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The safety of paternal and maternal use of 5-aminosalicylic acid during conception and pregnancy: a nationwide cohort study

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Summary

Background: Data on the safety of paternal use of 5-aminosalicylic acid (5-ASA) prior to conception are lacking, and the safety of maternal use of 5-ASA during pregnancy has not been examined in nationwide data.

Aims: To examine offspring outcomes after paternal pre-conception use of 5-ASA, and after maternal use during pregnancy

Methods: This nationwide cohort study was based on Danish health registries. The study population included live born singletons of patients with ulcerative colitis (UC) or Crohn's disease (CD). Paternal exposure included 2168 children fathered by men treated with 5-ASA, and 7732 unexposed. Maternal exposure included 3618 children exposed *in utero* to 5-ASA, and 7128 unexposed. The outcomes were pre-term birth, small for gestational age (SGA), low Apgar score and major congenital abnormalities (CAs) according to EUROCAT guidelines.

Results: The vast majority of fathers and mothers used mesalazine. In children fathered by men with UC using 5-ASA, we found no increased risk of pre-term birth, SGA or low Apgar score. The hazard ratio (HR) of CAs was 1.30 (95% CI 0.92–1.85). In children of fathers with CD, the odds ratio (OR) of SGA was 1.52 (95% CI 0.65–3.55). After maternal 5-ASA exposure, the OR of SGA in children of women with UC was 1.46 (95% CI: 0.93–2.30); for CAs in children of women with CD, HR was 1.44 (95% CI 0.84–2.47).

Conclusions: Paternal and maternal use of 5-ASA was safe across offspring outcomes; none of the findings reached statistical significance. The safety of 5-ASA formulations that are used infrequently cannot be settled here.

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1 | INTRODUCTION

Many therapeutic drugs are used by patients with inflammatory bowel disease (IBD), and the safety of drug therapy around the time of conception or during pregnancy is an important clinical concern. Both male and female patients with IBD are naturally concerned about the potential adverse effects of medical therapies on their offspring. Most drugs and metabolites cross the placenta to the fetal circulation, and therefore an association between maternal drug use during pregnancy and the risk of adverse birth outcomes has drawn significant attention. Unfortunately, there has been a paucity of research regarding paternal contributions to the health of the offspring.[1–6] It has now become increasingly evident, that fathers' health and fathers' use of medications prior to conception may have significant importance for the health of the offspring, and accumulating evidence has shown that environmental paternal exposures such as medications may induce epigenetic alternations in sperm which in turn increases the risk of adverse health outcomes in the offspring.[3,6–10]

5-aminosalicylic acid (5-ASA) therapeutics include mesalazine, sulfasalazine, olsalazine, and balsalazide and are the first-line anti-inflammatory drugs in the treatment of men and women with ulcerative colitis (UC). From the paternal perspective, no controlled studies have examined the impact of preconceptual paternal use of 5-ASAs and risk of different adverse offspring outcomes. Only one brief report has suggested an increased risk of congenital abnormalities (CAs) associated with the use of balsalazide.[11] From the maternal perspective, the safety of 5-ASA use during pregnancy has been examined,[12–15] and as stated in guidelines, 5-ASA is considered to be of low risk during pregnancy.[16] However, some of the results are still conflicting, and so far, no studies have been based on unselected nationwide data. Several former studies have been limited by selected study populations, small sample size and uncontrolled design.[17–20] A meta-analysis (based on 642 women receiving 5-ASAs in pregnancy) has suggested a 1.16-fold increase in CAs, a 2.38-fold increase in stillbirth, a 1.14-fold increase in spontaneous abortion, and a 1.35-fold increase in preterm delivery.[14]

Based on nationwide health registries including all relevant information on births, parental disease diagnoses, and prescribed medications, we retrieved data on singleton children born in Denmark. We aimed to examine whether (i) fathers' use of 5-ASA within 3 months prior to conception was associated with an increased risk of adverse offspring outcomes, and (ii) maternal use of 5-ASA during pregnancy was associated with an increased risk of adverse offspring outcomes. The examined outcomes were preterm birth, small for gestational age (SGA), low Apgar score, and major CAs.

2 | METHODS

2.1 | Study setting and design

In Denmark, healthcare is available free of charge for all citizens, and all citizens are assigned a unique civil registration number. All contacts in the health care system in Denmark are based on an individual's civil registration number, and thereby it is possible to perform a valid linkage on an individual level between national registries. Due to the mandatory registration of all health activities, we were able to conduct a population-based cohort study.

2.2 | Data sources

The study was based on nationwide Danish health registries, that is, the Danish National Patient Registry (NPR),[21] the Danish Medical Birth Registry (MBR),[22] the Civil Registration system[23] and the Nationwide Prescription Database.[24] The NPR has recorded all discharges from Danish hospitals since 1977 and all outpatient visits since 1994. Key data includes the patients' civil registration numbers, hospital, department, date of admission and discharge, procedures performed, and discharge diagnoses based on the International Classification of Diseases (ICD-8 before 1994, ICD-10 from 1994 onward). The MBR includes information on all births in Denmark, and includes data on the mother, the father, pregnancy-related information, and information on birth outcomes. Since 1995, data on out-patient drug prescriptions have been available from the Nationwide Prescription Database where key information includes the patient's civil registration number, the type of drug according to the anatomical therapeutical chemical (ATC) classification system, and the date of filled prescriptions. All pharmacies in Denmark are equipped with computerised accounting systems that sends key data on prescriptions directly to the Nationwide Prescription Database. By use of the civil registration number, it is therefore possible to obtain the prescription history of each person in Denmark. The Civil Registration system provides information on the civil registration number, death and immigration.

2.3 | Paternal exposure

2.3.1 | Study population

The study population comprises all live born singleton children (January 1, 1997 until December 31, 2018), who were born to fathers with a diagnosis of IBD before the time of conception. The children were identified in the MBR together with the registered father and mother of the child. Diagnoses of IBD were classified in the NPR according to Crohn's Disease (CD) ICD-10: K50*, ICD-8 56301 or UC ICD-10: K51*, ICD8 56319, 56904. The date of conception was based on information from either estimated or ultrasound measured gestational age in the MBR.

2.3.2 | Exposed cohort, children fathered by men treated with 5-ASA prior to conception

For the children in the study population, we retrieved information on paternal preconceptional use of 5-ASA (ATC A07EC) within

3 months before the date of conception. We included children fathered by men with at least one filled prescription for 5-ASA, and the exposed children were split into those fathered by men with UC or CD. Spermatogenesis takes 70–90 days in humans,[25] and a 3-month period prior to conception is used in studies looking at potential toxic effects of a drug on sperm development and adverse offspring outcomes. Data on 5-ASA were obtained from the Nationwide Prescription Database. Fathers were allowed to be treated with drugs other than 5-ASA.

2.3.3 | Unexposed cohort, children fathered by men not treated with 5-ASA prior to conception

The unexposed cohort consisted of all children fathered by men, who had not filled prescriptions for 5-ASA 3 months prior to the conception. The unexposed cohort was split into patients with UC or CD. Fathers were allowed to be treated with drugs other than 5-ASA.

2.4 | Maternal exposure

2.4.1 | Study population

The study population comprises all live born singleton children, born to mothers with IBD before the time of childbirth (1 January 1995 until 31 December 2015). For all children, we retrieved data related to the birth of the child, the mother of the child, and whether the child had been exposed in utero to 5-ASA.

2.4.2 | The exposed cohort, children exposed in utero to 5-ASA

The exposed cohort constituted children exposed in utero to 5-ASA in a period of 30 days before conception or during pregnancy. In this period of time, the mothers had at least one filled prescription for 5-ASA. The exposed cohort was split into women with UC or CD. The mothers were allowed to be treated with other drugs.

2.4.3 | The unexposed cohort, children not exposed in utero to 5-ASA

The unexposed cohort constituted children from the study population who were not exposed in utero for 5-ASA, that is, mothers had no filled prescriptions for 5-ASA in the period of 30 days before conception or during pregnancy. The exposed cohort was split into women with UC or CD. Women were allowed to be treated with drugs other than 5-ASA.

2.5 | Birth outcomes after paternal and maternal exposure

The information on outcomes was retrieved from the MBR and the NPR. The examined outcomes were (i) preterm birth (birth before 37 completed weeks of pregnancy), (ii) SGA estimated according to the Marsal algorithm, that is below the mean −2 SD according to gestational age and sex,[26] and (iii) low 5 min Apgar scores (<7).[27,28] The Apgar scores are assessed based on five components, each with a possible score between 0 and 2 points. The component parts are heart rate, respiratory effort, muscle tone, reflex irritability and skin colour. The fourth outcome was major CAs. These were identified in the Danish National Patient Registry, ICD-10 codes from chapter Q (congenital malformations, deformations and chromosomal abnormalities) and D18.1A (Cystic hygroma), D21.5 (Sacral teratoma) and D82.1 (Pharyngeal pouch syndrome) in line with EUROCAT criteria. Major CAs were identified by excluding minor CAs based on the EUROCAT's classification of CAs.[29,30]

2.6 | Data on possible confounders

From the MBR we obtained information on age of the father (<30 years, 31–40 years, ≥41 years) and mother (<30 years, 31–40 years, ≥41 years) at the time of delivery, parity (1 or more than 1), sex of the child, maternal body mass index (BMI, <18.5, 18.5–24.9, ≥25 kg/m^2), maternal smoking during pregnancy (yes/no) and calendar year of childbirth. BMI and information on smoking is recorded at the first antenatal visit in early pregnancy. Data on mothers' and fathers' additional use of medications were retrieved from the Nationwide Prescription Database and based on filled prescriptions for thiopurines (azathioprine/mercaptopurine, ATC code L04A X01 and L01B B02), systemic corticosteroids (ATC H02AB02, H02AB04, H02AB06, H02AB07, H02AB09) and anti-TNF-alfa (treatment code BOHJ18A). Information on maternal and paternal comorbidity was retrieved from the NPR and calculated according to Charlson Comorbidity Index (CCI) (no comorbidity or some comorbidity).

2.7 | Statistical analyses

For children born after paternal and maternal exposure, contingency tables were constructed for the main study variables according to the exposed and unexposed cohorts. Logistic regression analyses were used to compute crude and adjusted prevalence odds ratio [OR] with 95% confidence intervals [95% CI], for dichotomous outcomes, preterm birth, SGA, and low Apgar score. CAs, diagnosed within the first year after birth, were analysed as time to event data in a Cox regression, computing crude and adjusted hazard ratios [HR] with 95% CI. In all regression analyses, we used robust variance estimation to account for multiple children by the same man or woman. We estimated the risks following paternal use of 5-ASA prior to conception relative to

no paternal use of 5-ASA prior to conception, and the risks following maternal in utero exposure relative to no in utero exposure. In analyses after paternal exposure, adjustment was made for mothers and fathers age, parity, sex of the child, mother's BMI and smoking, fathers and mothers CCI, calendar year of birth, and paternal use of thiopurines, systemic corticosteroids or anti-TNF-alfa 3 months prior to conception. In analyses after maternal exposure, adjustment was made for maternal CCI, maternal age at childbirth, calendar year of childbirth, parity, sex of the child, maternal BMI and smoking, and use of thiopurines, systemic corticosteroids or anti-TNF-alfa 30 days before conception or during pregnancy. Patients who had missing data on confounder variables were excluded from the regression models.

In categories with ≤5 events in our main analyses, we did not calculate risk estimates due to low statistical precision.

In sub-analyses, we examined the risk of CAs according to subgroups of 5-ASA, that is, sulfasalazine ATC A07EC01, mesalazine ATC A07EC02, olsalazine ATC A07EC03 and balsalazide ATC A07EC04. Here, we relaxed the requirement for number of events among the exposed.

All calculations were performed using STATA Release 17.0 (StataCorp).

To confirm that patients in the unexposed cohort were really unexposed, we performed a sensitivity analysis. We increased the time period where patients were not allowed to have filled prescriptions for 5-ASA (paternal part: 3 months prior to conception plus additional 30 days. Maternal part: 60 days before conception or during pregnancy). The exposed cohorts remained unchanged.

2.8 | Permissions and ethics

The study was approved by the Danish Data Protection Agency (j.nr. 19/11743 and 20/4674). This study follows all currently applicable Danish laws regarding scientific research. According to Danish law, no ethical approvals of register-based studies are necessary. The study was non-interventional and did not require direct patient contact.

2.9 | Patient and public involvement

Patient representatives are part of the research council at the Center for Clinical Epidemiology, Odense University Hospital, and patient representatives have been involved in the processes of this study (discussion of the ideas of the study and the outcome assessments). Patient representatives have not been part of the design of the study, analyses of the data or in manuscript writing.

3 | RESULTS

3.1 | Paternal exposure

A total of 1824 singleton children were fathered by men with UC, and 344 children by men with CD, who filled a prescription with a 5-ASA within 3 months before conception (exposed). A total of 4519 children were fathered by men with UC, and 3213 children by men with CD, who had not filled a prescription with a 5-ASA before conception (unexposed). The characteristics of these cohorts are given Table 1. The vast majority of those exposed to 5-ASA were treated with mesalazine (94%). In both the exposed and unexposed cohorts, most fathers were aged 31–40 years at the time of childbirth and had no comorbid diseases. Compared to the unexposed cohorts, the use of corticosteroids was more prevalent in the exposed cohorts of fathers with UC and CD. In fathers with UC, the ORs for preconceptual use of 5-ASA leading to adverse birth outcomes, compared to fathers with no use of 5-ASA, are given in Table 2. We did not find an increased OR of preterm birth, SGA or low Apgar score. The adjusted HR for CAs was 1.30 (95% CI: 0.92–1.85). Table 2 also shows the results for fathers with CD. We did not find an increased OR of preterm birth or HR of CAs, and only two events for low Apgar score. The adjusted OR for SGA was 1.52 (95% CI: 0.65–3.55).

3.2 | Maternal exposure

In women with UC, a total of 2914 singleton children were born after in utero exposure to 5-ASA, and in women with CD, 704 children were born after in utero exposure. In women with UC, 3518 children were not exposed and in women with CD, 3610 children were not exposed. The characteristics of these cohorts are given in Table 3. In the exposed and unexposed cohorts, most women were non-smokers, had normal BMI and had no comorbid diseases. Compared to the unexposed cohorts, the use of corticosteroids was more prevalent in the exposed cohorts of women with UC and CD. In mothers with UC, the ORs for in utero exposure for 5-ASA leading to adverse birth outcomes, compared to children not exposed in utero, are given in Table 4. We did not find an increased OR of preterm birth, low Apgar score or HR of CAs. The adjusted OR for SGA was 1.46 (95% CI: 0.93–2.30). Table 4 also shows the results for mothers with CD. We did not find an increased OR of preterm birth or SGA and only few events of a low Apgar score. The adjusted HR for CAs was 1.44 (95% CI: 0.84–2.47).

3.3 | Subanalysis of 5-ASA subtypes

The HR of CAs was examined according to sub-types of 5-ASA (Table 5). In fathers and mothers with CD, there were too few data to subdivide into types of 5-ASA, and the subanalyses were made only on patients with UC (Table 5). In fathers with UC, preconceptual use of sulfasalazine, mesalazine or olsalazine was not associated with an increased HR of CAs in the offspring. A total of 19 fathers with UC filled a prescription for balsalazide prior to conception and 4 children had a CA (21%). Compared to fathers not using balsalazide prior to conception, the crude and adjusted HRs for CAs were 6.86 (95% CI 2.55–18.46) and 7.22 (95% CI 2.67–19.55), respectively. The CAs in the 4 children belonged predominantly to the EUROCAT category "Limb" (no further details are allowed due to anonymity), and each

TABLE 1 Characteristics of children according to paternal use of 5-ASA 3 months prior to the conception, singleton births from 1 January 1997 until 31 December 2019

	Ulcerative colitis		Crohn's disease	
	Children fathered by men treated with 5-ASA *N* = 1824	Children fathered by men not treated with 5-ASA *N* = 4519	Children fathered by men treated with 5-ASA *N* = 344	Children fathered by men not treated with 5-ASA *N* = 3213
Paternal age at childbirth, years				
−30	385 (21.1)	1025 (22.7)	94 (27.3)	906 (28.2)
31–40	1213 (66.5)	2779 (61.5)	215 (62.5)	1920 (59.8)
41–	226 (12.4)	715 (15.8)	35 (10.2)	387 (12.0)
Paternal CCI[a]				
0	1622 (88.9)	3889 (86.1)	306 (89.0)	2738 (85.2)
≥1	202 (11.1)	630 (13.9)	38 (11.0)	475 (14.8)
Maternal age at childbirth, years				
−30	706 (38.7)	1750 (38.7)	162 (47.1)	1446 (45.0)
31–40	1061 (58.2)	2599 (57.5)	169 (49.1)	1668 (51.9)
41–	57 (3.1)	170 (3.8)	13 (3.8)	99 (3.1)
Maternal CCI				
0	1700 (93.2)	4186 (92.6)	330 (95.9)	2937 (91.4)
≥1	124 (6.8)	333 (7.4)	14 (4.1)	276 (8.6)
Maternal smoking				
No	1631 (89.4)	3769 (83.4)	265 (77.0)	2620 (81.5)
Yes	109 (6.0)	522 (11.6)	52 (15.1)	451 (14.0)
Missing	84 (4.6)	228 (5.0)	27 (7.8)	142 (4.4)
Maternal BMI				
<18.5	73 (4.0)	130 (2.9)	10 (2.9)	114 (3.5)
18.5–24.9	875 (48.0)	2117 (46.8)	102 (29.7)	1551 (48.3)
≥25	415 (22.8)	1086 (24.0)	53 (15.4)	856 (26.6)
Missing	461 (25.3)	1186 (26.2)	179 (52.0)	692 (21.5)
Parity				
First child	766 (42.0)	1896 (42.0)	146 (42.4)	1428 (44.4)
Second or more	1038 (56.9)	2584 (57.2)	194 (56.4)	1756 (54.7)
Missing	20 (1.1)	39 (0.9)	4 (1.2)	29 (0.9)
Child sex				
Girl	869 (47.6)	2227 (49.3)	165 (48.0)	1555 (48.4)
Boy	955 (52.4)	2292 (50.7)	179 (52.0)	1658 (51.6)
Calendar year of birth				
1997–2002	353 (19.4)	914 (20.2)	147 (42.7)	492 (15.3)
2003–2008	490 (26.9)	1212 (26.8)	111 (32.3)	785 (24.4)
2009–2014	543 (29.8)	1304 (28.9)	56 (16.3)	1013 (31.5)
2015–2018	438 (24.0)	1089 (24.1)	30 (8.7)	923 (28.7)
Subtypes of 5-ASA and ATC[b]				
sulfasalazine A07EC01	88 (4.8)		27 (7.8)	
mesalazine A07EC02	1714 (94.0)		314 (91.3)	
olsalazine A07EC03	37 (2.0)		4 (1.2)	
balsalazide A07EC04	19 (1.0)		1 (0.3)	

(Continues)

TABLE 1 (Continued)

	Ulcerative colitis		Crohn's disease	
	Children fathered by men treated with 5-ASA N = 1824	Children fathered by men not treated with 5-ASA N = 4519	Children fathered by men treated with 5-ASA N = 344	Children fathered by men not treated with 5-ASA N = 3213
Other medications[c]				
azathioprine	210 (11.5)	148 (3.3)	60 (17.4)	421 (13.1)
corticosteroids	174 (9.5)	83 (1.8)	45 (13.1)	114 (3.5)
anti-TNF-alfa	43 (2.4)	88 (1.9)	5 (1.5)	295 (9.2)

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

[a]Charlson Comorbidity Index.

[b]Anatomical therapeutical chemical (ATC) classification system.

[c]3 months prior to conception.

TABLE 2 Paternal exposure. Crude and adjusted relative risk estimates, with 95% confidence interval (CI), for birth outcomes in singleton children fathered by men treated with 5-ASA within 3 months before conception

	Children exposed to 5-ASA		Children not exposed to 5-ASA			
	Events (%)	Total	Events	Total	Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Ulcerative colitis						
Preterm birth	100 (5.5)	1824	227 (5.0)	4519	1.10 (0.86–1.40)	0.94 (0.69–1.28)
Small for gestational age	40 (2.2)	1820	123 (2.7)	4507	0.80 (0.56–1.15)	0.83 (0.52–1.32)
Low Apgar score	7 (0.4)	1810	23 (0.5)	4489	0.75 (0.32–1.76)	0.48 (0.17–1.35)
	Events	Total time at risk (years)	Events	Total time at risk (years)	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Congenital abnormalities	64	1765	150	4379	1.06 (0.79–1.42)	1.30 (0.92–1.85)
	Children exposed to 5-ASA		Children not exposed to 5-ASA			
	Events	Total	Events	Total	Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Crohn's disease						
Preterm birth	17 (4.9)	344	172 (5.4)	3213	0.92 (0.55–1.53)	0.91 (0.41–2.02)
Small for gestational age	11 (3.2)	344	90 (2.8)	3203	1.14 (0.60–2.16)	1.52 (0.65–3.55)
Low Apgar score	2 (0.6)	344	21 (0.7)	3184	–	–
	Events	Total time at risk (years)	Events	Total time at risk (years)	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Congenital abnormalities	10	334	129	3097	0.72 (0.38–1.37)	0.85 (0.38–1.93)

[a]Adjusted for maternal age (≤30 years, 31–40 years, >40 years), paternal age (≤30 years, 31–40 years, >40 years), parity (1 or more than 1), sex of the child, maternal BMI (<18.5, 18.5–24.9, ≥25 kg/m^2), maternal smoking in pregnancy (yes/no), paternal and maternal Charlson Comorbidity Index, calendar year of birth (1997–2002, 2003–08, 2009–13, 2014–2019), paternal use of thiopurines, systemic corticosteroids or anti-TNF-alfa 3 months prior to conception in regression models.

of the 4 children only had a single CA. In mothers with UC who used mesalazine, there was no increased HR of CA. We had few mothers exposed to sulfasalazine, olsalazine or balsalazide, and few events of CAs (13, 5, and 1, respectively). The HR of CAs associated with maternal use of sulfasalazine was 1.81 (95% CI 0.99–3.31) and for olsalazine 1.85 (95% CI 0.76–4.53).

3.4 | Sensitivity analysis

Expanding the time period for no use of 5-ASA prior to conception excluded only a few patients from the unexposed cohorts, and this did not change any of the risk estimates in the paternal and maternal analyses.

TABLE 3 Children born to women with inflammatory bowel disease according to in utero exposure to 5-ASA or not. Characteristics of the study cohorts

	Ulcerative colitis		Crohn's disease	
	Children exposed in utero to 5-ASA *N* = 2914	Children not exposed in utero to 5-ASA *N* = 3518	Children exposed in utero to 5-ASA *N* = 704	Children not exposed in utero to 5-ASA *N* = 3610
Maternal age at childbirth, years				
–30	1384 (47.5)	1623 (46.1)	391 (55.5)	1884 (52.2)
31–40	1474 (50.6)	1825 (51.9)	308 (43.8)	1667 (46.2)
41–	56 (1.9)	70 (2.0)	5 (0.7)	59 (1.6)
Maternal BMI				
<18.5 (underweight), *N* (%)	88 (3.0)	125 (3.6)	8 (1.1)	143 (4.0)
18.5.24.99 (normal), *N* (%)	1315 (45.1)	1401 (39.8)	203 (28.8)	1513 (41.9)
25.00–29.99 (overweight), *N* (%)	343 (11.8)	443 (12.6)	65 (9.2)	529 (14.7)
≥30.00 (obese), *N* (%)	174 (6.0)	287 (8.2)	34 (4.8)	307 (8.5)
Missing	994 (34.1)	1262 (35.9)	394 (56.0)	1118 (31.0)
Maternal smoking at start of pregnancy				
Non-smoker, *N* (%)	2551 (87.5)	2818 (80.1)	490 (69.6)	2626 (72.7)
Smoker, *N* (%)	195 (6.7)	496 (14.1)	134 (19.0)	780 (21.6)
Missing, *N* (%)	168 (5.8)	204 (5.8)	80 (11.4)	204 (5.7)
Parity				
0, *N* (%)	1139 (39.1)	1329 (37.8)	316 (44.9)	1566 (43.4)
1+, *N* (%)	1587 (54.5)	1904 (54.1)	309 (43.9)	1788 (49.5)
Missing	188 (6.5)	285 (8.1)	79 (11.2)	256 (7.1)
Maternal CCI[a]				
No comorbidity, *N* (%)	2679 (91.9)	3137 (89.2)	639 (90.8)	3121 (86.5)
Some comorbidity, *N* (%)	235 (8.1)	381 (10.8)	65 (9.2)	489 (13.5)
Calendar year of childbirth				
1995–1999, *N* (%)	437 (15.0)	594 (16.9)	189 (26.8)	551 (15.3)
2000–2004, *N* (%)	636 (21.8)	737 (20.9)	233 (33.1)	680 (18.8)
2005–2009, *N* (%)	779 (26.7)	894 (25.4)	154 (21.9)	988 (27.4)
2010–2015, *N* (%)	1062 (36.4)	1293 (36.8)	128 (18.2)	1391 (38.5)
Sex of the child (boy), *N* (%)	1466 (50.3)	1774 (50.4)	358 (50.9)	1869 (51.8)
Paternal age at childbirth, years				
–30	1009 (34.6)	1138 (32.3)	304 (43.2)	1409 (39.0)
31–40	1613 (55.4)	2021 (57.4)	350 (49.7)	1892 (52.4)
41–	292 (10.0)	359 (10.2)	50 (7.1)	309 (8.6)
Subtypes of 5-ASA and ATC[b]				
sulfasalazine A07EC01	240 (8.2)		92 (13.1)	
mesalazine A07EC02	2712 (93.1)		623 (88.5)	
olsalazine A07EC03	84 (2.9)		8 (1.1)	
balsalazide A07EC04	22 (0.8)		4 (0.6)	
Other medications[c]				
thiopurines	184 (6.3)	64 (1.8)	80 (11.4)	382 (10.6)
corticosteroids	850 (29.2)	179 (5.1)	140 (19.9)	258 (7.1)
anti-TNF-alfa	41 (1.4)	32 (0.9)	18 (2.6)	178 (4.9)

[a]Charlson Comorbidity Index.

[b]Anatomical therapeutical chemical (ATC) classification system.

[c]30 days before conception or during pregnancy.

TABLE 4 Maternal exposure. Crude and adjusted odds ratio (OR), with 95% confidence interval (CI), for adverse birth outcomes children after in utero exposure to 5-ASA

	Children exposed in utero to 5-ASA		Children not exposed in utero to 5-ASA		Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
	Events	Total	Events	Total		
Ulcerative colitis						
Preterm birth	213 (7.3%)	2914	256 (7.3%)	3518	1.00 (0.82–1.23)	0.83 (0.63–1.10)
Small for gestational age	82 (2.8%)	2897	85 (2.4%)	3499	1.17 (0.85–1.62)	1.46 (0.93–2.30)
Low Apgar score	15 (0.5%)	2729	22 (0.7%)	3238	0.81 (0.41–1.58)	0.71 (0.24–2.06)
	Events	**Total time at risk (years)**	**Events**	**Total time at risk (years)**	**Crude hazard ratio (95% CI)**	**Adjusted hazard ratio[a] (95% CI)**
Congenital abnormalities	117	2807.0	153	3373.6	0.92 (0.72–1.17)	0.76 (0.56–1.04)
	Children exposed in utero to 5-ASA		**Children not exposed in utero to 5-ASA**			
	Events	**Total**	**Events**	**Total**	**Crude odds ratio (95% CI)**	**Adjusted odds ratio[a] (95% CI)**
Crohn's disease						
Preterm birth	53 (7.5%)	704	313 (8.7%)	3610	0.86 (0.63–1.17)	0.78 (0.50–1.22)
Small for gestational age	26 (3.7%)	702	117 (3.3%)	3595	1.14 (0.73–1.79)	0.89 (0.41–1.93)
Low Apgar score	5 (0.8%)	628	23 (0.7%)	3364	–	–
	Events	**Total time at risk (years)**	**Events**	**Total time at risk (years)**	**Crude hazard ratio (95% CI)**	**Adjusted hazard ratio[a] (95% CI)**
Congenital abnormalities	28	676.8	140	3479.3	1.03 (0.68–1.55)	1.44 (0.84–2.47)

[a]Adjusted for maternal Charlson Comorbidity Index, maternal age at time of child birth (≤30 years, 31–40 years, >40 years), calendar year of child birth (1995–99, 2000–04, 2005–09, 2010–2015), parity (1 or more than 1), sex of the child, use of immunomodulator therapy during pregnancy (thiopurines, corticosteroids or anti-TNF-alfa), maternal BMI (<18.5, 18.5–24.9, ≥25 kg/m^2), and maternal smoking in pregnancy (yes/no).

4 | DISCUSSION

This is the first controlled study to examine the effect of paternal preconceptual use of 5-ASAs on different birth outcomes, and it is the largest study to date on a range of outcomes after maternal use of 5-ASA during pregnancy. Mesalazine was used in 95% of all cases of fathers prescribed 5-ASA prior to conception. We showed that children fathered by men with UC, who used 5-ASAs prior to conception, did not have increased OR of preterm birth, SGA or low Apgar score, but the HR of CAs was 1.30-fold increased (although not statistically significant). Children fathered by men with CD, who used 5-ASA prior to conception, did not have statistically significantly increased OR/HR of the examined outcomes. If women used 5-ASA during pregnancy, mesalazine was used in 92% of all cases. In women with UC and CD, we did not find increased OR/HRs of the examined adverse outcomes, except an OR of 1.46 of SGA in women with UC, and a HR of 1.44 of CAs in women with CD (none of these were statistically significant).

There is no doubt that both maternal and paternal preconception health conditions and behaviours influence the health of the offspring.[31,32] This has also been supported in patients with IBD where a study from 2010 showed that both maternal and paternal IBD influenced the risk of preterm birth, OR 2.15 (95% CI: 1.36–3.39) and OR 3.02 (95% CI: 1.82–5.01), respectively.[9] In contrast, a Swedish study failed to show an association between fathers suffering from IBD and offspring birthweight.[33] These studies, however, did not examine an impact of paternal IBD medications prior to conception. Our study showed that the vast majority of fathers were treated with mesalazine, and as expected relatively few were treated with sulfasalazine because this is often stopped in men considering fatherhood. In addition, balsalazide was very rarely used. Most of our results after paternal use of 5-ASA cannot be compared to others as only case series exist, with many focusing on fertility and sulfasalazine and sperm parameters.[34–36] Expecting fathers are often advised to discontinue sulfasalazine 3–4 months before attempting conception given a negative impact on semen quality,[34,35,37] but the recommendations have been that other 5-ASA compounds can be used throughout conception.[38] One recent report from Denmark has suggested an increased adjusted OR of CAs after preconceptual use of balsalazide (7.7, 95% CI: 2.5–23).[11] Wensink et al hypothesized that the increased risk may be related to the 4-aminobenzoyl-β-alanine component part of balsalazide.[11] Our analytic approach was a little different, but we also found a 7-fold increased risk of CAs. However, our analyses are based on only 4 CAs, and we would indeed be cautious when interpreting this result as it could be vulnerable to differential misclassification of CAs. Our dataset shares some of the same data used by Wensink et al,[11] and therefore our result cannot be used to validate the findings related to balsalazide. The safety

TABLE 5 Crude and adjusted Hazard rates (HR), with 95% confidence interval (CI), for major congenital abnormalities in exposed patients with ulcerative colitis according to different 5-ASA compounds

	Children exposed to paternal use a specific subtype of 5-ASA		Children not exposed to paternal use of a specific subtype of 5-ASA			
Congenital abnormalities	**Events**	**Total time at risk (years)**	**Events**	**Total time at risk (years)**	**Crude HR (95% CI)**	**Adjusted HR[a] (95% CI)**
Paternal preconception use of 5-ASA						
sulfasalazine	3	85	211	6059	1.01 (0.32–3.15)	1.07 (0.34–3.34)
mesalazine	57	1661	157	4483	0.98 (0.72–1.33)	1.04 (0.76–1.42)
olsalazine	0	37	214	6107		
balsalazid	4	16	210	6129	6.86 (2.55–18.46)	7.22 (2.67–19.55)
	In utero exposure to a specific subtype of 5-ASA		**No in utero exposure to a specific subtype of 5-ASA**			
Congenital abnormalities	**Events**	**Total time at risk (years)**	**Events**	**Total time at risk (years)**	**Crude HR (95% CI)**	**Adjusted HR[b] (95% CI)**
Maternal use of 5-ASA during pregnancy						
sulfasalazine	13	228	257	5953	1.31 (0.75–2.29)	1.81 (0.99–3.31)
mesalazine	106	2614	164	3566	0.88 (0.69–1.13)	0.86 (0.66–1.13)
olsalazine	5	80	265	6100	1.42 (0.59–3.45)	1.85 (0.76–4.53)
balsalazid	1	21	269	6159		

[a]Adjusted for other subtypes of 5-ASAs, maternal age (≤30 years, 31–40 years, >40 years), paternal age (≤30 years, 31–40 years, >40 years), parity (1 or more than 1), sex of the child, paternal and maternal Charlson Comorbidity Index, calendar year of birth (1997–2002, 2003–08, 2009–13, 2014–2019), paternal use of thiopurins, systemic corticosteroids or anti-TNF-alfa 3 months prior to conception in regression models.

[b]Adjusted for maternal Charlson Comorbidity Index, maternal age at time of child birth (≤30 years, 31–40 years, >40 years), calendar year of child birth (1995–99, 2000–04, 2005–09, 2010–2015), parity (1 or more than 1), sex of the child, use of immunomodulator therapy during pregnancy (thiopurins, corticosteroids or anti-TNF-alfa).

of balsalazide should be examined in datasets from other countries where balsalazide is more commonly used.

The risk of adverse offspring outcomes following paternal use of IBD medications other than 5-ASA has been studied in few controlled studies, and the evidence is still scant. These studies have examined outcomes in children fathered by men on thiopurines prior to conception,[38–41] with very few studies on an impact of paternal use of biologic therapies,[41,42] and systemic steroids.[43]

This study adds to the evidence on the safety of maternal use of 5-ASAs during pregnancy, and compared to former studies, this study benefits from the increased power of nationwide data. Our study was based on 3618 children exposed in utero to 5-ASA and overall, our results were reassuring across the examined outcomes. Generally, 5-ASA has been considered safe for many years, but former studies have been hampered by small study populations and lack of consistency across the measured birth outcomes.[12,13,15,44,45] Some studies have suggested an increased risk of preterm birth, low birth weight and CAs, and sometimes the conclusions have been vague because of problems with the statistical precision. Concern has also been raised regarding the possible harmful effect of dibutyl phthalate (DBP) as DBP was initially an inactive part of the coating of Asacol (mesalazine). In animal studies, DBP has been suggested to increase CAs,[46] but DBP was removed from the coating in Denmark in 2007. Regarding CAs, a study from 2014, based on 551 5-ASA exposed women with IBD, did not find an increased overall risk, OR = 0.82 (95% CI 0.42–1.61).[47] In a meta-analysis from 2008, based on 642 women receiving 5-ASAs in pregnancy, Rahimi et al reported the ORs of CAs, preterm birth and low birth weight (1.16 (95% CI 0.76–1.77), 1.35 (95% CI 0.85–2.13), and 0.93 (95% CI 0.46–1.85), respectively). The study from Rahimi et al did not stratify the results according to UC and CD.

Our study has several strengths. We were able to study the risk of adverse birth outcomes based on nationwide data on all fathers with IBD who filled prescriptions for 5-ASAs prior to conception, and all women with IBD who filled prescriptions for 5-ASAs during pregnancy. The precision and the validity of our results depends on the size of the study, accurate classification of exposure and outcomes, and the ability to adjust for relevant confounders. The data from the used health care registries have a high completeness and validity. We extracted information on drug exposure from the Nationwide Prescription Database and this ensured exact ascertainment of drug exposure, that is, all fathers could be classified according to filled prescriptions for 5-ASAs prior to conception, and similarly, all mothers could be classified according to use of 5-ASA during pregnancy.[24] It is a strength that drug exposure was based on prescriptions and not on patient recall, as drug exposure based on self-reported use

may lead to recall bias or under ascertainment. Our outcome assessments were based on valid information from the MBR,[22] and this information was collected independently of the exposure, which prevents information bias. Due to ethics, randomised trials are not designed to examine the safety of drugs during pregnancy and conception. Therefore, clinical decisions on drug use during stages of gestation must be based on evidence from observational studies that might be vulnerable to bias and confounding. Notably, we were able to consider several important confounders related to both the mother and father. Based on the above, we believe that the external validity of our study is good and applicable to other populations of men and women with IBD.

The precision of the risk estimates is always a matter of concern when studying adverse birth outcomes because of a low prevalence of such outcomes. This is particularly relevant for CAs, because no known teratogens increase the risk of all CAs, but rather tend to affect selected CAs. Despite these nationwide data, some of our risk estimates were still vulnerable to low statistical precision. This was particularly true when examining subtypes of 5-ASAs and CAs.

Our study also has limitations. We had no information on drug compliance. However, any misclassification of 5-ASA exposure, due to patient non-compliance, is most probably not related to our outcome assessments, and would therefore tend to underestimate our risk estimates. Based on prescription data, we were not able to examine a possible 5-ASA dose-effect response. Ideally, the risk of specific CAs should be examined instead of overall rates but examining specific CAs would have a major impact on the sample size requirements. Estimating the risk of specific CAs were thus not possible based on our data. It is not possible to perform medical record reviews in this nationwide setting, and therefore we could not obtain further clinical details or information on disease activity or go through all cases of CAs in exposed and unexposed cohorts. Regarding disease activity and severity we were able to adjust the analyses for proxy measurement (use of corticosteroids) and use of immunomodulatory treatments. Hospitalizations were not used as a proxy for disease activity as only the most severely ill patients in Denmark are hospitalised and those who are mildly to moderately ill are treated in out-patient settings. Theoretically, other confounders might have an impact on our results, and in an observational study like this, one can never rule out an impact of unknown or residual confounding.

The health of the offspring after paternal and maternal drug exposure around the time of conception and during pregnancy is continuously relevant, and only observational cohort studies can provide data on drug safety. This study gives the first controlled results of different adverse birth outcomes after preconceptual paternal use of 5-ASA, and it has the largest number of prescribed 5-ASA during pregnancy to date. Based on our overall results, paternal use of 5-ASA prior to conception was not associated with a significantly increased risk of adverse outcomes in the offspring. Additionally, maternal use of 5-ASA during pregnancy was safe and there were no statistically significantly increased risks of adverse outcomes in the offspring. To study an impact of rarely used 5-ASA compounds such as olsalazine and balsalazine, other datasets are needed.

AUTHOR CONTRIBUTIONS

Bente Mertz Nørgård: Conceptualization (lead); data curation (supporting); formal analysis (supporting); methodology (lead); validation (equal); writing – original draft (lead); writing – review and editing (lead). **Sonia Friedman:** Conceptualization (supporting); validation (supporting); writing – review and editing (supporting). **Jens Kjeldsen:** Conceptualization (supporting); methodology (supporting); writing – review and editing (supporting). **Jan Nielsen:** Conceptualization (equal); formal analysis (lead); methodology (equal); validation (lead); writing – review and editing (equal).

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The use of Danish registers has been approved for this study. We are not allowed to share the patient data with other parties. Other researchers can have access to the Danish registries through an application to the Danish Data Authority (forskerservice@sundheds-data.dk). Access to data also requires approval form the Danish Data Protection Agency. The authors of this paper do not have special access privileges to the data used in the current study.

AUTHORSHIP

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