Executive summary

Background: Asthma is reported to occur in 3% to 14% of pregnancies and poorly controlled asthma has been found to be associated with a number of adverse pregnancy outcomes. Asthma management guidelines highlight the importance of maintaining good asthma control during pregnancy and inhaled corticosteroids are first line therapies in asthma treatment. Fluticasone propionate is an inhaled corticosteroid used for the treatment of asthma, often in combination with the long-acting β_2-agonist salmeterol. Owing to small numbers of pregnancy exposures in the past, little is known about the safety of fluticasone propionate when used during pregnancy.

Aims:

1. To evaluate the safety profile of fluticasone propionate (FP) compared with exposure to all other non-FP inhaled corticosteroids for the primary endpoint of all major congenital malformations (MCMs) combined, whilst taking into account potential confounders and exposure to other asthma medicines.

2. To provide an overall assessment of the risks of adverse pregnancy outcomes (MCMs, spontaneous pregnancy loss, preterm delivery, stillbirth and neonatal death) associated with asthma in general and with different levels of asthma control, irrespective of the products used for treatment.

Methods:

Data source: The General Practice Research Database (GPRD), which contains longitudinal data collected from within UK primary care.

Study design: Cohort study.

Study period: 1st January 2000 to 31st December 2010.

Study population: Females who had a pregnancy ending between January 2000 and December 2010 where the female was 11-50 years of age at the pregnancy start date and had been followed in the GPRD for the 6 months before pregnancy, throughout pregnancy and for at least 3 months following pregnancy. Females were also required to have a diagnosis of asthma and at least one prescription for an asthma medicine or ≥6 prescriptions for asthma

medicines if no asthma diagnosis was recorded. Females with a recorded diagnosis of any other chronic respiratory disease were excluded from the study.

Determining exposure to asthma medicines: Exposure to an inhaled corticosteroid during the first trimester of pregnancy was based on the issue of a prescription during the first trimester of pregnancy or the two weeks before the start of pregnancy. To determine asthma treatment intensity levels, all prescriptions for asthma medicines were identified and were mapped based on the quantity of tablets or inhalers and the recorded daily dose prescribed. Each treatment regimen and time period that an individual spent on that treatment regimen was then assigned to an asthma treatment step according to the British Thoracic Society prescribing guidelines.

Identification of outcomes: An algorithm generated at the University of Bath was used to identify pregnancies in the GPRD. For live born infants MCMs were identified based on a Read medical code relating to an MCM recorded in the infant's medical record. Supporting evidence and data from questionnaires sent to GPs were used to verify the diagnoses. For pregnancies that ended in an induced termination or stillbirth, non-coded free text comments recorded by GPs in association with the pregnancy outcome were requested to enable the identification of MCMs. The pregnancy algorithm was used to identify pregnancies that ended in a spontaneous pregnancy loss, stillbirth or preterm delivery.

Analyses:

Primary analyses: Patient characteristics were described for the 'fluticasone propionate alone' (Flixotide®), 'fluticasone propionate + salmeterol in fixed dose combination (FSC)' (Seretide®) and 'non-FP inhaled corticosteroid (ICS)' exposure groups. The absolute risk of a pregnancy outcome with an MCM was calculated for the different ICS exposure groups stratified by first trimester asthma treatment intensity level with 95% confidence intervals. The relative risk of a pregnancy outcome with an MCM following first trimester exposure to fluticasone propionate compared to non-FP ICS was calculated with 95% confidence intervals stratified by asthma treatment intensity level during the first trimester. Logistic regression was used to adjust for potential confounding variables. The prevalence of different types of MCMs and organ classes, identified in the different ICS exposure groups was calculated with 95% confidence intervals.

Secondary analyses: The patient characteristics were described for the entire asthma cohort stratified by asthma treatment intensity level during the first trimester of pregnancy. The absolute risk of a pregnancy outcome with an MCM was calculated for the entire asthma cohort with 95% confidence intervals stratified by asthma treatment intensity level. The prevalences of the different types of MCM and organ classes identified in the entire asthma cohort were calculated with 95% confidence intervals. The risk of a spontaneous pregnancy loss, a preterm delivery, a stillbirth and a neonatal death were calculated separately stratified by asthma treatment intensity level. The relative risk of each of these outcomes in females with a 'moderate' asthma treatment intensity level was calculated compared to the risk in females with a 'mild' asthma treatment intensity level. The same was calculated comparing those with 'considerable to severe' asthma treatment intensity to those with 'mild' asthma treatment intensity. Logistic regression was used to adjust for potential confounding variables.

Principal findings:

In this study, based on longitudinal electronic medical records with linked prescription data, we did not identify any increase in the overall risk of major congenital malformations following exposure to fluticasone propionate during the first trimester of pregnancy compared with exposure to non-fluticasone propionate inhaled corticosteroids. In addition, the risk of MCMs following first trimester exposure to FP alone (Flixotide®) was not found to differ to the risk following exposure to FP + salmeterol in fixed dose combination (Seretide®). This study did not identify any increase in the risk of an MCM, stillbirth or neonatal death in pregnancies to females categorised as having a 'moderate' or 'considerable to severe' asthma treatment intensity level compared to those categorised as having a 'mild' asthma treatment intensity level. This study did identify an increase in the risk of spontaneous pregnancy loss in pregnancies to females with 'moderate' or 'considerable to severe' asthma treatment intensity levels compared to females with 'mild' asthma treatment intensity. A small increase in the risk of preterm deliveries in females with a 'moderate' compared to 'mild' asthma treatment intensity level was also observed, but this was not present for those with a 'considerable to severe' asthma treatment intensity level.

Discussion and conclusions:

Our study did not find an increased risk of major congenital malformations following exposure to fluticasone propionate, during the first trimester of pregnancy, when compared to non-FP inhaled corticosteroids. This finding is in line with other studies evaluating the safety of ICS products. The results of this study add to the growing body of evidence on the safety of inhaled corticosteroids when used during the first trimester of pregnancy. The evidence available at present is reassuring and, given the risks of poorly controlled asthma, females with asthma who are pregnant should continue to aim for good asthma control and treatment at the lowest effective dose.