**PHARMACOEPIDEMIOLOGY UNIT**

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# Asthma treatment in pregnancy and the frequency of adverse pregnancy outcomes

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## Contents

# 1. Background / rationale

Asthma is reported to affect between 3-14%[1-4] of pregnancies making asthma medicines one of the most commonly used classes of medicines during pregnancy. Maternal asthma and in particular poorly controlled asthma has been found to be associated with a number of adverse perinatal outcomes including preterm delivery, low birth weight and pre-eclampsia.[5,6] At present little is known about the safety in humans of many anti-asthma medicines when used during pregnancy. As a result all inhaled corticosteroids, with the exception of budesonide which is category B, have an FDA pregnancy category C, indicative of the fact there are no adequate and well controlled studies in humans.

Fluticasone is an inhaled corticosteroid used for the treatment of asthma, often in combination with the long-acting β-agonist salmeterol. Owing to small numbers of pregnancy exposures in the past, little is known about the safety of fluticasone when used during pregnancy. A recent feasibility study, however, has shown that there are sufficient numbers of first trimester exposed pregnancies on the General Practice Research Database (GPRD) to allow the overall risk of major congenital malformations (MCMs) to be evaluated. This study also demonstrated that using data from the GPRD it is possible to determine an individual's exposure to anti-asthma medicines during pregnancy and to categorise their treatment in terms of the British Thoracic Society treatment steps.

When evaluating the safety of a particular product it is, however, important to evaluate the overall safety profile of the uncontrolled disease. This enables the information on the harm of asthma and uncontrolled asthma on pregnancy outcomes, to be balanced with the potential harm associated with use of anti-asthma medicines.

# 2. Aims and objectives

### 2.1 Aim

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

To test the null hypothesis that exposure to fluticasone propionate during the first trimester of pregnancy is not associated with increased overall risk of all major congenital malformations when compared to the risk in those exposed to other inhaled corticosteroids during the first trimester of pregnancy.

## 2.2 Objectives

**Primary objectives**

1. To calculate the absolute risk of all major congenital malformations following first trimester exposure to fluticasone propionate alone (Flixotide®) and in combination (Seretide®). If appropriate and there is no heterogeneity absolute risks will be calculated for the two groups combined.
2. To calculate the prevalence with 95% confidence intervals of different major congenital malformations identified – this is because it is recognised that the risk of all major congenital malformations combined is not usually sensitive enough to detect a teratogenic association and this study will not be powered to detect a moderate increase in risk of specific malformations. This will be done separately for FP alone (Flixotide®) and in combination (Seretide®) and if appropriate for the two groups combined.
3. To calculate the relative risk of all major congenital malformations following first trimester exposure to fluticasone propionate alone (Flixotide®) and in combination (Seretide®). If appropriate relative risks will be calculated for the two groups combined.

**Secondary objectives**

The following objectives aim to give an overall picture of the risks of adverse pregnancy outcomes associated with asthma in general and different levels of asthma control, irrespective of the products used for treatment. This will then help us interpret any potential risks associated with asthma medicines in the context of those associated with poor asthma control.

1. To calculate the risk of a major congenital malformation in pregnancies to women with 'considerable to severe' asthma activity and 'moderate' asthma activity during the first trimester of pregnancy and compare them to those with 'mild' asthma activity during the first trimester of pregnancy.
2. To describe the prevalence of specific major congenital malformations identified within the entire treated asthma population (women who received ≥1 prescription for an anti-asthma medicine during the year before, during or the year following pregnancy)
3. To calculate the risk of a spontaneous pregnancy loss to women with 'considerable to severe' asthma activity and 'moderate' asthma activity during the first trimester of pregnancy and compare them to those with 'mild' asthma activity during the first trimester of pregnancy. This risk of spontaneous pregnancy losses will also be calculated for pregnancy losses that occurred in the second trimester before 24 weeks gestation and will be calculated based on asthma activity in the second trimester.
4. To calculate the risk of a pre-term delivery to women with 'considerable to severe' asthma activity and 'moderate' asthma activity in the third trimester of pregnancy and compare it to those with 'mild' asthma activity in the third pregnancy trimester. This will also be done comparing 'moderate' asthma severity with 'mild' asthma severity.

5. To calculate the risk of a stillbirth to women with 'considerable to severe' asthma activity and 'moderate' asthma activity in the third trimester of pregnancy and compare it to those with 'mild' asthma activity during the first trimester. This will also be calculated separately based on asthma activity levels in the second trimester

## 3. Study design and data source

The study will be a retrospective cohort study and will use data from the United Kingdom's General Practice Research Database (GPRD). The GPRD contains longitudinal medical records collected within UK primary care. All medical symptoms and diagnoses are recorded in the database, including those relating to pregnancy, in the form of Read Codes. In addition to coded data GPs have the option of recording un-coded comments, such as more detailed descriptions of diagnoses or treatments along with information provided to them via hospital letters, referrals and discharge summaries. This so called 'free text' is not readily available to researchers and needs to be requested from the database provider, at a fee, owing to the need for anonymisation.

## 4. Sample size and power considerations

**Primary objective**
From preliminary investigations we expect to capture approximately 30,000 pregnancies to women with asthma between 01/01/2000 and 31/12/2010. Of these, about 1,200 first trimester exposures to fluticasone propionate and 3,600 first trimester exposures to other inhaled corticosteroids (ICS) are expected.

Assuming no increase in the risk of all major congenital malformations is associated with exposure to all other inhaled corticosteroids, an overall major congenital malformation frequency of 2% on the GPRD and a ratio between exposure to an all other inhaled corticosteroid and exposure to fluticasone propionate of 3:1, this study would require 3,126 other ICS and 1,042 fluticasone propionate exposed pregnancies to have 90% power to detect a 2-fold increase in risk. To have 95% power the numbers required would increase to 3,894 and 1,298 (Table 1).

**Table 1** Sample size and power considerations

| Confidence level (%) | Power (%) | Unex:Exp | Disease in unexposed | Risk ratio to detect | Number of unexposed (other ICS) | Number of exposed (Fluticasone) |
|---|---|---|---|---|---|---|
| 95 | 90 | 3:1 | 2.0 | 2.5 | 1,617 | 539 |
| 95 | 95 | 3:1 | 2.0 | 2.5 | 2,019 | 673 |
| 95 | 99 | 3:1 | 2.0 | 2.5 | 2,898 | 966 |
| 95 | 90 | 3:1 | 2.0 | 2.0 | 3,126 | 1,042 |
| 95 | 95 | 3:1 | 2.0 | 2.0 | 3,894 | 1,298 |
| 95 | 99 | 3:1 | 2.0 | 2.0 | 5,571 | 1,857 |
| 95 | 80 | 3:1 | 2.0 | 1.5 | 7,731 | 2,577 |

The study will not, however, be powered to evaluate any differences in risk of individual defects such as spina bifida or oral clefts that have a frequency of ~0.1% in the general population. Based on the estimated number of other ICS exposed and fluticasone propionate exposed pregnancies the study would only have 60% power to detect a 5-fold increase in risk of a specific defect with a frequency of ~0.1% in the general population.

**Secondary objectives**

In England and Wales the frequency of stillbirths is about 5 in every 1000 deliveries. Between 12-15% of clinically recognised pregnancies end in a spontaneous pregnancy loss; on the GPRD we find around 12% of pregnancies end in a spontaneous pregnancy loss. Finally, about 7% of babies born each year in England are born prematurely (before 37 weeks gestation). Based on estimates of ~half of the study population having mild, 35% having moderate, and 15% having considerable to severe asthma activity, the study will be powered to detect differences in risk for all of these outcomes between different asthma activity levels in pregnancy.

## 5. Source and study populations

### 5.1 Source population

The source population will be all pregnancies identified on the GPRD that started and ended between 1 January 2000 and 31 December 2010. All pregnancy outcomes will be identified including live births, stillbirths, spontaneous pregnancy losses and induced terminations of pregnancy.

Identification of pregnancies

Pregnancies will be identified in the GPRD using an algorithm created at the University of Bath that has been described elsewhere.[7,8]

Exclusion criteria

- Pregnancies will be excluded if the female was not registered with a practice contributing up-to-standard data to the GPRD for the 6 months before the start of pregnancy, throughout pregnancy and for the 3 months following the pregnancy end date.

- Pregnancies will be excluded if the female was not 11-50 years of age on the pregnancy start date
- Pregnancies will be excluded if they result in a multiple birth (twins, triplets) and will be restricted to singleton births only.

**5.2 Study population**

The study population will consist of all eligible pregnancies identified from the source population where the female is considered to have asthma.

Females with asthma will be identified based on one of the following:

a) an asthma related medical code recorded anytime before the pregnancy start date and at least one prescription for an asthma medicine in the 6 months before the pregnancy start date or during pregnancy. (asthma medicines are defined as Section BNF chapter 3.1-3.3)

b) no asthma related Read medical code but at least 6 prescriptions for an asthma medicine in their record before the pregnancy start date, including one in the 6 months before the pregnancy start date or during pregnancy.

<u>Exclusion criteria</u>

- Pregnancies will be excluded if the female has a medical code for a diagnosis of chronic obstructive pulmonary disease (COPD) or any other chronic respiratory condition (e.g. cystic fibrosis) recorded at anytime before the pregnancy end date.

<u>Linking the mother and the child</u>

For live births an algorithm will be used to link the mother's medical record with that of the offspring based on family number, mothers date of delivery and child's month and year of birth. In previous studies this has been possible for approximately 80% of deliveries.

<u>Exclusion criteria</u>

- Live births will be excluded from the final study population for the major congenital malformation section of the study if it is not possible to link the mother's medical record to the medical record of the offspring. They will, however, be included in the analyses evaluating premature delivery.

## 6. Exposure definition and measurement

### a. Exposure to anti-asthma medicine prescriptions

Definition

Anti-asthma medicines will be defined as all prescriptions issued by a GP for short-acting $\beta_2$ agonists (SABA), inhaled corticosteroids (ICS), long-acting $\beta_2$ agonists (LABA), compound bronchodilator preparations, cromoglicates, leukotriene receptor antagonists, antimuscarinic bronchodilators and theophylline products. Prescriptions for oral corticosteroids will also be identified.

Determining exposure

For the primary endpoint, exposure status will be determined based on the individual receiving a prescription for the drug of interest (fluticasone or another inhaled corticosteroid) in the 2 weeks immediately before the LMP date or during the first trimester of pregnancy.

Sensitivity analysis will be carried out categorising exposure based on mapping the duration of prescriptions based on the number of inhalers, number of puffs within an inhaler and the prescribed daily dose as outlined below.

**Mapping of anti-asthma medicine prescriptions**

To calculate asthma activity levels for each pregnancy, in an attempt to be able to control for asthma severity, all prescriptions for an anti-asthma medicine will be mapped using the steps outlined below.

Determining prescription duration

For each prescription information is available on the date it was issued, the name of the product, the quantity prescribed and information on daily dosage.
The duration of each prescription will be estimated based on the following –

a) Short-acting $\beta_2$ agonist: it is expected that the majority of prescriptions will have the prescribed dose 'as needed' or 'as directed' (British Guidelines for the Management of Asthma 2004; personal communication with M Thomas 2010) and that each patient will have multiple inhalers. It is therefore considered not feasible to calculate the average daily dose of this group of products. Once a person has received at least one prescription for a short-acting $\beta_2$ agonist therefore, it will be assumed they have $\beta_2$ agonists at their disposal.
b) Other medicines, such as ICS: the duration of each prescription will be calculated based on a combination of the prescribed daily dosage and the number of puffs/tablets in an inhaler/pack, taking into account where ≥1 inhaler was prescribed in a single prescription. Where the daily dose and/or quantity information has not been recorded, the missing values will be imputed based on the value recorded for the nearest prior prescription for the same product. Where this is not available the modal value for that particular product will be taken.
c) Oral corticosteroids: The dose and duration of each oral corticosteroid prescription will be established from prescribing instructions; where these are not

available, the modal duration for that quantity within the study population will be assumed. If it is deemed feasible to use stratum-specific modal durations for different levels of asthma severity then we shall do so. This feasibility will depend on the extent to which duration determines the asthma severity level attributed to study participants.

Determining timing of exposure

Once the duration of each prescription has been calculated all prescriptions will be mapped based on their calculated duration to identify the different treatment combinations individuals were exposed to at different time periods. When individuals receive a new prescription for a product in the same drug class before the previous prescription's expected end date, it will be assumed that the individual had either used the product more frequently than the documented prescribing information or discontinued using the product and the first prescription will be truncated on the date the following prescription was issued. For oral corticosteroid prescriptions, only those indicating continuous exposure periods of >60 days duration will be included in the mapping. All other prescriptions for oral corticosteroid will be taken as evidence of short-term use for the treatment of an asthma exacerbation.

Assigning product combinations to a British Thoracic Society (BTS) treatment step

The aim of anti-asthma medication is to provide adequate control of asthma symptoms, to reduce or prevent the chronic inflammatory process in this lung disease and to prevent exacerbation. There is a stepped programme of asthma management (Table 2). Patients can move either up or down between and within these steps based on the control of their asthma and should be maintained on the lowest possible doses of medication to provide adequate control. For each pregnancy, using the BTS guidelines on the management of asthma, the prescription mapping will be used to establish which asthma treatment steps females are being prescribed (e.g. a SABA and a standard dose ICS = Step 2). For product combinations that do not directly translate to a specific treatment step, the most comparable treatment step will be assigned with guidance from a respiratory clinician. As oral corticosteroids can be used to treat a range of conditions, a review of medical codes in the individual's record will be undertaken to ensure those prescriptions issued to treat a condition other than asthma are excluded when assigning product combinations to an asthma treatment step and activity level.

**Table 2** Step management of asthma (British Guidelines)[9]

| | |
|---|---|
| Step 1<br>Mild intermittent asthma | Inhaled short-acting $\beta_2$ agonist (SABA) |
| Step 2<br>Regular preventer therapy | Add inhaled corticosteroid (ICS) at a dose appropriate to the severity of the disease (usually 200 – 800µg /day*) |
| Step 3<br>Add-on therapy | 1. Add a long-acting $\beta_2$ agonist (LABA)<br>2. Assess response<br>a. If good response: continue LABA<br>b. Benefit but not adequately controlled : continue LABA, increase ICS to 800µg/day<br>c. No response: stop LABA. Trial other therapies e.g. Leukotriene receptor antagonist, Slow Release Theophylline<br>d. Double dose of ICS |
| Step 4<br>Persistent poor control | Consider trials of ICS to 2000µg / day* and / or addition of a 4th drug e.g. Leukotriene receptor antagonist, Slow Release Theophylline, $\beta_2$ agonist tablets, Omalizumab |
| Step 5<br>Continuous or frequent use of oral corticosteroids | Use daily oral corticosteroid at the minimum dose required for adequate control<br>Maintain ICS at 200µg / day<br>Consider other treatments to minimise the use of oral corticosteroids<br>Refer for specialist management |

* beclomethasone dipropionate– for other inhaled corticosteroids the dose will vary.

**b. Exposure to asthma exacerbations**

Asthma exacerbations will be identified as outlined below

a) A 'definite' exacerbation - an asthma exacerbation or asthma attack or an asthma diagnosis on the same date as a hospitalisation or accident and emergency visit
b) A 'probable' exacerbation – a prescription for short-term oral corticosteroid treatment associated with a record of asthma (but not explicitly an exacerbation) on the same day
c) A 'possible' exacerbation – a prescription for short-term oral corticosteroid treatment without any record of the indication for treatment

All exacerbations will be taken as evidence of oral corticosteroid exposure.

All exposure to anti-asthma medicines, categorisation of treatment steps and identification of asthma exacerbations will be carried out blinded to major congenital malformation case status.

## 7. Outcome definition and measurement

The primary outcome of interest will be all major congenital malformations (MCMs) combined

Definition

MCMs will be defined according to the EUROCAT (European network of population-based registers for the epidemiological surveillance of congenital anomalies) classification scheme. Malformations that spontaneously resolve, such as some less severe ventricular septal defects, will not be counted as a MCM. In addition the EUROCAT classification excludes malformations that are related to preterm births (e.g. a patent ductus arteriosus in infants <37 weeks gestation). MCMs will also exclude all chromosomal defects, congenital malformations known to be of a genetic origin and malformations where there is evidence that it is not drug induced (e.g. hydrocephalus secondary to an intraventricular haemorrhage). If there is a syndrome then the MCMs will not be counted separately, unless there is an MCM present that is not usually part of that syndrome.

Identification

- For live births, MCMs will be identified based on a Read medical code relating to an MCM recorded in the infant's medical record.
- For all pregnancy losses identified by the algorithm as potentially being induced for medical reasons or where the induced reason or type of pregnancy loss was unknown, MCMs will be identified by requesting and reviewing all free text that had been recorded in the mother's medical record in association with that pregnancy.
- For stillbirths, MCMs will be identified by requesting and reviewing free text comments that had been recorded in association with a pregnancy related medical code in the 2 weeks before and 10 weeks following the stillbirth date.

Verification

Each major congenital malformation identified in live born infants will be verified using one of the methods below in that order of priority -

- Additional supporting evidence in the form of medical codes within the infant's electronic medical record e.g. a medical code relating to the repair of a cleft lip in addition the cleft lip diagnosis
- Requesting and reviewing the free text comments recorded in the infant's or mother's medical record (if diagnosed soon after birth) associated with medical codes for the malformation of interest or medical codes relating to a letter from a specialist etc.
- Sending a questionnaire to the infant's GP asking if the infant had the congenital malformation of interest and to provide a letter from a specialist as supporting evidence
- Requesting full photocopied medical records for the individual

MCMs identified solely from the free text comments associated with a stillbirth or pregnancy loss will be taken as a true MCM and will not undergo any further verification.

Secondary outcomes will include:

**a.** Spontaneous pregnancy losses

Spontaneous pregnancy losses will be defined as spontaneous pregnancy losses that occurred before 24 weeks gestation from the date of the first day of the last menstrual period (LMP). Spontaneous pregnancy losses will be identified based on the pregnancy algorithm. For pregnancy losses where the type of loss is unknown any free text comments associated with the pregnancy loss code will be requested and reviewed.[10]

**b.** Pre-term births

A pre-term birth will be defined as a live birth delivered at <37 complete weeks gestation from the date of the first day of the LMP. Pre-term births will be identified based on medical codes for a pre-term delivery in addition to information on gestational age and the first day of the LMP.

**c.** Stillbirths and neonatal deaths

Stillbirths will be defined as spontaneous pregnancy loss or delivery of a foetus at any time later than 24 weeks gestation that shows no evidence of life. Stillbirths will be identified based on a medical code in the mother's medical record.
Neonatal deaths will be defined as the death of an infant during the first four weeks of life and will identified based on a medical code in the mother's medical record, a medical code in the infant's medical record or by the date of death recorded in the infant's medical record.

As the recording of stillbirths, neonatal deaths and pre-term births on the GPRD has not been verified, a verification exercise will be carried out. This will involve requesting and reviewing free text comments for 100 stillbirths, 100 neonatal deaths and 100 pre-term births. Free text comments will be requested if they are associated with a medical code related to pregnancy, delivery, post natal visits, death, post mortem, hospital letters and other forms of communication. If the free text is not found to be informative we will send questionnaires to the woman's GP.

All outcomes will be identified and verified blinded to asthma treatment and severity levels.

## 8. Covariate definitions and measurement

Data will be collected, where available, on the following potential confounding variables

a. smoking status
b. alcohol intake
c. body mass index (nearest recorded before pregnancy start)
d. socio-economic status (based on quintiles of Townsend and IMD scores)
e. maternal age at LMP
f. asthma activity/severity level – for this an average treatment step will be calculated for each of the pregnancy trimesters and for the entire pregnancy period as outlined below

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

Based on the average treatment step value pregnancies will be assigned to one of the 3 asthma activity levels listed below

Mild = average treatment step ≤1
Moderate = average treatment step >1 and ≤2
Considerable to severe = average treatment step >2

g. Change in average BTS asthma treatment step between the 3 month period before pregnancy and the first trimester. This will be categorised as >0.5 increase; >1.0 increase; Remained the same; >0.5 decrease; >1.0 decrease
h. asthma exacerbation in the 6 months before the start of pregnancy will be included as a binary variable Sensitivity analyses will be carried out to evaluate the impact on the risk estimates of including definite, probable and possible exacerbation definitions.
i. Prescription for an oral corticosteroid (yes/no), regardless of indication for prescribing, or an asthma related emergency hospital admission/A&E visit during the first trimester of pregnancy. If numbers allow we will look at stratifying by cumulative oral corticosteroid exposure.
j. co-medications – for all major congenital malformations identified the woman's prescription record will be reviewed to identify any non-asthma medicines that she was exposed to during the first trimester of pregnancy that are known to increase the risk of particular congenital malformations (e.g. valproate) and exposure to these will be reported. There will, however, be insufficient exposure in the study population to enable inclusion of such risk factors as a covariate in any statistical model as it will make the model unstable.
k. other risk factors for the pregnancy outcomes to be evaluated such as a diagnosis of an autoimmune condition, diabetes, or epilepsy.

l. past pregnancy history – information will be collected where available on previous preterm births, spontaneous abortions, parity, gravidity, pregnancy complications (e.g. preeclampsia related to preterm births).

## 9. Analysis plan

**Primary objectives**

- The population characteristics in terms of maternal age, smoking status, alcohol intake, BMI and SES will be described for the 'fluticasone propionate alone' 'fluticasone propionate in combination' and 'other inhaled corticosteroids (ICS)' exposure groups. (Table A1)

- The absolute risk of a pregnancy outcome with a major congenital malformation will be calculated for 'fluticasone propionate alone', 'fluticasone propionate in combination' and 'other ICS' exposure groups stratified by first trimester asthma activity level with 95% confidence intervals. (Table A2)

The absolute risk of a pregnancy outcome with an MCM will be calculated as

$$\frac{\text{The n}^{o}\text{ of live births with an MCM + the n}^{o}\text{ of pregnancy losses with an MCM}}{\text{The total n}^{o}\text{ of live births + the n}^{o}\text{ of pregnancy losses with an MCM}}$$

For live births, all major congenital malformation calculations will be carried out separately for infants still present on the GPRD at 3 months, 1 year and 5 years of age. Pregnancy losses without an MCM will be excluded from the denominator because of the likelihood of inconsistent identification of defects across pregnancy losses; this is the approach commonly taken by pregnancy registries.

For all MCM analyses sensitivity analyses will be carried out, including and excluding those malformations that it was not possible to verify (e.g. those where the GP did not respond).

- The relative risk of a pregnancy outcome with a major congenital malformation following first trimester exposure to fluticasone compared to all other ICS will be calculated with 95% confidence intervals stratified by asthma activity level during the first trimester. This will be carried out using logistic regression adjusting for maternal age, alcohol consumption, smoking status, socioeconomic status, body mass index, change in asthma treatment step, oral corticosteroid use and exacerbation occurrence. (Table A2) This will be carried out separately for FP alone and FP in combination exposures and if appropriate for the 2 groups combined.

Exploratory analyses will be carried out to analyse the distribution of fluticasone exposure across the spectrum of asthma severity and to determine whether fluticasone exposure is more common at the severe end of the 'considerable to severe' strata (as expected based on information regarding prescribing in clinical

practice, and based on the fact fluticasone is available as a combination product with a LABA).

- The prevalence of different types of major congenital malformations and organ classes, as outlined in output Table A3, identified in the fluticasone propionate alone and in combination groups and other ICS exposure groups will be calculated with 95% confidence intervals. (Table A3). Relative risks will be calculated for individual major congenital malformations where the prevalence is found to be at least 5 times higher than expected (based on prevalence figures reported by EUROCAT) and the number of cases of the specific malformation is ≥5. For the relative risk calculations 'other ICS' will be the reference category.

**Secondary objectives**

- The population characteristics in terms of maternal age, smoking status, alcohol intake, BMI and SES will be described for the entire asthma cohort stratified by asthma activity level. (Table A4)

- The absolute risk of a pregnancy outcome with a major congenital malformation will be calculated for the entire asthma cohort with 95% confidence intervals stratified by asthma activity level. (Table A5)

- The prevalence of the different types of major congenital malformations and organ classes as outlined in output Table A3 identified in the entire asthma cohort will be calculated with 95% confidence intervals. (Table A1)

- The risk of a spontaneous pregnancy loss will be calculated for the entire asthma cohort stratified by asthma activity level. The relative risk of a spontaneous pregnancy loss in women with a 'considerable to severe' asthma activity level will be calculated compared to the risk in those with a 'mild' asthma activity level during the first trimester. This will also be done comparing the risk in those with 'moderate' asthma activity to those with 'mild'. Relative risks will be presented with 95% confidence intervals. This will be carried out using logistic regression adjusting for maternal age, alcohol consumption, smoking status, socioeconomic status, body mass index, change in asthma treatment step, oral corticosteroid use and exacerbation occurrence. (Table A6)

- The risk of a pre-term delivery will be calculated for the entire asthma cohort stratified by asthma activity level. The relative risk of a pre-term delivery in women with a 'considerable to severe' asthma activity level will be calculated compared to the risk in those with a 'mild' asthma activity level during the third trimester. This will also be done comparing the risk in those with 'moderate' asthma activity to those with 'mild'. Relative risks will be presented with 95% confidence intervals. This will be carried out using logistic regression adjusting for maternal age, alcohol consumption, smoking status, socioeconomic status, body mass index, change in asthma treatment step, oral corticosteroid use and exacerbation occurrence. (Table A7)

- The risk of a stillbirth will be calculated for the entire asthma cohort stratified by asthma activity level. The relative risk of a stillbirth in women with a 'considerable to severe' asthma activity level will be calculated compared to the risk in those with a 'mild' asthma activity level during the third trimester. This will also be done comparing the risk in those with 'moderate' asthma activity to those with 'mild'. Relative risks will be presented with 95% confidence intervals. This will be carried out using logistic regression adjusting for maternal age, alcohol consumption, smoking status, socioeconomic status, body mass index, change in asthma treatment step, oral corticosteroid use and exacerbation occurrence. (Tables A8-9)

All analyses will be carried out using Stata statistical software in the latest version available for use by us.

## 10. Study limitations

- **Selection bias**

The population based nature of the GPRD cohort combined with the fact that asthma is mainly treated in general practice will mean that this study is unlikely to suffer from selection bias.

- **Information bias**

1. Outcomes - it is likely that not all outcomes (e.g. all cases of major congenital malformations, spontaneous pregnancy losses etc.) will be captured, owing to incomplete recording; if this is non-differential between the different exposure groups then this will lead to underestimated risk estimates. For most outcomes we anticipate the misclassification will be non-differential; for early spontaneous loss it may be differential.

2. Exposure

a) Exposure to asthma medicines - exposure information is recorded independently by the GP before the pregnancy outcome which removes the problem of recall bias. Exposure assessment is, however, based purely on the issue of a prescription and it is not possible to know whether it was dispensed or whether the individual actually used the medication and inhaled successfully. The nature of asthma and the known high levels of poor compliance to treatment mean that there will be some misclassification of exposure.

b) Exposure to asthma exacerbations – given the nature of asthma and asthma exacerbations women may stockpile oral corticosteroids so they have some at home in case of an asthma exacerbation. As a result the timing of an oral corticosteroid prescription may not equal the timing of an asthma exacerbation. Sensitivity analyses will be carried out in which the different levels of certainty with which exacerbations were identified will be considered.

- **Confounders**

Attempts will be made to control for asthma severity although this is unlikely to be perfect. It is likely that those prescribed fluticasone propionate will have more severe disease than those prescribed other generic inhaled corticosteroids. Analyses will be carried out stratified by asthma activity level during the relevant trimester of interest and exploratory analyses will be carried out across the spectrum of severity to determine whether fluticasone propionate exposure is concentrated at the more severe end of the 'considerable to severe' strata.

There is the possibility of confounding by indication for oral corticosteroid use so adjustment will be made for autoimmune conditions if the numbers allow. If the numbers are too small, sensitivity analyses will be carried out excluding pregnancies where the female had a diagnosis of an autoimmune condition.

No information will be available on over-the-counter medicines including 400mcg folic acid

Highly selective information, if any, will be available on a family history of congenital malformations and therefore it is not considered usable.

- **Effect modifiers**

None anticipated.

- **Other limitations**

<u>Pooling of all major congenital malformations</u>

This study will evaluate the risk of all major congenital malformations combined and it is recognised that this is usually insufficiently sensitive for detecting teratogenic associations. This study will not be powered to detect a moderate increase in risk of specific malformations. The prevalence of specific major congenital malformations identified will however be reported. It is envisaged the study may provide some reassurance of absence of major teratogenic risk, if no increased risk is found.

<u>Comparing to all other inhaled corticosteroids</u>

This study will involve comparing exposure to fluticasone propionate with exposure to all other inhaled corticosteroids at comparable doses, and therefore one limitation could be that if a class effect of an increased risk of major congenital malformations associated with corticosteroid exposure truly exists then this may not be identified.

## 11. Ethical issues

In 2006, Trent MREC gave ethics approval for drug safety studies on the GPRD subject to scrutiny by the GPRD's advisory committee. The study protocol will be submitted for approval by the GPRD's Independent Scientific Advisory Committee (ISAC). In order to ensure that patients remain unidentifiable, in all publications/ presentations we will not state the calendar year of birth of the offspring, the sex of the offspring or the maternal age. All results relating to terminations will be reported in an aggregated

fashion and not at an individual level to ensure that no individual woman can be potentially identified.

All data will be anonymised and stored on a secure server with restricted access.

If we find evidence of a potential adverse association / increased risk then the procedures adopted in the FP7 funded SOS, ARITMO and SAFEGUARD studies will be followed, which will involve liaising with both GlaxoSmithKline and the regulatory authorities.

## 12. Data storage

All data will be anonymised and stored on a secure server with restricted access at the University of Bath in the research environment for epidemiology in the following directory: \Projects\Asthma in pregnancy and will be available for audit and data sharing on site. All data will be stored in accordance with national data protection legislation.

## 13. Quality assurance

Code identification for drug and medical codes will be undertaken by two people independently. Discrepancies will be identified and agreement will be reached by consensus. Where this is difficult, expert opinion will be consulted. Clinicians and pharmacists will be involved in this process to ensure all correct codes have been identified.

Where pragmatically feasible, double-programming will be undertaken by two people independently. Where this is not feasible, one person will identify the study population using a computer algorithm, the underlying principles of which will have been designed and agreed upon by at least two people. A person other than the person who wrote the extraction program will assess the code used for the extraction procedure.

## 14. Plans for disseminating and communicating study results

Monthly conference calls will be held with GlaxoSmithKline to keep the funders up to date with study progress. The results of the study will be written up and submitted for publication in peer reviewed journals. In addition they will be submitted for presentation at the annual International Conference for Pharmacoepidemiology and they will be reported within GlaxoSmithKline. GlaxoSmithKline will record the study in the clinical trials registry (clinical trials.gov), report the information to regulatory agencies and make publically available the results on the clinicaltrials.gov. The University of Bath will do the same in the ENCePP registry of studies.

## 15. Study timelines

**Gantt chart illustrating the proposed work schedule**

| | | Months after start of project | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **task** | **task summary** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| 1 | Identify population base | | | | | | | | | | | | |
| 2 | Identify cohort study population | | | | | | | | | | | | |
| 3 | Exposure & asthma severity classification | | | | | | | | | | | | |
| 4 | MCM identification | | | | | | | | | | | | |
| 5 | MCM verification[1] | | | | | | | | | | | | |
| 6 | Secondary endpoint identification | | | | | | | | | | | | |
| 7 | Secondary endpoint verification | | | | | | | | | | | | |
| 8 | Coding for covariates | | | | | | | | | | | | |
| 9 | Analyses | | | | | | | | | | | | |
| 10 | Write report | | | | | | | | | | | | |
| 11 | Write publication | | | | | | | | | | | | |

[1] Allowing for time for free text and questionnaires to be requested, received and reviewed.

## 16. References


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8. Charlton RA, Weil JG, Cunnington M, et al. Comparing the General Practice Research Database and the UK Epilepsy and Pregnancy Register as tools for postmarketing teratogen surveillance: anticonvulsants and the risk of major congenital malformations. Drug Safety. 2011;34(2):157-71.

9. British guideline on the management of asthma. A national clinical guideline. British Thoracic Society and Scottish Intercollegiate Guidelines Network. 2011
10. Charlton RA, Snowball JM, de Vries CS. The identification and classification of pregnancy losses on the General Practice Research Database. In preparation

## 17. Future protocol amendments

Any amendments to the protocol will be listed here

## 18. Shell output tables

**Table A1** Patient characteristics for women exposed to fluticasone propionate (FP) or another inhaled corticosteroid during the first trimester of pregnancy

| Characteristic | First trimester exposure to | | | |
|---|---|---|---|---|
| | FP alone (flixotide®) N (%) | FP in combination (seretide®) N (%) | Any FP product N (%) | Non-FP inhaled corticosteroids N (%) |
| Number of pregnancy outcomes | | | | |
| Distinct number of females | | | | |
| Type of pregnancy outcome - deliveries<br>- spontaneous losses<br>- induced terminations | | | | |
| Mean age at LMP (years: (SD))<br>- deliveries<br>- spontaneous losses<br>- induced terminations | | | | |
| Age at LMP<br>• <20<br>• 20-24<br>• 25-29<br>• 30-34<br>• 35-39<br>• 40+ | | | | |
| Smoking status<br>• non-smoker<br>• current smoker<br>• ex-smoker<br>• unknown | | | | |
| Alcohol drinking status<br>• teetotal<br>• drinks alcohol<br>• heavy drinker<br>• ex-drinker<br>• unknown | | | | |
| Body mass index (nearest before pregnancy start date)<br>• <20<br>• 20 - 24<br>• 25 - 29<br>• 30 - 34<br>• >34<br>• Unknown | | | | |
| Socioeconomic status (practice level)<br>• quintile 1 – least deprived<br>• quintile 2<br>• quintile 3<br>• quintile 4<br>• quintile 5 – most deprived | | | | |
| Comorbidities<br>• epilepsy<br>• diabetes<br>• autoimmune disease<br>• psychiatric disorders | | | | |

**Table A2** Risk of a pregnancy outcome with a major congenital malformation for fluticasone propionate exposed pregnancies compared to all other inhaled corticosteroid pregnancies separately stratified by asthma activity level

| Asthma activity level and first trimester exposure type | Number of exposed pregnancies* N (%)** | Unique pregnancies with MCMs N | Absolute risk of an MCM (95% CI) | Relative risk of an MCM (95% CI) |
|---|---|---|---|---|
| **Mild**<br>Non-fluticasone propionate ICS<br>Fluticasone propionate alone | | | | Reference |
| **Moderate**<br>Non-fluticasone propionate ICS<br>Fluticasone propionate alone | | | | Reference |
| **Considerable to severe**<br>Non-fluticasone propionate ICS<br>Fluticasone propionate alone | | | | Reference |
| **Mild**<br>Non-fluticasone propionate ICS<br>Fluticasone propionate in combination | | | | Reference |
| **Moderate**<br>Non-fluticasone propionate ICS<br>Fluticasone propionate in combination | | | | Reference |
| **Considerable to severe**<br>Non-fluticasone propionate ICS<br>Fluticasone propionate in combination | | | | Reference |
| **Mild**<br>Non-fluticasone propionate ICS<br>Any Fluticasone propionate | | | | Reference |
| **Moderate**<br>Non-fluticasone propionate ICS<br>Any Fluticasone propionate | | | | Reference |
| **Considerable to severe**<br>Non-fluticasone propionate ICS<br>Any Fluticasone propionate | | | | Reference |

* ending in either a delivery or an induced termination of pregnancy following a prenatal diagnosis of an MCM

** proportion treated with this ICS (category) within this asthma activity level

**Table A3** Prevalence of major congenital malformations stratified by first trimester ICS exposure

| **Major congenital malformation** | **Entire asthma cohort**<br>**N (95% CI) (%)** | **First trimester exposure to non-FP ICS**<br>**N (95% CI) (%)** | **First trimester exposure to FP alone**<br>**N (95% CI) (%)** | **First trimester exposure to FP in combination**<br>**N (95% CI) (%)** |
|---|---|---|---|---|
| **Nervous system** | | | | |
| Anencephalus and similar | | | | |
| Encephalocele | | | | |
| Spina bifida | | | | |
| Hydrocephalus | | | | |
| Microcephaly | | | | |
| Arhinencephaly/holoprosencephaly | | | | |
| **Eye** | | | | |
| Micropthalmos | | | | |
| Anophthalmos | | | | |
| Congenital cataract | | | | |
| Congenital glaucoma | | | | |
| **Ear, face and neck** | | | | |
| Anotia | | | | |
| **Congenital heart defects** | | | | |
| Severe CHD | | | | |
| Common arterial truncus | | | | |
| Transposition of great vessels | | | | |
| Single ventricle | | | | |
| Ventricular septal defect | | | | |
| Atrial septal defect | | | | |
| Atrioventricular septal defect | | | | |
| Tetralogy of Fallot | | | | |
| Tricuspid atresia and stenosis | | | | |
| Ebstein's anomaly | | | | |
| Pulmonary valve stenosis | | | | |
| Pulmonary valve atresia | | | | |
| Aortic valve atresia/stenosis | | | | |
| Hypoplastic left heart | | | | |
| Hypoplastic right heart | | | | |
| Coarctation of aorta | | | | |
| Total anomalous pulm venous return | | | | |
| PDA as only CHD in term infants (>=37 weeks) | | | | |
| **Respiratory** | | | | |
| Choanal atresia | | | | |
| Cystic adenomatous malformation of lung | | | | |
| **Oro-facial clefts** | | | | |
| Cleft lip with or without palate | | | | |
| Cleft palate | | | | |

| | | | | |
|---|---|---|---|---|
| **Digestive system**<br>Oesophageal atresia with or without tracheooesophageal fistula<br>Duodenal atresia or stenosis<br>Atresia or stenosis of other parts of small intestine<br>Ano-rectal atresia and stenosis<br>Hirschsprung's disease<br>Atresia of bile ducts<br>Annular pancreas<br>Diaphragmatic hernia<br>Abdominal wall defects<br>Gastroschisis<br>Omphalocele | | | | |
| **Urinary**<br>Bilateral renal agenesis including Potter syndrome<br>Renal dysplasia<br>Congenital hydronephrosis<br>Bladder exstrophy and/or epispadia<br>Posterior urethral valve and/or prune belly | | | | |
| **Genital**<br>Hypospadias<br>Indeterminate sex | | | | |
| **Limb**<br>Limb reduction<br>Upper limb reduction<br>Lower limb reduction<br>Complete absence of a limb<br>Club foot - talipes equinovarus<br>Hip dislocation and/or dysplasia<br>Polydactyly<br>Syndactyly | | | | |
| **Other anomalies / syndromes**<br>Skeletal dysplasias<br>Craniosynostosis<br>Congenital constriction bands/amniotic band<br>Situs inversus<br>Conjoined twins<br>Congenital skin disorders | | | | |
| **Teratogenic syndromes with malformations**<br>Foetal alcohol syndrome<br>Valproate syndrome | | | | |

**Table A4** Patient characteristics for all women in the asthma cohort with a pregnancy, stratified by asthma activity level

| Characteristic | Asthma activity level | | |
|---|---|---|---|
| | Mild | Moderate | Considerable to severe |
| | N (%) | N (%) | N (%) |
| Number of pregnancy outcomes | | | |
| Distinct number of females | | | |
| Type of pregnancy outcome - deliveries<br>- spontaneous losses<br>- induced terminations | | | |
| Mean age at pregnancy outcome (years: (SD))<br>- deliveries<br>- spontaneous losses<br>- induced terminations | | | |
| Age at LMP<br>• <20<br>• 20-24<br>• 25-29<br>• 30-34<br>• 35-39<br>• 40+ | | | |
| Smoking status<br>• non-smoker<br>• current smoker<br>• ex-smoker<br>• unknown | | | |
| Alcohol drinking status<br>• teetotal<br>• drinks alcohol<br>• heavy drinker<br>• ex-drinker<br>• unknown | | | |
| Body mass index (nearest before pregnancy start date)<br>• <20<br>• 20 - 24<br>• 25 - 29<br>• 30 - 34<br>• >34<br>• Unknown | | | |
| Socioeconomic status (practice level)<br>• quintile 1 – least deprived<br>• quintile 2<br>• quintile 3<br>• quintile 4<br>• quintile 5 – most deprived | | | |
| Comorbidities<br>• epilepsy<br>• diabetes<br>• autoimmune disease<br>• psychiatric disorders | | | |

**Table A5** Absolute risk of a pregnancy outcome with a major congenital malformation (MCM) stratified by asthma activity level for the entire asthma cohort

| Asthma activity level | Number of pregnancies* | Unique pregnancies with MCMs N | Absolute risk of an MCM (95% CI) |
|---|---|---|---|
| Mild<br>Moderate<br>Considerable to severe | | | |

* ending in either a delivery or an induced termination of pregnancy following a prenatal diagnosis of an MCM

**Table A6** Risk of a pregnancy loss stratified by asthma activity level during the first trimester for the entire asthma cohort

| First trimester asthma activity level | Number of pregnancies | Pregnancies ending a spontaneous loss N (%) | Relative risk of a spontaneous loss (95% CI) |
|---|---|---|---|
| Mild<br>Moderate<br>Considerable to severe | | | Reference |

**Table A7** Risk of a pre-term delivery stratified by asthma activity level in the 30 days leading up to delivery for the entire asthma cohort

| Asthma activity level | Number of deliveries | Pregnancies ending in a pre-term delivery N (%) | Relative risk of a pre-term delivery (95% CI) |
|---|---|---|---|
| Mild<br>Moderate<br>Considerable to severe | | | Reference |

**Table A8** Risk of a stillbirth stratified by asthma activity level in the 30 days leading up to delivery for the entire asthma cohort. The numbers will be reported separately for those born before and after 37 weeks gestation. Relative risks will be calculated for all gestational ages combined.

| Asthma activity level | Number of pregnancies at >24 weeks gestation | Pregnancies ending in a stillbirth N (%) | Relative risk of a stillbirth (95% CI) |
|---|---|---|---|
| Mild<br><br>Moderate<br><br>Considerable to severe | | | Reference |

**Table A9** Risk of a neonatal death stratified by asthma activity level in the 30 days leading up to delivery for the entire asthma cohort

| Asthma activity level | Number of live deliveries | Pregnancies ending in a neonatal death N (%) | Relative risk of a neonatal death (95% CI) |
|---|---|---|---|
| Mild<br><br>Moderate<br><br>Considerable to severe | | | Reference |

**Table A10** Results of the verification study of stillbirth and neonatal death recording on the GPRD

| | Stillbirths N (%) | Neonatal deaths N (%) | Pre-term births N (%) |
|---|---|---|---|
| **Free text confirms the type of pregnancy outcome** | | | |
| **Free text confirms the type of pregnancy outcome** | | | |
| **Free text does not provide evidence to confirm or refute the type of pregnancy outcome** | | | |