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Cryptorchidism and Steroid Hormones

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1. Introduction

Two important functions of testis are production of spermatozoa and synthesis of steroids. These functions depend on anatomical, hormonal and constitutional homeostasis and begin during the first stage of gestation. Cryptorchidism can be defined as an abnormal localization of one or both testes. It's the failure of one or both testes descent into the scrotal sac. The third trimester in humans is crucial for the testis descent. When the testis is not found in normal location it may be palpable or nonpalpable. The palpable testis may be cryptorchid, ectopic or retractile. Non-palpable testis may be cryptorchid, atrophic or absent. Cryptorchidism occurs when the testis fails to descend into its normal postnatal location and may be found in the abdomen, in the inguinal canal or just reaching the external ring (prescrotal) (Nguyen 1999). Before sex determination, both female and male embryonic gonads are located in the same high intra-abdominal position. During mammalian development, the cranial suspensory ligament (CLS) and the caudal ligament (or gubernaculum) is responsible for a sexual dimorphic position of the testis and ovary. In males, regression of the CLS, along with the outgrowth of the gubernaculum and its migration to the scrotum, results in the extraabdominal position of the testis (AgoulNIK 2005). Androgens induce regression of the cranio-suspensory ligament to release the testis to descent. The inguinoscrotal descent of the normal testicle takes place between 26 and 35 weeks of gestation. In preterm males with cryptorchidism the testes may descend postnatally (Berkowitz 1993, Cortez 2008). Cryptorchidism is one of the most common urogenital disorders in boys. Cryptorchidism can occur as an isolated disorder or may be associated with other congenital anomalies. The intraabdominal temperature is dangerous for germ cells and cryptorchidism may be a risk factor for male infertility and for testicular malignancy in adulthood. The decrement in intratesticular temperature in adult males is 2-4°C lower compared with body temperature (Thonneau 1998). This temperature difference is necessary to maintain spermatogenesis. The lower temperature in the scrotum is essential for normal spermatogenesis. Dangerous effects of increased temperature on spermatogenesis are well documented. For undescended testis abnormal spermatogenesis may be related with degenerative changes connected with high temperature (Mieussed 1993). This condition affects both morphology and function of the Sertoli and Leydig cells of the testis (Farrer 1985) The association of cryptorchidism with testicular cancer is also well

documented (Giwerzman 1989). The prevalence of cryptorchidism among boys is 2-4% in full - term male birth and 2-8.4% among boys with premature births. The incidence of cryptorchidism is significantly increased in premature males (Berkowitz 1993). Presently we observe an increased trend in the incidence of congenital cryptorchidism. Sometimes statistics includes testis in a high scrotal position (as normal descent) or cryptorchid testis may spontaneously descent in the first months after birth, therefore the incidence of cryptorchidism decreases from 1% to 0.5% by age of 1 year due to spontaneous descent (Barthold 2003). In earlier studies it has been speculated that the late spontaneous testicular descent occurs in more than half (Boisen 2004) or 70% of newborns with cryptorchidism. On the contrary the data obtained by Wenzler et al. (Wenzler 2004) showed that in patients with cryptorchidism spontaneous testicular descent occurs infrequently during the first year of life. They found that in patients with cryptorchidism before 12 months only 6.9% of the cryptorchid testicles reached the acceptable scrotal location at age of 1 year or later (Wenzler 2004). There are large regional differences in incidence of cryptorchidism. The study on the prevalence of congenital cryptorchidism in Denmark and Finland was also performed and much higher incidence of congenital cryptorchidism in Denmark was found. In Denmark an increase in reproductive health problems is explained by environmental factors, including endocrine disrupters and a lifestyle (Boisen 2004). In the meantime the incidence of cryptorchidism has increased in many countries. In two comparable British studies the incidence of cryptorchidism delivered at term boys approximately doubled between the 1950s and the 1980s. (Toppari 2001). However the report by Cortes (2008) has shown that the incidence of cryptorchidism in Denmark has not changed and is similar to the previous reports obtained in the 1950s. They have pointed out the general difficulties to compare the frequency of cryptorchidism as reported in different publications, since the definition of cryptorchidism is not yet uniform (Cortes 2008). The International Clearinghouse for Birth Defects Monitoring System has collected data on cryptorchidism, but they are unreliable, because of a discrepancy with the data from cohort studies (Toppari 2001). The present incidence may be even higher than reported one because of under-reporting tendency (Kaleva 2005).

Cryptorchidism is a risk factor for male infertility in adulthood and for the male health (testicular cancer). Cryptorchidism uni- or bilateral is associated with degenerative changes in Sertoli cells and germ cells and is the most common etiologic factor of azoospermia (Hadziselimovic 2001). 89% of untreated cryptorchid patients with bilateral maldescent develop azoospermia and 32% treated medically or 46% boys treated surgically develop azoospermia (Hadziselimovic 2001). Hormonal treatment with human chorionic gonadotropin (HCG) or gonadotropin releasing hormone may be given initially for cryptorchidism. Very often a surgical intervention is needed to protect function of seminiferous tubules and to prevent degenerative changes in Sertoli and germ cells saving the man's future fertility potential.

2. Pathogenesis of cryptorchidism

The etiology of cryptorchidism remains mostly unclear (Foresta 2008). The main risk factor is preterm birth, low birth weight, disrupted endocrine regulations, several gene defects and environmental factors (endocrine disruptors). Preterm birth and small size for gestational age are risk factors for cryptorchidism (Pierik 2004). Cryptorchidism is considered to be indirectly related to birth weight. The incidence of cryptorchidism is about 20-25% in infants

with birth weight less than 2.5 kg (Scorer 1964). Androgens play a crucial role in the development of male external genital organs and testicular descent. Hormonal dysregulation can be one out of many etiological factors of cryptorchidism (Suomi 2006). Testicular descent is at least partly dependent on fetal testicular testosterone, which in turn is initiated and maintained by human chorionic gonadotropin produced by the placenta (Biggs 2002). An increased risk of cryptorchidism in cases with placental abnormalities is noted (Biggs 2002). The increasing incidence of reproductive abnormalities in human males may be associated with increased estrogen exposure during gestation. The increased expression of estradiol in the syncytiotrophoblast may have impact on testicular descent (Hadziselmovic 2000). Industrial and agricultural chemicals acting as endocrine disrupters might have a deleterious effect on normal male sexual differentiation. These chemicals may occur in our close environments of work and life, drinking water, a food. Humans can also be exposed to natural phytoestrogens through consumption of food products derived from the plants (Toppari 1996, Sultan 2001). Various groups of chemicals, including pesticides and phthalate esters, have been identified as being weakly estrogenic or antiandrogenic (Sharpe 2003). Ferlin has proposed a distinction between intrinsic and extrinsic causes of cryptorchidism. In the first group frequently displayed bilateral cryptorchidism is associated with progressive testicular damage and increased risk of infertility or testicular damage. In these cases early orchidopexy may reduce the risk of these consequences but does not eliminate it definitely. Genetic alterations are more frequent in this group (Klinefelter syndrome, RXFP2 gene mutations) (Ferlin 2008). In the group with extrinsic causes of cryptorchidism (low birth weight, prematurity, maternal diabetes or preeclampsia during pregnancy) a spontaneous descent in the first months of age is noted. The early orchidopexy can reduce almost completely risk of testicular damage (Trisnar 2009). The possible genetic background of cryptorchidism still remains unresolved and genetics causes are rarely found (Ferlin 2008).

The following genetic abnormalities may be associated with cryptorchidism:

- mutations in the gene coding for insulin-like factor 3,

The mutation R102C was detected in a boy with unilateral persistent cryptorchidism (Ferlin 2008). The other mutation (T86M) was detected in a boy with bilateral cryptorchidism and spontaneous descent in the first months of age (Ferlin 2008).

- mutations in INSL3 receptor gene (RXFP2).
- mutations in the gene coding for receptor for insulin-like factor 3, INSL3/LGR8,
- mutations in the androgen receptor gene,
- chromosomal alterations in Klinefelter syndrome.

Familial occurrence – cryptorchidism is heritable susceptibility.

Seasonal variation in the incidence of cryptorchidism suggest that environmental factors may have the importance in its etiology. Cryptorchidism can be often the consequence of testicular dysgenesis, a developmental disorder of the gonads due to disruption of embryonal programming and gonadal development during fetal life. Testicular dysgenesis syndrome (TSD) can result in maldescent, reduced fertility and an increased risk for malignant development, increased frequency of incomplete descent of a testis into the scrotum and hypospadias (Skakkebaek 2001). TSD can arise due to environmental factors including endocrine disruptors (potential endocrine disruptors in diet, in place of occupation; lifestyle, dietary phytoestrogens, present in food, water, air) or genetic defects.

The contralateral testis in men with unilateral testis cancer (Berthelsen 1983) or unilateral cryptorchidism (Kaki 1999) can be often damaged as well. There is also clear confirmation of testicular dysgenesis syndrome. Fetal exposure to endocrine disruptors (EDs) with estrogen-like or antiandrogen-like activity has been suggested as a cause for TDS (Sharpe 1993).

Environmental or genetic defects can influence Leydig cell function and result in androgen insufficiency which may cause testicular maldescent (Skakkebaek 2001).

Uterine exposure to environmental endocrine disruptors can have also deleterious effects on male reproductive system development in embryos. Environmental endocrine disruptors (EEDs) are defined as exogenous substances which can disrupt endocrine homeostasis and reproduction. EEDs include xenoestrogens, synthetic hormones, natural hormones or substances affecting endocrine signaling (Vidaeff 2005).

Chemicals have been found to possess either weak estrogenic, anti-androgenic or other hormonal activities, which are often referred to as endocrine disrupters. Fetal or perinatal exposure to endocrine disrupters results in disturbed sexual differentiation, urogenital malformations and decreased reproductive health in adult life (Sharpe 1993).

The significantly increased risk of bilateral cryptorchidism in boys whose mothers smoked heavily during pregnancy may indicate that heavy maternal smoking can be included in the pathogenesis of cryptorchidism (Throup 2005). Altered hormonal levels in smokers may have a casual role in cryptorchidism. Paternal pesticide exposure may be also associated with cryptorchidism. The investigation of circulating androgens bioactivity in 3-month-old boys suggests that infant boys are exposed to biological effects of androgens during the postnatal activation of the hypothalamic-pituitary-testicular axis, and the degree of the exposure may result in testis location superior to the scrotum (Raivio 2003)

3. Hormonal regulation of testicular descent

Testicular descent is hormonally regulated. Regulation of testicular descent is not yet completely understood. There are various forms of cryptorchidism (congenital with or without spontaneous descent, mild versus severe, acquired). These forms may reflect distinct hormonal patterns which differ in each situation (Suomi 2006). Apart from anatomical configuration and hormonal stimulation, genetic control of testis descent is very important. Major regulators of testicular descent are insulin-like factor 3 and testosterone. Testes migrate from initial intraabdominal position into the scrotal sac in two distinct hormonally regulated phases. During the first transabdominal phase (androgen independent) (10-23th week gestation) the CLS (cranial suspensory ligament) regresses while the gubernaculum shortens and develops caudal segment into the gubernaculum bulge. The second inguinoscrotal phase (depends on androgens) is normally completed by the 35th week – the gubernaculum extends caudally into the scrotum and involutes, following the passage of the testis through the inguinal canal.

The first phase of testis descent (transabdominal) is regulated essentially by insulin-like factor 3 (INSL3), a peptide, product of the pre- and postnatal Leydig cells. INSL3 controls the passage through its receptor Lgr8 (leucine-rich-containing repeats G protein-coupled receptor). Genetic disruption of the *Insl3* gene or its receptor (*Lgr8*) in mice has led to high intraabdominal cryptorchidism (Adham 2004). In the second phase (inguinoscrotal) androgens (testosterone) are the major mediators of testis descent (Foresta 2008). The inguinoscrotal phase is at least partly dependent on fetal testicular testosterone secretion, which in turn is initiated and maintained by human chorionic gonadotropin produced by

placenta. In mutation analysis of the human homologs of INSL3, LGR8 or HOXA10 genes in patients with cryptorchidism there were rarely found mutations or polymorphisms (Bogatcheva 2005, Bertini 2004).

For a normal descent and testicular development of the testes, a normal hypothalamo-pituitary-gonadal axis is essential. Certain androgens:estrogens ratio is required for physiological function of the testis. Steroid hormones act through specific receptors: ARs, ER α , ER β .

Insl-3 is under estrogenic control. Mutations in insl-3 gene showed a low incidence at 1.3% in patients with cryptorchidism. Estrogens may affect insl-3 expression and may have a role in regulation of testicular descent (Tomboc, 2000).

Androgen receptors (ARs) mediate the biological effects of both T and 5 α -dihydrotestosterone. AR mutations are not a frequent cause of isolated cryptorchidism (Ashim 2004, Ferlin 2006, Ferlin 2008). AR mutations in men with history of cryptorchidism are connected rather with infertility. The AR is highly polymorphic due to a glutamine repeat (CAG) and a glycine repeat (GGN). Polymorphic CAG and GGN segments regulate AR function. A clear associations were observed between shorter CAG repeats and disorders dependent on enhanced androgen action. Longer CAG repeats have been associated with undescended testes, idiopathic hypospadias and decreased sperm counts. In result of combined analysis of CAG and GGC repeat lengths the stronger association with cryptorchidism was found (Ferlin 2005). The CAG repeat length has been also assessed in males with cryptorchidism, but no association between CAG repeat length and undescended testes was found in Japanese population (Sasagawa 2000) or Caucasian population (Aschim 2004). It was indicated rather association between GGN length and cryptorchidism or hypospadias (Aschim 2004). Median GGN lengths were significantly higher (24 vs. 23) among subjects with cryptorchidism, compared with controls and subjects with hypospadias. GGN length 23 is the most prevalent in males from general population. A majority of individuals with cryptorchidism demonstrated GGN numbers of 24 or more (Aschim 2004).

4. Hypothalamic-pituitary-testicular axis

Androgens regulate testicular descent, but androgen action alone is not sufficient for normal testicular descent. A proper hypothalamus-pituitary-testis axis function together with normal synthesis and action is a prerequisite for normal testicular descent. Various defects in this axis may result in cryptorchidism (Toppari 2007). Regulation of androgen production depends on hCG (placental human chorionic gonadotropin) and LH (pituitary luteinizing hormone) actions. INSL3 (insulin-like hormone-3) is the main regulator of gubernaculum development and testicular descent. Reduced levels of INSL3 may cause cryptorchidism (Toppari 2007). INSL3 production is also related to LH levels. Cryptorchid boys have normal testosterone and elevated LH levels (Toppari 2007). The first postnatal months of boys are characterized by activation of the hypothalamic-pituitary-testicular axis that results in the well depicted surge of reproductive hormones. Serum testosterone levels at that time are high, but infants do not display signs of virilization, and subsequently there is only indirect evidence that circulating androgens during the surge are biologically active. Three-month-old boys are exposed to biological effects of androgens during the postnatal activation of the hypothalamic-pituitary-testicular axis, and this exposure may be reduced in boys with at least 1 testis located superior to the scrotum. Functional integrity of the HPG

axis is fundamental for testicular descent. Gonadotropin-releasing hormone (GnRH) regulates the production of pituitary gonadotropins FSH and LH. Gonadotropins FSH and LH are the main regulators of postnatal testicular activity. LH stimulates Leydig cells to produce testosterone while FSH regulates Sertoli cell functions (Toppari 2006). Human fetal testis binds hCG and physiological levels hCG stimulate testosterone production at least from 14 weeks of gestation (Huhtaniemi 1977). LH becomes more important regulator of fetal testosterone synthesis in the late pregnancy (Quinton 2001). The high percentage of cryptorchidism cases resolves spontaneously during the period of high serum gonadotropin and steroid hormone levels at the age of 1-3 months (Anderson 1998).

Testosterone is one of the main regulators of testicular descent. It is the main androgen in the circulation, mainly protein-bound, either strongly to sex hormone binding globulin (SHBG), or loosely to albumin. Only about 2% of this hormone is unbound; this is called free testosterone and is considered to be the most biologically active form of testosterone. In the target tissue testosterone can either bind directly to the androgen receptor (AR) or, if the tissue expresses the enzyme 5 α -reductase, can be converted to dihydrotestosterone (DHT). Testosterone is produced by Leydig cells and low testosterone level is a consequence of a reduced ability of the Leydig cells to synthesize T.

Impaired testosterone biosynthesis or distinct increase in testosterone metabolism is observed in cryptorchidism. Aromatase may convert androgens into estradiol. Testosterone is converted by aromatase CYP 19 to estradiol in many tissues of healthy men. The development of internal male genitalia is testosterone dependent, and 5 α -dihydrotestosterone (synthesized from T by the enzyme 5 α -reductase 2) is essential for normal external masculinization. DHT is produced from circulating testosterone, which is manufactured by the fetal testis under stimulation of hCG.

Estrogens Estrogens are necessary for maintaining functional integrity of the male reproductive tract. Estrogens and ER α are important for fertility. Excess of estrogens can affect function of the cells of male reproductive system. The excess of estrogens was reported to be associated with cryptorchidism, epididymal defects, impaired fertility. Estradiol however is an essential hormone for male reproduction. The maternal and placental estradiol is elevated in children with cryptorchidism. The increased expression of estradiol in the syncytiotrophoblast may have an impact on testicular descent (Hadziselmovic 2000). Low estrogen levels in mothers may mean that a placental defect increases the risk of cryptorchidism (Mc Glynn 2005). Estrogens are synthesized in the male reproductive system by at least four different cell types: Leydig cells, Sertoli cells, germ cells and epithelial cells of the epididymis. Estrogens are synthesized in a cortex of the adrenal gland, too. In the immature testis, the main source of estrogens are Sertoli cells.

In horse and mouse *in vivo* cryptorchidism is associated with the increase in conversion of androgens to estrogens in the testis (Hejmej 2008), epididymal duct and the prostate. Increase in testosterone metabolism rather than an impairment of testosterone production is proposed to explain incidence of cryptorchidism. Testicular descent is significantly inhibited by estradiol. The estrogen effect might be mediated through suppression of fetal Leydig cell development, with resulting decrease of androgens and INSL3 production.

5. Estrogen receptor α , ERs

The association of cryptorchidism with a specific haplotype of the estrogen receptor 1 gene was reported (Yoshida 2005). The specific haplotype AGATA located within the 3' end of

human ESRI1 is associated with cryptorchidism in the Japanese population. The AGATA haplotype was frequently found to be significant in cryptorchid children. Homozygosity for the AGATA haplotype was found only among cryptorchid boys (Yoshida 2005). ER α and PR (progesterone receptor) expressed in paratesticular tissues are important for normal testicular descent. ER α was overexpressed in boys with undescended testis previously treated with human chronic gonadotropin (Przewratil 2004).

The analysis of the whole AGATA haplotype is possible by testing only the SNP12 (the tag SNP for the AGATA haplotype). Results obtained by Galan indicated that SNP 12 is the tag SNP for the AGATA haplotype also in Caucasians, but is not connected with cryptorchidism and infertility. Surprisingly ESR1 SNP12 may have a protective effect on cryptorchidism in the Italian populations, since it was found more frequently among healthy populations (Galan 2007).

Progesterone influences spermiogenesis, sperm capacitation/acrosome reaction and testosterone biosynthesis in the Leydig cells. The detection of progesterone receptor (PR) isoforms have a diagnostic value in prostate cancer (Oettel 2004). The position of the undescended testis did not appear to influence progesterone metabolism (Läckgren 2008). PRs density was higher in paratesticular tissues (cremaster muscle and processus vaginalis) obtained from boys with undescended testis compared to the control group (Przewratil 2005)

6. Steroid hormones, male immune system and reproductive system

Steroid hormones especially testosterone, progesteron and estradiol can modulate the immune system. The relationship between the immune system and reproduction is very strict. The immune response may be involved in reproductive processes what may interfere with fertility. A role of estrogens and testosterone in (auto)antibody production was proved. Estrogens increase, while testosterone decreases antibody production. Immune disorders have been formulated to take part in etiology of cryptorchidism.

The significant associations of cryptorchidism with HLA class I antigens were found. Some associations of HLA class I alleles (HLA-A11, A23, A29) with cryptorchidism were explained by their crossreactivity with receptors for LH and hCG present on fetal Leydig cells and/or interference with the hormone-binding sites through a mechanism of "molecular mimicry" (Martinetti 1992). Most likely the "molecular mimicry" between hormonal receptors and HLA surface antigens may also play a role in etiopathogenesis of cryptorchidism. The human major histocompatibility complex class II HLA molecules, by presenting antigens to helper T cells, play a decisive role in induction of antibody production (Chen 2008). Antisperm antibodies (AsA) in serum samples from prepubertal boys with testicular failure were substantially reported (Lenzi 1991, Kurpysz 1996, Sinisi 1998). We have investigated the frequency of HLA class II alleles to recognize possible genetic predisposition for antisperm antibodies development in prepubertal boys with diagnosed cryptorchidism. We have found, a strong correlation between the presence of some HLA-antigens in patients with unilateral and bilateral cryptorchidism, and a formation of antisperm antibodies. We have observed that boys suffering from bilateral cryptorchidism differed from controls in their HLA-DRB1*11 frequency. Associations of cryptorchidism with some HLA-DRB1 and HLA-DQB1 alleles, very rare in Caucasians, were described only for a Japanese population (Tsuji 2000). No correlation with HLA class II polymorphism, however, was observed in a study of Italian population. We have observed strong difference between

cryptorchidism with history of infertility within these families and healthy controls, showing a high risk for HLA-DRB1*11 bearers. This result may suggest that sporadic and familial cryptorchidism may have different genetic background. HLA-DRB1*11 was also, albeit weakly, associated with bilateral cryptorchidism. Predisposition to produce anti-sperm antibodies seems to be only weakly associated with HLA class II genes.

Autoimmune reactions, particular directed to testicular elements and/or spermatozoa have been found to be often associated with cryptorchidism. Antisperm immunization has been proposed as possible additional factor associated with late surgery in prepubertal boys with cryptorchidism. Cryptorchidism in young boys can induce immune reactions against sperm-specific antigens. Future fertility status thus may be endangered, because antisperm antibodies can impair fertility at different levels. The relationship between the presence of antisperm antibodies and male infertility has been documented in large number of earlier studies (Krause 2009). There are some reports on high frequency of antisperm antibodies (AsA) in infertility patients who have suffered in the past from cryptorchidism. In healthy men seminiferous epithelium is anatomically sequestered from the systemic immunity. There exist multiple elements of active tolerance. An increased ability for induction of antisperm antibodies in men has been observed in various testicular pathologies: varicocele, testicular torsion, vasectomy and genital tract infections. An induction of antisperm antibodies in adult males may take place because of a break in the anatomical “blood-testis” barrier or because of the failure of an immunosuppressive mechanism providing tolerance to sperm. Sometimes, such antibodies can arise without a known reason. Pathologic conditions within the urogenital tract may predispose to antisperm antibody formation. In prepubertal boys, testicular failures may cause an activation of destructive to testes humoral immune response, because the anatomical testicular barrier is then not completely formed and immunosuppression not fully activated due to the absence of male germ cells. Diminished levels of testosterone observed in prepubertal boys may be an additional reason for inefficient immunosuppression at young age and may contribute to the rise of autoantibody development (Jones 1994). It is difficult to argue whether it is mainly anatomical sequestration or rather active immunosuppression playing a dominant role in preserving intact spermatogenic differentiation. It was earlier reported that 20-60% of individuals with a history of maldescended testis have circulating antisperm antibodies and most of them demonstrates oligoasthenozoospermia (Urry 1994). Evaluating the immune status of prepubertal boys with testicular failures, we have previously found detectable levels of AsA predominantly in boys with pathology of both gonads (Kurpisz 1996). One possible explanation for the induction of immune response to spermatozoa (testis) may be an increase of testicular temperature in boys with cryptorchidism, which may initiate the degenerative changes in spermatogenesis and alter testicular functions. A unique exposure of membrane antigens on testicular cells can be thus noted. Changes in the Leydig cells function may provoke the disturbances in the levels of locally secreted hormones, e.g. diminished levels of testosterone. Altogether, this multifactorial machinery may create a “vicious circle” that will perpetuate intratesticular inflammation leading to the inhibition of spermatogenesis that was to be triggered at the onset of puberty.

7. Final remarks

Cryptorchidism is one of the most common urogenital disorders found in postnatal boys. Main predisposing factor are: preterm birth, dysfunctional endocrine regulations, gene

defects and environmental factors (endocrine disruptions). It is believed that testicular descent is hormonally regulated and although genetic contribution is observed, the number of genes/mutations responsible for testis descent is relatively rare. Changed environment in testis located in abdomen may induce pathological reactions mainly resulted in immune response induction. This, however, seems to be a secondary phenomenon. Despite this, once triggered immune response may persist and underlie future infertility in adulthood. Early surgical intervention in cryptorchidism can be therefore recommended.

8. References

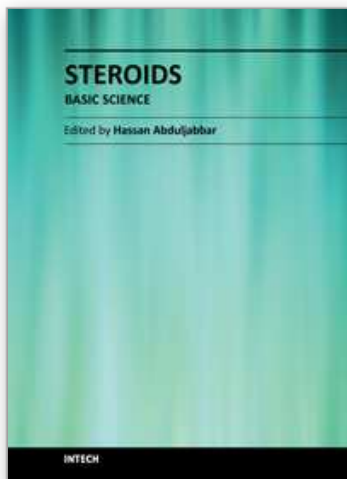
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Steroids - Basic Science

Edited by Prof. Hassan Abduljabbar

ISBN 978-953-307-866-3

Hard cover, 234 pages

Publisher InTech

Published online 11, January, 2012

Published in print edition January, 2012

This book explains the basic science of steroids and is targeted towards professionals engaged in health services. It should be noted that medical science evolves rapidly and some information like the understanding of steroids and their therapeutic use may change with new concepts quickly. Steroids are either naturally occurring or synthetic fat-soluble organic compounds. They are found in plants, animals, and fungi. They mediate a very diverse set of biological responses. The most widespread steroid in the body is cholesterol, an essential component of cell membranes, and the starting point for the synthesis of other steroids. Since the science of steroids has an enormous scope, we decided to put the clinical aspects of steroids in a different book titled "Steroids-Clinical Aspects". The two books complete each other. We hope that the reader will gain valuable information from both books and enrich their knowledge about this fascinating topic.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Marzena Kamieniczna, Anna Havrylyuk and Maciej Kurpisz (2012). Cryptorchidism and Steroid Hormones, Steroids - Basic Science, Prof. Hassan Abduljabbar (Ed.), ISBN: 978-953-307-866-3, InTech, Available from: <http://www.intechopen.com/books/steroids-basic-science/cryptorchidism-and-steroid-hormones>

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