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Effect of Inhaled Corticosteroids on Growth and Puberty in Egyptian Asthmatic Children and Adolescents

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Abstract: Growth suppression and delayed puberty may be major concerns for Inhaled Corticosteroids (ICS) treatment in children. Thus, we aimed to assess the effect of long-term ICS on growth and pubertal status in 30 asthmatic children and adolescents in comparison to 20-matched healthy subjects. Auxological measurements, Tanner staging and bone age assessment were performed. Measurements of basal and Lutenizing hormone releasing hormone (LHRH) stimulated follicle stimulating hormone (FSH) and Lutenizing hormone (LH) were done for patients only. In addition, pelvic ultrasound for measurements of uterine length and right ovarian volume was done for females aged >11 years. Patients' height, bone age and their Standard Deviation Scores (SDSs) were significantly lower, while weight SDSs were significantly higher than controls. ICS at doses >400 μg/day negatively affected height and its SDS (OR: 8.5, 95% CI: 2.15-33.8), whereas the use of ICS for >1 year significantly affected all auxological parameters with a particular risk on height SDS (OR: 9, 95% CI = 3.10-10.64) and weight for height SDS (OR: 6.82, 95% CI: 1.36-34.27). Significantly lower stimulated gonadotropins were encountered at doses >400 μg/day, while a duration >1 year was associated with significantly lower basal and stimulated gonadotropins. Logistic analysis revealed that the use of ICS for >1 year carried the highest risk of association with low stimulated FSH (OR: 5.80, 95%, CI: 1.54-33.70) and LH (OR: 8.31, 95% CI: 1.83-50.47). In conclusion, ICS at doses >400 μg/day carry a significant risk of retarding height of asthmatic children while their continuous use for >1 year carries significant risks of short stature, weight gain and delayed puberty.

Key words: Asthma, Egyptian, growth, inhaled steroids, puberty

INTRODUCTION

Asthma is the most common chronic disease of childhood; it is a worldwide problem that affects approximately 100 million people worldwide. During the past several decades, this prevalence has been increasing by 5 to 6% per year reaching rates of 30 to 40% in many countries. Therefore, it is important to assess accurately the impact of such a wide spread illness and its treatment regarding efficacy and safety (National Heart, Lung and Blood Institute, 2002).

As in other chronic childhood diseases, impairment of growth may often be seen in children with asthma. Rarely, poor asthma control is the cause. Factors that participate in the affection of growth parameters among asthmatic cases are variable. These include severity and duration of illness, hypoxemia, recurrent respiratory infections, age at onset of the disease and frequency of hospitalization. These are in addition to demographic and social factors such as age of the child, mother's education, hormonal, nutritional and psychological factors. The most important factors, however, may be asthma severity and treatment with exogenous corticosteroids (Agertoft and Pedersen, 2000).

ICS are recommended as first line anti-inflammatory therapy for the treatment of asthma. Also, they are the most effective controller therapy and are therefore the recommended treatment for asthma in children of all ages (Global Initiative for Asthma, 1995). However, concerns persist regarding their potential effect on growth and, most importantly, final height. Moreover, ICS can decrease the level of adrenal androgens, which in consequence leads to decreased growth hormone (GH) secretion and affects the hypothalamo-pituitary-gonadal axis. The whole process can cause growth arrest and pubertal delay (Doull, 2004). All these factors have resulted in reluctance of many physicians and parents to use ICS (Altintas *et al*., 2005).

Several studies have addressed the effect of ICS on linear growth and final height of asthmatic children

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(Doull, 2004). Allen (2005, 2007) concluded that the dosage, type of inhaler device used, patient technique and characteristics of individual drug all influence the systemic side effects of ICS especially on height. Visitsunthorn *et al*. (2002) confirmed that the average dose and duration of ICS had no significant effects on growth in prepubertal asthmatic children. Allen (2004) found that dose related inhibition of growth is detectable as ICS dose increases and Allen (2006) concluded that detectable suppression of childhood growth can occur when ICS with relatively poor first pass activation are administered at doses greater than 400 μg/day for more than 1 year.

With this background, we were stimulated to assess growth and pubertal status among asthmatic children and adolescents on long-term ICS therapy.

MATERIALS AND METHODS

Study population: This case-control study was carried out on 30 asthmatic children and adolescents who had bronchial asthma diagnosed according to the criteria of GINA, 2006 and who were receiving ICS therapy. Patients were recruited from the Pediatric Allergy and Immunology Clinic, Children's Hospital, Ain Shams University during the period from September 2006 until June 2008. They were 18 males (60%) and 12 females (40%). Their ages ranged from 9 to 16 years with a mean of 12.445±1.895 years.

Asthmatic patients were studied in comparison to 20 healthy age- and sex-matched control children who had no clinical findings suggestive of any endocrinal disorder or any disease that might affect growth or puberty. They were recruited from the outpatient clinic of the same hospital. They were 12 males and 8 females and their ages ranged from 10.0 to 15.9 years with a mean of 12.36±1.91 years.

An informed written consent for participation in the study was signed by the parents or legal guardians of the studied subjects.

Study measurements

Clinical evaluation of patients: This was based on clinical history taking from caregivers, reviewing follow-up sheets and clinical examination. Special emphasis was done on duration of illness, detailed history of ICS therapy including dose and duration of therapy. According to the dose, patients were classified into those who took a dose of >400 μg/day of beclomethasone dipropionate equivalent and those who took a dose of ≤400 μg/day. In addition, according to duration of therapy, they were classified into those who took ICS for >1 year and those who took ICS for ≤1 year. Clinical examination included auxological measurements (height and weight and their SDSs) which were calculated according to the norms of Sempe *et al*. (1979) and Tanner Pubertal staging which was applied to girls aged ≥11years and to boys aged ≥11.5 years; the age at which puberty is expected to have started according to Marshall and Tanner (1969).

Assessment of serum FSH and LH levels (for patients only): Both basal and stimulated serum FSH and LH levels after LHRH stimulation test were measured by immunochemiluminometric assay (ICMA) based on direct sandwich technique on the Immulite 2000 apparatus using commercial kits (Diagnostic Products Corp-Med lab, Los Angeles, CA) (Babson, 1999). Samples for measurement of FSH and LH were withdrawn before and 4 hours after subcutaneous injection of 0.1 mg/m^2 of LHRH analogue (Styne, 1997). Both basal and stimulated values were compared to standard reference values in normal Egyptian children (El-Sedfy and Shahin, 2001).

Assessment of bone age (for patients and controls): This was done by performing plain x-ray left hand and wrist with calculation of bone age SDS using the method of Greulich and Pyle (1959).

Measurements of uterine length and right ovarian volume by using pelvic ultrasound (for patients only): This was applied for girls aged ≥11 years by using Acouson Computed Sonography with an SL 1 Ultrasonographer (Sono Line; Siemens, Erlangen, Germany) with 3.5 and 5 MHz linear transducer. Ovarian volume was calculated according to the formula for ellipsoid bodies where V = longitudinal diameter× anteroposterior diameter×transverse diameter×0.5233. Calculation of SDS of uterine length and right ovarian volume was done and compared to age-matched values (Griffin *et al*., 1995).

Statistical analysis: Analysis of data was done on an IBM computer system using SPSS (statistical program for social science) Version 10 as follows: quantitative variables were presented as Mean±SD, median and range while qualitative variables as frequency and percentage. Student t-test was used to compare parametric data, whereas Mann Whitney and Wilcoxon tests were used for non-parametric data. Chi-square test was used to compare qualitative variables. Risk estimation was done by using the odd's ratio which compares the odds of 2 events, where the odds of an event equals the probability that the event occurs divided by the probability that it does not occur. A 95% confidence interval for the odds ratio was

also calculated. If the value of 1 is not in the range of confidence interval, it can be concluded that there is an increased relative risk in one group compared to the other. A p-value of <0.05 was considered significant.

RESULTS

Out of our 30 studied asthmatic patients, 17 (56.67%) received ICS for ≤1 year and 13 (43.33%) for >1 year. Also, 17 patients were receiving ICS at a dose of ≤400 μg/day and the remaining 13 were receiving a dose of >400 μg/day.

Auxological parameters and bone age of asthmatics versus controls: A significant reduction was noticed in each of the height and height SDS of patients in comparison to controls (133.64±9.41 cm versus 142.97±7.05 cm, respectively and -2.09, mean rank: 16.17 versus +0.55, mean rank: 29.42, respectively, p<0.05) while there was a significant increase in the weight for height SDS of patients (+1.20, mean rank: 39.50 versus -0.42, mean rank: 19.63, p<0.05). Bone age and its SDS were significantly lower among cases when compared to controls (10.62±2.12 years versus 12.52±1.88 years and -1.470±1.25 versus +0.241±0.33, respectively, p<0.05).

Growth in relation to dose and duration of ICS therapy: The height was significantly lower in patients who took ICS at doses of >400 μg/day when compared to those who took ≤400 μg/day (Mean±SD: 125.44±7.70 versus 135.24±10.34 cm, p<0.05). Also, a significantly lower SDS of height for age was noticed at doses of >400 μg/day groups in comparison to doses of ≤400 μg/day (Table 1). The weight (Mean±SD: 32.53±10.07 kg versus 30.65±10.41, respectively), weight for height SDS, bone age and bone age SDS did not differ between the two groups (p>0.05, Table 1).

Regarding the duration of ICS therapy, height was significantly lower while weight was significantly higher in patients who took ICS for >1 year in comparison to those who took ICS for ≤1 year (130.37±9.19 versus 138.18±8.10 cm and 36.48±12.21 versus 28.31±6.83 kg, respectively, p<0.05). In addition, significantly lower SDS of height for age, higher SDS of weight for height and lower bone age were noticed in patients who took ICS therapy for >1 year (Table 2).

Therefore, doses of ICS of >400 μg/day affected height and its SDS only with no effect on other auxological parameters (weight and its SDS and bone age and its SDS) whereas the use of ICS for >1 year affected all auxological parameters (height and its SDS, weight and its SDS and bone age).

Also, we found that each of the height and its SDS, weight and its SDS and bone age and its SDS did not significantly differ in patients receiving ICS therapy at doses ≤400 μg/day and those receiving ICS therapy for ≤1year from those of controls (p>0.05). This means that ICS at doses ≤400 μg/day and for ≤1 year are safe.

Pubertal development in relation to dose and duration of ICS therapy: Among the 30 asthmatic patients, 23 (76.66%) were expected to be pubertal (Tanner stages 2-5) based on their ages. These were girls aged ≥11.5 years and boys aged ≥11 years. However, 7/23 (30.43%) were still prepubertal (Tanner 1).

Table 1: The effect of the dose of ICS on SDS of height for age, SDS of weight for height, bone age and its SDS in patients' group

	Dose							
	≤400 μg/day (n = 17)			>400 μg/day (n = 13)				
ICS therapy	Range	Median	Mean rank	Range	Median	Mean rank	z-value	p-value
SDS of height for age	-4.90-0.47	-2.05	26.77	-4.90-0.47	-2.20	17.84	-2.25	0.02*
SDS of weight for height	-2.43-8.25	0.74	22.44	-2.43-8.25	1.27	23.76	-0.33	0.74
Bone age (years)	10.6-15.0	13.00	25.48	7.00-12.60	10.00	19.61	-1.50	0.13
SDS of bone age	-3.40-0.80	-1.10	11.10	-3.40-1.94	-1.94	7.50	-1.43	0.15

SDS: Standard deviation score. ICS: Inhaled corticosteroids, *p<0.05: Significant

Table 2: Duration of ICS therapy in relation to SDS of height for age, SDS of weight for height, bone age and its SDS among patients' group

	Duration							
	≤one year (n = 17)			>one year (n = 13)				
ICS therapy	Range	Median	Mean rank	Range	Median	Mean rank	z-value	p-value
SDS of height for age	-4.90-0.47	-2.16	25.03	-4.90-1.05	-3.05	21.52	-0.89	0.038*
SDS of weight for height	-2.43-4.09	0.74	22.38	-2.35-8.25	2.13	23.84	-0.37	0.041*
Bone age (years)	7.1-15.00	11.60	18.36	7.0-13.0	10.50	12.00	-2.56	0.040*
SDS of bone age	-3.40-0.80	-0.96	10.31	-3.40-1.94	-1.92	8.85	-0.58	0.560

SDS: Standard deviation score. ICS: Inhaled corticosteroids, *p<0.05: Significant

Table 3: Basal and stimulated gonadotropins in relation to the dose of ICS in patients' group

	Dose							
	≤400 μg/day (n = 17)			>400 μg/day (n = 13)				
ICS therapy	Range	Median	Mean rank	Range	Median	Mean rank	z-value	p-value
Basal FSH (uIU/mL)	0.14-8.70	2.90	24.77	0.14-5.31	2.42	20.58	-1.06	0.29
FSH (after LHRH, uIU/mL)	2.00-40.00	13.91	26.69	2.00-15.60	3.90	17.95	-2.21	0.03*
Basal LH (uIU/mL)	0.06-7.95	2.98	24.06	0.06-4.91	2.90	21.55	-0.63	0.40
LH (after LHRH, uIU/mL)	3.02-37.60	14.16	26.29	2.89-15.91	5.17	18.50	-1.97	0.04*

FSH: Follicle stimulating hormone, LH: Lutenizing hormone, LHRH: Lutenizing hormone releasing hormone, ICS:L Inhaled corticosteroids, *p<0.05: Significant

Table 4: Basal and stimulated gonadotropins with respect to duration of ICS in the patients' group

	Duration							
	≤one year (n = 17)			>one year (n = 13)				
ICS therapy	Range	Median	Mean rank	Range	Median	Mean rank	z-value	p-value
Basal FSH (uIU/mL)	0.14-8.70	3.50	28.00	0.14-4.43	2.38	19.35	-2.18	0.03*
FSH (after LHRH, uIU/mL)	2.30-40.00	14.01	29.11	2.00-25.80	3.25	18.54	-2.67	0.01*
Basal LH (uIU/mL)	0.06-7.95	3.27	26.84	0.06-7.07	2.77	20.19	-1.68	0.03*
LH (after LHRH, uIU/mL)	4.18-37.60	15.12	29.21	2.89-36.40	4.60	18.46	-2.71	0.01*

FSH: Follicle stimulating hormone, LH: Lutenizing hormone, LHRH: Lutenizing hormone releasing hormone, ICS: Inhaled corticosteroids, *p<0.05: Significant

All the 7 cases (100%) with delayed puberty were detected among those receiving ICS doses of >400 μg/day for > 1 year.

Uterine length and right ovarian volume did not differ significantly with respect to the dose of ICS (>400 μg/day versus ≤400 μg/day) (3.98±1.30 versus 5.05±1.36 cm and 1.66±0.36 versus 1.41±0.81 mL, respectively, p>0.05). Moreover, SDSs of both parameters did not differ significantly (-1.21, mean rank: 7.63, versus -0.14, mean rank: 11.00 and -1.27, mean rank: 19.71 versus +0.35, mean rank: 25.40 respectively, p>0.05). The same was seen with basal FSH and LH (p>0.05) whereas after LHRH stimulation, FSH and LH were significantly lower among those who received ICS therapy at doses of >400 μg/day (p<0.05, Table 3).

The duration of ICS therapy did not have a significant impact on uterine length and right ovarian volume (>1year versus ≤1 year duration: 4.92±1.4 versus 4.29±1.36 cm and 2.23±0.78 versus 1.96±0.72 mL, respectively, p>0.05). The SDSs of both parameters followed the same pattern (-0.38, mean rank: 10.50 versus -1.16, mean rank: 8.70 and +0.35, mean rank: 25.18 versus -1.21, mean rank: 21.40, respectively, p>0.05). Basal and stimulated FSH and LH were significantly lower among those who received ICS therapy for >1 year (p<0.05, Table 4).

Frequency of low basal and/or stimulated gonadotropins among asthmatic children expected to be pubertal: Of the 23 patients expected to be pubertal, seven (30.44%) had low FSH (basal and after LHRH stimulation). Only one case had low basal LH (4.35%) and seven cases (30.44%) had low LH after LHRH stimulation. All cases with low basal and stimulated FSH and low basal and stimulated LH were detected among asthmatics who took ICS at doses of >400 μg and for >1 year.

Risk estimation for the association of ICS doses of >400 μg/day with short stature (height SDS <-2), overweight (weight for height SDS >+2), low stimulated FSH and LH: ICS doses of >400 μg/day had a significant risk (p<0.05) for association with short stature with an estimated relative risk of 8.5 (95% CI: 2.15-33.8). On the other hand, ICS doses of >400 μg/day did not have a significant risk (p>0.05) for association with overweight (OR: 0.8, CI = 0.47-2.6), low stimulated FSH (OR: 1.13, CI = 0.85 -1.52) and low stimulated LH (OR: 0.3, CI = 0.03 -2.60).

Risk estimation for the association of ICS use for >1 year with short stature (height SDS <-2), overweight (weight for height SDS >+2), low stimulated FSH and LH: The use of ICS for >1 year had a significant risk (p<0.05) for association with short stature (OR: 9, 95% CI = 3.10-10.64), overweight (OR: 6.82, 95% CI = 1.36-34.27), low stimulated FSH (OR: 5.80, 95% CI = 1.54-33.70), low stimulated LH (OR: 8.31, 95% CI = 1.83-50.47).

DISCUSSION

In this study, height and its SDS were significantly lower and the weight for height SDS was significantly higher in asthmatic children than in controls. Therefore,

both weight and height were considerably affected in asthmatic children: a negative impact on height and a positive one on weight. It is to be noted that the mean age of our study sample was insignificantly different from that of the control group. So, the differences in our results could not be attributed to differences in age.

The reduction in linear growth noticed in our study is in accordance with a randomized double-blind study that compared inhaled beclomethasone dipropionate with placebo in 94 asthmatic children. Those on beclomethasone dipropionate grew significantly less than those on the placebo (2.66 versus 3.66 cm) (Doull, 2004). Again, our work is in accordance with the study of Skoner *et al.* (2000) who reported the results of a multicenter, randomized, open-label, active-controlled, parallel-group study that was designed to evaluate the effect of ICS therapy on growth after 52 weeks of follow-up. The subjects were 0.5 to 8 years old; all had a pre-existing diagnosis of asthma. Changes in height SDS differed significantly between groups receiving budesonide inhalation suspension and their counterparts who received conventional asthma therapy [excluding glucocorticoids (GCs)]. At 52 weeks, the height SDS was significantly lower by 0.19 SD among the ICS group and their growth velocity was reduced by 0.8 cm/year. In 2001, the Food and Drug Administration (FDA) recommended that all ICSs should carry a warning regarding their potential effects on growth (Food and Drug Administration, 2001).

It has been reported that children with chronic asthma start to show growth retardation at the age of 10 years which is most marked at the age of 14 years (Doull, 2004). Both asthma and its therapy could account for the suppression in linear growth. A study done in Alexandria University to assess whether long standing asthma affects growth in prepubertal Egyptian children before initiation of long-term ICS therapy showed no significant major effect of asthma on physical growth, apart from skeletal maturation, which was found to be significantly retarded in asthmatics compared to normal children (Ismail *et al.*, 2006). Phelan *et al.* (1994) found that the disease itself had no effect on growth in children with infrequent episodic asthma, but those with frequent asthma were found to have minor effects. Growth suppression due to poor asthma control may depend on long-term catabolic stress and severe sleep disturbances interfering with the diurnal secretion of anabolic hormones (Agertoft and Pedersen, 2000).

The susceptibility to growth suppression by ICS could be explained by the interactions of GCs with hypothalamo pituitary adrenal axis (HPA) axis, either GH or adrenal hormones. Acute exposure to GCs can enhance GH release, but long-term exposure impairs its release, both by direct and indirect mechanisms. GCs appear to augment hypothalamic somatostatin secretion, which exerts an inhibitory effect on pituitary pulsatile GH secretion. Directly, GCs regulate the expression and binding of the GH receptor downward. Furthermore, exogenous GCs appear to interfere with the bioactivity of insulin-like growth factor-1 (IGF-1), the primary second messenger of GH, probably by altering protein binding of IGF-1 to limit the circulation of free IGF-1 (Allen, 2006).

In the prepubertal child, GH secretion is generally confined to nighttime, usually beginning after sleep onset, which coincides with the normal nadir in blood cortisol levels. The risk for adverse effects of ICS therapy is increased either when systemic exposure exceeds normal endogenous cortisol production or when the pattern of cortisol effect is sufficiently abnormal to disrupt other normal hormone secretion (Allen, 2006). In addition, GCs have a direct inhibitory effect on the synthesis of new connective tissue and at certain ages, diminish androgen production by the adrenal gland, normally a critical stimulator of growth during the early phase of the pubertal growth spurt (Todd *et al.*, 2002).

In our series, the significantly increased weight for height of asthmatic patients can be attributed to either asthma itself or ICS therapy. Obesity may develop as a consequence of asthma if the disease leads to sedentary lifestyle (Mathew *et al.*, 2009). Meanwhile, interventions that reduce obesity in asthmatics are followed by improvements in asthma control (El-Helaly *et al.*, 2009). ICS lead to impaired insulin tolerance, increased glucose and hyperlipidaemia with rise in total and high density lipoprotein cholesterol. It also leads to increased appetite, fluid retention and consequently weight gain (Maniscalco *et al.*, 2008). Contrary to our findings, Todd *et al.* (2002) reported that poor weight gain is seen commonly in patients with asthma. Also, British Thoracic Society (1993) stated that children receiving step 4 treatment in the British Thoracic Society's guidelines who use hospital services are shorter and lighter than expected and also have comparatively poor growth rates. The decrease in body weight and body mass index despite the administration of high dose of ICS in some asthmatic children may be related to the improvement of pulmonary function that may lead to improvement in life style and decrease in fatness.

One of the greatest concerns of corticosteroid therapy for asthma is its potential for adverse effects on bone age. In the current study, we found a significant lowering in patients bone age and its SDS as compared to those of controls. Similar to our results, short-and medium-term studies of healthy volunteers and asthmatic

patients receiving ICS have been able to detect its effect causing delayed bone age, which occurs less frequently than with oral corticosteroids (Saravi *et al*., 2000). However, Agertoft and Pedersen (2000), found no differences in bone age among asthmatic patients and controls.

In the current study, a dose of >400 μg/day was associated with a significant lowering in height and its SDS whereas doses of ≤400 μg/day were not. This was confirmed by a study done by Childhood Asthma Management Research Group (2000), who found that doses of less than 400 μg had no effect on growth and bone age. Also, high daily doses of ICS (>400 μg/day) had a statistically significant effect on reduction in both height and bone age in another study (Priftis *et al*., 2006). Therefore, ICS when administrated in low doses seem to be safe. In any case, patient monitoring allows early detection of possible side effects associated with ICS (Allen, 2006).

Allen *et al*. (1994) studied the growth curve of the patients at the age of 15 years who used inhaled beclomethasone at a dose of >400 μg daily. Their growth curve showed typical delayed pubertal growth spurt and the reduction of growth velocity appeared to commence at the age of 8 years, at about the time the ICS therapy was started. Over the 5 years that followed, the patients' height SDS went from around zero (the population mean) to -1.45 at the age of 13 years. Also, Doull (2004) found that those who received ICS had significantly lower final adult height compared to their predicted adult height based on mid parental height.

On the other hand, other studies by Harmanci *et al*. (2001) and Shonoey *et al*. (2006) reported no effect on growth of children treated with a dose of >400 μg of ICS. Hence, the reports on the effect of ICS dose have been very variable. Most studies, however, are of the view that there is no significant evidence of adverse effects on growth when conventional doses (<400 μg/day) of ICS are used. This situation reflects also the extreme variability of individual sensitivity and the need for careful surveillance for all asthmatic children treated with steroid therapy, which may necessitate dose reduction or drug replacement (Doull, 2004).

The risk of growth rate suppression due to use of corticosteroids, was examined with respect to the duration of ICS treatment. We found that the height and bone age and their SDSs were significantly lower while weight and its SDS were significantly higher in patients who received ICS for more than one year. ICS for a duration of less than a year had no such impact. Similarly, studies submitted to the FDA with several different active corticosteroid moieties demonstrated reduced growth velocities over a 1 year time period of approximately 1 cm/year among active treatment groups exposed to oral or inhaled or intranasal corticosteroids as compared to control groups (placebo or non-corticosteroid asthma treatments such as beta-agonists). Moreover, It has been reported that daily treatment with any dose of corticosteroids (CSs) suppresses the growth rate for as long as, the treatment is maintained. The longer the duration of treatment, the more is the effect on growth. When treatment is withdrawn, catch-up growth may occur, compensating for some, if not all, of the retardation (Reid *et al*., 1996). Agertoft and Pedersen (2000) reported that growth rates were significantly reduced during the first years of budesonide treatment but were not significantly associated with adult height. Also, reduced bone age z-scores was reported in asthmatics on long term treatment >1 year with ICS (Altintas *et al*., 2005).

In adolescents with chronic asthma, as in any chronic illness, the progress of puberty may be abnormal. The basis of abnormal physical development in adolescence is multifactorial. Genetic factors, nutritional deficiency, hormonal abnormalities or concomitants of treatment all may contribute to disordered growth (Rosen, 1991). In the present series examined cross sectionally, 7 out of the 23 (30.43%) patients who were expected to have had started puberty were still prepubertal. This was evident only in patients on ICS doses of >400 μg/day. Similarly, Doull (2004) found a significant delay in menarchal age in asthmatic girls. They explained the delay in pubertal age associated with asthma may be a consequence of increased weight as has been found in our study. Moudiou *et al*. (2003) found that the growth of asthmatic children before any long-term treatment with inhaled ICS is not different from the control population, except for the asthmatic girls of pubertal age who are shorter than control girls probably because of delay in pubertal maturation. Untreated asthma results in a delay of puberty by approximately 1.3 years and pubertal delay is likely to explain the majority of apparent growth failure in asthmatics, including retardation in height (Rosen, 1991).

Normally, a single dose of LHRH agonist stimulates release of LH within 4 hours in teenage prepubertal children as well as in sexually mature group. The initial rise in LH occurs earlier and is of greater magnitude in adults than in the immature groups. The subsequent pattern of LH secretion differs markedly according to stage of sexual development. FSH responses tend to parallel those of LH but change less consistently with pubertal maturation. This is compatible with earlier findings that FSH responsiveness to both LHRH bolus or infusion increases very little during puberty (Styne, 1997).

The present work revealed significantly lower mean FSH and LH levels after LHRH stimulation in patients who took a steroid dose of more than 400 μg/day but not in the basal state. High doses of ICS decrease the production of LHRH which decreases the production of LH, which leads to secondary hypogonadism, decreased testosterone or estradiol production, with decreased bone formation and increasing bone resorption (Styne, 1997). Also, in our study, ICS therapy for a duration of more than one year had a negative effect on FSH and LH, lowering their levels both in the basal and stimulated state. This was previously shown by Doull (2004), who found a delay in sexual maturation by approximately 1.3 years, at an ICS duration of more than one year.

Comparison of each of the basal and stimulated FSH and LH of our studied children supposed to be pubertal with standard levels in normal Egyptian children (El-Sedfy and Shahin, 2001) showed that 7 (30.44%) had low basal FSH and low FSH after LHRH stimulation, one case had low basal LH (4.35%) and 7 (30.44%) had low LH after LHRH stimulation. All cases with low FSH (basal and after LHRH stimulation) and low LH (basal and after LHRH stimulation) were detected among those who took steroids doses of >400 μg and for >1 year. This supports earlier findings by Rosen (1991).

Uterine length and right ovarian volume did not differ with respect to the dose of ICS (>400 μg/day versus ≤400 μg/day) and its duration (>1 year versus ≤1 year). To the best of our knowledge, we could not trace data in literature regarding the latter issue to compare our results. One of the crucial problems of ICS therapy is the suppression of hypothalamic-pituitary-adrenal function. Morever, ICS show direct effects on the gonads and the target tissues of gonadal steroids. ICS also reduce the action of FSH on granulosa cells and inhibit the response of LH to LHRH (Todd *et al*., 2002).

It can finally be concluded that ICS when used at higher doses of >400 μg/day have a significant risk of adverse effects on growth leading to retarded height while their use continuously for long periods, at least 1 year, has significant risk of short stature, weight gain as well as delayed puberty due to reduction of FSH and LH. This highlights the importance of using ICS at the lowest effective dose and for the shortest possible durations. Regular follow-up of growth and puberty parameters among asthmatic children on ICS therapy is mandatory especially those on doses of >400 μg/day and/or for more than 1 year. The need is growing for newer effective therapies that can provide a better chance for normal growth of asthmatic children.

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