Original Article

Safety of Fluticasone Propionate Prescribed for Asthma During Pregnancy: A UK Population-Based Cohort Study

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What is already known about this topic? Little is known about the safety of many inhaled corticosteroids when used during pregnancy, and with the exception of the Swedish Medical Birth Register study of budesonide, there is limited data from studies in humans.

What does the article add to our knowledge? This study found no increase in the overall risk of major congenital malformations after exposure to fluticasone propionate during the first trimester of pregnancy compared with exposure to nonfluticasone propionate inhaled corticosteroids.

How does the study impact current management guidelines? This study supports the findings of studies evaluating the safety of other inhaled corticosteroids and provides reassurance to women and clinicians that fluticasone propionate is not a major teratogen.

BACKGROUND: Asthma is commonly treated during pregnancy, yet data on the safety of asthma medicines used during pregnancy are sparse.

OBJECTIVE: The objective of this study was to evaluate the safety of the inhaled corticosteroid (ICS) fluticasone propionate (FP), alone and in fixed-dose combination with salmeterol (FSC) in terms of the risk of all major congenital malformations (MCMs), compared with all other non-FP ICS.

METHODS: Women with asthma who had a pregnancy between January 1, 2000, and December 31, 2010, were identified in the United Kingdom's Clinical Practice Research Datalink. Exposure to asthma medicines during the first trimester of pregnancy was based on issued prescriptions. The mothers' and infants' medical records were linked where possible, and pregnancy outcomes with an MCM diagnosed by age 1 year were identified based on medical codes in the mother's and infant's medical records, including those MCMs prenatally diagnosed that ended in an induced pregnancy termination. The absolute and relative risks of an MCM after different ICS exposures, stratified by the asthma treatment intensity level, were calculated.

RESULTS: A total of 14,654 mother-infant pairs were identified, of which 6,174 received an ICS prescription during the first trimester, in addition to 13 first trimester ICS exposed pregnancies that ended in an induced termination after a prenatal MCM diagnosis. In total, 5,362 pregnancies were eligible for the primary analysis at age 1 year. The absolute risk of an MCM after any first trimester FP exposure was 2.4% (CI_{95} 0.8-4.1) and 2.7% (CI_{95} 1.8-3.6) for the "moderate" and "considerable/severe" asthma treatment intensity levels, respectively. The adjusted odds ratios when compared with non-FP ICS were 1.1 (CI_{95} 0.5-2.3) and 1.2 (CI_{95} 0.7-2.0) for the "moderate" and "considerable/severe" intensity levels; risks for any FP and for FSC did not differ substantially.

CONCLUSION: No increase in the overall risk of MCMs was identified after first trimester FP exposure compared with non-FP ICS. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: *Pregnancy; Asthma; Anti-asthmatic agents; Congenital abnormalities; Electronic medical records; Teratogens*

Asthma affects between 3% and 14% of pregnancies.[1-5] Maternal asthma, and in particular poorly controlled asthma, is associated with a number of adverse perinatal outcomes including preterm delivery and pre-eclampsia.[6,7] Consequently, asthma treatment guidelines highlight the importance of maintaining good asthma control during pregnancy, with inhaled corticosteroids (ICS) recommended as first-line controller therapies.[8] Pregnant women, however, are typically excluded from randomized controlled trials, and at present there is little knowledge about the safety of many asthma medicines when used during pregnancy. As a result, all ICS with the exception of

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Abbreviations used
BDP- Beclometasone dipropionate
CPRD- Clinical Practice Research Datalink
FP- Fluticasone propionate
FSC- Fluticasone propionate in fixed dose combination with salmeterol (Seretide)
GP- General Practitioner
GPRD- General Practice Research Database
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist
MCM- Major congenital malformations

budesonide, which is category B based on data from the Swedish Medical Birth Register, have a Food and Drug Administration pregnancy category C, indicative of the fact that there are no adequate and well-controlled studies in humans.

Fluticasone propionate (FP) is an ICS used for the treatment of asthma, as monotherapy and in fixed-dose combination with the long-acting β_2-agonist (LABA) salmeterol. Owing to small numbers of pregnancy exposures in the past, little is known about its safety when used during pregnancy. A recent feasibility study,[5] however, demonstrated that there are now sufficient numbers of first trimester exposed pregnancies in the Clinical Practice Research Datalink (CPRD) to allow the overall risk of major congenital malformations (MCMs) to be evaluated. This study aimed to evaluate the safety profile of FP, in terms of the risk of MCMs, compared with all other non-FP ICS exposures, while taking into account potential confounders.

METHODS

The CPRD, previously the General Practice Research Database, contains anonymized patient medical and prescribing records from UK primary care.[9] Within the CPRD, it is possible to link a mother's medical record to her infant's, which enables the evaluation of data on both maternal drug exposure and pregnancy outcomes.[10-12] Data are entered as Read clinical codes and general practitioners (GPs) can record additional noncoded free text comments, which researchers can request from the database provider. This protocol was approved by the CPRD Independent Scientific Advisory Committee, and there is a single Multi-Centre Ethics approval for observational studies using CPRD data.

Women with a pregnancy starting and ending between January 1, 2000, and December 31, 2010, were identified, who were aged 11-50 years at the start of pregnancy. Pregnancies were identified using algorithms previously developed and utilized at the University of Bath.[5,13] The pregnancy start date was estimated based on medical codes in the woman's record; where information was not available, a defaulted pregnancy duration of 40 weeks for live and stillbirths and 10 weeks for pregnancy losses was used. The defaulted duration was used for approximately 40% of deliveries and 70% of pregnancy losses. Women were required to have had a singleton birth and have been followed in the CPRD for the 6 months before, throughout, and for at least 3 months after pregnancy. A more detailed description of the methods has been described previously.[5]

Women were considered to have asthma if they had:

(a) an asthma diagnosis at any time in their medical record and 2 or more prescriptions for any asthma medicine during the study period *or*

(b) 6 or more prescriptions for any asthma medicine during the study period

Asthma medicines included short-acting β_2-agonists, ICS, LABA, compound bronchodilator preparations, cromoglycate and related therapy, leukotriene receptor antagonists, antimuscarinic bronchodilators, and theophylline products, and did not include the use of intranasal steroids. Women were required to receive 1 or more prescriptions during the 6 months before or during pregnancy. Women with a diagnosis of any other chronic respiratory disease were excluded.

For all asthma medicines, the duration of each prescription was calculated.[5] In addition to those described above, oral corticosteroid prescriptions were identified where there was no evidence that they had been prescribed for a condition other than asthma. Each prescription was given a start and end date, and the prescriptions were mapped, taking into account the switching of products.[5] Periods of long-term oral corticosteroid use ($\geq$90 days) were included in the mapping, whereas short courses (<90 days) were used to identify acute asthma exacerbations. The mapped prescription data were then used to determine the combination of products a patient was exposed to during each day of the study period.[5]

Women were assigned to treatment steps based on the combination of products prescribed and the British Thoracic Society and Scottish Intercollegiate Guidelines on the management of asthma.[8] Women were only allocated to step 5 if long-term oral corticosteroid use was combined with a current prescription for high-dose ICS (>800 μg for beclometasone dipropionate [BDP] or budesonide and >400 μg for FP).

Each treatment step was assigned a value and an average treatment step value was calculated for each woman for the entire pregnancy, for each trimester, and for the 3 months before pregnancy as shown below.

$$\frac{\sum(\text{number of days on each treatment step} \times \text{step value})}{\text{total number of days in time period}}$$

Individuals were categorized into 1 of 3 "asthma treatment intensity levels" based on their average British Thoracic Society and Scottish Intercollegiate Guidelines treatment step value during each particular time period ("mild": $\leq$step 1; "moderate": >step 1 and $\leq$step 2; "considerable to severe": >step 2). The category "considerable to severe" included a wide range, with 51.2% classified as >step 2 and $\leq$step 3, 47.9% classified as >step 3 and $\leq$step 4, and the remainder being >step 4 and $\leq$step 5.

First trimester ICS exposure was defined as the issue of a prescription for any ICS during the first trimester or the 2 weeks preceding. FP exposure was categorized into "FP alone" (Flixotide), "FP in fixed-dose combination with salmeterol" (Seretide [FSC]) and "any FP." Women who received both "FP alone" and "FSC" were eligible for inclusion in both groups but only counted once in the "any FP" category. Women were included in the non-FP ICS category if they received a non-FP ICS prescription and no prescriptions for an FP product, regardless of the prescribing of any other asthma medicine classes. All exposure was determined masked to pregnancy outcome status.

For live deliveries, the mother's medical record, where possible, was linked to that of the infant; this was possible for approximately 80% of deliveries. MCMs were identified based on a Read code relating to an MCM in the infant's record. MCMs were defined according to the EUROCAT classification.[14,15] In infants diagnosed with a syndrome, syndrome-related MCMs were excluded as these