Title: Safety of fluticasone propionate prescribed for asthma during pregnancy: A UK population-based cohort study

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Abstract

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

Objective 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 1-Jan-2000 and 31-Dec-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 mother 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 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 following different ICS exposures, stratified by asthma treatment intensity level, were calculated.

Results 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 following 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 following 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 to 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 following first trimester FP exposure compared with non-FP ICS.

Highlights box (35 words max per questions)

What is already known about this topic? (N = 35)

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? (N = 32)

This study found no 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.

How does the study impact current management guidelines? (N = 29)

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.

Key words (Max 10)

pregnancy; asthma; anti-asthmatic agents; congenital abnormalities; electronic medical records; teratogens;

Abbreviations

BDP	Beclometasone dipropionate
BTS	British Thoracic Society
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
LMP	Last menstrual period
MCM	Major congenital malformations
N^o	Number
SABA	Short-acting β_2-agonist

Introduction

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 randomised 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 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 there are no adequate and well controlled studies in humans.

Fluticasone propionate (FP) is an ICS used for the treatment of asthma, as mono-therapy 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, whilst taking into account potential confounders.

Methods

The CPRD, previously the General Practice Research Database, contains anonymised 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, enabling the evaluation of data on both maternal drug exposure and pregnancy outcomes.[10-12] Data is entered as Read clinical codes and general practitioners (GPs) can record additional non-coded 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 01-Jan-2000 and 31-Dec-2010 were identified, who were aged 11-50 years at the start of pregnancy. Pregnancies were identified using algorithms previously developed and utilised 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 six months before, throughout and for at least three months following 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 prescriptions for any asthma medicine during the study period *or*

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

Asthma medicines included short-acting β_2-agonists (SABA), ICS, LABA, compound bronchodilator preparations, cromoglicate 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 prescription during the six 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 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 (≥90 days) were included in the mapping whilst short courses (<90 days) were used to identify acute asthma exacerbations. The mapped prescription data was 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 a Step 5 if long term

oral corticosteroid use was combined with a current prescription for high dose ICS (>800µg for beclomethasone dipropionate (BDP) or budesonide and >400µg 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 three months before pregnancy as shown below.

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

Individuals were categorised into one of three 'asthma treatment intensity levels' based on their average British Thoracic Society and Scottish Intercollegiate Guidelines treatment step value during each particular time period ('mild': ≤Step 1; 'moderate': >Step 1 and ≤Step 2; 'considerable to severe': >Step 2). The category 'considerable to severe' included a wide range, with 51.2% classified as >Step 2 and ≤Step 3, 47.9% classified as >Step 3 and ≤ Step 4 and the remainder being > Step 4 and ≤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 categorised 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. Major congenital malformations (MCMs) were defined according to the EUROCAT classification.[14, 15] In infants diagnosed with a syndrome, syndrome-related MCMs were excluded as these were unlikely to be drug induced but any MCMs that were not reported in the literature as being part of that syndrome were included. Each potential MCM was verified using either supporting medical codes in the infant's record (e.g. surgery code), free text comments or by sending a questionnaire to the infant's GP. MCMs were identified in pregnancies that ended in a stillbirth or induced termination by requesting and reviewing free text comments recorded in association with a pregnancy related medical code in the mother's record.

Analyses

The maternal patient characteristics were reported for all pregnancies where the woman received a prescription for an ICS, stratified by type of ICS. For pregnancies where the mother's medical record could be linked to that of the child or the pregnancy had ended in a pregnancy termination, the absolute risk of a pregnancy outcome with an MCM diagnosed by 1 year of age was calculated as shown below for each ICS exposure group, stratified by first trimester asthma treatment intensity level. Stillbirths and pregnancy losses without an MCM were excluded from the

denominator because of the likelihood of inconsistent identification of defects across these types of outcome; this approach is commonly taken by pregnancy registries.[16] To be eligible for the analyses at one year of age infants had to still be registered in the CPRD at, or had died before, the time of their first birthday.

$$\frac{\text{N}^{\text{o}} \text{ of live deliveries with MCM} + \text{n}^{\text{o}} \text{ of stillbirths with MCM} + \text{n}^{\text{o}} \text{ of pregnancy losses with MCM}}{\text{Total n}^{\text{o}} \text{ of live deliveries} + \text{n}^{\text{o}} \text{ of stillbirths with MCM} + \text{n}^{\text{o}} \text{ of pregnancy losses with MCM}}$$

The relative risk of a pregnancy outcome with an MCM, diagnosed by 1 year of age, following first trimester exposure to FP compared to all non-FP ICS was calculated, stratified by first trimester asthma treatment intensity level. Multivariate logistic regression was used to adjust for maternal age, alcohol consumption, smoking status, socioeconomic status, body-mass-index, change in asthma treatment step, oral corticosteroid use and exacerbation occurrence. This was carried out separately for FP alone and FSC and also for the 'any FP' category as there was no heterogeneity between exposure groups.

The primary outcome was an MCM diagnosed by one year of age because previous research had demonstrated that approximately only two-thirds of MCMs were recorded in an infant's medical record by 3 months of age. Sensitivity analyses were, however, carried out to evaluate the risks of an MCM diagnosed by 3 months of age and by 5 years of age in order to assess any impact on the risk estimates of loss to follow-up and to look at the impact of any malformations diagnosed later in life. Further sensitivity analyses were carried out by excluding MCMs where it was not possible to confirm or refute the diagnosis following the verification exercise. All

analyses were carried out using Stata version 12.[17] To investigate the impact of non-independent pregnancies, where one woman contributed more than one pregnancy to the study cohort, sensitivity analyses were carried out for the primary outcome of interest (an MCM diagnosed by 1 year of age), restricting the analyses to the first pregnancy of each woman.

The prevalence of MCM organ classes, identified in the different FP exposure groups, were calculated and compared to those reported by the UK contributing EUROCAT registries.[18]

Results

In total, 25,247 pregnancies in 18,674 women with asthma were identified, of which 18,120 (71.8%) ended in a delivery. An ICS prescription had been issued during the first trimester in 10,770 pregnancies. Of these, 3,311 (30.7%) had received a prescription for FP; 807 for FP alone and 2,558 for FSC (Figure 1a). Non-FP ICS use consisted of beclomethasone dipropionate (~80%), budesonide in a single inhaler (~10%) and budesonide in a fixed-dose combination with the LABA formoterol (~10%). The demographic patient characteristics of women prescribed FP during the first trimester were comparable with those prescribed a non-FP ICS (Table 1). In general, women prescribed FSC did not differ from those prescribed FP alone on demographic features, although FSC users were more likely to be smokers (p<0.01). With respect to differences in asthma, women receiving FP were more likely to be at the more severe end of the asthma treatment severity strata than women prescribed a non-FP ICS (Table 1). Women prescribed FP were also more likely to have experienced an asthma exacerbation in the six months before pregnancy (p<0.01) and to have received an oral corticosteroid prescription during the first trimester (p<0.01) than those prescribed a non-FP ICS.

Within the asthma cohort 14,654 mother-infant pairs were identified, of which 6,174 were exposed to an ICS during the first trimester and 5912, 5362 and 2062 pregnancies were eligible for the primary and sensitivity analyses at 3 months, 1 year and 5 years of age respectively (Figure 1b). A total of 622 potential MCMs in 514 pregnancies were identified (including 43 chromosomal defects and 35 syndrome related). Figure 2 shows the results of the verification exercise.

Of the 5,362 ICS exposed pregnancies eligible for the primary analysis at 1 year of age, 131 pregnancies were identified with an unrefuted MCM diagnosed by aged 1 year (including MCMs where it was not possible to verify or refute the diagnosis and excluding chromosomal defects and defects part of a syndrome). There was no evidence of an increase in MCM risk for the offspring of women who received a prescription for FP during the first trimester compared to women who received a non-FP ICS product (Table 2). In addition, no substantial differences were observed in those prescribed FP alone compared to those prescribed FSC. Restricting the analysis to only verified MCMs did not substantially change the risk estimates (Online repository Table E1).

No meaningful differences were observed when sensitivity analyses restricted MCMs to those diagnosed by 3 months of age (Table E2). When the analyses were restricted to MCMs diagnosed by 5 years, the absolute risks for FP exposed women were slightly higher than those prescribed a non-FP ICS. The differences observed, however, were not statistically significant and the number of exposures in some groups was low (Table E2). Restricting the primary analyses to the first pregnancy of each woman reduced the point estimates below the null for those with moderate asthma treatment intensity but did not substantially change the confidence intervals or the overall study findings (Table E3).

For all MCM subgroups, with the exception of the 'urinary subgroup' in the non-FP ICS exposed group where the prevalence was higher, comparison of the prevalences in the CPRD with data from UK contributing EUROCAT registries, restricted to the

same study period, did not demonstrate any evidence of an increase in risk following ICS exposure (Table E4).

Discussion

This study did not identify any increase in the overall risk of MCMs following exposure to FP during the first trimester of pregnancy compared with exposure to non-FP ICS. In addition, the risk of MCMs following first trimester exposure to FP alone was not found to differ to the risk following exposure to FSC. To our knowledge, this is one of the first large population-based studies to evaluate the safety of FP when used during pregnancy in relation to the risk of MCMs and also to specifically evaluate the safety of an ICS delivered as part of a fixed-dose combination product with a LABA.

This study included over 25,000 pregnant women with asthma, including over 10,000 who received an ICS prescription during the first trimester. The prevalence of asthma and the frequency of asthma medicine prescribing in the GPRD has been demonstrated to be similar to that described elsewhere,[5] implying that the cohort is reasonably representative of the wider pregnant population with asthma.

Data on asthma medicines were recorded prospectively and independently by the prescriber, preventing maternal recall bias. Exposure was, however, based on the issue of a prescription and it was not possible to know whether it was dispensed and used, or used as directed with proper inhaler technique. The nature of asthma and the high levels of poor treatment compliance will have resulted in some non-

differential exposure misclassification and this would likely have resulted in a bias towards the null. Inclusion of prescriptions issued during the two weeks before the start of pregnancy will have helped to identify some, but not all, women who were exposed during the early stages of pregnancy but did not receive a prescription during the pregnancy itself. Misclassification of exposure may also have resulted from limitations in estimating the start of pregnancy and subsequently the precise timing of exposure. The lack of patient reported information (e.g. Asthma Control Test) in electronic medical databases is a limitation. Although this study attempted to take into account treatment intensity, the level of symptom control provided by a particular treatment regimen will vary between women. Within the CPRD, data on changes in symptom control that may not have been associated with a change in treatment regimen or required intervention with oral steroids were not available. No information was also available on medicines bought without a prescription, including 400mcg folic acid which is known to reduce the risk of some MCMs when taken during the peri-conception period.[19, 20]

This study identified a wide range of MCMs and had the strength of capturing prenatally diagnosed MCMs resulting in an induced termination. It is possible some MCMs may not have been recorded in a patient's record but this is unlikely to be differential between exposure groups. This study, like the budesonide study,[21] did however evaluate the risk of all MCMs combined, and it is recognised that this is usually insufficiently sensitive for detecting specific teratogenic associations. Although this study attempted to control for effects of varying 'asthma severity' this measure was based on asthma treatment patterns and did not take into account

treatment compliance or additional clinical asthma symptoms that are not routinely recorded in the CPRD. It is possible this will have resulted in some confounding by indication which may not have been fully adjusted for in the stratified analyses and multivariate modelling.

This study compared FP exposure with exposure to all other non-FP ICS, and therefore one limitation is that if a class effect of an increased risk of MCMs associated with ICS exposure exists, then this study design would not have been able to identify such a class-effect. Given that treatment step guidelines recommend ICS as the backbone of persistent asthma maintenance therapy beginning in Step 2, in an observational study design it is not feasible to study a class-effect without potential confounding by severity.

A small number of studies have reported on first trimester ICS exposure and the risk of congenital malformations.[21-28] Many of these, however, have grouped all ICS products and have been limited by small numbers. Based on the studies available, there is general consensus that the use of ICS products during early pregnancy does not appear to be associated with an increased risk of congenital malformations overall when compared to either users of non-ICS asthma medicines[23, 25] or the general population.[21, 22] The findings of our study are in line with the published data. A recent study by Eltonsy *et al.,* compared the use of long-acting β_2-agonists and inhaled corticosteroids in combination with higher-dose inhaled corticosteroid monotherapy and found the risk of MCMs was similar for the two groups.[29]

Neither our study nor the Swedish study looked at ICS dose and its relationship with MCM risk. A study using Canadian electronic healthcare data[24] has suggested that higher ICS dose (>1,000µg/d BDP equivalent) may be associated with an increased risk of congenital malformations when compared to low/moderate doses (≤1,000µg/d). The adjusted odds ratios were 1.66 (CI_{95}1.02-2.68) and 1.67 (CI_{95}0.91-3.06) for all congenital malformations and MCMs respectively, when high-dose ICS was compared to low/moderate doses. No increase in risk was observed when low/moderate exposures were compared to no ICS. The number of high-dose exposures was, however, small (N=154) and it was not possible to rule out confounding by disease severity as a possible explanation for the observed increased risk.

Conclusion

In our population-based cohort study, FP users were at the more severe end of the asthma severity spectrum and therefore would be less likely to successfully discontinue their asthma medicines during pregnancy without the increased risk of asthma exacerbations and other symptoms. Our study found no evidence of an increased risk of MCMs following exposure to FP during the first trimester of pregnancy when compared to non-FP ICS. This is reassuring and in line with other studies evaluating the safety of ICS products. This study had 90% power to detect a two-fold increase in the risk of all MCMs diagnosed by one year of age but was not powered to detect smaller increases in risk. In addition to providing information on the safety profile of FP and other ICS, this study also in part evaluated the safety of the LABA salmeterol used in a fixed-dose combination with FP. Whilst FP exposures

were mostly in combination with salmeterol in this study (77.9%) and the preliminary findings were reassuring, further data on the safety of LABA-containing regimens used during pregnancy are required to increase the precision of the risk estimates and further inform prescribers and patient decision making aiming to optimize asthma control during pregnancy.[30]

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Table 1 Patient characteristics of women exposed to fluticasone propionate (FP) or another inhaled corticosteroid during the first trimester of pregnancy

Patient characteristic	Non-FP inhaled corticosteroids		FP alone (Flixotide®)		FSC (Seretide®)		Any FP product	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of pregnancy outcomes	7,459		807		2,558		3,311	
Mean age at LMP (years [SD])	29.4	[6.6]	29.9	[6.3]	29.7	[6.4]	29.7	[6.4]
Age at LMP (years)								
<20	669	(9.0)	42	(5.2)	178	(7.0)	217	(6.6)
20-24	1,160	(15.6)	121	(15.0)	411	(16.1)	521	(15.7)
25-29	1,779	(23.9)	210	(26.0)	631	(24.7)	834	(25.2)
30-34	2,071	(27.8)	245	(30.4)	725	(28.3)	952	(28.8)
35-39	1,369	(18.4)	138	(17.1)	470	(18.4)	600	(18.1)
40+	411	(5.5)	51	(6.3)	143	(5.6)	187	(5.7)
Smoking status								
non-smoker	3,589	(48.1)	436	(54.0)	1,199	(46.9)	1,606	(48.5)
current smoker	2,390	(32.0)	211	(26.2)	801	(31.3)	997	(30.1)
ex-smoker	1,469	(19.7)	159	(19.7)	556	(21.7)	705	(21.3)
unknown	11	(0.2)	1	(0.1)	2	(0.1)	3	(0.1)
Alcohol drinking status								
teetotal	1,020	(13.7)	127	(15.7)	362	(14.2)	480	(14.5)
drinks alcohol	4,969	(66.6)	548	(67.9)	1,716	(67.1)	2,229	(67.3)
heavy drinker	129	(1.7)	10	(1.2)	44	(1.7)	54	(1.6)
ex-drinker	352	(4.7)	24	(3.0)	124	(4.9)	145	(4.4)
unknown	989	(13.3)	98	(12.1)	312	(12.2)	403	(12.2)
Body mass index (before LMP)								
<20	797	(10.7)	82	(10.2)	258	(10.1)	337	(10.2)
20 - 24	2,680	(35.9)	280	(34.7)	933	(36.5)	1,189	(35.9)
25 - 29	1,656	(22.2)	198	(24.5)	600	(23.5)	789	(23.8)
30 - 34	823	(11.0)	89	(11.0)	286	(11.2)	366	(11.1)
>34	519	(7.0)	39	(4.8)	230	(9.0)	264	(8.0)
Unknown	984	(13.2)	119	(14.8)	251	(9.8)	366	(11.1)
Socioeconomic status (practice level)								
quintile 1 – least deprived	1,257	(16.9)	152	(18.8)	480	(18.8)	624	(18.9)
quintile 2	1,399	(18.8)	199	(24.7)	436	(17.0)	621	(18.8)
quintile 3	1,539	(19.4)	122	(15.1)	481	(18.8)	593	(17.9)
quintile 4	1,595	(21.4)	146	(18.1)	489	(19.1)	628	(19.0)
quintile 5 – most deprived	1,759	(23.6)	188	(23.3)	672	(26.3)	845	(25.5)
Pregnancy history[1]								
Nº of Previous deliveries 0	3,504	(47.0)	401	(49.7)	1,146	(44.8)	1,518	(45.8)
1	2,484	(33.3)	287	(35.6)	881	(34.4)	1,152	(34.8)
2	1,027	(13.8)	92	(11.4)	376	(14.7)	461	(13.9)
>2	444	(6.0)	27	(3.3)	155	(6.1)	180	(5.4)
Previous pre-term delivery	283	(3.8)	19	(2.4)	94	(3.7)	112	(3.4)
Previous spontaneous loss	1,203	(16.1)	125	(15.5)	466	(18.2)	585	(17.7)

[1] Recorded in the GPRD

Table 1 continued

Patient characteristic	Non-FP inhaled corticosteroids		FP alone (Flixotide®)		FSC (Seretide®)		Any FP product	
	N	(%)	N	(%)	N	(%)	N	(%)
Asthma treatment intensity level								
Mild	162	(2.2)	10	(1.2)	12	(0.5)	22	(0.7)
Moderate	5,139	(68.9)	274	(34.0)	350	(13.7)	623	(18.8)
Considerable to severe	2,158	(28.9)	523	(64.8)	2,196	(85.8)	2,666	(80.5)
Change in average BTS treatment step[2]								
>1.0 decrease	141	(1.9)	41	(5.1)	145	(5.7)	186	(5.6)
>0.5 and ≤1.0 decrease	217	(2.9)	32	(4.0)	118	(4.6)	146	(4.4)
Remained the same	4,967	(66.6)	514	(63.7)	1,568	(61.3)	2,050	(61.9)
>0.5 and ≤1.0 increase	1,489	(20.0)	98	(12.1)	232	(9.1)	322	(9.7)
>1.0 increase	645	(8.6)	122	(15.1)	495	(19.4)	607	(18.3)
Asthma exacerbation in 6 months before pregnancy								
Yes	754	(10.1)	155	(19.2)	505	(19.7)	638	(19.3)
No	6,705	(89.9)	652	(80.8)	2,053	(80.3)	2,673	(80.7)
Prescription for an oral corticosteroid during the first trimester*								
Yes	385	(5.2)	78	(9.7)	230	(9.0)	299	(9.0)
No	7,074	(94.8)	729	(90.3)	2,328	(91.0)	3,012	(91.0)

* either as part of a Step 5 treatment regimen or issued for less than a 90 day duration in relation to the treatment of an exacerbation.

[2] Between the 3 month period before pregnancy and the first trimester

Table 2 Risk of a pregnancy outcome with a major congenital malformation (MCM) diagnosed by 1 year of age for first trimester FP exposed pregnancies compared to all other non-FP ICS exposed pregnancies, stratified by first trimester asthma treatment intensity level

Asthma treatment intensity level and first trimester exposure type	Nº of exposed pregnancies* N	(%)**	Nº of pregnancies with an MCM†	Absolute risk of an MCM (95% CI)	Adjusted odds ratio‡ (95% CI)
Mild					
Non-FP ICS	72	(1.2)	4	5.6 (0.3 – 10.8)	
FP alone (Flixotide®)	7	(0.1)	0	0.0	
FSC (Seretide®)	3	(0.0)	0	0.0	
Any FP exposure	10	(0.2)	0	0.0	
Moderate					
Non-FP ICS	2,598	(64.1)	60	2.3 (1.7 – 2.9)	1
FP alone (Flixotide®)	152	(3.8)	3	2.0 (0.0 – 4.2)	0.9 (0.3 – 2.9)
FSC (Seretide®)	177	(4.4)	5	2.8 (0.4 – 5.3)	1.3 (0.5 – 3.2)
Any FP exposure	328	(8.1)	8	2.4 (0.8 – 4.1)	1.1 (0.5 – 2.3)
Considerable to severe					
Non-FP ICS	1,080	(43.0)	25	2.3 (1.4 – 3.2)	1
FP alone (Flixotide®)	273	(10.9)	8	2.9 (0.9 – 4.9)	1.3 (0.6 – 3.0)
FSC (Seretide®)	1,032	(41.1)	27	2.6 (1.6 – 3.6)	1.1 (0.6 – 2.0)
Any FP exposure	1,274	(50.7)	34	2.7 (1.8 – 3.6)	1.2 (0.7 – 2.0)

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

** Percentage treated with this category of ICS within this asthma treatment intensity level

† Including MCMs where it was not possible to verify or refute the diagnosis

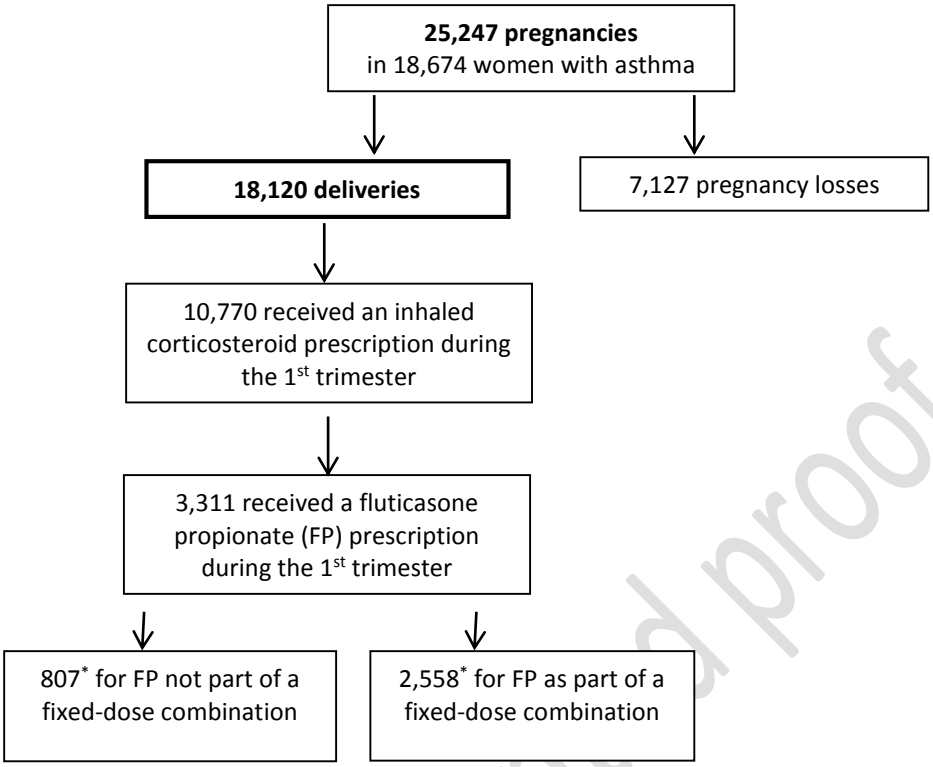
‡ Adjusted for maternal age, socioeconomic status and maternal smoking status

Figure legends

Figure 1 Flow diagram of the asthma study cohort showing a breakdown of pregnancy outcome status and inhaled corticosteroid prescribing

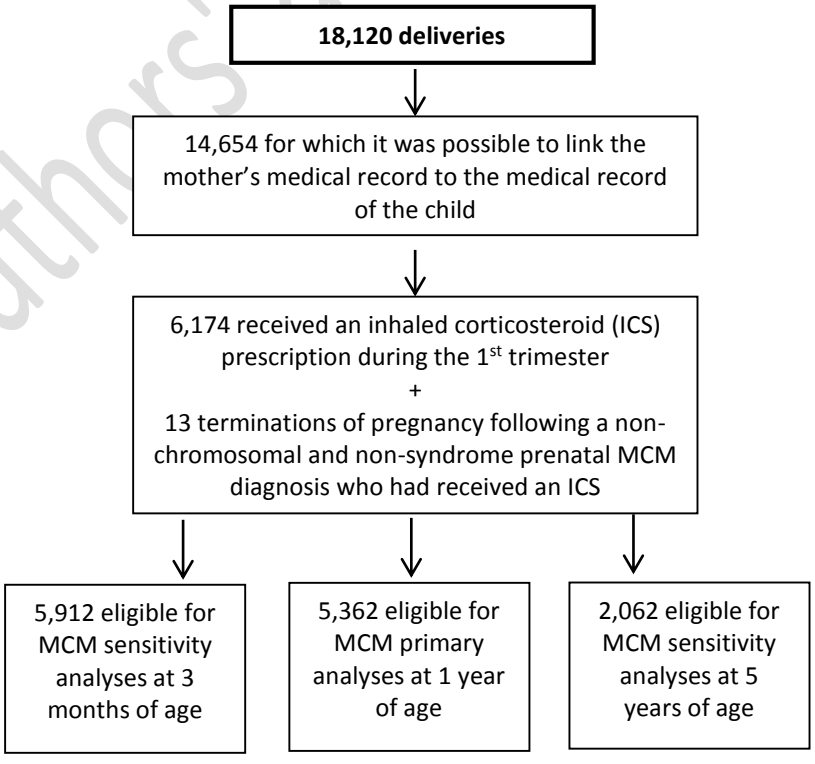
Figure 2 Flow diagram of the asthma study cohort showing the identification of pregnancies eligible for the congenital malformation analyses

Figure 3 Verification of potential major congenital malformations



* 54 women received a prescription for FP both as part of a fixed-dose combination and as an inhaler not part of a fixed-dose combination during the 1st trimester

Figure 1.



MCM = major congenital malformation

Figure 2.

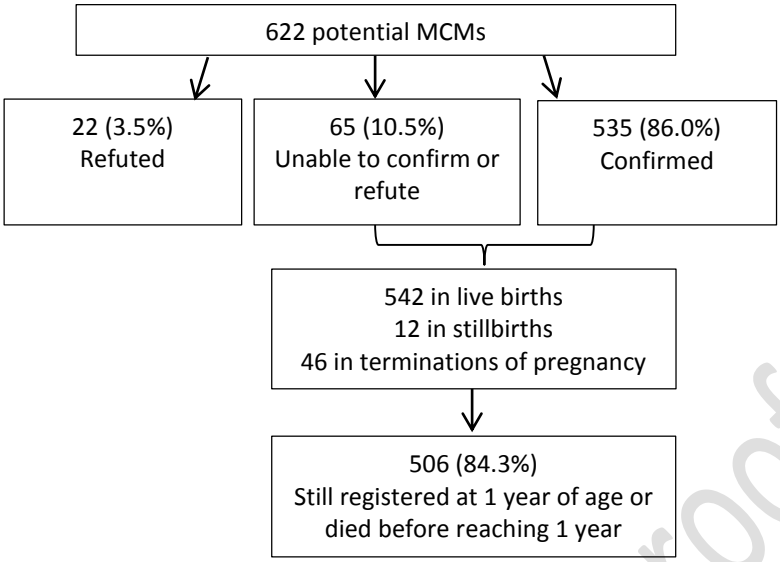


Figure 3

Repository E tables

Table EI Risk of a pregnancy outcome with a major congenital malformation (MCM) diagnosed by 1 year of age for first trimester FP exposed pregnancies compared to all other non-FP ICS exposed pregnancies stratified by first trimester asthma treatment intensity level restricted to MCMs that could be verified.

Asthma treatment intensity level and first trimester exposure type	Nº of exposed pregnancies* N	(%)**	Nº of pregnancies with an MCM	Absolute risk of an MCM (95% CI)	Adjusted odds ratio± (95% CI)
Mild					
Non-FP ICS	72	(1.2)	4	5.6 (0.3 – 10.8)	
FP alone (Flixotide®)	7	(0.1)	0	0.0	
FSC (Seretide®)	3	(0.0)	0	0.0	
Any FP exposure	10	(0.2)	0	0.0	
Moderate					
Non-FP ICS	2,598	(64.1)	56	2.2 (1.6 – 2.7)	1
FP alone (Flixotide®)	152	(3.8)	3	2.0 (0.0 – 4.2)	0.9 (0.3 – 2.9)
FSC (Seretide®)	177	(4.4)	5	2.8 (0.4 – 5.3)	1.3 (0.5 – 3.2)
Any FP exposure	328	(8.1)	8	2.4 (0.8 – 4.1)	1.1 (0.5 – 2.4)
Considerable to severe					
Non-FP ICS	1,080	(43.0)	22	2.0 (1.2 – 2.9)	1
FP alone (Flixotide®)	273	(10.9)	7	2.6 (0.7 – 4.4)	1.5 (0.6 – 3.4)
FSC (Seretide®)	1,032	(41.1)	26	2.5 (1.6 – 3.5)	1.2 (0.7 – 2.2)
Any FP exposure	1,274	(50.7)	32	2.5 (1.7 – 3.4)	1.2 (0.7 – 2.1)

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

** percentage treated with this category of ICS within this asthma treatment intensity level

± Adjusted for maternal age, socioeconomic status and maternal smoking status

Table EII Risk of a pregnancy outcome with a major congenital malformation (MCM) for first trimester FP exposed pregnancies compared to all other non-FP ICS exposed pregnancies, stratified by first trimester asthma treatment intensity level

a) diagnosed by 3 months of age

Asthma treatment intensity level and first trimester exposure type	Nº of exposed pregnancies* N	(%)**	Nº of pregnancies with an MCM†	Absolute risk of an MCM (95% CI)	Adjusted odds ratio± (95% CI)
Mild					
Non-FP ICS	82	(1.2)	3	3.7 (0.00 – 7.7)	
FP alone (Flixotide®)	7	(0.1)	0	0.0	
FSC (Seretide®)	3	(0.0)	0	0.0	
Any FP exposure	10	(0.1)	0	0.0	
Moderate					
Non-FP ICS	2,868	(64.0)	47	1.6 (1.2 – 2.1)	1
FP alone (Flixotide®)	159	(3.6)	3	1.9 (0.0 – 4.0)	1.2 (0.4 – 3.9)
FSC (Seretide®)	203	(4.5)	5	2.5 (0.3 – 4.6)	1.6 (0.6 – 4.0)
Any FP exposure	361	(8.1)	8	2.2 (0.7 – 3.7)	1.4 (0.7 – 3.0)
Considerable to severe					
Non-FP ICS	1,169	(42.2)	18	1.5 (0.8 – 2.2)	1
FP alone (Flixotide®)	283	(10.2)	2	0.7 (0.0 – 1.7)	0.5 (0.1 – 2.1)
FSC (Seretide®)	1,171	(42.2)	24	2.1 (1.2 – 3.0)	1.3 (0.7 – 2.5)
Any FP exposure	1,422	(51.2)	25	1.8 (1.1 – 2.4)	1.1 (0.6 – 2.1)

b) diagnosed by 5 years of age

Asthma treatment intensity level and first trimester exposure type	Nº of exposed pregnancies* N	(%)**	Nº of pregnancies with an MCM†	Absolute risk of an MCM (95% CI)	Adjusted odds ratio± (95% CI)
Mild					
Non-FP ICS	24	(1.1)	0	0.0	
FP alone (Flixotide®)	4	(0.2)	0	0.0	
FSC (Seretide®)	0	(0.0)	0	0.0	
Any FP exposure	4	(0.2)	0	0.0	
Moderate					
Non-FP ICS	1,080	(67.1)	39	3.6 (2.5 – 4.7)	1
FP alone (Flixotide®)	66	(4.1)	3	4.6 (0.0 – 9.6)	1.3 (0.4 – 4.4)
FSC (Seretide®)	51	(3.2)	1	2.0 (0.0 – 5.8)	0.5 (0.1 – 3.9)
Any FP exposure	117	(7.3)	4	3.4 (0.1 – 6.7)	0.9 (0.3 – 2.7)
Considerable to severe					
Non-FP ICS	446	(49.4)	14	3.1 (1.5 – 4.8)	1
FP alone (Flixotide®)	155	(17.2)	8	5.2 (1.7 – 8.6)	1.7 (0.7 – 4.3)
FSC (Seretide®)	248	(27.5)	12	4.8 (2.2 – 7.5)	1.6 (0.7 – 3.5)
Any FP exposure	391	(43.3)	19	4.9 (2.7 – 7.0)	1.6 (0.8 – 3.3)

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

** Percentage treated with this category of ICS within this asthma treatment intensity level

† Including MCMs where it was not possible to verify or refute the diagnosis

± Adjusted for maternal age, socioeconomic status and maternal smoking status

Table EIII Prevalence of major congenital malformations diagnosed by 1 year of age stratified by first trimester ICS exposure and grouped according to the EUROCAT criteria

( ) = additional MCMs where it was not possible to confirm or refute the diagnosis
* = observed to be higher than the prevalence reported by EUROCAT and 95% confidence intervals for the two data sources did not overlap.

Major congenital malformation	Non-FP inhaled corticosteroid N = 3,750		FP alone (Flixotide®) N = 432		FSC (Seretide®) N = 1,212	
	N¥	(%)†	N¥	(%)†	N¥	(%)†
Nervous system	6	0.16 (0.03-0.29)	≤5	≤1.16 (0.15-2.17)	≤5	≤0.41 (0.05-0.77)
Eye	≤5	≤0.13 (0.02-0.25)	0		0	
Ear, face and neck	0		0		0	
Congenital heart defects	(3) 27	0.72 (0.45-0.99)	≤5	≤1.16 (0.15-2.17)	13	1.07 (0.49-1.65)
Respiratory	0		0		0	
Oro-facial clefts	≤5	≤0.13 (0.02-0.25)	0		≤5	≤0.41 (0.05-0.77)
Digestive system	(1) 7	0.21 (0.07-0.36)	≤5	≤1.16 (0.15-2.17)	≤5	≤0.41 (0.05-0.77)
Abdominal wall defects	≤5	≤0.13 (0.02-0.25)	0		0	
Urinary	(2) 20	0.59 (0.34-0.83)*	0		6	0.50 (0.10-0.89)
Genital	6	0.16 (0.03-0.29)	≤5	≤1.16 (0.15-2.17)	≤5	≤0.41 (0.05-0.77)
Limb	(2) 18	0.53 (0.30-0.77)	≤5	≤1.16 (0.15-2.17)	6	0.50 (0.10-0.89)
Other anomalies / syndromes	(2) 4	0.16 (0.03-0.29)	(≤5)	≤1.16 (0.15-2.17)	(≤5) ≤5	<0.41 (0.05-0.77)
Teratogenic syndromes with malformations	≤5	≤0.13 (0.02-0.25)	0		(≤5)	<0.41 (0.05-0.77)
MCM type unknown – pregnancy ended in an induced termination	≤5	≤0.13 (0.02-0.25)	0		≤5	<0.41 (0.05-0.77)

† Includes MCMs where it was not possible to confirm or refute the diagnosis
¥ Reported as N ≤5 to ensure patient anonymity