The Impact of Age and Laterality on the Response of Gonadotropin Hormone Therapy (HCG) in Undescended Testes

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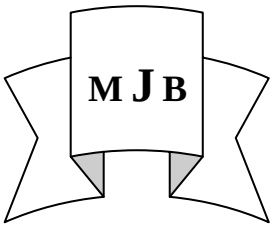

Abstract

Purpose: To evaluate the role of Gonadotropin (HCG) Hormone in bilateral and unilateral undescended testis in young and old age children, and its benefit for descent, with surgical out come results after therapy.

Material and Method: A prospective study on 117 patients (147 testis) with cryptorchidism, evaluated in AL-KUT general hospital from April 2005 to April 2009.Thirty of them with bilateral undescended (60 testis), and 87 patients with unilateral undescended testis,19 testis were impalpable and 128 testis were palpable. Patients divided into two group according to their age, from one years to five years 85 patients (110 testis) [25 bilateral (50 testis) and 60 unilateral], given 500 IU of HCG weekly intramuscularly for five weeks, and second group 32 patients (37testis) [5 bilateral(10 testis) and 27 unilateral] from five years to eight years, given1500 IU of HCG weekly intramuscularly for five weeks. Then patients were evaluated clinically, for descent and palpability. All patient not response to therapy and those with partial descent, orchiopexy done for them, and surgical out come results were evaluated.

Results: Descent occur more in bilateral undescended testis (33.3%) than unilateral group (10.3%), and more in younger age group (22.7%) than older age group (10.8%). We found that 5 testis (26.3%) were palpable from 19 impalpable testis, all of them young age group, while 50 low canalicular palpable testis become prescrotal (39%). We achieve success rate of 19.7% dropped after one year to (10%) due to relapse in 15 testis. The surgical out come was objective as easily descent to scrotum with short time of manipulation due to long spermatic cord with easily hernial sac isolation.

Conclusion: HCG treatment should be limited to those young children with bilateral low undescended testes and as combination therapy with surgery to facilitate surgical descent, otherwise HCG treatment in older age will delay the operative procedure.

اهمية استخدام هرمون الكوريونك كونادوتروفين في الخصية الهاجره وتأثره بالعمر والجانبية

الخلاصة

دراسة لتقييم استخدام هرمون الكوريونك كونادوتروفين في الغرض الخصية الهاجره عند الاطفال الصغار والاطفال الاكبر سنا والجانب الواحد والجانبيين :

دراسه اجريت في م.الكوت العام على ١١٧ مريض (١٤٧ ألطريقه خصية) يعانون من خصية هاجره من نيسان ٢٠٠٥ الى نيسان ٢٠٠٩ ، ثلاثون منهم مع خصية مزدوجة (٦٠ خصية) و ٨٧ مع خصية احادية و١٩خصية غير ملموسه و١٢٨ خصية ملموسة قسم المرضى الى مجموعتين حسب العمر ، المجموعة الاولى من سنه الى ٥ سنوات احادية تم اعطائهم ٥٠٠ وحدة من هرمون الكوريونك كونادوتروفين اسبوعيا لمدة ٥ أسابيع والمجموعه الثانية من ٥ سنوات الى ٨ سنوات وعددهم ٣٢ مريض (٣٧ خصية) منهم ٥ مزدوجه (١٠ خصية) و ٢٧ أحادي الجانب تم اعطائهم ١٥٠٠ وحدة من هرمون الكوريونك كونادوتروفين اسبوعيا لمدة ٥ اسابيع ثم تم متابعتهم سريريا لغرض نزول الخصية او احساسها . المرضى الغير مستجيبين للعلاج والاستجابه الجزئيه تم اجراء عملية انزال الخصية لهم وتم تقييم النتائج الجراحية لهم :

النزول الكامل كان اكثر في المزدوجة (٣٣,٣ %) من الاحادية (النتائج ١٠,٣ %) واكثر في الاطفال الصغار (٢٢,٧ %) من الكبار (٢٠,٨ %) نسبة النجاح كانت ١٩,٧ % نزلت بعد سنة الى ١٠% تقييم النتائج الجراحيه لهم كان سهولة انزال الخصبة الى كيس الصفن نتيجة طول الحبل المنوي مع سهولة عزل الفتق المصاحب مع قصر وقت العلمية
هرمون الكوريونك كونادوتروفين يجب ان يستخدم للاطفال الصغار مع عدم النزول المزدوج وكعلاج كصاحب للعملية لتسهيل انزال الخصية الى كيس الصفن عدا ذلك هرمون يونك كونادوتروفين في الاطفال الكبار لوحدة يودي الى تأخير العلاج الجراحي.

Introduction

Cryptorchidism 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 [1,2]. 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 [3]. By three months of age, the incidence is reduced to 0.8 percent, between three months of age and adulthood, the incidence does not change [4,5]. Watchful waiting is not an option because true undescended testicles rarely descend spontaneously after three months of age. Undescended testicles can be categorized on the basis of physical and operative findings**:** **True undescended testicles**, which divided into, high type including intra-abdominal, and high canalicular testes at the internal inguinal ring and low type including low canalicular and prescrotal testes, which exist along the normal path of descent and have a normally inserted gubernaculums. **Ectopic testicles**, which have an abnormal gubernacular insertion in the femoral region or perineum, and **Retractile testicles**, which are not truly undescended [3].

Men who have had an undescended testicle have lower sperm counts, poorer quality sperm and lower fertility rates than men whose testicles descended normally[5,6]. The likelihood of subfertility increases with bilateral involvement and increasing age at the time of orchiopexy. However, there seems to be an advantage to early orchiopexy for protection of fertility [7,8]. Through testicular biopsy at the time of orchiopexy, germ cell density has been shown to decrease over time, beginning as early as one year of age [9,10]. For this reason, treatment of the undescended testicle is recommended as early as six months of age and should be completed before age two [5].

It has been well documented that men with a history of undescended testicle have a higher-than-expected incidence of testicular germ cell cancers, the incidence among men with an undescended testicle is approximately one in1,000 to one in 2,500 [5,11]. Although significantly higher than the risk among the general population (1:100,000), this level of risk does not warrant radical therapy, such as removal of all intra-abdominal testes. About 20% of testicular tumors in men with unilateral cryptorchidism occur on the side with the normally descended testicle [12].This finding supports the argument against indiscriminate removal of undescended testes. Cryptorchidism and testicular cancer may also be manifestations of a genetic testicular abnormality; therefore, the development of cancer in an undescended testis may not be caused by testicular malposition. Although there is no proof that orchiopexy reduces the risk of testicular cancer, it is performed to ease detection through testicular self-examination [5, 13].

The incidence of testicular torsion is thought to be higher in undescended testes than in normal scrotal testes [14]. Torsion of an undescended testicle often occurs with the development of a testicular tumor, presumably caused by increased weight and distortion of the normal dimensions of the organ [15].
Most true cases of undescended testicles are associated with a patent processes vaginalis [3]. If an overt hernia is present, expeditious hernia repair with orchiopexy at the age of presentation is undertaken. Otherwise, the hernia should be repaired at the time of orchiopexy. A man with an untreated undescended testicle and an occult inguinal hernia may present at any time with symptoms and complications typical of any inguinal hernia.

Material and Method: A prospective study on 117 patients (147 testis) with cryptorchidism evaluated in AL-KUT general hospital from April 2005 to April 2009 , 30 of them with bilateral undescended (60 testis), and 87 patients with unilateral undescended testis, after physical examination and ultrasonography (U\S) for all of them, magnetic resonance imaging (MRI) for two with impalpable high abdominal testes and exclude ectopic and retractile testis. Then testis were divided into impalpable 19 testis (high abdominal 2 and high canalicular 17) and palpable 128 testis (low canalicular 86 testis and prescrotal 42 testis). Patients divided into two group according to their age, from one years to five years 85 patients (110 testis)(25 bilateral(50 testis) and 60 unilateral), given 500 IU of HCG weekly intramuscularly for five weeks, and second group 32 patients (37testis)(5 bilateral(10 testis) and 27 unilateral), from five years to eight years, given1500 IU of HCG weekly intramuscularly for five weeks , then patients were evaluated clinically, for descent and palpability. All patient not response to therapy and those with partial descent, inguinal orchiopexy operation is done for the palpable undescended testicle, the incision is extended, and the peritoneum is entered in a search for an intra-abdominal impalpable testis and surgical out come results were evaluated. Figure-1.

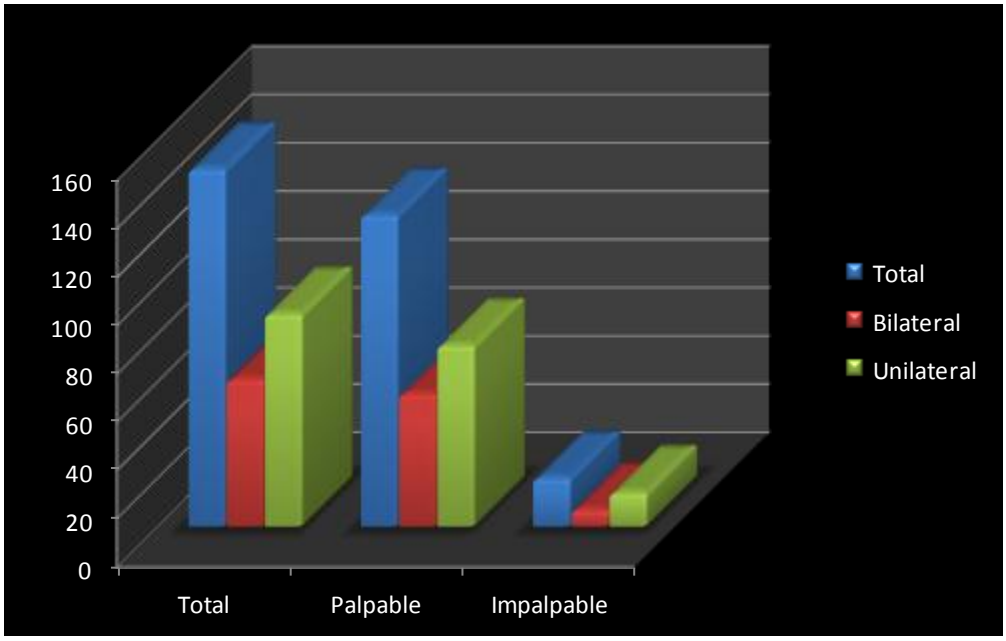

Figure 1 The Total No. and Type of UND.

Results

Descent occur more in bilateral undescended testis (all of them prescrotal) (33.3%) (20 from 60 testis)(9 young and 1 old) than unilateral group (10.3%)(9 from 87)(7 young and 2 old) (all of them prescrotal), and more in younger age group(22.7%)(9 bilateral and 7 unilateral) (25 testis from 110 testis) than older age group (10.8%)(4 from37 testis)(1 bilateral and 2 unilateral). We found that 5 testis (26.3%) were palpable from 19 impalpable testis(5 high canalicular become low canalicular) 2 testis bilateral and 3 testis unilateral, all of them young age group, while 50 low canalicular palpable testis become prescrotal (39%),16 testis from bilateral young age and 34 from unilateral undescended testis, 7 of them old age group. Some side effects of hCG was occur during administration, these includes, enlargement of the penis in 10 patients, pubic hair growth in 2 patient and aggressive behavior in 5 patients ,all of them from older age group. The success rate was dropped after one year to (10%) due to relapse in 15 testes (10 bilateral and 5 unilateral 6 young and 3 old). The surgical out come was objective as easily descent to scrotum with short time of manipulation due to long spermatic cord with easily hernial sac isolation. Figure (2, 3, and 4).

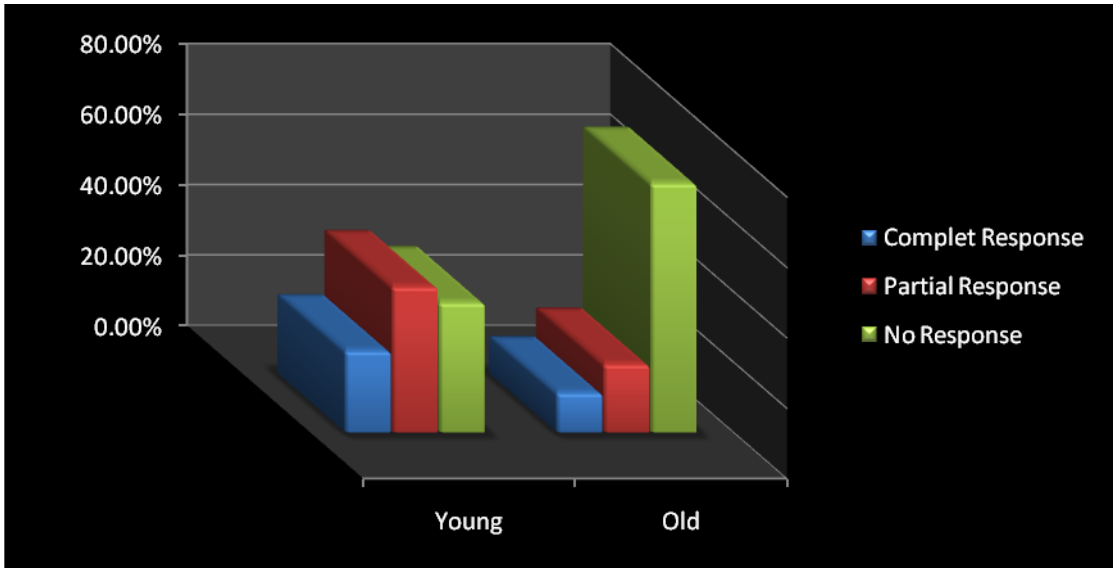

Figure 2 Percentage of HCG therapy response according to the age.

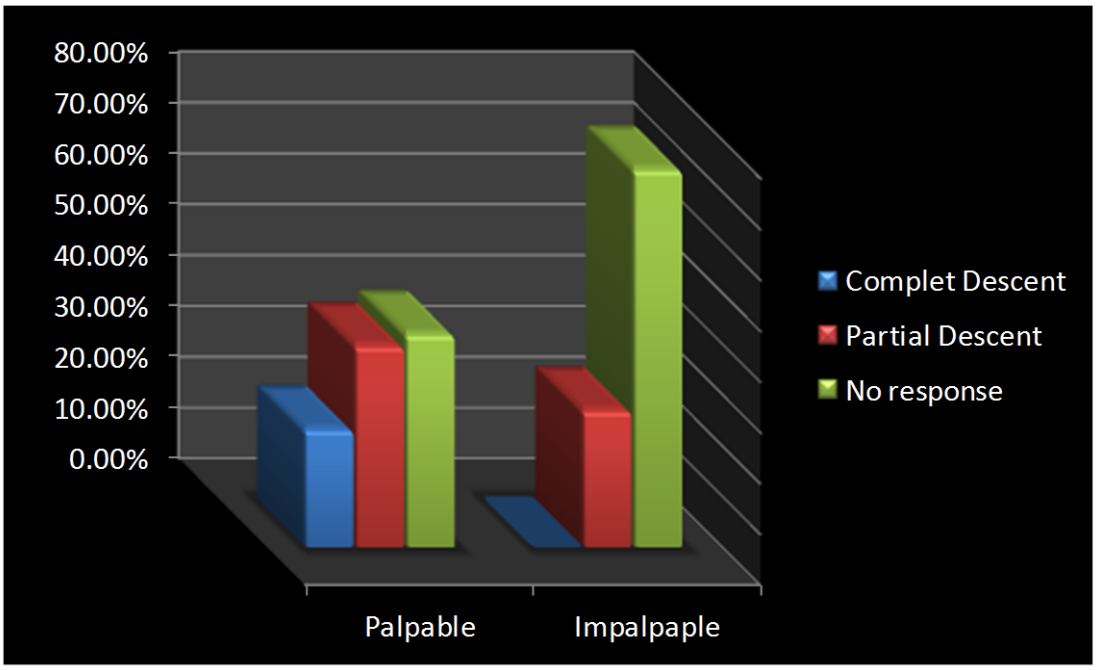

Figure 3 Percentage of hCG Therapy response According to Palpability..

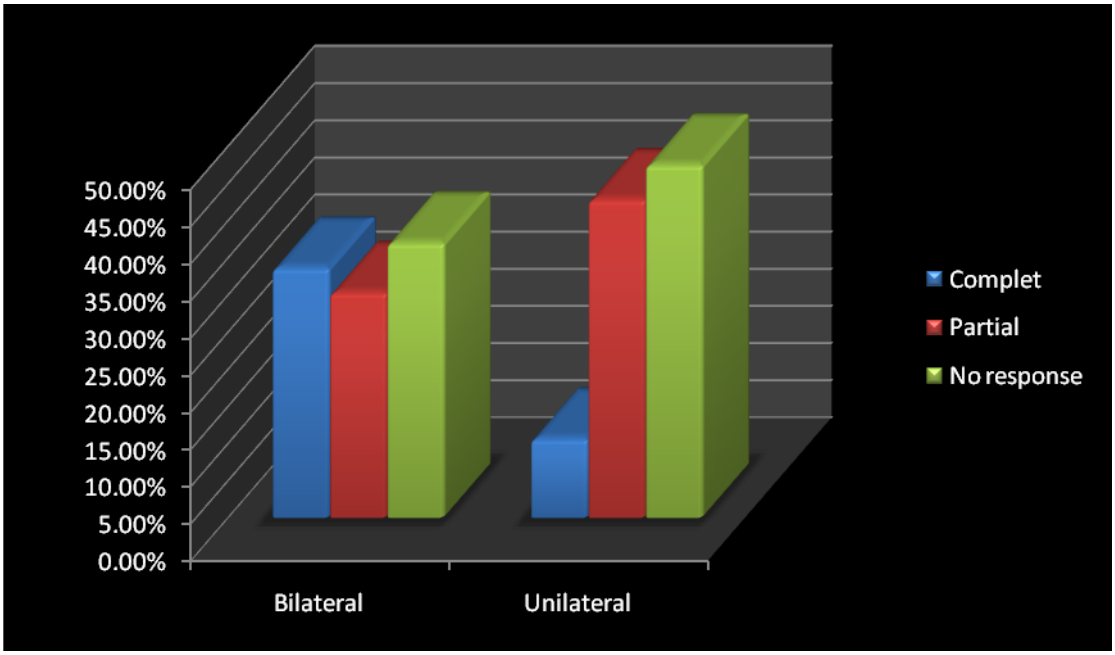

Figure 4 Percentage of hCG therapy response according to laterality.

Discussion

Correction of cryptorchidism can be possible for improving fertility, self-examination of testicular mass (cancer), correction of associated hernia, prevention of testicular torsion, avoidance of injury against pubic bone and remove psychological effects of empty scrotum.

Treatment for cryptorchidism can be hormonal, surgical or a combination of the two. The most significant complication of orchiopexy is testicular atrophy, dissection of the testicular vessels and/or postoperative swelling and inflammation can result in ischemic injury and testicular atrophy. A meta-analysis of the

urologic literature suggested an 8% failure rate of orchiopexy, even in the distal undescended testis, and failure of more than 25% of orchiopexies for intra-abdominal testes [16]. Other potential complications include ascent of the testis (which would require a second orchiopexy), infection and bleeding.

Hormone therapy has been used, because the process of testicular descent is hormonally mediated, endocrine factors play the major role in testicular descent. Testosterone and Dihydro-testosterone under the influence of hypothalamic- pituitary axis play this role [17]. Administration of systemic testosterone is minimally effective in achieving testicular descent because the process depends on a paracrine effect ,high local levels of testosterone that cannot be achieved systemically [18]. Exogenous Human Chorionic Gonadotropin (HCG) since 1930 and Gonadotropin Realizing Hormone (GnRH) since 1974 have been used for promoting testicular descent. The action of HCG is virtually identical to that of pituitary LH. It stimulates production of gonadal steroid hormones by stimulating the Leydig cells to produce androgens. Hormone response may differ according age and laterality [19,20]. Hormone therapy also makes impalpable testis to become palpable and orchiopexy easier thus improving surgical outcome [21, 22].

Generally, the only hormone labeled for the treatment of cryptorchidism is HCG, which is administered intramuscularly [23]. There are many protocols for the use of HCG. One such protocol is the administration of 1,500 to 2,500 IU two times per week for four weeks, The World Health Organization suggests treatment with 250 IU HCG twice a week for five weeks for children up to 12 months old, 500 IU HCG twice a week for five weeks for children 1 to 5 years of age and 1000 IU HCG twice a week for five weeks in older children, and recommends a total optimal dose of 10,000 IU. Our protocol was 500 IU weekly for 5 weeks in those less than 5 years and 1500 IU weekly for 5 weeks in those more than 5 years. Whatever protocol is used, the likelihood of success is greatest in the most distal true undescended testicles. A high undescended testis is unlikely to descend completely, if it does it will probably ascend after the hormone stimulation is withdrawn [23]. Studies suggest that gonadotropin-releasing hormone (GnRH) which given intranasaly is more effective than HCG in achieving testicular descent. Unfortunately, the reported results of hormonal therapy in the United States and Europe vary widely, probably because of the inclusion of variable numbers of boys with retractile testes. At any rate, GnRH is not currently labeled for use in the treatment of cryptorchidism [25].

There is a high controversy between studies regard results of HCG therapy in cryptorchidism between 0-50% [23]. Our data shows success rate of 19.7% of complete descent, better results in bilateral undescended testes(33.3%) as compared to(10.3%) in unilateral undescended testes. We found that HCG was more effective in young age group and caused complete descent in (22.7%) compared to (10.8%) in older age group, although more than half of them ascent after one year. Bierich showed 63% descent in children less than 4-6 years and 33% descent in children 6-7 years [20]. Ingersleve(1991)found 50% descent in bilateral undescended testes and 35% with unilateral by HCG therapy [26]. We observed that 26.3% impalpable testes became palpable.Timothy(2001) in his study found that 80% of

impalpable testes became palpable after HCG [22]. Best results were shown when the testis are prescrotal , low canalicular and young age children. Similar results were observed by Roberto Lala(1997) and Orkiszewskvi(1989) [27,28]. Bertelloni(2001) achieve success rate of 19.3% and relapse 23.3% [29]. There is a high relapse rate 51% from complete descent, and some side effects of hCG, these include enlargement of the penis, pubic hair growth and aggressive behavior mostly in older age children, and risk of premature puberty.

We determined that in our patients with cryptorchidism, which we believe is a public health problem for our country, due to late diagnosis, hCG treatment should be limited to those young children with bilateral low undescended testes and as combination therapy with surgery to facilitate surgical descent to scrotum with short time of manipulation, due to elongation of spermatic cord with easily hernial sac isolation especially the high impalpable testes. HCG treatment should be limited to those young children with bilateral low undescended testes and as combination therapy with surgery to facilitate surgical descent to the scrotum with short time of manipulation. Otherwise HCG treatment in older age will delay the operative procedure.

Conclusion

HCG treatment should be limited to those young children with bilateral low undescended testes and as combination therapy with surgery to facilitate surgical descent. Otherwise, HCG treatment in older age will delay the operative procedure.

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