
Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide

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Background: Budesonide is the only inhaled corticosteroid to be given a category B pregnancy rating by the US Food and Drug Administration, based on observational data from the Swedish Medical Birth Registry. However, data from large randomized controlled trials are lacking.

Objective: To compare pregnancy outcomes among patients with recent-onset mild-to-moderate persistent asthma receiving low-dose budesonide vs placebo.

Methods: In a randomized, double-blind, placebo-controlled trial, 7,241 patients aged 5 to 66 years with mild-to-moderate persistent asthma for less than 2 years and no previous regular corticosteroid therapy received once-daily budesonide or placebo via dry powder inhaler in addition to their usual asthma medication for 3 years. This trial was followed by a 2-year open-label treatment period. The daily dose of budesonide was 400 μ g for adults. The study included 2,473 females aged 15 to 50 years at randomization. Pregnancy was not an exclusion criterion (except for US patients).

Results: Of 319 pregnancies reported, 313 were analyzed. Healthy children were delivered in 81% and 77% of all pregnancies in the budesonide and placebo groups, respectively. Of the 196 pregnancies reported by participants taking budesonide, 38 (19%) had adverse outcomes: 23 (12%) had miscarriages, 3 (2%) had congenital malformations, and 12 (6%) had other outcomes. Of the 117 pregnancies reported in the placebo group, 27 (23%) had adverse outcomes: 11 (9%) had miscarriages, 4 (3%) had congenital malformations, and 12 (10%) had other outcomes.

Conclusions: Treatment with low-dose inhaled budesonide in females with mild-to-moderate persistent asthma does not seem to affect the outcome of pregnancy.

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INTRODUCTION

Asthma commonly complicates pregnancy, sometimes with serious consequences.¹ Inadequate control of asthma during pregnancy has been associated with adverse outcomes, such as higher rates of premature births, intrauterine growth retardation, lower birth weight, perinatal mortality, and pre-eclampsia, which may be due to fetal hypoxia.^{2,3} However, pregnancy in well-controlled asthmatic women has been associated with outcomes that are not significantly different from those of the nonasthmatic population.^{4–6} Therefore, treatment guidelines emphasize the importance of maintaining asthma control during pregnancy, and inhaled corticoste-

roids (ICSs) are recommended as first-line regular therapy in pregnant individuals with moderate-to-severe asthma.⁷

Nevertheless, ICSs are labeled with a pregnancy warning based on reproductive toxicologic studies in animals in which a teratogenic effect (cleft palate) has been reported.^{8–10} Whether this effect is relevant in humans remains controversial.^{11–16}

Three large, population-based observational studies^{17–19} using the Swedish Medical Birth Registry have provided reassuring data on the use of inhaled budesonide for the treatment of asthma during pregnancy. These studies detected neither an increased risk of congenital malformation (based on 2,534 budesonide-exposed pregnancies) nor an increased rate of premature birth, stillbirth, multiple births, or decreased birth weight or length (based on 2,968 budesonide-exposed pregnancies). The value of these epidemiologic data and the quantity of safety and efficacy data available have been recognized by the American College of Allergy, Asthma and Immunology and by the American College of Obstetricians and Gynecologists.⁷ Furthermore, budesonide is the only ICS assigned a category B pregnancy rating by the US Food and Drug Administration (ie, no risk in controlled animal studies plus sufficient clinical safety data in pregnancy).²⁰ However, precise data on dose and duration were lacking in the epide-

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miologic studies of inhaled budesonide, and potential confounding factors were not allowed for. A recent observational study²¹ failed to show any association between birth weight and corticosteroid dose given during pregnancy but pointed out that a randomized controlled trial was needed to avoid bias.

START (inhaled Steroid Treatment As Regular Therapy), the largest asthma trial ever reported, is a randomized, double-blind study investigating early intervention with inhaled budesonide in patients with recent-onset mild-to-moderate persistent asthma.²² The START study included 7,241 patients (aged 5–66 years) from 32 countries during a 3-year double-blind period (part A), during which patients were randomly allocated to receive either budesonide or placebo in addition to their usual asthma medication, followed by a 2-year open-label period (part B), during which all patients received budesonide.²² The purpose of the present study was to compare the pregnancy outcomes among patients treated with budesonide vs placebo.

METHODS

Patients and Schedule of Visits

Between October 1, 1996, and January 31, 1998, 7,241 patients aged 5 to 66 years from 32 countries were enrolled in a randomized controlled trial. Patients had symptoms such as wheeze, cough, dyspnea, and chest tightness at least weekly, but not as often as daily, during the 3 months before entering the study. All the patients had reversible airway obstruction, defined as an increase in forced expiratory volume in 1 second (FEV₁) of more than 12% after receiving a short-acting bronchodilator or as a decline in FEV₁ of more than 15% on exercise testing or as a variation of more than 15% between the 2 highest and the 2 lowest peak expiratory flow rates recorded during a 14-day period. Patients were excluded if (1) they had asthma symptoms or had received asthma treatment for more than 2 years before entry, (2) they had received more than 30 days of corticosteroid treatment or more than 1 depot corticosteroid injection per year, (3) delaying ICS treatment was judged to be inappropriate by the treating physician, (4) prebronchodilator FEV₁ was less than 60% of predicted, (5) postbronchodilator FEV₁ was less than 80% of predicted, or (6) they had another clinically significant disease. The patients or their parents signed an informed consent form approved by the institutional review board at their local study site. Follow-up visits occurred 6 and 12 weeks after randomization and then every 3 months for 3 years during part A and at 2 years during part B.

Treatment

In the 3-year double-blind phase of the study (part A), patients were randomly assigned to receive once-daily budesonide (Pulmicort; AstraZeneca, Lund, Sweden) or placebo, delivered via a dry powder inhaler (Turbuhaler; AstraZeneca), in addition to their usual asthma treatment. The daily dose of budesonide was 400 µg in patients 11 years or older at randomization. The placebo consisted of lactose. Changes

in concurrent medication use, including introducing inhaled or systemic corticosteroids, were permitted during the study at the investigator's discretion if necessary to achieve asthma control. In the 2-year open-label period (part B), all participants received a daily dose of 400 µg of budesonide in addition to their usual therapy.

Pregnancy Outcome Measures

The outcome of pregnancy was a secondary aim of the START study. Pregnancy outcome data for patients who became pregnant during the START study were collected using a separate study-specific pregnancy form. All pregnancies that occurred during treatment in the 3-year double-blind phase of the study (part A) or in the 2-year open-label period (part B) were followed up to the end point (including dropouts) and are reported herein. Birth weight and gestational age were not recorded. The pregnancies were entered into and analyzed in a separate database. Summary statistics were used to calculate the number and frequencies of the pregnancy outcomes.

RESULTS

Study Population

In total, 3,642 patients were randomized to receive budesonide and 3,599 were randomized to receive placebo in this worldwide study. Of these, 2,010 patients did not complete the 3-year follow-up owing to adverse events (46 in the budesonide group and 44 in the placebo group), asthma deterioration (3 and 6), lost to follow-up (105 and 106), withdrawal of informed consent (509 and 507), not fulfilling the randomization criteria (155 and 151), noncompliance with study procedures (71 and 97), or other reasons (82 and 89); in addition, 39 patients who became pregnant during the study were excluded from the main clinical study for regulatory reasons (US regulations) but are included in this pregnancy study. The dropout rate and the mean time in the randomized phase of the study were comparable for the budesonide and placebo treatment arms (2.47 and 2.44 years). The baseline characteristics were similar in the 2 treatment groups and have been described previously.²² Overall, 5,150 patients entered the open-label phase of the study (part B), and 4,712 patients completed the full 5-year study. The dropout rate during the open-label phase was 8.5%.

Pregnancy During Part A

The study included 2,473 females (1,250 in the budesonide group and 1,223 in the placebo group) aged 15 to 50 years (there were no pregnancies in patients aged <15 years). In total, 223 participants reported that pregnancy began during part A of the study; 4 of these patients (3 taking budesonide and 1 taking placebo) were lost to follow-up. The data set thus includes 219 pregnancies (102 in the budesonide group and 117 in the placebo group). Healthy children were delivered in 76% of all pregnancies for budesonide and 77% for placebo. Adverse outcomes are listed in Table 1. The category "other outcome" included 1 hydatidiform mole and 1

Table 1. Outcomes of the 313 Pregnancies Analyzed

	Budesonide part A (n = 102)	Budesonide total (n = 196)*	Placebo part A (n = 117)
Healthy children, No. (%)	78 (76)	158 (81)	90 (77)
Adverse outcomes, No. (%)	24 (24)	38 (19)	27 (23)
Spontaneous abortion	15	23	11
Congenital abnormality	1	3	4
Extrauterine pregnancy	3	4	3
Induced abortion	3	6	6
Other outcome	2	2	3

*Includes all pregnancies in the budesonide group in part A plus all pregnancies in part B (open-label budesonide).

case of “premature separation of the placenta plus intrauterine necrosis” in the budesonide group. The corresponding placebo cases are 1 hydatidiform mole, 1 case of “hepatitis in mother; child died,” and 1 preterm delivery in which the child died after 3 months owing to intestinal complications without leaving the neonatal intensive care unit. Of the 102 pregnancies in the budesonide group, there were 5 preterm labors and 11 were caesarian sections. The corresponding figures for the 117 pregnancies in the placebo group were 8 and 4, respectively. During part A, 2 patients in the budesonide group had used ICSs for less than 14 days, and 17 patients in the placebo group had used ICSs for more than 14 days. However, reanalyzing the data after shifting these patients to the opposite group did not change the main results.

Pregnancy During Part B

During open-label budesonide therapy, 96 participants reported that pregnancy started during part B of the study. Two of these patients (1 taking budesonide in parts A and B and 1 taking placebo in part A and budesonide in part B) were lost to follow-up. The data set thus includes 94 pregnancies (51 in the budesonide group during parts A and B and 43 in the placebo group during part A and the budesonide group during part B). Healthy children were delivered in 81% of all pregnancies in patients receiving budesonide during parts A and B and in 79% of those receiving placebo during part A and budesonide during part B. During part B, there were 2 preterm labors and 17 caesarian sections.

Comparing Budesonide With Placebo

There were 3 congenital abnormalities in 196 births (2%) in patients receiving budesonide and 4 congenital abnormalities in 117 births (3%) in patients receiving placebo when all patients taking budesonide in parts A and B were compared with those taking placebo in part A. The proportion of pregnancies that terminated because of spontaneous abortion, extrauterine pregnancy, and induced abortions was identical at 17% in these 2 groups (Table 1). Hypertension developing during pregnancy was reported in only 3 patients, 1 taking budesonide and 2 taking placebo, all of whom delivered healthy children.

DISCUSSION

The results of this large, international, randomized, double-blind, prospective asthma study showed that treatment with low-dose budesonide had no adverse effects on the outcome of pregnancy in patients with mild-to-moderate persistent asthma. There is insufficient information on many of the medications that may sometimes be used in pregnancy, such as antibiotics and drugs to treat seizure disorders, hypertension, and psychiatric conditions. For most products, whether newly marketed or commercially available for an extended period, laboratory animal studies and isolated case reports may provide the only information on potential health effects during human pregnancy. Randomized controlled studies of health effects during pregnancy require the deliberate administration of these products to pregnant patients and are often not feasible.²³ In practice, during the clinical development of most products, pregnant individuals are explicitly excluded from trials. If pregnancy occurs during a trial, the usual procedure is to discontinue treatment and drop the patient from the study. Consequently, at the time of a product's marketing, there are seldom meaningful human data on the effects of that product during pregnancy.

Although studies with corticosteroids have demonstrated that they are teratogenic in animals, as a group they have not been associated with congenital malformations in humans.¹⁶ A review¹¹ of published case reports and case series published between 1952 and 1994 of maternal treatment with corticosteroids in the first 70 days after conception within an analysis of reported congenital malformations in the infants born to these mothers also supports this conclusion. Although there were few congenital malformations in our study, it may seem that the overall outcome for healthy pregnancy is low (81%). The figure is affected by the large number of reported spontaneous abortions. This is a feature of pregnancies studied from conception rather than from later in gestation, the usual time for recruitment into studies.

In a systematic review²⁴ of studies investigating the risk of congenital malformations associated with asthma treatment during the first trimester of pregnancy, only 3 eligible studies met the quality criteria defined by the authors of the review. One study did not even include ICSs, another study²⁵ included 137 pregnant patients exposed to inhaled beclomethasone, and a further study¹⁷ included 2,014 pregnant individuals exposed to inhaled budesonide. Neither study reported a significant increase in the proportion of congenital malformations with ICS use. A recent observational study²¹ supports these conclusions. We did not collect data on birth weight, but there are reassuring observational data concerning fetal growth during maternal ICS treatment for asthma.^{19,21} No evidence of impaired intrauterine growth was found.

Despite these observations, practitioners have been reluctant to prescribe ICSs to pregnant patients in part because of general constraints in prescribing any medication during pregnancy and also because of concerns raised by the label warning that maternal adverse effects and adverse perinatal

outcomes may result from any type of corticosteroid administration. In addition, some patients may be reluctant to take their prescribed medication for fear of possible adverse effects. This may, in turn, impair asthma control and thereby increase the risk of adverse outcomes, such as premature birth, intrauterine growth retardation, low birth weight, increased perinatal mortality, and preeclampsia.^{2,3}

The unique contribution of the START study is its randomized controlled design. The results showed no difference in the rate of malformation between the budesonide and placebo groups, although the study was underpowered to identify small differences in pregnancy outcome, a secondary aim of the START study. Nevertheless, it supports large observational studies of the Swedish Medical Birth Register.^{17,18} The START study, however, is also unique in providing precise information on dose and duration and in the fact that exposure was throughout the entire pregnancy, beginning at conception. It is also the first truly international study, including a wide mix of ethnicity, which renders the results more widely generalizable.

Results of the large studies with inhaled budesonide should be applied with caution to other ICSs because the systemic effects of different ICSs vary owing to differences in the potency and bioavailability of the drugs and their metabolites.^{26,27} Unlike budesonide, some ICSs are 9-fluorinated or 9-halogenated and do not undergo marked inactivation by the placenta²⁸ and thus, in theory, could potentially exert a greater effect on the fetus. The one comparative data set did not show any differences in outcome between different ICSs, but total numbers were small (25–201 for different agents), and there was no control group.²¹

In conclusion, the results of the START study support the finding that treatment with low-dose budesonide during the full course of pregnancy in individuals with mild-to-moderate persistent asthma has no adverse effects on the fetus or newborn. This finding corroborates various asthma treatment guidelines⁷ and the Food and Drug Administration pregnancy labeling for budesonide (Pulmicort Turbuhaler and Pulmicort Respules).²⁰

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