Send Orders for Reprints to reprints@benthamscience.ae

The Open Respiratory Medicine Journal, 2014, *8*, (Suppl 1: M2) 59-65

Open Access

Systemic Effects of Inhaled Corticosteroids: An Overview

Dhruti Pandya[1], Amar Puttanna[*,1] and Viswanatha Balagopal[2]

[1]*Department of Endocrinology, Walsall Manor Hospital, West Midlands, WS2 9PS, UK*

[2]*Department of Respiratory Medicine, Walsall Manor Hospital, Walsall, West Midlands, WS2 9PS, UK*

Abstract: Inhaled corticosteroids (ICS) are common medications, used in respiratory medicine for controlling conditions such as asthma and other obstructive airway diseases. The systemic effects of oral corticosteroids are well known and established; inhaled steroids have been known to cause relatively minor and localized adverse effects such as oral candidiasis. However, less attention has been paid to their systemic effects. Although currently there is a paucity of prospective studies demonstrating the systemic effects of inhaled corticosteroids, there are numerous retrospective studies adding evidence to this link. Inhaled corticosteroids can affect the hypothalamo-pituitary-adrenal axis, bone density and growth, eyes, skin and immunity including an increased risk of pneumonia. Clinicians are recommended to aim for the lowest possible dose to avoid these systemic side effects. Fluticasone is more likely to cause systemic effects compared to budesonide. Newer ICS molecules such as ciclesonide may be more beneficial in reducing such systemic complications on prolonged use. This paper provides an updated overview of the common systemic effects encountered with ICS treatment.

Keywords: Asthma, chronic obstructive pulmonary disease (COPD), diabetes progression, hypothalamo-pituitary-adrenal axis, inhaled corticosteroids (ICS), systemic adverse effects.

INTRODUCTION

Inhaled corticosteroids (ICS) are frequently used to treat chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). They are effective by reducing inflammation and airway hyper-responsiveness and therefore reduce the risk of exacerbations [1].

There are four main types of inhaled steroids that are widely available for treating patients, namely; beclometasone dipropionate, budesonide, fluticasone propionate and mometasone furoate. Relatively newer inhaled steroid molecules include ciclesonide and flunisolide.

Systemic effects can vary depending on the type of steroid and the dosage used. Other factors include pharmaco-kinetics, type of inhaler and method of administration with inter-patient differences in susceptibility and response [2].

Although prolonged exposure to oral steroids has long been associated with systemic side effects that are well established, the systemic effects of inhaled preparations are less often considered. As ICS are recommended for the management of common respiratory conditions such as asthma and COPD, and inhaled steroids being step 2 on the asthma management ladder [3] it is imperative that their systemic complications are highlighted and reviewed regularly by the prescribing clinician.

There is a substantial amount of data suggesting that inhaled corticosteroids are effective at managing respiratory conditions and thus will continue to remain the mainstay of treatment. However, clinicians must appreciate and recognize their widespread effects. The main objective of this article is to provide an overview of the systemic complications and effects that may occur in patients on long-term ICS. It aims to provide the clinician with an understanding of these effects so as to aid clinical management and knowledge when dealing with such patients.

ICS may exert their effects and cause complications in the hypothalmo-pituitary-adrenal (HPA) axis, bones, skin, eyes, growth and immunity. This paper will also address effects of ICS use in pregnancy.

EFFECTS ON HYPOTHALAMO-PITUITARY-ADRENAL (HPA) AXIS

ICS have been found to affect the hypothalamo-pituitary-adrenal axis [4]. Exogenous corticosteroids act on the hypothalamus and anterior pituitary gland, and cause a negative feedback which attenuates the release of cortisol from the adrenal cortex [5]. This hypo-stimulation causes shrinkage of the adrenals due to disuse. This suppressive effect of corticosteroids is only problematic if the exogenous stimulus is removed suddenly (i.e. inhalers discontinued), or if a greater cortisol response is required during the introduction of stressful stimuli e.g. infection, surgery, or trauma. The lack of an adequate endogenous glucocorticoid response (due to adrenal atrophy) would result in an adrenal insufficiency crisis.

Several studies have compared the effects of different ICS on the HPA axis and have assessed for a dose response

*Address correspondence to this author at the Department of Endocrinology, Walsall Manor Hospital, West Midlands, WS2 9PS, UK; Tel: +44-7850329633; E-mail: amarputtanna@doctors.org.uk

1874-3064/14

relationship. Low dose ICS (0.4 mg/day), regardless of the device or drug, have not shown to cause adrenal suppression [6]. Contrasting results do exist however as these studies were conducted over a short period of only two weeks [7] and one of these was not blinded [8] leading to potential confounders.

With higher doses (>0.4 mg/day), Clark *et al*. showed fluticasone administered to asthmatic children *via* a large volume spacer caused adrenal suppression as measured by urinary cortisol. Budesonide however at the same dose did not have this effect [9]. In a similar test in asthmatic adults comparing fluticasone and budesonide administered *via* metered-dose inhalers, only 8.3% patients had low urinary cortisol levels with budesonide, whilst 58% of patients on fluticasone were seen to have low urinary cortisol levels [10].

On comparing high dose ICS given *via* the same device, fluticasone propionate and beclomethasone dipropionate have more of an effect on the HPA axis than budesonide [9, 11]. Thus it can be concluded that fluticasone is more potent at inhibiting the HPA axis than budesonide and also this suppression is dose related.

In order to assess whether patients on ICS would be able to mount a response to stressful situations, stimulation with high dose exogenous corticotropin such as cosyntropin is required. Such studies have been conducted with long term beclomethasone dipropionate with no concomitant use of oral corticosteroids. Of the 11 patients on higher doses of ICS, 4 had low serum cortisol levels pre- and post-cosyntropin test [12]. Thus ICS at higher doses upset the response required to stressful stimuli.

Todd carried out a survey to inquire whether ICS caused adrenal crisis in children and adults. Of the 28 children meeting the study criteria, 22 had an episode of acute hypoglycemic events where they presented with reduced conciousness, coma or convulsions. In one case, the child's death was thought to be caused by adrenal insufficiency as demonstrated by adrenal hemorrhages and cushingoid features. In the study population (n=33), 30 subjects were found to have an impaired response to the short synacthen stimulation test. Moreover there were 37 episodes of adrenal crisis. The cause was found to be related to cessation or a reduction in the ICS dose [13]. This observation is consistent with the studies that prove ICS diminish the ability of the adrenals to mount a response to stress. 76% of adrenal crisis episodes in this survey were in patients on high dose ICS. In addition most of the episodes include the use of fluticasone despite it being the least prescribed ICS in the patient population [14, 15]. This is consistent with a meta-analysis showing that fluticasone was more effective in suppressing the adrenals *vs* budesonide [5, 15]. The higher lipophilic properties and longer half-life [16] of fluticasone may explain this difference. Fluticasone is able to distribute effectively due to its highly lipophilic nature, and its long half-life means it is able to exert its adrenal suppressive effects for an extended period [17]. This may also explain why fluticasone can be used to wean patients off oral corticosteroids i.e. high dose fluticasone has systemic effects comparable to that of oral corticosteroids [18].

With the abundance of data suggesting that ICS do affect the HPA axis, clinicians should regularly assess adrenal function particularly in patients on high doses of fluticasone [13]. Though budesonide may have a lesser effect on HPA, ciclesonide and flunisolide, which are newer ICS molecules, have been assessed for effects on the HPA, and have been found to possess reduced effects on the HPA [19, 20] and may be better treatment options in patients where this is of concern.

EFFECTS ON BONE

The link between systemic steroids and osteoporosis is well established. Glucocorticoids affect bone in a number of ways; they reduce the lifespan of osteoblasts and osteoclasts by inducing apoptosis as well as reducing recruitment of these cells from progenitor cells (thereby affecting bone formation and resorption). They also affect calcium absorption and excretion either by direct effects on the renal tubule or by affecting calcium binding in the intestines [21].

There is much controversy surrounding the effects of ICS on bone health. There are conflicting studies on the effects ICS have on bone density, and whether they increase fracture risk [22]. Some studies show that it is not the use of ICS that increase fracture risk, but rather the chronic respiratory disease process itself. This is demonstrated by Staa *et al.* [23]. Their study composed of three cohorts: patients on ICS, patients on non-corticosteroid bronchodilators and a control group. Those on systemic steroids were not included in the study. The relative rates of vertebral, non-vertebral and hip fractures were higher in the cohorts on ICS and those on non-corticosteroid bronchodilators compared to the control group. There was no difference however, between the ICS and non-corticosteroid cohort. This suggests that COPD patients are at a greater risk of developing osteoporosis and thus fractures independent of ICS use. The factors responsible for this may include hypercapnea, low BMI and the likelihood of COPD patients being heavier smokers [24]. Other studies such as the TORCH study also did not show an increase in fracture risk with the use of ICS [25].

Gonnelli compared the fracture risk of ICS compared with β2-agonists in COPD patients [26]. The parameters assessed were bone status of the calcaneus using ultrasound and vertebral fractures using radiography. This large study revealed that at higher doses (>1500 μg/day) of ICS is associated with an increase in the risk of vertebral fractures. Osteoporosis risk was higher in COPD patients on ICS versus COPD patients on other medications such as β2-agonists but not including ICS. In this study there was no correlation between β2-agonists and osteoporosis or a dose response relationship with fracture risk.

This is corroborated by Pujades-Rodriguez who also found an increased risk, albeit small, of fractures of any bone with higher doses of ICS [27]. Studies investigating the link between ICS and osteoporosis have found a negative correlation in asthmatics treated with ICS with regards to total minimized dose and Bone Mineral Density (BMD) up to 0.16SD [28]. Fracture risk and osteoporosis is of particular concern in the elderly in whom fractures can almost double the mortality rate for 5-10 years post fracture [29].

The systemic effects of ICS are not just limited to bone but have also been observed to affect the dental arch and palate. An increased frequency of malocclusion and an open-bite in children using ICS has also been found [30].

EYES

Cataracts are well known complications of systemic steroids and tend to be of central posterior location in the eyes. However, the etiology is still unclear [31]. The main postulated mechanism is gene transcription induced by glucocorticoids in the lens epithelium, though other indirect mechanisms acting on growth factors affecting lens development and homeostasis are suggested [32]. Also suggested is fluid build up in the lens fibers and lens protein agglutination as a result of inhibition of the sodium-potassium pump at the lens epithelium is postulated to be the relevant mechanism *via* which corticosteroids exert their cataract forming effect [33].

Many earlier studies did not exclude subjects who had been exposed to oral corticosteroids thus confounding their results [34]. A cross-sectional study by Cumming concluded that the use of ICS is associated with the growth of nuclear and sub-capsular cataracts [35]. A greater lifetime exposure to ICS was also related to higher risk of cataract formation with severity being measured through analyses of lens photographs. However, there was no significant increase in the risk of cortical cataract with the use of ICS [34].

There have been reports of ICS causing other serious ocular complications such as open angle glaucoma, which can lead to permanent eye damage if not managed appropriately. Garb *et al*. found that regular and long term (3 months or more) ICS or intranasal corticosteroid use lead to an increased risk of open angle glaucoma [36]. Several conflicting studies have been carried out in children, in whom cataracts are uncommon, and thus a significant increase in risk may not be observed [37]. Furthermore, some of these studies have also been confounded by previous exposure to oral corticosteroids [38].

Cataracts are one of the leading causes of blindness in the world [39]. It is thus important to establish *via* prospective studies whether ICS increase risk of cataracts as patients would benefit from regular monitoring of their ocular health.

EFFECTS ON IMMUNITY

There is a plethora of data evidencing the suppression of cell-mediated immunity by oral corticosteroids [40]. Thus far it is uncertain whether ICS do the same. Case reports have suggested that ICS may cause a recurrence of viral infections and tuberculosis [41, 42]. Lee *et al*. assessed the effects of high dose ICS on cell mediated immunity, using delayed type hypersensitivity skin testing as the measure of impaired cellular immunity. This small study among 18 subjects found that asthmatics on ICS for a duration of at least six months, did not have an impaired immunity compared with asthmatics on medications other than ICS [43]. England *et al*., who carried out a similar study, also did not find a suppression of cell mediated immunity with the use of high dose inhaled corticosteroids in healthy subjects [44]. However, the duration of ICS use was short (only 28 days). Moreover the prolonged use of low dose ICS has not been shown to affect cell mediated immunity either [45].

On the contrary, studies showed that fluticasone and budesonide, in COPD patients increased the risk of pneu=monia [46, 47]. Two recent studies have further cemented the association of inhaled corticosteroids and increased risk of pneumonia. The PATHOS study [48] assessed the yearly pneumonia events as well as hospital admissions and deaths due to pneumonia in patients with combinations of inhaled steroid and long acting beta 2 agonists. The study revealed that patients taking fluticasone and salmeterol were more likely to be admitted with pneumonia or pneumonia-related events compared to those on budesonide and formoterol. A further recent study by Suissa *et al*. [49] analysed a cohort of Canadian patients to assess the effects of inhaled corticosteroids. They confirmed that all ICS molecules are associated with an increased risk of serious pneumonia infections with fluticasone the most commmonly associated ICS type and having a dose-related risk.

EFFECTS ON GROWTH/LINEAR GROWTH

Several factors affect growth such as chronic disease, genetic background, suppression of the HPA axis and onset of puberty, and therefore it is difficult to fully assess the effects of steroids on growth [5]. Severe asthma therefore may confound the results of several studies which aim to determine whether ICS suppress growth. The limitations in studies exploring this field are: a short study duration which would not include final height, and the measure of growth such as knemometry whereby the length between the knee and heel is measured. Such studies confirm that oral prednisolone suppress lower leg growth as measured by knemometry and to a lesser degree, high dose ICS (>0.4 mg/day) also suppressed growth [50]. Beclomethasone compared with theophylline albeit more effective at disease control, has been shown to reduce height velocity, particularly in boys [51]. This study however did not follow up the patients to assess final growth.

Long term studies in this field are rare. However, they have shown that although ICS such as high dose beclomethasone result in delayed puberty and slower growth velocity, catch up growth allows them to reach their growth potential (predicted adult height) [52]. Another long-term study comparing asthmatics and non-asthmatics found that after accounting for mid-parental height, predicted height for asthmatics was comparable to healthy controls and that ICS had no effect on growth [53].

A recent study assessed the effects of inhaled steroids on bone density and growth. The authors found that children on budesonide and beclomethasone dipropionate had reduced linear growth and this did persist for up to two years from treatment commencement [54].

A recent Cochrane review [55] found that regular ICS use even at low to medium doses was associated with a 0.48 cm/year reduction in linear growth in children with mild to moderate asthma. They found that the effect decreased after the first year however there was limited long-term data and therefore could not ascertain whether ICS affected long-term growth.

PREGNANCY

Asthma affects a significant number of young women [56]. Optimal control of asthma in pregnancy is prudent to avoid complications in both the mother and fetus. ICS are the medications of choice for treating asthma in pregnancy and there are reports suggesting that their use in pregnancy reduces acute exacerbations and frequency of visits to primary care services [57]. Thus it is important to ensure that there are no major complications with their use.

Clinicians, particularly general practitioners, are often cautious about treating asthmatic pregnant women and feel that they do not have a good understanding on how to manage the condition safely [58]. A recent study [59] has also looked into non-pharmacological methods of treating asthma perhaps suggesting the hesitant nature among healthcare professionals surrounding the use of corticosteroids during pregnancy.

It is difficult to discern whether the reported maternal complications of asthma such as pre-eclampsia [60] are due to the medications used to treat asthma or the condition itself. Earlier studies suggest an association with peri-natal mortality and ICS [61], although this has been disproved by several more recent studies. One study does show however that there is an increased risk of preterm births with the use of ICS [62].

However, longer term effects of ICS on the offspring of women using ICS during pregnancy has not been explored sufficiently. Animal studies have shown that the cardiovascular and metabolic systems of fetus can be affected if exposed to glucocorticoids in-utero [63]. Therefore, the implications of ICS use on the fetus should be considered by the clinicians while prescribing the medications.

A prospective study by Marion *et al*. evaluated the effects of intrauterine glucocorticoid exposure in the offspring of 4083 women with asthma against a control group. The offspring were followed up to the median age of 6.1 years. This study revealed an increased risk of metabolic and endocrine disorders in the in-utero ICS exposed cohort versus control. Risk of other disorders however was not increased [64].

It is possible that glucocorticoids exert their effects on the fetus by crossing the placenta and acting on glucocorticoid regulated pathways. Hodyl however reports that these pathways are not affected by ICS [65]. This study aims to continue to follow up their cohort that may reveal development of further complications and whether the metabolic and endocrine disorders persist. There is a lack of reports corroborating Marion *et al*. and furthermore, the association between dosage of ICS and outcome was not assessed, therefore subsequent studies will need to address this.

Large cohort studies in Swedish populations have specifically assessed steroid use in pregnant women and found that in general anti-asthmatic drugs carry no risk for congenital malformations [66] and specifically budesonide is unlikely to cause any teratogenic risk to offspring [67].

SKIN EFFECTS

Corticosteroids cause a reduction in collagen synthesis by the skin and this is true of both oral and inhaled steroids. Thinning of the dermis and increased bruising/purpura have been noted in patients on high dose ICS [68].

What is difficult to ascertain once again is the influence of oral corticosteroids on these studies as in the study by Capewell *et al*., low dose ICS did not cause increase in purpura or skin bruising whereas the patients on high dose inhaled steroids also had oral steroid treatment. However, a slightly larger study looked at the effects of high dose ICS on skin bruising found that there was increased bruising compared to the control group and that this bruising was commoner in the elderly [69].

Although one case report has suggested a link between ICS and acne, no subsequent studies have analyzed this association [70].

The implications of these findings are more related to patient and physician awareness rather than adverse event prevention. However, skin tears and the increased risk of infection are potential concerns. As with the other systemic effects, using the lowest possible dose of ICS is expected to reduce this risk.

INHALED CORTICOSTEROIDS AND DIABETES RISK OR PROGRESSION

Glucocorticoids cause hyperglycaemia by two main mechanisms, namely, increased gluconeogenesis in the liver (including increased glucagon release which stimulates gluconeogenesis) and decreased glucose uptake in the liver and adipocytes *via* reduced insulin binding [71].

As with oral corticosteroids, ICS have been associated with an increased risk of developing diabetes and also worsening of glycemic control in patients with known diabetes.

There have been few case reports acknowledging the worsening of glycaemic control in patients commenced on high dose ICS including worsening of HbA1c [72]. However, a small prospective double-blind randomized controlled trial (n=12) found no difference in HbA1c values in patients with known asthma or COPD and diabetes on inhaled steroids at six weeks [73].

A large Canadian study looking at a cohort of patients with COPD treated with ICS found an increased risk of development and progression of diabetes in ICS users, especially at high doses. They found a statistically significant 34% mean increase in the incidence of type 2 diabetes in those patients on inhaled steroids [74].

There is enough evidence to suggest that patients with diabetes commenced on inhaled steroids should be monitored for worsening of glycemic control, and this is more important when higher doses of steroids are administered.

OTHER COMPLICATIONS

It has been difficult to confirm that ICS use is associated with an increased psychiatric morbidity. A study conducted

in Netherlands in 2006 [75] analysed adverse drug reporting patterns in pediatric populations found that alterations in behavior were the commonest reported effects. The authors suggested that this provides more evidence of the link between ICS and behavioral alterations. Another study in an adult population on high dose ICS suggested a negative association with mental well being. However, it was difficult to conclude that this was solely due to ICS rather than severity of disease [76].

A recent study has looked into the risk of gastrointestinal side effects: ulceration, gastritis and bleeding in patients taking ICS [77]. The study found a slight increase in the risk in patients on ICS, though this was reduced on using a spacer. This differs from previous suggestions that there was no link, although further studies are required to ascertain whether there is an actual increase in the risk.

CONCLUSION

ICS are one of the common medications prescribed in both primary and secondary care. Whilst not having the same potency or systemic effects as oral steroids, their systemic effects cannot be disputed. It is imperative that clinicians are aware of these effects to ensure that they can be minimized and patients can be monitored effectively and promptly. There are areas with lack of sufficient evidence with regards to the effects of ICS, especially whether there is a link between psychiatric or gastrointestinal side effects, and further studies will allow for a more detailed assessment.

It is important to note that for the most part, low dose steroids have reduced side effect profile and there is a dose response relationship with regards to systemic effects. Also worth noting is the difference in patient susceptibility to systemic effects regardless of steroid type. From current evidence we can conclude that budesonide has the least systemic effects with fluticasone having a higher risk especially at doses above 400 mcg/day. Other ICS molecules such as ciclesonide and flunisolide still lack sufficient evidence to comprehensively conclude whether they have a better side effect profile, although initial studies are promising.

Thus, clinicians should be watchful about increasing ICS doses and perhaps consider other methods of improving control such as pharmacological and non pharmacological methods to ensure that the risk does not outweigh benefit. Clinicians should also try and taper doses to find the lowest effective dose.

KEY POINTS

- ICS have demonstrable systemic effects, especially on the hypothalamo-pituitary-adrenal axis.
- Among ICS molecules, fluticasone has greater systemic side effects than other steroids, with budesonide having a better systemic adverse effect profile.
- Newer ICS such as ciclesonide might be of better beneficial effects in reducing the risk of systemic effects.
- Clinicians should use the lowest effective dose (ideally less than 400 mcg/day) when commencing patients on ICS, and be aware of the dose-dependant nature of the systemic effects.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Van Rensen EL, Straathof KC, Veselic-Charvat MA, Zwinderman AH, Bel EH, Sterk PJ. Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma. Thorax 1999; 54: 403-8.

[2] Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids new developments. Am J Respir Crit Care Med 1998; 157: S1-53.

[3] British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma: A national clinical guideline. https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-guideline-on-the-management-of-asthma/ (accessed 25 June 2014).

[4] White M, Crisalida T, Li H, Economides A, Kaliner M. Effects of long term inhaled corticosteroid on adrenal function in a patient with asthma. Ann Allergy Asthma Immunol 2006; 96: 437-44.

[5] Moghaddam KG, Rashidi N, Meybodi HA, *et al*. The effect of inhaled corticosteroids on hypothalamic-pituitary-adrenal axis. Indian J Pharmacol 2012; 44: 314-8.

[6] Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systemic review and meta-analysis. Arch Intern Med 1999; 159: 941-55.

[7] Agertoft L, Pedersen S. Short-term knemometry and urine cortisol excretion in children treated with fluticasone propionate and budesonide: a dose response study. Eur Respir J 1997; 10: 1507-12.

[8] Nicolaizik WH, Marchant JL, Preece MA, Warner JO. Endocrine and lung function in asthmatic children treated with inhaled budesonide. Am J Respir Crit Care Med 1994; 150: 624-8.

[9] Clark DJ, Clark RA, Lipworth BJ. Adrenal suppression with inhaled budesonide and fluticasone propionate given by a large volume spacer in asthmatic children. Thorax 1996; 51: 941-3.

[10] Clark DJ, Lipworth BJ. Adrenal suppression with chronic dosing of fluticasone propionate compared with budesonide in adult asthmatic patients. Thorax 1997; 52: 55-8.

[11] Pedersen S, Fugslang G Urine cortisol excretion in children treated with high doses of inhaled corticosteroids: a comparison of budesonide and beclomethasone. Eur Respir J 1988; 1: 433-5.

[12] Smith MJ, Hodson ME. Effects of long term inhaled high dose beclomethasone dipropionate on adrenal function. Thorax 1983; 38: 676-81.

[13] Allen A. The relationship between fluticasone furoate systemic exposure and cortisol suppression. Clin Pharmacokinet 2013; 52: 885-96.

[14] Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. J Allergy Clin Immunol 1996; 97(1 Pt 2): 169-76.

[15] Thorsson L, Dahlstrom K, Edsbacker S, *et al*. Pharmacokinetics and systemic effects of inhaled fluticasone propionate in healthy subjects. Br J Clin Pharmacol 1997; 43: 155-61.

[16] Fahim A, Faruqi S, Wright CE, Kastelik JA, Morice AH. Comparison of the effect of high-dose inhaled budesonide and fluticasone on adrenal function in patients with severe chronic obstructive pulmonary disease. Ann Thorac Med 2012; 7: 140-4.

[17] Casale TB, Nelson HS, Stricker WE, *et al*. Suppression of hypothalamic-pituitary-adrenal axis activity with inhaled flunisolide and fluticasone propionate in adult asthma patients. Ann Allergy Asthma Immunol 2001; 87: 379-85.

[18] Noonan M, Chervinsky P, Busse WW, *et al*. Fluticasone propionate reduces oral prednisolone use while it improves asthma control and quality of life. Am J Respir Crit Care Med 1995; 152: 1467-73.

[19] Rohatagi S, Luo Y, Shen L, *et al*. Protein binding and its potential for elliciting minimal systemic side effects with a novel inhaled corticosteroid, ciclesonide. Am J Ther 2005; 12: 201-9.

[20] Casale TB, Nelson HS, Stricker WE, Raff H, Newman KB. Suppression of hypothalamic-pituitary-adrenal axis activity with inhaled flunisolide and fluticasone propionate in adult asthma patients. Ann Allergy Asthma Immunol 2001; 87: 379-85.

[21] Jehle PM. Steroid-induced osteoporosis: how can it be avoided? Nephrol Dial Transplant 2003; 18: 861-4.

[22] Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. J Allergy Clin Immunol 1995; 96: 571-9.

[23] van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res 2001; 16: 581-8.

[24] Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk in patients with chronic lung diseases treated with bronchodilator drugs and inhaled and oral corticosteroids. Chest 2007; 132: 1599-607.

[25] Ferguson GT, Calverley PM, Anderson JA, *et al*. Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. Chest 2009; 136: 1456-65.

[26] Gonnelli S, Caffarelli C, Maggi S, *et al*. Effect of inhaled glucocorticoids and b2 agonists on vertebral fracture risk in COPD patients: The EOLO study. Calcif Tissue Int 2010; 87: 137-43.

[27] Pujades-Rodrı´guez M, Smith CJ, Hubbard RB. Inhaled corticosteroids and the risk of fracture in chronic obstructive pulmonary disease. QJM 2007; 100: 509-17.

[28] Wong CA, Walsh LJ, Smith CJP, *et al*. Inhaled corticosteroid use and bone mineral density in patients with asthma. Lancet 2000; 355(9213): 1399-403.

[29] Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009; 301: 513-21.

[30] Kumar S S, Nandlal B. Effects of Asthma and Inhalation corticosteroids on the dental arch morphology in children. J Indian Soc Pedod Prev Dent 2012; 30: 242-9.

[31] Urban RC Jr, Cotlier E. Corticosteroid-induced cataracts. Surv Ophthalmol 1986; 31: 102-10.

[32] James ER. The etiology of steroid cataract. J Ocul Pharmacol Ther 2007; 23: 403-20.

[33] Karim AK, Jacob TJ, Thompson GM. The human lens epithelium: morphological and ultrastructural changes associated with steroid therapy. Exp Eye Res 1989; 48: 215-24.

[34] Fraunfelder FT, Mayer SM. Posterior subcapsular cataracts associated with nasal or inhaled corticosteroids. Am J Ophthalmol 1990; 109: 489-90.

[35] Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med. 1997; 337: 8-14.

[36] Garb E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA 1997; 277: 722-7.

[37] Simons FER, Persaud MP, Gillespie CA, Cheang M, Shuckett EP. Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids. Lancet 1993; 342(8874): 776-8.

[38] Abuekteish F, Kirkpatrick JNP, Russell G. Posterior subcapsular cataract and inhaled corticosteroid therapy. Thorax 1995; 50: 674-6.

[39] Javitt JC, Wang F, West SK. Blindness due to cataract: epidemiology and prevention. Annu Rev Public Health 1996; 17: 159-77.

[40] Janis EM, Allen DW, Glesby MJ, *et al*. Tuberculin skin test reactivity, anergy, and HIV infection in hospitalized patients. Am J Med 1996; 100: 186-92.

[41] Abzug MJ, Cotton MF. Severe chickenpox after intranasal use of corticosteroids. J Pediatr 1993; 123: 577-9.

[42] Shaikh WA. Pulmonary tuberculosis in patients treated with inhaled beclomethasone. Allergy 1992; 47(4 Pt 1): 327-30.

[43] Lee C, Klaustermeyer WB. Effect of high dose inhaled corticosteroids on cell mediated immunity in patients with asthma. Allergol Immunopathol (Madr) 2012; 40: 100-3.

[44] England RW, Nugent JS, Grathwohl KW, Hagan L, Quinn JM. High dose inhaled fluticasone and delayed hypersensitivity skin testing. Chest 2003; 123: 1014-7.

[45] Levy J, Zalkinder I, Kuperman O, *et al*. Effect of prolonged use of inhaled steroids on the cellular immunity of children with asthma. J Allergy Clin Immunol 1995; 95: 806-12.

[46] Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014; 3: CD010115.

[47] Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. Arch Intern Med 2009; 169: 219-29.

[48] Janson C, Larsson K, Lisspers KH, *et al*. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β2 agonist: observational matched cohort study (PATHOS). BMJ 2013; 346: f3306.

[49] Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax 2013; 68: 1029-36.

[50] Wolthers OD, Pedersen S. Short term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate. Arch Dis Child 1993; 68: 673-6.

[51] Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. Pediatrics. 1993; 92: 64-77.

[52] Balfour-Lynn L. Growth and childhood asthma. Arch Dis Child 1986; 61 : 1049-55.

[53] Silverstein MD, Yunginger JW, Reed CE, *et al*. Attained adult height after childhood asthma: effect of glucocorticoid therapy. J Allergy Clin Immunol 1997; 99: 466-74.

[54] Fuhlbrigge AL, Kelly HW. Inhaled corticosteroids in children: effects on bone mineral density and growth. Lancet Respir Med 2014; 2: 487-96.

[55] Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. Cochrane Database Syst Rev 2014; 7: CD009471.

[56] Skadhauge LR, Baelum J, Siersted HC, *et al*. The occurrence of asthma among young adults. A population-based study in five west Danish counties. Ugeskr Laeger 2005; 167: 648-51.

[57] Schatz M, Leibman C. Inhaled corticosteroid use and outcomes in pregnancy. Ann Allergy Asthma Immunol 2005; 95: 234-8.

[58] Lim AS, Stewart K, Abramson MJ, George J. Management of asthma in pregnant women by general practitioners: a cross sectional survey. BMC Fam Pract 2011; 12: 121.

[59] Murphy VE, Gibson PG, Talbot PI, *et al*. Asthma self-management skills and the use of asthma education during pregnancy. Eur Respir J 2005; 26: 435-41.

[60] Lehrer S, Stone J, Lapinski R. Association between pregnancy-induced hypertension and asthma during pregnancy. Am J Obstet Gynecol 1993; 168: 1463-6.

[61] Gelber M, Sidi Y, Gassner S, *et al*. Uncontrollable life-threatening status asthmaticus: an indicator for termination of pregnancy by cesarean section. Respiration 1984; 46: 320-2.

[62] Schatz M, Zeiger RS, Hoffman CP, *et al*. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. Am J Respir Crit Care Med 1995; 151: 1170-4.

[63] Seckl JR, Meaney MJ. Glucocorticoid programming. Ann N Y Acad Sci 2004; 1032: 63-84.

[64] Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Inhaled glucocorticoids during pregnancy and offspring pediatric diseases: a national cohort study. Am J Respir Crit Care Med 2012; 185: 557-63.

[65] Hodyl NA, Stark MJ, Osei-Kumah A. Fetal glucocorticoid-regulated pathways are not affected by inhaled corticosteroid use for asthma during pregnancy. Am J Respir Crit Care Med 2011; 183: 716-22.

[66] Kallen B, Otterblad OP. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infatnts. Eur J Clin Pharmacol 2007; 63: 383-8.

[67] Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999; 93: 392-5.

[68] Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high-dose inhaled corticosteroids. BMJ 1990; 300(6739): 1548-51.

[69] Roy A, Leblanc C, Paquette L, *et al*. Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function. Eur Respir J 1996; 9: 226-31.

[70] Monk B, Cunliffe WJ, Layton AM, Rhodes DJ. Acne induced by inhaled corticosteroids. Clin Exp Dermatol 1993; 18: 148-50.

[71] Marco J, Calle C, Roman D, Diaz-Fierros M, Villanueva ML, Valverde I. Hyperglucagonism induced by glucocorticoid treatment in man. New Engl J Med 1973; 288: 128-31.

[72] Faul JL, Cormican LJ, Tormey VJ, Tormey WP, Burke CM. Deteriorating diabetic control associated with high-dose budesonide. Eur Respir J 1999; 14: 242-3.

[73] Faul JL, Wilson SR, Chu JW, Canfield J, Kuschner WG. The effect of an inhaled corticosteroid on glucose control in type 2 diabetes. Clin Med Res 2009; 7(1-2): 14-20.

[74] Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. Am J Med 2010; 123: 1001-6.

[75] de Vries TW, De Langden-Wouterse JJ, Van Puijenbroek E, Duiverman EJ, De Jong-Van den Berg LT. Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. Eur J Clin Pharmacol 2006; 62: 343-6.

[76] Bonala SB, Pina D, Silverman BA, Amara S, Bassett CW, Schneider AT. Asthma severity, psychiatric morbidity, and quality of life: correlation with inhaled corticosteroid dose. J Asthma 2003; 40: 691-9.

[77] Hansen RA, Tu W, Wang J, Ambuehl R, McDonald CJ, Murray MD. Risk of adverse gastrointestinal events from inhaled corticosteroids. Pharmacotherapy 2008; 28: 1325-34.

Received: October 10, 2014 Revised: October 21, 2014 Accepted: October 21, 2014