INFLAMMATION AND INFLAMMATORY BOWEL DISEASE

Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study

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Background: 5-Aminosalicylic acid (5-ASA) preparations are the firstline drugs in the treatment of inflammatory bowel disease. Data on the safety of these drugs in pregnancy are sparse.
Aims: To examine the risk of adverse birth outcome in women who were prescribed 5-ASA drugs during pregnancy.
Patients: Women were included in the study if they were prescribed 5-ASA drugs immediately before or during pregnancy. To examine the risk of malformations, we included 60 pregnancies exposed to 5-ASA drugs 30 days before pregnancy or in the first trimester. To examine stillbirths, preterm births, and low birth weight, we included 88 pregnancies exposed during the entire pregnancy. Outcomes were compared with those of 19 418 pregnancies in which no drugs were prescribed for mothers during the study period.
Methods: We conducted a Danish cohort study based on data from a population based prescription registry, the Danish Birth Registry, and the Hospital Discharge Registry in North Jutland County.
Results: Odds ratios for malformations, stillbirth, preterm birth, and low birth weight in women who received prescriptions for 5-ASA drugs were 1.9 (95% confidence interval 0.7–5.4), 6.4 (1.7–24.9), 1.9 (0.9–3.9), and 1.2 (0.4–3.3), respectively. The increased risk of stillbirth and preterm birth were found only in patients with ulcerative colitis.
Conclusions: We found an increased risk of stillbirth and preterm birth in women who had been prescribed 5-ASA drugs during pregnancy but no substantial increased risk of malformations. It was difficult to distinguish the specific effects of disease activity and 5-ASA drugs.

During the past decades pure 5-aminosalicylic acid (5-ASA) preparations have been the firstline drugs in the treatment of inflammatory bowel diseases (IBD), thereby avoiding the use of sulphasalazine, which is associated with several adverse effects.[1] IBD often affect women of child bearing age. Careful treatment during pregnancy is an important task as active IBD may be associated with poor obstetric outcome.[2 3]

Until the thalidomide disaster it was believed that the placenta protected the fetus from adverse drug effects.[4] The realisation that drugs taken during pregnancy may harm the fetus has had a major impact on clinical behaviour and considerations about risk and benefit. Most studies of drug treatment during pregnancy have been based mainly on case reports or small observational studies influenced by bias, and animal studies are in general uncertain and not predictive of human teratogens.[5] Therefore, the demand for large observational epidemiological studies on drug safety remains considerable.

The 5-ASA preparations, and in particular the metabolite *N*-acetyl-5-ASA, cross the placenta,[6–8] and only one study is available on their safety during pregnancy. The only study with a control group included 146 women with a live born child in which the mother had received 5-ASA drugs during pregnancy, 127 with exposure during the first trimester.[9] In that study there was an increased risk of preterm birth but no increased risk of major malformations.[9] The remaining studies were small with no control groups.[10–12]

We therefore examined the risk of congenital malformations, stillbirth, preterm birth, and low birth weight in women who were prescribed 5-ASA drugs during pregnancy in a population based design.

METHODS

Study population

We conducted the study in the Danish county of North Jutland (population approximately 490 000). It included data on all women who, between 1 January 1991 and 31 December 2000, had a live birth or a stillbirth after the 28th week of gestation (58 328 pregnancies). Data on drug use and outcome data were obtained from the population based registries in North Jutland County.

Use of 5-ASA drugs

The population based Pharmaco-Epidemiological Prescription Database of North Jutland was used to identify all prescriptions for 5-ASA drugs in the county from 1 January 1991 to 31 December 2000. The county is served by 33 pharmacies equipped with computerised accounting systems from which data are sent to the Danish National Health Service. The National Health Service provides tax supported health care for all inhabitants of the country. Apart from guaranteeing free access to general practitioners, hospitals, and public clinics, the insurance programme refunds part of the costs associated with the purchase of most prescribed drugs. Data are transferred to the prescription database from the accounting system that is maintained by the pharmacies and includes the patient's civil registry number (which incorporates date of birth), type of drug prescribed according to the anatomical therapeutic chemical (ATC) classification system, and the date of the prescription. The present study identified all prescriptions with the ATC codes A07E C02 (mesalazine) and A07E C03 (olsalazine). To examine the impact of disease activity, we stratified according to concomitant use of steroids (local or systemic) using the following ATC codes: H02A B06 (prednisolone), H02A B07 (prednisone), A07E A01 (prednisolone), A07E A02 (hydrocortisone), and A07E A06 (budesonide).

Abbreviations: 5-ASA, 5-aminosalicylic acid; ATC, anatomical therapeutic chemical; CD, Crohn's disease; IBD, inflammatory bowel diseases; OR, odds ratio; UC, ulcerative colitis.

Table 1 Characteristics of the study cohort

	Exposed to 5-aminosalicylic acid*		
	In the 1st trimester or 30 days before pregnancy (n=60)	During pregnancy (n=88)	Not exposed* (n=19 418)
Mother's age (y)			
Mean (SD)	30.1 (4.8)	30.7 (4.4)	28.7 (4.7)
Range	21–42	21–42	13–47
Smokers (n (%))	9 (15.0)	14 (15.9)	5102 (26.3)
Parity >1 (n (%))	30 (50.0)	53 (60.2)	9191 (47.3)
Preterm birth (gestational age <37 weeks) (n (%))	6 (10.0)	8 (9.1)	1062 (5.5)
Birth weight (g)			
Mean (SD)	3564 (639)	3567 (579)	3503 (587)
Range	1310–5550	1310–5550	500–6230
Low birth weight (< 2500 g) (n (%))	3 (5.0)	4 (4.6)	844 (4.4)
Congenital malformation (n (%))	4 (6.7)	5 (5.7)	711 (3.7)
Stillbirth (n (%))	2 (3.3)	3 (3.4)	109 (0.6)

*Represents 52 women exposed during the first time period, 74 during the second time period, and 16 486 different unexposed women.

Table 2 Adjusted odds ratios (OR) and 95% confidence limits (CL) for birth outcome in patients treated with 5-aminosalicylic acid (5-ASA) in pregnancy, including stratification for concomitant use of steroids

	Treated with 5 ASA (overall)		Stratification for concomitant use of steroids			
			Treated with 5-ASA and steroids		Treated with 5 ASA but no steroids	
	Events/total (%)	OR (adjusted‡) (95% CL)	Events/total (%)	OR (adjusted‡) (95% CL)	Events/total (%)	OR (adjusted‡) (95% CL)
LBW*	4/88 (4.6)	1.2 (0.4–3.3)	1/27 (3.7)	1.1 (0.2–8.1)	3/61 (4.9)	1.2 (0.4–4.0)
Preterm birth**	8/88 (9.1)	1.9 (0.9–3.9)	1/27 (3.7)	0.8 (0.1–5.7)	7/61 (11.5)	2.4 (1.1–5.3)
Stillbirth	3/88 (3.4)	6.4 (1.7–24.9)	2/27 (7.4)	20.4 (3.4–122.9)	1/61 (1.6)	2.8 (0.3–23.8)
Malformation†	4/60 (6.7)	1.9 (0.7–5.4)	2/16 (12.5)	3.9 (0.9–17.2)	2/44 (4.5)	1.3 (0.3–5.3)

*LBW, birth weight less than 2500 g.
**Preterm birth, gestational age less than 37 weeks.
†Different exposure window when examining congenital malformations (exposed in the period 30 days before conception to the end of first trimester).
‡Adjusted for mother's age (below 25 years, 25–29 years, and 30 years or more), parity (1 or more than 1), smoking (yes/no) in a logistic regression model. LBW and stillbirths also for gestational age (32 weeks or less, 33–36 weeks, and 37 weeks or more).

Outcome data

The Danish Medical Birth Registry

The Danish Medical Birth Registry contains information on all births in Denmark since 1 January 1973; data are recorded by the midwives and doctors responsible for the deliveries.[13] The main variables in the registry are maternal age, birth weight, length at birth, parity, gestational age, sex of the child, stillbirth, and smoking status of the mother. Information on smoking is collected at the first antenatal care visit. We identified all singleton pregnancies in North Jutland County during the study period.

The County Hospital Discharge Registry

Data on type of congenital malformation and underlying disease (Crohn's disease (CD) and ulcerative colitis (UC)) were extracted from the County Hospital Discharge Registry. Established in 1977, the County Registry transfers data to the nationwide registry in which 99.4% of all discharges from Danish medical hospitals are recorded. Data include dates of admission and discharge, surgical procedures performed, and up to 20 discharge diagnoses, classified according to the Danish version of the ICD-8 (International Classification of Diseases, 8th revision) until the end of 1993, and the ICD-10 after this date.[14 15] The codes for congenital malformations were 740.00–759.99 in ICD-8 and Q0.00–Q99.9 in ICD-10. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their low validity.

The codes 563.01 (ICD-8) and K50 (ICD-10) were used to identify patients with CD, and 563.19, 569.04 (ICD-8), and K51.0-K51.3 (ICD-10) to identify patients with UC. When a patient had been discharged with both CD and UC the sequence of admissions was studied; for example, a patient who had one admission diagnosed as UC and all subsequent as CD was classified as CD. If there was any doubt about the classification of IBD, the hospital record was reviewed. Thus all women exposed to 5-ASA drugs were classified as either CD or UC.

The unique 10 digit civil registry number, which is assigned to all citizens shortly after birth, was used to link prescription records with both outcome registries. Follow up ended on 31 December 2000.

The study was approved by the Danish Data Protection Agency (record No 1995-1200-362) and the regional ethics committee (record No 1995/104).

Statistical analysis

The association between the use of 5-ASA drugs and adverse birth outcome was studied in a cohort of women who had a live birth or stillbirth after the 28th week of gestation. Women were classified according to stage of gestation (based on ultrasound or last menstrual period) at which they had been prescribed 5-ASA drugs: (1) the "early pregnancy" group comprised women who had been prescribed 5-ASA drugs from 30 days before conception to the end of first trimester, and (2) the "entire pregnancy" group comprised women who had been prescribed 5-ASA drugs during the first to the third trimesters.[16] The first control group comprised all pregnant women who had not been prescribed any kind of reimbursed medicine from three months before conception to the end of pregnancy. A second control group comprised all pregnant women, apart from those treated with 5-ASA drugs from three months before conception to the end of pregnancy, thereby

Table 3 Adjusted odds ratios (OR) and 95% confidence limits (CL) for birth outcome in patients treated with 5-aminosalicylic acid (5-ASA) in pregnancy, stratified by type of underlying disease (Crohn's disease or ulcerative colitis)

	Patients with Crohn's disease treated with 5-ASA		Patients with ulcerative colitis treated with 5-ASA	
	Events/total (%)	OR (adjusted‡) (95% CL)	Events/total (%)	OR (adjusted‡) (95% CL)
LBW*	1/23 (4.3)	0.9 (0.1–6.7)	3/65 (4.6)	1.4 (0.4–4.3)
Preterm birth**	1/23 (4.3)	0.8 (0.1–5.6)	7/65 (10.8)	2.4 (1.1–5.3)
Stillbirth	0/23 (0.0)	—	3/65 (4.6)	8.4 (2.0–34.3)
Malformation†	1/18 (5.6)	1.5 (0.2–11.4)	3/42 (7.1)	2.1 (0.7–6.9)

*LBW, birth weight less than 2500 g.
**Preterm birth, gestational age less than 37 weeks.
†Different exposure window when examining congenital malformations (exposed in the period 30 days before conception to the end of first trimester).
‡Adjusted for mother's age (below 25 years, 25–29 years, and 30 years or more), parity (1 or more than 1), smoking (yes/no) in a logistic regression model. LBW and stillbirths also for gestational age (32 weeks or less, 33–36 weeks, and 37 weeks or more).

Table 4 Crude and adjusted odds ratios (OR) and 95% confidence limits (CL) for birth outcome in patients treated with 5-aminosalicylic acid (5-ASA) in pregnancy, using a control group of women treated with 5-ASA before or after pregnancy (control group of women with inflammatory bowel disease)

	Exposed: treated with 5-ASA in pregnancy	Controls: treated with 5-ASA outside pregnancy (ie, more than 3 months before or after pregnancy)		
	Events/total (%)	Events/total (%)	OR (crude) (95% CL)	OR (adjusted‡) (95% CL)
LBW*	4/88 (4.6)	9/243 (3.7)	1.2 (0.4–4.1)	1.7 (0.5–6.4)
Preterm birth**	8/88 (9.1)	14/243 (5.8)	1.6 (0.7–4.0)	2.0 (0.8–5.0)
Stillbirth	3/88 (3.4)	2/243 (0.8)	4.3 (0.7–25.9)	7.1 (0.2–205.1)
Malformation†	4/60 (6.7)	10/243 (4.1)	1.7 (0.5–5.5)	1.5 (0.4–5.1)

*LBW, birth weight less than 2500 g.
**Preterm birth, gestational age less than 37 weeks.
†Different exposure window when examining congenital malformations (exposed in the period 30 days before conception to the end of first trimester).
‡Adjusted for mother's age (below 25 years, 25–29 years, and 30 years or more), parity (1 or more than 1), smoking (yes/no) in a logistic regression model. LBW and stillbirths also for gestational age (32 weeks or less, 33–36 weeks, and 37 weeks or more).

allowing use of other drugs in the control group. A third control group comprised pregnant women treated with 5-ASA drugs outside pregnancy—that is, more than three months before or after pregnancy (IBD control group).

To examine whether disease activity had an impact on birth outcome, we obtained information on concurrent use of steroids (local or systemic) prescribed during the same periods as 5-ASA prescriptions—that is, according to the "early pregnancy" group and the "entire pregnancy" group (see above).

We performed logistic regression analyses to estimate the risk of congenital malformations, stillbirth, preterm birth (fewer than 37 completed weeks of gestation), and low birth weight (< 2500 g) associated with 5-ASA drugs, adjusted for maternal age, parity, and smoking. The risk estimates for low birth weight and stillbirth were furthermore adjusted for gestational age. Every pregnancy was included in the analyses as an independent event. We used data from the "early pregnancy" group to estimate the risk of congenital malformations as this is the period where the organs are especially vulnerable to teratogenic exposure. Data from the "entire pregnancy" group was used to estimate the risk of stillbirth, preterm delivery, and low birth weight.

It is well known that the validity of malformations is often misclassified, and after hospital record review of those exposed to 5-ASA could not confirm all cases of congenital malformations. However, to avoid an asymmetrical pattern in the data, we included all cases of malformations in the main analyses. Restricted to a subanalysis we estimated the risk of congenital malformations by including only confirmed diagnoses of malformations in users of 5-ASA.

In the analyses, we stratified for concurrent use of steroids in order to examine this as a surrogate measure of disease activity.

Finally, to evaluate whether the disease itself may influence birth outcome, we used two strategies—that is, we stratified for type of disease, and we used the IBD control group of women who had not been prescribed 5-ASA drugs, thereby comparing patients with the same underlying diseases. Both strategies used the logistic regression models, taking the same potential confounders into consideration.

RESULTS

The 5-ASA exposed women were classified according to disease. Outpatient records of seven women were reviewed because they had never been admitted to hospital, and three of them did not fulfill the criteria for IBD (unspecific IBD or irritable colon). 5-ASA drugs had been prescribed in 60 pregnancies in the "early pregnancy" group (18 CD pregnancies, 42 UC pregnancies) and in 88 pregnancies in the "entire pregnancy" group (23 CD pregnancies, 65 UC pregnancies). The first control group comprised 19 418 pregnancies (table 1). Women who had been prescribed 5-ASA drugs were older, smoked less, and were more often multipara. After stratifying by

disease, the prevalence of smokers with CD and UC was 41% and 8%, respectively. Malformations, stillbirth, and preterm birth were more prevalent in users of 5-ASA drugs than in non-users (table 1).

Four malformations were registered in the "early pregnancy" group but review of hospital records confirmed only two (diagnoses: aphakia and atresia of the lacrimal duct). One of the mothers (with CD) had also received azathioprine for six weeks during the first trimester. The other mother (with UC) had received only 5-ASA. None had disease activity during pregnancy.

There were three cases of stillbirth among women who had been prescribed 5-ASA drugs during pregnancy. After review of the hospital records, no obvious cause was given for two of the three stillbirths in the "entire pregnancy" group (one male, born at a gestational age of 33.6 weeks, weight 2340 g, length 49 cm; and one female, dead at a gestational age of 28.6 weeks, weight 1310 g, length 42 cm). The third, born at a gestational age of 43 weeks, probably died because of strangulation by the umbilical cord.

There were eight cases of preterm birth in the "entire pregnancy" group, including two of the stillbirths. Of the other six, two were medically induced (increasing liver enzymes in one, severe UC activity in the other) and four were spontaneous.

Table 2 shows the adjusted odds ratios (OR) for different adverse birth outcomes in women who had been prescribed 5-ASA drugs, including stratification for concomitant use of steroids. We found an increased risk of congenital malformations, particularly among those who had been prescribed 5-ASA drugs and steroids. There were three stillbirths, two in women who had been prescribed 5-ASA drugs and steroids, giving a 20-fold increased risk, but with a statistical imprecise risk estimate. Furthermore, we found an increased risk of preterm birth, particularly in those who had been prescribed 5-ASA drugs alone. The risk of low birth weight was not substantially increased, and when the analysis was restricted to full term pregnancies (gestational age ⩾37 weeks), we found no children with low birth weights. In a subanalysis, we included only the two confirmed cases of congenital malformations in women who had been prescribed 5-ASA drugs and found no increased risk of malformations (OR 0.9 (95% confidence interval (CI) 0.2–3.8)).

If the second control group was used—the whole cohort (including women who had been prescribed all types of drugs except 5-ASA)—the overall estimates were only slightly lower (data not shown).

Table 3 shows the results after stratifying for underlying type of disease. The main estimates were that the risk of preterm birth was only increased in patients with UC (OR 2.4 (95% CI 1.1–5.3)), and the three stillbirths were all in patients with UC, giving an eightfold increased risk among those who had been prescribed 5-ASA drugs (OR 8.4 (95% CI 2.0–34.3)).

In table 4, we used the IBD control group—that is, women who had been prescribed 5-ASA drugs before or after but not during this pregnancy. Using these controls, the risk of preterm birth was still increased (OR 2.0 (95% CI 0.8–5.0)), and the risk of stillbirth showed a sevenfold increased risk in women who had been prescribed 5-ASA drugs (OR 7.1 (95% CI 0.2–205.1)).

DISCUSSION

We found an increased risk of stillbirth and preterm birth in women who had been prescribed 5-ASA drugs during pregnancy. The risk of stillbirth and preterm birth was equally increased when we used IBD patients as controls (women who had been prescribed 5-ASA drugs before or after but not during pregnancy). The risk of stillbirth was highest among women with UC who had been prescribed 5-ASA drugs and steroids, and the risk of preterm birth was highest in women with UC who used only 5-ASA drugs. These increased risks however may be due to confounding by disease activity and not by the medication. Furthermore, we found no substantial increased risk of low birth weight and no significantly increased risk regarding the overall rate of congenital malformations.

When prescribing drugs for women with IBD, one has to consider the benefits and risks. The fetus may benefit from the drugs due to lessening of disease activity but the therapy may also lead to adverse birth outcome and malformations in the fetus. For ethical reasons no randomised trials have been designed to evaluate the safety of 5-ASA drugs during pregnancy. Therefore, we have to base our clinical decisions on observational studies that are vulnerable to bias, confounding, and problems with statistical precision because of the low frequency of adverse birth outcomes. The literature on the safety of 5-ASA drugs during pregnancy is sparse, as only one controlled study exists in which, for example, the risk of congenital malformations and preterm birth (but not the risk of stillbirth) was estimated.[9] Other studies include two case series of 19 and 18 children born to 5-ASA exposed women,[11 12] and one study with an internal comparison between women treated with high dose versus low dose mesalazine.[10]

Our registry based study comprised a complete prescription database, which prevents selection bias. A strength of the study is that exposure measurement was based on prescriptions and not on recall. Drug exposure based on self reported use may lead to recall bias or under ascertainment[17] which is a serious threat in case control studies. Another strength is that the outcome data were obtained independently of exposure measurement, and most outcome data from the Medical Birth Registry have been shown to be valid.[18] On the other hand, we have no information on compliance. Patient non-compliance may influence the results but this potential misclassification of exposure will tend to underestimate our risk estimates. Another weakness of the study is that most of our estimates were influenced by low statistical precision.

It is well known that congenital malformations are misclassified.[19–21] The risk of congenital malformation may have been overestimated as we included all four of the registered cases in the analysis. However, some of the malformations in the control group may also have been misclassified, thereby giving a risk of imbalance of misclassification in the groups if we excluded the two unconfirmed cases. Studies of teratogenesis require special attention as malformations cannot be regarded as a single homogenous outcome because teratogens do not uniformly increase the rates of all malformations but rather increase rates of selected malformations. Therefore, under ideal circumstances one should consider specific rather than overall rates of malformations.[22] Thus cohort studies can only detect considerable increases in the risk of specific defects, and most cohort studies are limited in their ability to provide assurance of safety. Therefore, it is important to report all data on birth outcomes in IBD women to increase our experience.

The finding of an increased risk of stillbirth, particularly in patients with UC, is new. After reviewing the hospital records of the stillbirths in women who had been prescribed 5-ASA drugs, we found no specific pattern in the cause of death. The risk of stillbirth was not estimated in the 5-ASA study by Diav-Citrin and colleagues.[9] Previous studies have suggested an association between patients with IBD and an increased risk of stillbirth.[23–25] However, none of these studies was designed to examine potential adverse drug effects, and in fact the studies had no data on drug use. In our analysis of women who had been prescribed 5-ASA drugs and steroids, as a surrogate of disease activity, the risk of stillbirth increased further, and this may in fact indicate the importance and disadvantage of disease activity.

The increased risk of preterm birth in patients treated with 5-ASA drugs is in agreement with the only other 5-ASA study

with a control group (that is, by Diav-Citrin and colleagues[9]). However, we also found that the increased risk of preterm birth related only to women with UC who had been prescribed 5-ASA drugs. This association has not been found in other studies as they gave no information on the use of 5-ASA drugs.[2 23 25 26] With respect to preterm births in women who had been prescribed 5-ASA drugs, some were medically induced and some were spontaneous, a pattern that we would also probably have found after reviewing the records of the controls. The risk of preterm birth was still increased using IBD patients as controls, which may indicate that use of 5-ASA drugs plays a role in outcome. An alternative explanation is that the apparent effect of 5-ASA drugs is confounded by disease activity. In the analysis of women who had been prescribed 5-ASA drugs and steroids, as a surrogate of disease activity, the increased risk of preterm birth disappeared, and this may indicate that treatment is effective in patients with disease activity.

We found no substantial increased risk of low birth weight in women with UC or CD disease who had been prescribed 5-ASA drugs. No earlier study has examined this aspect. In agreement with Diav-Citrin and colleagues,[9] we found no increased risk of low birth weight after restricting the analysis to full term births.

In conclusion, our data strongly linked IBD with adverse birth outcome, a finding that has been suggested in previous studies without data on drug intake. Information on drug use in our study may be difficult to interpret. Whether the increased risk of stillbirth and preterm birth is caused, at least partly, by disease activity is uncertain. Analyses of concomitant use of steroids indicated that disease activity was an important risk factor for birth outcome because the use of 5-ASA drugs together with steroids gave a further increased risk of stillbirth. As disease activity may be a risk factor for adverse birth outcome, our data cannot exclude the fact that drugs with effect on disease activity may have a protective effect on the fetus.

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