

ASTHMA AND GROWTH

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ABSTRACT

Inhaled corticosteroids (ICS) are first-line therapy in persistent asthma and are being used earlier, at higher doses and in younger children. The main side-effect of concern is the effect of ICS on growth. Asthma itself may cause growth stunting, which is associated with poor control and asthma severity; delayed maturation is a possible cause. Systemic steroids are known to cause growth suppression. Studies assessing the effects of ICS on growth should take into account the growth phases of childhood. The study duration should be more than 12 months, and there should be a control group, which poses ethical problems. Knemometry, which measures short-term growth, has shown dose-related suppression by ICS. Evidence from studies on budesonide and beclomethasone dipropionate (BDP) indicates impaired growth velocity during the first 1-2 years of treatment, but no effect on final adult height. Growth retardation may occur with all ICS if they are given in high doses for long periods, especially in prepubertal children. However, ICS are safe if used at appropriate doses with step-down to the lowest effective dose once control of symptoms is achieved.

INTRODUCTION

Worldwide, guidelines addressing maintenance treatment of childhood asthma recommend inhaled corticosteroids (ICS) as first-line therapy in all grades of persistent asthma.^{1,3} This is a relatively new development: as recently as 1994 the South African consensus suggested as-needed bronchodilators for mild asthma and sodium cromoglycate for moderate asthma.⁴ The result has been a tendency to treat children with ICS at younger ages and earlier in the course of their disease. This has led to concerns regarding the side-effects of ICS in children, and particularly their potential effect on growth.

GROWTH: TERMINOLOGY

Growth is an increase in the size, composition and distribution of tissues and is associated with changes in their proportions, shape and functions. *Growth velocity* is the speed at which the process takes place over a period of time. A *growth spurt* is an increase in growth velocity; *growth lag* is a decrease in the rate or velocity of normal expected growth. *Catch-up growth* is a return towards the size that would have been attained if the growth lag had not occurred.

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GROWTH PHASES

There are three growth phases during childhood. It is important to take these phases into consideration when assessing the effects of disease or therapy on growth. During *infancy* there is rapid growth, with body length increasing by 50% in 1 year. The height at the end of this phase depends on genetic and nutritional factors. Birth weight is an important factor; preterm and some small-for-gestation infants demonstrate catch-up growth during the first 2 years after birth.

The next phase, from *2 years until puberty*, is characterised by gradually decelerating growth, although very few children cross height percentiles. This phase is influenced mainly by growth hormone secretion. The growth phase associated with *puberty* involves an initial period of slow growth, followed by a growth spurt lasting approximately 2 years. This phase is controlled by the sex steroids and growth hormone.

Biological, constitutional, hereditary and environmental factors all influence growth (Fig. 1).

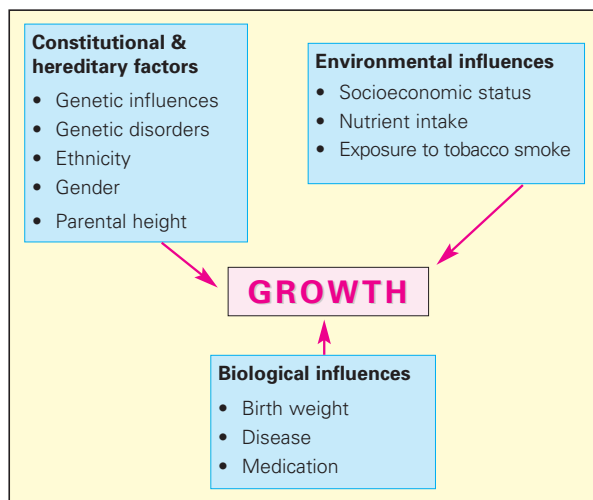


Fig. 1. Factors affecting growth.

ASSESSMENT OF GROWTH

Various parameters may be used to assess growth. Length is used during the first 2 years, and height after the age of 2 years. Stadiometry is used to measure height during childhood; if measured over 12 or more months it reflects intermediate-term growth, and if measured over 3 or more years it reflects long-term growth. Other height measures used to assess growth are predicted adult height and final adult height. Growth velocity is used to assess the speed of growth over time. Knemometry, the measurement of lower leg length growth, is used in studies to reflect short-term growth. The problem with this measurement is that it has poor reproducibility, and is difficult to relate to long-term statural growth.

ASTHMA AND GROWTH

Any review of asthma and growth has to take into account the effect of asthma itself on growth, as well as the effect of the treatment of asthma on growth.

The effect of asthma on growth

It has been recognised for some time that asthma itself may cause growth impairment. Hyde Salter wrote in 1868 'if the asthma has come on young, he is *generally* below the average height. Some asthmatics, however... have nothing whatever the matter with their appearance, and would be taken for perfectly healthy people.'⁵ Subsequently researchers noted that uncontrolled allergy in children was associated with growth impairment. Control of the allergic disease resulted in satisfactory growth.⁵

Russell⁶ reviewed the literature on growth and asthma and found that there were very few published data on asthma as a cause of growth impairment. He found comments on growth of asthmatic children in three types of paper: reports on asthma treatment; reports on selected populations of children with severe asthma; and hospital records of children attending allergy and asthma clinics. Several authors included data on the growth of their asthmatic patients once it became apparent that corticosteroids caused growth stunting. Several of these studies reported an association between asthma and poor growth; this was independent of any treatment that these patients received. In a study done by Ninan and Russell⁶ the patients showed impaired growth only during periods of poor asthma control, suggesting that the growth impairment is related to asthma severity.

Murray *et al.*⁷ reported that the proportion of small children attending their clinic was about twice that in the normal population. Factors related to growth impairment included onset of asthma before the age of 3 years and chronic hypoxaemia. In a subsequent paper the same authors confirmed that the children in their study had delayed bone age, suggesting that growth retardation in asthma is a maturational phenomenon, with the long-term prognosis being good.⁸ Balfour-Lynn⁹ also supported the view that puberty is delayed in children with asthma.

There are several possible explanations for the association between asthma and growth retardation. The first is the association with delayed maturation, with prolongation and deepening of the prepubertal growth nadir.⁵ This would be in keeping with the observation that final adult height is normal in asthmatics. Severe asthma may be associated with hypoxaemia, which may lead to impaired growth. There is no evidence to support postulates that growth hormone secretion is impaired or that there is other endocrine dysfunction.⁵

Assessing the effect of asthma treatment on growth

In order to determine clinically relevant systemic side-effects of drugs, studies should consist of controlled, long-term clinical trials, using clinically appropriate doses of drugs in patients with age and severity of disease similar to the groups in which the drugs would normally be prescribed. Such studies are difficult to conduct and require large numbers of patients.¹⁰

One problem with assessing the effects of ICS on growth in asthmatic children is that many of the studies are poorly designed with inconclusive results. The ideal study design recommended by the FDA includes comparison with non-steroidal treatment, which is clearly not ethically acceptable in children with persistent asthma. The fact that childhood growth occurs in three distinct phases as explained above must be taken into account when assessing the effect of therapy on growth. In addition, the fact that asthma itself can affect growth also complicates the interpretation of studies.

Confounding factors in studies evaluating therapy are illustrated in Figure 1. Others are concomitant administration of systemic or topical corticosteroids for asthma, allergic rhinitis or eczema.

According to Price *et al.*,¹¹ the key requirements for any study assessing growth are duration ≥ 12 months, height measured by a trained investigator using stadiometry, confounders taken into account, and a control group.

In order to assess the effect of exogenous CS on growth, the studies may be divided into the following categories:^{9,10,12}

- Studies of *growth markers*, which measure the effects of CS on markers of bone and collagen formation/degradation or growth
- *Short-term studies*, which assess growth over 6-month periods or less
- *Intermediate-term studies*, which evaluate growth over periods longer than 6 months but which do not assess final adult height
- *Long-term studies*, which assess growth for many years and include final adult height in relation to predicted adult height.

The growth markers and short-term studies are very sensitive to the presence of CS but correlate poorly with final height. The predictive value of studies for assessing clinically relevant effects of ICS on growth improves with increasing duration of the study.

The effect of asthma treatment on growth

CS are potent anti-inflammatory agents, and have become established as the most effective treatment for asthma. However, soon after they were used regularly for asthma control it became apparent that they have significant systemic side-effects in children when taken orally. Their major effects were central obesity and reduced growth velocity.¹³ This led to the development of ICS, of which BDP, developed in the early 1970s, was the first. The fact that smaller doses could be used and delivered directly to the airways reduced the potential for side-effects. The principal ICS side-effect causing concern for patients, parents and treating doctors is their effect on final height.

Covar *et al.*¹⁴ indicated that ICS reduced the growth suppression associated with asthma by reducing the use of oral CS and also by improving asthma control. However, the trend has been to use progressively higher doses of ICS earlier, in milder forms of asthma, and in younger children. It has been shown that the effect of systemic CS on growth is dose-dependent, and therefore, ICS can cause growth impairment if administered at high enough doses.¹¹

At present, no controlled studies have reported any clinically relevant systemic side-effects with orally inhaled CS in the dose range of 100-200 $\mu\text{g}/\text{day}$.¹⁰

Numerous studies have demonstrated clear dose-related growth suppression as measured by knemometry for BDP 200 and 400 $\mu\text{g}/\text{day}$, budesonide 400 and 800 $\mu\text{g}/\text{day}$, as well as for nebulised steroids. The clinical significance of these short-term growth suppressant effects is uncertain.

Studies comparing ICS with non-steroidal therapy have shown reduced growth velocity with BDP, but no significant differences in those treated with fluticasone propionate or budesonide vs cromones.¹⁵ In a prospective randomised study, children treated with BDP showed significantly slower growth than those treated with salmeterol (4.7 cm/year vs 6.1 cm/year), although the BDP-treated group experienced fewer asthma exacerbations.¹⁶ This effect was only significant for prepubertal children.

A study reporting on the follow-up of a cohort of 3 347 children with asthma in general practice found no growth impairment in children receiving ICS at doses <400 µg/day.¹⁷ Only children who received ≥400 µg/day showed impaired growth. However, this effect was less than the effect of poor socio-economic status or severe asthma on growth. This emphasises the importance of taking into account confounding factors in the assessment of growth in asthma studies.

The Childhood Asthma Management Program (CAMP) study was a multicentre trial, which included 1 041 children with mild to moderate asthma between the ages of 5 and 12 years.¹⁸ They were randomised to receive budesonide 400 µg/day, nedocromil or placebo, and were treated for 4-6 years (mean 4.3 years). This implies that many children entered puberty during the study. In this study oral CS were permitted; their use was greatest in the placebo and nedocromil groups and significantly lower in the budesonide group. The use of systemic CS therefore probably affected the results of the study. In the CAMP study growth velocity was reduced in the budesonide group compared with placebo and nedocromil; this reduction was most notable in the first year of ICS treatment and was persistent but not progressive. The estimation of final adult height was comparable for all three of the treatment groups.

Agertoft and Pedersen¹⁹ prospectively examined the effect on adult height of budesonide in 142 children with asthma. The children in the budesonide group received a mean daily dose of 412 µg (range 110-877 µg) for a mean duration of 9.2 years (range 3-13). They attained normal adult height when compared with control asthmatics who had never received ICS, and with 51 healthy siblings of patients in the budesonide group. In this study too, the growth velocity was significantly reduced during the first years of treatment, but after 2 years this was no longer significant.

Essentially the evidence from studies, flawed as their designs may be, indicates impaired growth velocity with budesonide and BDP in comparison with placebo, non-steroidal therapy and fluticasone propionate during the first 1-2 years of treatment, but no effect on final adult height.¹⁵ Two meta-analyses of growth studies have been published.^{13,20} In general, the findings from these studies concur with the previous statement, although Sharek and Bergman²⁰ did not include any studies that assessed final adult height in their meta-analysis.

Comparing different inhaled corticosteroids

Pedersen and O'Byrne²¹ emphasise that one cannot extrapolate from conclusions of studies investigating one ICS to other ICS. Growth retardation may be seen with all ICS if administered in sufficiently high doses for long periods without adjusting for disease severity. Younger children appear to be more susceptible to growth retardation from ICS than pubertal children. However, there are important differences in the growth-retarding effect of various ICS and inhalers. For example, in one study in prepubertal children, the growth rate during treatment with 400 µg/day of fluticasone propionate was significantly higher than with BDP 400 µg/day (4.99 cm/year vs 4.09 cm/year).²²

CONCLUSION

Conclusions from various studies addressing the question of final adult height are consistent regarding several issues. There is evidence that uncontrolled or severe asthma adversely affects growth and final adult height.¹⁰

ICS may be used for long periods of time in a large number of children and therefore safety issues have to

be taken into account. The following points are apparent:^{10,12}

- ICS in small doses pose no significant risk for systemic side-effects
- If ICS are used at higher doses for long periods of time, differences in the characteristics of the drug affect the ratio of the therapeutic to the systemic effect of the individual ICS
- Detectable suppression of growth can occur if ICS with poor first-pass metabolism are used at doses exceeding 400 µg/day
- Administration of ICS alone has not been associated with significant effects on final adult height
- ICS-induced changes in growth velocity during the first year of treatment do not predict adult height
- Cumulative steroid doses must be taken into account if intranasal or other topical CS are administered
- ICS remain far safer than oral glucocorticosteroids.

In summary, the studies evaluating ICS suggest that they are not only efficacious but also safe. In real life only children with moderate or severe asthma receive continuous daily ICS doses of 400 µg or more, and they may be less susceptible to their systemic effects than children with mild asthma. In addition, adherence to therapy would probably be poorer than in controlled drug trials. However, one should always use the lowest dose of ICS that achieves control of the child's asthma, and additional therapy may be preferable to increasing the ICS dose in case of poor control. Recommendations for the use of ICS in children are summarised in Table I.

Table I. Correct use of inhaled corticosteroids in children*

- Use in persistent asthma only
- Start with an appropriate (vs high) dose
- Step down to the lowest effective dose once control of symptoms has been achieved
- Use once-daily ICS
- Use an appropriate delivery system
- Use adjunctive alternative anti-inflammatory agents rather than increasing the ICS dose
- Choose the ICS carefully if high dose required
- Limit steroid therapy for co-morbid conditions
- Monitor the child's growth

*Adapted from Pedersen¹⁹ and Allen¹²

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