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# The role of hormone in male genital abnormalities: Understanding the link between hypospadias and cryptorchidism

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**Abstract**
This study was conducted to understand the role of androgens (testosterone, dihydrotestosterone, and dehydroepiandrosterone) in addition to estrogen and their effect on the growth of the male reproductive organs and the relationship of these hormones, in the event of their decrease or increase, to deformities of the male reproductive system organs during fetal development or after birth. The study included 45 male children aged from 6 months to 12 years from Mosul city. They were divided into three groups. The first group included 15 children who did not suffer from this type of deformity and had no family history of this defect. They were used as a control group. The other group included 15 children who suffered from cryptorchidism and 15 children who suffered from hypospadias.
**Result:** Decreased levels of both testosterone and DHT and increased levels of DHEAS and estrogen in children with these abnormalities.

**Keywords:** Genital abnormalities, androgens, estrogen

## Introduction
Congenital abnormalities or malformations are structural or functional disorders that occur during the period of fetal developmental and can be detected during prenatal care, delivery, or after birth (Junior *et al*.,2017) [7]. Studies have shown that the rate of congenital malformations is widespread, and the genitourinary system was the most common system in terms of congenital malformations, followed by the musculoskeletal system and then the cardiovascular system (Shrestha *et al.,* 2020) [13]. Cryptorchidism and hypospadias are among the most common male genital abnormalities. Air pollution is one of the biggest problems in developing and developed countries, as there are many environmental factors such as radiation, heat and chemicals that affect the reproductive system of various living organisms and may contribute to genetic defects that are passed down through generations (Yasir, Janan.,2018). The development of the reproductive organs in the early embryonic stages is under the influence of several hormones, This specialized and unique hormonal environment results in the differentiation of the male and female reproductive organs (Kinter *et al*., 2023) [8]. Androgen deficiency or androgen resistance leads to the failure of the midline between the folds of the urethra and the scrotum to fuse, leading to hypospadias (Bhat.,2022) [3]. Androgens are endogenous steroid hormones that include DHEA, testosterone, and DHT. In males, testosterone, anti-Mullerian hormone, and dihydrotestosterone inhibit the development of female reproductive organs, while these hormones promote the development of male reproductive organs (Kinter *et al*.,2023) [8]. Testosterone also participates in the regulation of secondary male characteristics, such as the appearance of facial hair and voice changes (Nassar *et al*., 2018) [10], Leydig cells secrete testosterone under the influence of HCG, which is secreted from the placenta during the 60 days of embryonic development and is converted by an enzyme into dihydrotestosterone, which plays a crucial role in the formation of the external genitalia (penis, scrotum, and testes) (Farraj *et al*.,2017) [5] Testosterone level disturbance affects semen quality(Shaya *et al*.,2013).DHT is also considered one of the most important androgens and is classified as a pure androgen because it does not convert to estrogen. DHT is primarily produced in the peripheral tissues of the body that are affected by it and is present in small quantities in the circulatory system. The testicles continue to grow normally but fail to descend into the scrotum due to a deficiency in the hormone DHT. Patients suffer from an increase in the production of the hormone testosterone that is not converted from the testicles, which leads to the development of many secondary sexual characteristics (Kinter *et al*., 2023) [8]. While DHEA is a steroid hormone derived from cholesterol and is itself an intermediate for sex hormones such as estradiol and testosterone, it is found in the bloodstream as its sulfate ester (DHEA-S) (Jia *et al*.,2020) [6]. Estrogen is classified as a steroid hormone, it is primarily synthesized and secreted by the ovaries and placenta in mammals, it regulates the differentiation of the sex organs and contributes to the development of the reproductive system, furthermore estrogen exhibits physiologic functions in non-reproductive tissues and organs, including the cardiovascular, nervous, immune, and musculoskeletal systems (Kenta Yoh *et al*., 2023) [15]. Estrogen comprises three types: estrone (E1), estradiol (E2), and estriol (E3), (Xu *et al*., 2022) [14]. Low levels of estriol E3 in the second trimester examination may lead to Down syndrome, congenital malformations, some fetal hormonal disorders, or even fetal death (Yönetilir *et al*., 2022) [16].

## Material and Methods
### Study Area
This research was carried out in the Department of Biology/ Faculty of Science/ University of Mosul, Iraq.

### Experimental Design
The study included 45 male children aged from 6 months to 12 years with a body mass index ranging from 6 kg to 50

kg. The subjects were stratified into three cohorts of 15 individuals each, as follows:

1. Group 1 served as the control group Those who do not have a family history of the disease.
2. Group 2 included patients who have cryptorchidism.
3. Group 3 included patients who have hypospadias.

Biological samples were collected from the patients and their clinical status was monitored over a period of four months. Patients with chronic diseases such as hypertension, animia, diabetes, and cardiovascular diseases were excluded from the study.

**Sample Collection**

Blood samples were collected to determine the levels of testosterone, dihydrotestosterone, dehydroepiandrosterone, and estrogen from the serum of children with cryptorchidism and hypospadias to determine the increase and decrease in the levels of these hormones that affect the nature of the development of the male reproductive organs in children. About 3 ml were drawn into) gel tubes and then left to clot at room temperature and then separated in a centrifuge at speed of 3000 rpm for 15 minutes to obtain the serum used for the required analyses.

**Result**

There are 45 patients, and values are presented as mean and standard deviation. At the probability level (P≤0.05), shapes and various letters indicate a significant difference.

Figure (1): It shows a decrease in testosterone concentration in the group of patients with hypospadias and the group of patients with cryptorchidism compared to the control group. The mean and standard deviation of testosterone in the hypospadias group was (2.4 ± 0.12) ng/dL, the mean and standard deviation of testosterone in the cryptorchidism group was (1.6 ± 0.03) ng, while the mean standard deviation of testosterone in the control group was (32.7 ± 2.4) ng/dL.

Figure (***2***): It shows an increase in the concentration of the hormone DHEA in the group with hypospadias and in the group with cryptorchidism compared to the control group.The mean and standard deviation of DHEA in the hypospadias group was (2.4±0.2) ng/dL, and the mean and standard deviation of DHEA in the cryptorchidism group was (1.7±0.5) ng, while the mean and standard deviation of DHEA in the control group was (1.2±0.04) ng/dL.

Figure (3): It shows a decrease in the level of DHT in the group with hypospadias and in the group with cryptorchidism compared to the control group. The mean and standard deviation of DHT in the hypospadias group was (19.7±1.5) ng/dL, the mean and standard deviation of DHT in the cryptorchidism group was (41.5±6.4) ng, while the mean and standard deviation of DHT in the control group was (45.7±4.6) ng/dL.

Figure (4): It shows an increase in the level of estrogen in the group with hypospadias and in the group with cryptorchidism compared to the control group. The mean and standard deviation of estrogen in the hypospadias group was (258±31.1) ng/dL, the mean and standard deviation of estrogen in the cryptorchidism group was (430± 16.2) ng, while the mean and standard deviation of estrogen in the control group was (163± 13.8) ng/dL.

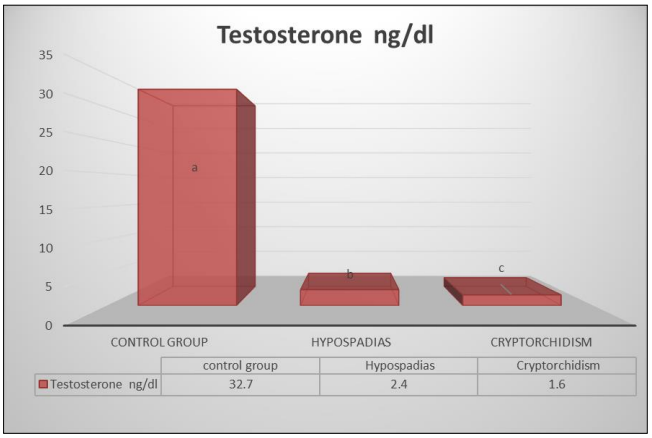


**Fig 1:** Show Testosterone Hormone Level

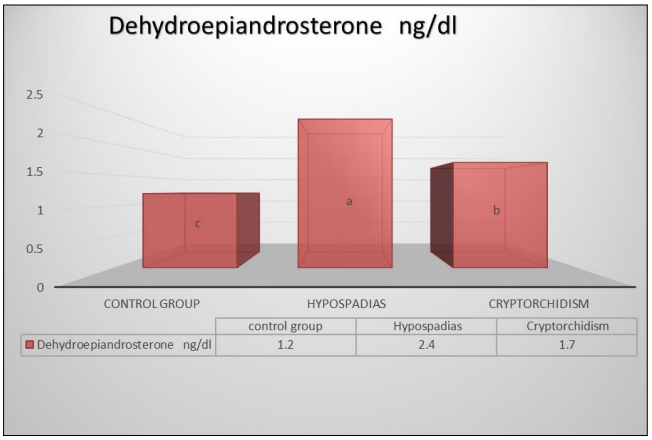


**Fig 2:** Show Dihydroepiendrosterone Hormone Level

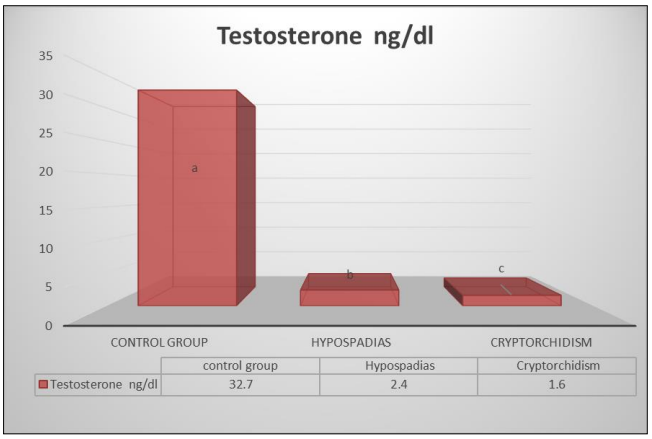


**Fig 3:** Show Dihydrotestesterone Hormone Level

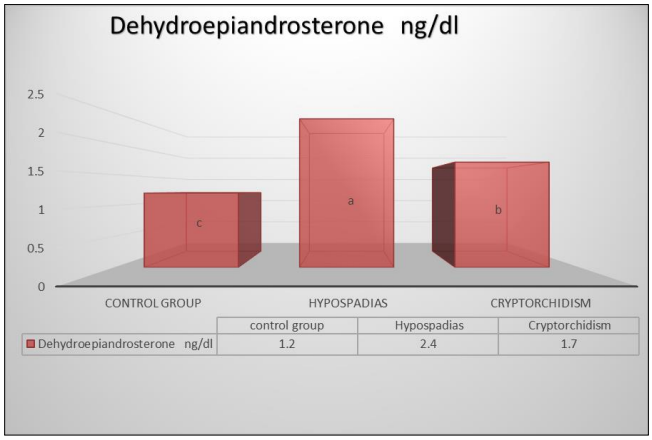


**Fig 4:** Show Estrogen Hormone Level

## Discussion

The results of the study showed a decrease in the levels of both testosterone and dihydrotestosterone in the group of children with hypospadias and the group of children with cryptorchidism compared to the control group. This result is consistent with that of a study conducted in the United Kingdom, which showed that levels of testosterone and dehydrotestosterone were lower in children with undescended testicles compared to the control group. As for the hormone dehydroepiandrosterone, it was high in children suffering from undescended testicle and penile dysplasia compared to the control group, despite the decrease in both testosterone and dehydrotestosterone, due to the presence of an enzyme block in the cholesterol cycle within Leydig cells (Ratan *et al*., 2012) [12]. Cholesterol is the basic raw material for the synthesis of all steroid hormones, including DHEA, in the adrenal gland and in the testes. The production of DHEA in the testes depends on the availability of cholesterol and the enzymes responsible for converting it to androgens (testosterone dihydrotestosterone). In the testes, cholesterol is imported from the mitochondria via the Steroidogenic Acute Regulatory Protein. (STAR) undergoes several enzymatic reactions to produce dehydroepiandrosterone. Increased activity of the CYP17A1 enzyme, which converts pregnenolone to 17-hydroxypregnenolone and then to dehydroepiandrosterone, leads to an increase in dehydroepiandrosterone levels, but with a deficiency in its conversion to testosterone and dihydrotestosterone due to a defect in the enzymes subsequent to the formation process, which affects the nature of hormonal production in the testicles (Prough *et al*., 2016) [11]. Our study showed a significant increase in estrogen levels in both the group of children with undescended testicles and the group with penile dysplasia compared to the control group. Maternal estrogen levels are significantly elevated, yet approximately 90% of the mother's endogenous estrogens are effectively sequestered by binding to sex hormone-binding globulin (SHBG) It is a protein produced by the liver and binds to sex hormones in the blood, such as testosterone, dihydrotestosterone, and estrogen, which reduces their free activity and helps regulate their effect on the body. Thus, the fetus is relatively protected from them. On the other hand, estradiol does not bind well with SHBG, which is present in the compounds of some medical drugs that the mother takes, such as contraceptives, because it has a high biological strength when taken orally, therefore its connection with SHBG is weak, and because of its lipid-loving nature, it is transferred to the fetus during pregnancy or to the newborn during breastfeeding. Thus, the estrogen level is high in children who suffer from undescended testicle deformity or penile dysplasia whose mothers were taking contraceptive drugs (Martin *et al*., 2008) [9]. High estrogen levels in children with undescended testicles and penile hypoplasia are also due to maternal exposure to EDC, It is ethylene dichloride found in pesticides, plastics, cosmetics, and flame retardants. These substances target the endocrine glands through direct and indirect mechanisms to suppress the production of androgens and cause an imbalance in estrogen levels by increasing or decreasing them, which affects the growth of the testicle and its hormonal production, which indirectly causes an imbalance in the growth of the penis or targets the process of forming the urethral opening in the penis (Mattiske *et al*.,2021).

## Conclusions

We conclude from this study that the occurrence of hormonal disorders during the fetal stage or after birth causes a defect in the nature of the formation of the male reproductive organs, which are under hormonal control, causing deformities that require therapeutic and surgical intervention.

## Conflicts of interest

The authors declare that they have no financial or personal relationships that could be perceived as creating a conflict of interest related to the research and information presented in this paper.

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