. *Int J Androl*. 2011;34(4 pt 2):e68–e84.

4. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod*. 2001;16:972–978.
5. Jørgensen N, Rajpert-De Meyts E, Main KM, Skakkebaek NE. Testicular dysgenesis syndrome comprises some but not all cases of hypospadias and impaired spermatogenesis. *Int J Androl*. 2010;33(298–303):2010.
6. Brucker-Davis F, Pointis G, Chevallier D, Fenichel P. Update on cryptorchidism: endocrine, environmental and therapeutic aspects. *J Endocrinol Invest*. 2003; 26(6):575–587.
7. Mathers MJ, Sperling H, Rübben H, Roth S. The undescended testis: diagnosis, treatment and long-term sequelae. *Dtsch Arztebl Int*. 2009;106(33):527–532.
8. Hadziselimovic F, Hoecht B. Testicular histology related to fertility outcome and postpubertal hormone status in cryptorchidism. *Klin Padiatr*. 2008;220(5): 302–307.
9. Toppari J, Kaleva M. Maldescensus testis. *Horm Res*. 1999;51:261–269.
10. Docimo S, Silver RI, Crome W. The undescended testicle: diagnosis and treatment. *Am Fam Physician*. 2000;62(9):2037–2044, 2047–2048.
11. Berkowitz GS, Lapinski RH, Dolgin SE, Gazella JG, Bodian CA, Holzman IR. Prevalence and natural history of cryptorchidism. *Pediatrics*. 1993;92:44–49.
12. Trussell JC, Lee PA. The relationship of cryptorchidism to fertility. *Curr Urol Rep*. 2004;5:142–148.
13. Ferlin A, Zuccarello D, Garolla A, Selice R, Foresta C. Hormonal and genetic control of testicular descent. *Reprod Biomed Online*. 2007;15(6):659–665.
14. Robin G, Boitrelle F, Marcelli F, et al. Cryptorchidism: from physiopathology to infertility. *Gynecol Obstet Fertil*. 2010;38(10):588–599.
15. de Sanctis C, Lala R, Canavese F. Cryptorchidism, La Pediatria Medicae Chirurgica: Medical and Surgical Pediatrics 1995;17(1):23–28.
16. Cobellis G, Noviello C, Nino F, et al. Spermatogenesis and cryptorchidism. *Front Endocrinol (Lausanne)*. 2014;5:63.
17. Lee PA. Fertility in cryptorchidism. Does treatment make a difference? *Endocrinol Metab Clin North Am*. 1993;22(3):479–490.
18. Ivell R, Heng K, Anand-Ivell R. Insulin-like factor 3 and the HPG axis in the male. *Front Endocrinol (Lausanne)*. 2014;5:6.
19. Ivell R, Wade JD, Anand-Ivell R. INSL3 as a biomarker of Leydig cell functionality. *Biol Reprod*. 2013;88(6):147.
20. Bay K, Andersson AM. Human testicular insulin-like factor 3: in relation to development, reproductive hormones and andrological disorders. *Int J Androl*. 2011; 34(2):97–109.
21. Kaushik P, Kaushik G. An assessment of structure and toxicity correlation in organochlorine pesticides. *J Hazard Mater*. 2007;143(1–2):102–111.
22. McBride ML, van den Steen N, Lamb CW, Gallagher RP. Maternal and gestational factors in cryptorchidism. *Int J Epidemiol*. 1991;20:964–970.
23. Bennett GW, Ballee DL, Hall RC, Fahey JE, Butts WL, Osmun JV. Persistence and distribution of chlordane and dieldrin applied as termiticides. *Bull Environ Contam Toxicol*. 1974;11:64–69.
24. Seegal RF, Fitzgerald EF, Hills EA, et al. Estimating the half-lives of PCB congeners in former capacitor workers measured over a 28-year interval. *J Expo Sci Environ Epidemiol*. 2011;21(3):234–246.
25. Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P. Risk of breast cancer and organochlorine exposure. *Cancer Epidemiol Biomarkers Prev*. 2000;9:271–277.
26. Thorup J, Cortes D. Surgical treatment and follow up on undescended testis. *Pediatr Endocrinol Rev*. 2009;7(1):38–43.
27. Walsh TJ, Dall'Era MA, Croughan MS, Carroll PR, Turek PJ. Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer. *J Urol*. 2007;178(4 pt 1):1440–1446. [discussion 1446].
28. Xi M, Cheng L, Wan YP, Hua W. Incidence of depression and its related factors in cryptorchidism patients after surgical treatment. *Zhonghua Nan Ke Xue*. 2015; 21(1):57–60.
29. Kojima Y, Hayashi Y, Mizuno K, et al. Future treatment strategies for cryptorchidism to improve spermatogenesis. *Hinyokika Kiyo*. 2007;53(7):517–522.
30. Kobayashi H, Nagao K, Nakajima K. Therapeutic Advances in the Field of Male Infertility: Stem Cell Research. *Advanced Studies in Medical Sciences*. 2013;1(1): 39–54. HIKARI Ltd, www.m-hikari.com.
31. Lee PA. Fertility after cryptorchidism: epidemiology and other outcome studies. *Urology*. 2005;66(2):427–431.
32. Fallon B, Kennedy TJ. Long-term follow-up of fertility in cryptorchid patients. *Urology*. 1985;25:502–504.
33. Hadziselimovic F, Zivkovic D, Bica DT, Emmons LR. The importance of minipuberty for fertility in cryptorchidism. *J Urol*. 2005;174:1536–1539. [discussion 1538–1539].
34. Biers SM, Malone PS. A critical appraisal of the evidence for improved fertility indices in undescended testes after gonadotrophin-releasing hormone therapy and orchidopexy. *J Purol*. 2010;6(3):239–246.
35. Huff DS, Hadziselimovic F, Snyder HM III, Blythe B, Ducket JW. Histologic maldevelopment of unilaterally cryptorchid testes and their descended partners. *Eur J Pediatr*. 1993;52(suppl 2):S11–S14.
36. Hadziselimovic F, Herzog B. The importance of both and early orchidopexy and germ cell maturation for fertility. *Lancet*. 2001;358:1156–1157.
37. Sinisi AA, Pasquali D, Papparella A, et al. Antisperm antibodies in cryptorchidism before and after surgery. *J Urol*. 1998;160(5):1834–1837.
38. Hadziselimovic F. Successful treatment of unilateral cryptorchid boys risking infertility with LH-RH analogue. *Int Braz J Urol*. 2008;34(3):319–328.
39. Hadziselimovic F. Höcht B: prospectives. In: Hadziselimovic F, ed. *Cryptorchidism: Management and Implications*. Berlin: Springer-Verlag; 1983:135.
40. Grasso M, Buonaguidi A, Lania C, Bergamaschi F, Castelli M, Rigatti P. Postpubertal cryptorchidism: review and evaluation of the fertility. *Eur Urol*. 1991; 20(2):126–128.
41. Okuyama A, Nonomura N, Nakamura M, et al. Surgical management of undescenced testis: retrospective study of potential fertility in 274 cases. *J Urol*. 1989; 142(3):749–751.
42. Thorup J, Petersen BL, Kvist K, Cortes D. Bilateral undescended testes classified according to preoperative and postoperative status of gonadotropins and inhibin B in relation to testicular histopathology at bilateral orchiopexy in infant boys. *J Urol*. 2012;188(4 suppl):1436–1442.
43. Hanerhoff BL, Welliver C. Does early orchidopexy improve fertility? *Transl Androl Urol*. 2014;3(4):370–376.
44. Hadziselimovic F, Huff D, Duckett J, et al. Treatment of cryptorchidism with low doses of buserelin over a 6-months period. *Eur J Pediatr*. 1987;146(suppl 2):S56–S58.
45. Hadziselimovic F, Hoecht B, Herzog B, Girard J. Does long term treatment with buserein improvemthe fertility chances of cryptorchid testes? In: Labrie F, Belanger A, Dupont A, eds. *LH-RH and its Analogues*. Amsterdam: Elsevier; 1984:457.
46. Zivkovic D, Bica DT, Hadziselimovic F, Bay K, Andersson AM. Relationship between adult dark spermatogonia and secretory capacity of Leydig cells in cryptorchidism. *BJU Int*. 2007;100(5):1147–1149. [discussion 1149].
47. Ong S, Hasthorpe JM, Hutson C. Germ cell development in the descended and cryptorchid testis and the effects of hormonal manipulation. *Pediatr Surg Int*. 2005; 21(4):240–254.
48. Chilvers C, Dudley NE, Gough MH, Jackson MB, Pike MC. Undescended testis: the effect of treatment on subsequent risk of subfertility and malignancy. *J Pediatr Surg*. 1986;21:691–696.
49. Kravarusic D, Freud E. The impact of laparoscopy in the management of nonpalpable testes. *Pediatr Endocrinol Rev*. 2009;7(1):44–47.
50. Hadziselimovic F, Hecker E, Herzog B. The value of testicular biopsy in cryptorchidism. *Urol Res*. 1984;12:171–174.
51. Hadziselimovic F, Hocht B, Herzog B, Buser MW. Infertility in cryptorchidism is linked to the stage of germ cell development at orchidopexy. *Horm Res*. 2007; 68:46–52.
52. Thorup J, Kvist K, Clasen-Linde E, Petersen BL, Cortes D. The relation between adult dark spermatogonia and other parameters of fertility potential in cryptorchid testes. *J Urol*. 2013;190(4 suppl):1566–1571.
53. Argos Rodriguez MD, Unda Freire A, Ruiz Orpez A, Garcia Lorenzo C. Diagnostic and therapeutic laparoscopy for nonpalpable testis. *Surg Endosc*. 2003; 17(11):1756–1758.