Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review

R Rahimi¹, S Nikfar² and M Abdollahi*¹

¹Faculty of Pharmacy, and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran;
²Iran Drug Selecting Committee Secretariat, Deputy of Food and Drug, Ministry of Health and Medical Education, Tehran, Iran

Inhaled corticosteroids (ICs) are the drug of choice for asthmatic women during pregnancy, but the results on the effects of these medications on obstetrical and perinatal outcomes are not conclusive. Meta-analysis is the statistical analysis of a collection of analysis results from individual studies for the purpose of integrating the findings. Meta-analysis techniques are necessary because only summary statistics are available in the literature. In order to determine the risk of exposure to ICs, we pooled data from all clinical studies that evaluated the pregnancy and perinatal outcomes in women exposed to this group of drugs during pregnancy by the meta-analytic technique.

PUBMED, OVID, EMBASE and SCOPUS databases were searched for studies that investigated birth outcome following exposure to ICs during pregnancy. Data were collected from 1997 to 2005 (up to 31 December). Types of outcome investigated were major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension. The criteria for inclusion of studies in this meta-analysis were exposure of women to any therapeutic dosage of any ICs (fluticasone, beclomethasone, budesonide, triamcinolone and flunisolide) during pregnancy.

The results showed that ICs do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension. In conclusion, ICs do not increase the rates of any obstetrical outcomes investigated in the present study and interestingly improve the symptoms and are helpful in the management of asthma and thus can be used comfortably during pregnancy.

Key words: asthma; inhaled corticosteroids; meta-analysis; perinatal outcome; pregnancy; pregnancy outcome

Introduction

Asthma is a common and potentially serious complication of pregnancy.¹ It has been determined that the prevalence of asthma among pregnant women in the USA is between 3.7% and 8.4%. A rising trend in the prevalence of asthma has also been observed.² It is estimated that asthma complicates the course of 200000 to 376000 pregnancies every year.³

Few results have demonstrated that asthma was not associated with a significant increase in preterm delivery,⁴ gestational diabetes,⁴ fetal death⁶ or other adverse perinatal outcomes.⁴,⁷ Most studies have shown that the incidence of preterm delivery,⁸-¹⁰ gestational diabetes,⁶,¹⁰ intrauterine growth restriction,⁶,¹¹ congenital malformations,¹² fetal death,¹⁰,¹² hypertensive disorders,⁶,⁷,⁹,¹⁰ pre-eclampsia⁹,¹² and premature rupture of membranes⁶,¹⁰ in asthmatic pregnant women is higher than in non-asthmatic ones.⁶ Higher rates of caesarean deliveries have been found among asthmatic patients as compared to controls.⁴,⁶,⁹,¹⁰,¹²,¹⁵ Murphy has shown that although there are no significant differences between mild and moderate–severe asthmatic and non-asthmatic pregnant women in regards to preterm delivery and gestational diabetes, severe asthmatic ones have a significantly elevated risk of these outcomes.¹³ Treatment guidelines therefore emphasize the importance of maintaining asthma control during pregnancy.¹
of the National, Heart, Lung, and Blood Institute (NHLBI) of the USA, a working group on asthma and pregnancy developed treatment guidelines. These guidelines recommended anti-inflammatory medications such as inhaled corticosteroids (ICs) as the first-line therapy for asthma. In general, there are many studies evaluating the safety of corticosteroid use during pregnancy. Some reported adverse effects are orofacial clefts, maternal infections and reduction of fetal head circumference. There are also some studies on the safety of ICs and their effects on pregnancy and perinatal outcomes, but the safety of use of these drugs during pregnancy is not well understood. Although narrative reviews had been used for this purpose, the narrative review is largely subjective and thus different experts can come to different conclusions and it becomes impossibly difficult when there are more than a few studies involved. Meta-analysis is the statistical procedure for combining data from multiple studies and is necessary because only summary statistics are available in the literature. No meta-analysis has been done on the safety of use of ICs on pregnancy yet. Therefore, we were interested in collecting all studies about the effects of ICs on obstetrical outcomes and determining whether the use of this type of medication is harmful or safe during pregnancy, using the meta-analysis technique.

Methods

PUBMED, OVID, EMBASE and SCOPUS databases were searched for studies that investigated birth outcome following exposure to ICs during pregnancy. Data were collected from 1997 to 2005 (up to 31 December). The keywords used to search were: ICs or inhaled glucocorticoids with pregnancy, birth outcome or obstetric outcome. The reference lists from retrieved articles were also reviewed for additional applicable studies. Types of outcomes investigated were major malformation, preterm delivery (≤37 week), low birth weight and pregnancy-induced hypertension. Studies that had compared these outcomes in asthmatic women receiving ICs during pregnancy with asthmatic ones who did not receive this type of drug during pregnancy were included. Three reviewers independently reviewed the retrieved articles. The criteria for inclusion of studies in this analysis were exposure of women to any therapeutic dosage of any ICs (fluticasone, beclomethasone, budesonide, triamcinolone and flunisolide) during pregnancy. Studies that were reviewed, had not investigated the effects of ICs alone, had not determined our desirable outcomes, did not have a control group or had a control group made up of non-asthmatic women were excluded. Data from accepted studies were extracted in the form of 2 × 2 tables. All included studies were pooled and weighted. Odds ratio (OR) was derived from outcomes, a fixed-effect model was used for meta-analysis of major malformations and a random-effect model was used for meta-analysis of preterm delivery. Data were analysed using Statsdirect. OR and 95% confidence intervals (95% CI) were calculated using the Mantel–Haenszel method for fixed-effects model and DerSimonian–Laird method for random-effects model. A Breslow-Day test was used to test non-combinability of ORs.

Results

The majority of the retrieved articles were reviews and thus were excluded. Only four related studies were reviewed for additional applicable trials. Four studies did not investigate the effects of ICs independently, one had not determined our desirable outcomes, five did not have a control group and one had a control group consisting of non-asthmatic women; thus these trials were excluded. Four studies met our inclusion criteria and were included in the meta-analysis (Table 1).

The summary OR for major malformations in two studies was 0.96 with a 95% CI of 0.51–1.83 and a non-significant OR (P = 0.9582, Figure 1). The summary OR for preterm delivery in three studies was 0.99 with a 95% CI of 0.8–1.22 and a non-significant OR (P = 0.9687, Figure 2). The

Table 1 Outcomes (major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension) of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Major malformations</th>
<th>Preterm delivery</th>
<th>Low birth weight</th>
<th>Pregnancy-induced hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ex</td>
<td>Non-ex</td>
<td>Ex</td>
<td>Non-ex</td>
</tr>
<tr>
<td>Bracken et al., 2003</td>
<td>–</td>
<td>–</td>
<td>15/176</td>
<td>136/2029</td>
</tr>
<tr>
<td>Schatz et al., 2004</td>
<td>14/722</td>
<td>28/1401</td>
<td>140/722</td>
<td>277/1401</td>
</tr>
<tr>
<td>Martel et al., 2005</td>
<td>–</td>
<td>–</td>
<td>3/125</td>
<td>6/100</td>
</tr>
<tr>
<td>Otsuka et al., 2005</td>
<td>0/125</td>
<td>0/100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>14/847</td>
<td>28/1501</td>
<td>158/1023</td>
<td>419/3530</td>
</tr>
</tbody>
</table>

Ex, asthmatic pregnant women exposed to ICs; non-ex, asthmatic pregnant women not exposed to ICs.
summary OR for low birth weight delivery in two studies\textsuperscript{5,33} was 0.89 with a 95\% CI of 0.7 – 1.14 and a non-significant OR ($P = 0.4013$, Figure 3). The summary OR for pregnancy-induced hypertension in three studies\textsuperscript{33 – 35} was 0.97 with a 95\% CI of 0.84 – 1.2 and a non-significant OR ($P = 0.9932$, Figure 4). The Breslow-Day tests for heterogeneity ($P = 0.9249$, $P = 0.2521$, $P = 0.6146$ and $P = 0.0013$ respectively) indicated that the studies for major malformation, preterm delivery and low birth weight were not significantly heterogeneous and could be combined but because of significant heterogeneity of included papers for the study of pregnancy-induced hypertension, the random effects for individual and summary of OR for meta-analysis of this study has been applied.

\textbf{Discussion}

Although NAEPP new guidelines stress ICs as first-line therapy in controlling asthma during pregnancy, Kallen \textit{et al.} have studied the teratogenic risk of inhaled budenoside in 2014 infants whose mothers had used this drug during pregnancy. No increase in the general rate of congenital malformations was observed: 3.8\% (95\% CI 2.9, 4.6) of the infants had a congenital malformation diagnosed, which is similar to the population rate (3.5\%). After exposure to budesonide, four infants were born with orofacial clefts; this also is similar to the expected number (3.3).\textsuperscript{29} Namazy \textit{et al.} have evaluated the adverse outcomes of IC use during pregnancy on infants of 396 mothers. They have demonstrated that
the incidence of infants with low birth weight, preterm birth and congenital malformations was not greater than expected in the general population. Bakhireva et al. have examined the effect of ICs on fetal growth in infants born to women with asthma compared with infants born to controls without asthma and have shown that ICs during pregnancy do not impair fetal growth. Norjavaara and de Verdier have investigated information about 2968 mothers who reported use of inhaled budesonide during early pregnancy and demonstrated that they gave birth to infants of normal gestational age, birth weight and length, with no increased rate of stillbirths or multiple births. Only the rate of caesarean births was higher among mothers who used asthma medication during their pregnancy than among the control group. Martel et al. have shown that ICs are not associated with an increased risk of pregnancy-induced hypertension or pre-eclampsia during pregnancy. Schatz et al. found no significant relationship between the use of ICs and gestational hypertension, preterm delivery, low birth weight and small for gestational age. Otsuka et al. have shown ICs to be safe and useful for asthma during pregnancy because of decreasing perinatal abnormalities such as preterm delivery and pregnancy-induced hypertension. To our knowledge, no systematic analysis investigating the relationship between exposure to ICs during pregnancy and rates of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension has been published. The

Figure 3  Individual and summary odds ratio for the outcome of “low birth weight” for studies including IC exposure during pregnancy.

Figure 4  Individual and summary odds ratio for the outcome of “pregnancy-induced hypertension” for studies including IC exposure during pregnancy.
meta-analysis refers to the statistical analysis of a collection of analysis results from individual studies for the purpose of integrating the findings. The meta-analysis technique is necessary because only summary statistics are available in the literature. In other words, meta-analysis is the statistical procedure for combining data from multiple studies. The results from the present meta-analysis showed that the use of ICs during pregnancy has not been associated with an increase in the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension. As ICs have been shown to be useful in controlling asthma during pregnancy and decrease unwanted symptoms of asthma, they can be used safely in this period. In this study, our control group was asthmatic women who had not used ICs during pregnancy. It is suggested to do clinical trials on the effects of ICs on pregnancy and birth outcomes with a control group of non-asthmatic women. In this way, more conclusive results about the safety of IC use during pregnancy would be obtained. Until now, there has been only one study that compared the obstetrical outcomes in asthmatic women who used ICs during pregnancy with non-asthmatic controls. The results of that study indicated that there was no significant difference in the rates of pregnancy-induced hypertension and neonatal birth weight between the two groups, but there was a significant increase in the rate of major structural anomalies in IC users in comparison to non-asthmatic controls. This observed increase in the rate of major anomalies seems to be a consequence of asthma, not the result of IC use.

One might think that severity of asthma or other complications during pregnancy in this kind of patient could confound the results of this study. In addition, some might think that the small number of included studies may reduce the impact of the present systematic meta-analysis review. In answer to both of these questions, it should be emphasized that the most important parameter in meta-analysis is the inclusion and it is more than necessary to select shared outcomes of different studies and exclude those that had a different study design. Thus, the small number of included studies in the present meta-analysis does not bias the conclusion of this study. All included studies were pooled and weighted, OR was derived from outcomes, a fixed-effect model was used for meta-analysis of major malformations and a random-effect model was used for meta-analysis of preterm delivery. In a fixed-effect model, the true magnitude of the effect is assumed to be a constant, whose value is unknown but is estimated by the values from the included studies. In a random-effect model, the magnitude of effect can vary between studies. Therefore, the severity of asthma or other confounding parameters cannot be biased for this meta-analysis.

In conclusion, ICs do not increase the rates of any obstetrical outcomes investigated in the present study and, interestingly, improve the symptoms and are helpful in the management of asthma and thus can be used comfortably during pregnancy.

References


