The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: fluticasone propionate + salmeterol

Study Number: 114593 (WEUSRTP4850)

Title: Asthma treatment in pregnancy and the frequency of adverse pregnancy outcomes

Rationale:

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 (FP) is an inhaled corticosteroid used for the treatment of asthma, often in combination with the long-acting β2-agonist salmeterol (FSC). Owing to small numbers of pregnancy exposures in the past, little is known about the safety of fluticasone propionate when used during pregnancy. A recent feasibility study, however, has shown that there are sufficient numbers of first trimester exposed pregnancies in the General Practice Research Database to allow the overall risk of major congenital malformations (MCMs) to be evaluated.

This study was a non-mandated Post-authorisation Safety Study (PASS) for the European Medicines Agency (EMA).

The full protocol and results will be posted to the ENCePP Electronic Register of Studies after the study is complete.

Study Period: 20 July 2012 until 4 December 2013

Objectives:

1. To evaluate the safety profile of fluticasone propionate compared with exposure to all other non-FP inhaled corticosteroids for the primary endpoint of all major congenital malformations 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.

Indication: Asthma

Study Investigators/Centers:

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Research Methods

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

Study Design: Observational retrospective cohort study

Study Population:

Females who had a pregnancy ending between January 2000 and December 2010 (n=25,247 eligible singleton pregnancies, in 18,674 distinct females) 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.

Study Exposures, Outcomes:

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 (BTS) 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.

Data Analysis Methods:

Primary analyses: Subject characteristics were described for the 'fluticasone propionate alone (FP)', 'fluticasone propionate + salmeterol in fixed dose combination (FSC)' 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 (CI). 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 subject 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 prevalence 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.

Limitations:

The prescribing information relating to asthma medicines was recorded prospectively and independently by the prescriber, before the pregnancy outcome and malformation status was known. This is an advantage of electronic healthcare databases and removes the possibility of recall bias that can be a concern when data are collected via maternal interview. Exposure information was, however, based purely on the issue of a prescription during the first trimester of pregnancy or the two weeks leading up to the start of pregnancy; it is not possible to know whether it was dispensed or whether the individual actually used the medication as directed with proper inhaler technique. Inclusion of prescriptions issued during the two weeks before the start of the pregnancy will have helped identify females who may have been exposed during the early stages of pregnancy who did not actually receive a prescription during the pregnancy itself. It is likely however, that there may be some females who received a prescription more than two weeks before the start of pregnancy where the prescription continued into the first trimester and in these cases some misclassification of exposure may have occurred. The nature of asthma and the known high levels of poor compliance to treatment will also mean there will have been some misclassification of exposure and the direction of this potential misclassification would result in a bias towards the null. Misclassification of exposure may also have resulted from limitations relating to the precision of the estimation of the date of the first day of the last menstrual period and subsequently the dates of the first trimester and the precise timing of exposure. No information was available on medicines bought over-the-counter without a prescription, including 400mcg folic acid which is known to reduce the risk of some congenital anomalies when taken during the peri-conceptional period.

Although this study attempted to control for effects of varying 'asthma severity' this measure was based purely on asthma treatment patterns and did not take into account the effects of treatment compliance, asthma exacerbations or additional clinical asthma symptoms. It is therefore possible that some confounding by indication may have occurred. This study did not look directly at ICS dose although the ICS dose was used in the calculation of average BTS treatment steps that were used to assign subjects to their asthma treatment intensity levels.

Finally this study involved comparing FP exposure with exposure to all other non-FP inhaled corticosteroids, and therefore one limitation is that if a class effect of an increased risk of MCMs associated with inhaled corticosteroid exposure truly exists then this study design would not have been able to identify such a class-effect.

Study Results:

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 was not found to differ to the risk following exposure to FP + salmeterol in fixed dose combination. 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.

Overall Pregnancy Characteristics

Pregnancy outcomes where the female received a prescription for an inhaled corticosteroid during the first trimester of pregnancy

Subject characteristic	Non-FP inhaled corticosteroids		FP alone * N		FSC * N		Any FP product* N	
Number of pregnancy outcomes	7,459		807		2,558		3,311	
Distinct number of females	6,264		673		2,059		2,628	
Type of pregnancy outcome		%		%		%		%
- Delivery	5,238	70.2)	567	(70.3)	1,782	(69.7)	2,309	(69.7)
- Spontaneous abortion	1,106	(14.8)	139	(17.2)	410	(16.0)	543	(16.4)
- Induced termination	710	(9.5)	65	(8.1)	239	(9.3)	299	(9.0)
- Ectopic	84	(1.1)	9	(1.1)	29	(1.1)	37	(1.1)
- Hydatidiform mole	3	(0.0)	2	(0.2)	1	(0.0)	3	(0.1)
- Type of loss unknown	318	(4.3)	25	(3.1)	97	(3.8)	120	(3.6)

*Females who received a prescription for both FP alone and FSC were included in both categories but only counted once in the 'Any FP product' category.

Pregnancy outcomes for the entire asthma cohort stratified by asthma treatment intensity level during the first trimester

Subject characteristic	Mild[a]		Moderate[b]		Considerable to severe[c]	
	N	(%)	N	(%)	N	(%)
Number of pregnancy outcomes	12,001		8,065		5,181	
Distinct number of females	10,089		6,872		4,111	
Type of pregnancy outcome						
- Delivery	8,893	(74.1)	5,676	(70.3)	3,551	(68.5)
- Spontaneous pregnancy loss	1,430	(11.9)	1,152	(14.3)	887	(17.1)
- Induced termination	1,085	(9.0)	798	(9.9)	462	(8.9)
- Ectopic	105	(0.9)	81	(1.0)	71	(1.4)
- Hydatidiform mole	9	(0.1)	3	(0.0)	4	(0.1)
- Type of loss unknown	479	(4.0)	355	(4.4)	206	(4.0)

a. BTS treatment step ≤1; b. BTS treatment step >1 and ≤2; c. BTS treatment step >2

Primary Outcome

Risk of a pregnancy outcome with a major congenital malformation 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[a] N	(%)[b]	Nº of pregnancies with an MCM[c]	Absolute risk of an MCM (95% CI)	Adjusted odds ratio[d] (95% CI)
Mild					
Non-FP ICS	72	(1.2)	4	5.6 (0.3 – 10.8)	
FP alone	7	(0.1)	0	0.0	
FSC	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	152	(3.8)	3	2.0 (0.0 – 4.2)	0.9 (0.3 – 2.9)
FSC	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	273	(10.9)	8	2.9 (0.9 – 4.9)	1.3 (0.6 – 3.0)
FSC	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)

a. Ending in either a delivery or an induced termination of pregnancy following a prenatal MCM diagnosis
b. Percentage treated with this category of ICS within this asthma treatment intensity level
c. Including MCMs where it was not possible to verify or refute the diagnosis
d. Adjusted for maternal age, socioeconomic status and maternal smoking status

Secondary Outcomes

Absolute risk of a pregnancy outcome with a major congenital malformation (MCM) diagnosed by 1 year of age stratified by first trimester asthma activity level for the entire asthma cohort

Asthma activity level	Number of pregnancies[a]	Unique pregnancies with MCMs N	Absolute risk of an MCM (95% CI)
Mild	6,167	163	2.6 (2.2 – 3.0)
Moderate	4,037	97	2.4 (1.9 – 2.9)
Considerable to severe	2,513	62	2.5 (1.9 – 3.1)

a. Ending in either a delivery or an induced termination of pregnancy following a prenatal diagnosis of an MCM and for live deliveries were registered in the GPRD at 3 months of age

Risk of spontaneous pregnancy loss stratified by first trimester asthma treatment intensity level for the entire asthma cohort

Asthma activity level	Number of pregnancies	Pregnancies ending in a spontaneous loss N	%	Adjusted odds ratio[a] (95% CI)
Mild	12,001	1,430	(11.9)	1
Moderate	8,065	1,152	(14.3)	1.2 (1.0 – 1.5)
Considerable to severe	5,182	887	(17.1)	1.4 (1.2 – 1.7)

a. Adjusted for maternal age at LMP, socioeconomic status, maternal smoking status, pre-pregnancy BMI and a history of spontaneous pregnancy loss

Risk of a preterm delivery, stillbirth and neonatal death stratified by asthma treatment intensity level in the 30 days leading up to delivery for the entire asthma cohort

Preterm Delivery				
Asthma activity level	Number of deliveries	Deliveries ending in a preterm delivery N	%	Adjusted odds ratio[a] (95% CI)
Mild	9,861	433	(4.4)	1
Moderate	4,508	222	(4.9)	1.1 (1.0 – 1.4)
Considerable to severe	3,751	180	(4.8)	1.1 (0.9 – 1.3)
a. Adjusted for maternal age at LMP, socioeconomic status, maternal smoking status and pre-pregnancy BMI				
Still Birth				
Asthma activity level	Number of deliveries at >24 weeks gestation	Deliveries ending in a stillbirth N	%	Adjusted odds ratio[a] (95% CI)
Mild	9,858	59	(0.6)	1
Moderate	4,507	27	(0.6)	1.0 (0.6 – 1.6)
Considerable to severe	3,751	20	(0.5)	0.9 (0.5 – 1.5)
a. Adjusted for maternal age at LMP, socioeconomic status, and maternal smoking status				
Neonatal death				
Asthma activity level	Number of live deliveries N	Neonatal death following a live delivery N	%	Adjusted odds ratio[a] (95% CI)
Mild	9,802	11	(0.1)	1
Moderate	4,481	4	(0.1)	0.8 (0.3 – 2.6)
Considerable to severe	3,731	3	(0.1)	0.7 (0.2 – 2.6)
a. Adjusted for maternal age at LMP, socioeconomic status, and maternal smoking status				

Conclusion:
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, women should continue to aim for good asthma control and treatment at the lowest effective dose during pregnancy.