Use of medications to treat inflammatory bowel diseases before and during pregnancy in Switzerland between 2012 and 2019: an observational study using the claims-based MAMA cohort.

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Abstract

Background: Effective management of Inflammatory bowel diseases (IBD) before and during pregnancy is crucial as women with well-controlled IBD at conception tend to remain in remission throughout pregnancy, experiencing outcomes similar to women without IBD. Most IBD medications are considered safe during pregnancy, except for methotrexate. Despite reassuring data, previous studies have highlighted that women often have negative perceptions and fears related to IBD medications, leading to poor adherence. There is a lack of data regarding how IBD is treated before and during pregnancy in Switzerland.

We aimed to assess the prevalence and usage patterns of various IBD medications in Switzerland before and during pregnancy over time.

Methods: A descriptive study using the MAMA cohort based on Swiss health insurance claims from 2012 to 2019. We identified pregnancies with a pharmaceutical cost group (PCG) indicating IBD and at least one prescribed IBD medication before pregnancy. We defined three groups based on dispensation timing: continuers (dispensation in pre-pregnancy and in or after trimester 2), switchers (different dispensation between pre-pregnancy and in or after trimester 2), and discontinuers (dispensation in pre-pregnancy but no dispensation in or after trimester 2).

Results: Among 104,098 deliveries, 0.3% had a PCG code for IBD with an IBD medication dispensed in pre-pregnancy. Over half of these pregnancies were exposed to Aminosalicylates, with a consistent proportion over time. Pregnancies exposed to biologics increased over time, while immunosuppressant use remained steady. Roughly one-third with IBD medication before pregnancy discontinued treatment, a consistent rate throughout the study.

Conclusions: Aminosalicylates were the most prescribed medication to treat IBD despite the lack of evidence to support their use as first-line therapy. The increase in biologics' prescriptions likely reflects the growing evidence on the safety of these medications during pregnancy. One in three women discontinued all treatment during pregnancy, with a stable proportion over time. It is not known whether women discontinued treatment due to quiescent disease or concerns about medication harm. If the latter, these women should be identified and counseled, preferably during the pre-conception period, about the risks and benefits of disease and treatment.

1. Background

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic inflammation and subsequent lesions of the gastrointestinal tract [1]. IBD can severely impact a person's life, often resulting in hospitalizations, surgeries, and increased mortality [2, 3], and are responsible for substantial societal and economic costs [4]. The prevalence of IBD has been estimated to be approximately 0.3% in North America, Australia, and Western Europe [5]. The highest incidence rate has been reported in young adults aged 15 to 29 years [6, 7].

Optimal disease control prior to and at the onset of pregnancy is important, as it has been shown that women with well-controlled IBD at conception and during the first trimester are likely to remain in remission during pregnancy and have similar outcomes to women without IBD [8]. Active disease before and at conception has been associated with an increased risk of caesarean section, preterm delivery, and low birth weight [9, 10, 11].

Current Swiss [12–14] and international [15] guidelines recommend aminosalicylates (ASAs) as the standard medical maintenance therapy for UC in the general adult population [13, 15]. Patients have traditionally been treated with thiopurines (azathioprine, mercaptopurine) in case of ASA failure or corticosteroid-dependent UC. The British Society of Gastroenterology (BSG) now recommends either thiopurines or biologics due to the lower biological toxicity and decreasing costs since biosimilars have become available [15]. The choice between different TNF-alpha inhibitors, vedolizumab, ustekinumab, or tofacitinib should be based on patients' characteristics and preferences. For maintenance treatment in patients with moderate to severe CD, the BSG recommends thiopurines (azathioprine, mercaptopurine) or methotrexate as first-line therapy. Patients with CD refractory to immunomodulatory therapy should be considered for biologic therapy (anti TNF-alpha, vedolizumab, ustekinumab). Aminosalicylates are no longer recommended in international guidelines as a treatment for CD [12, 16]. In Switzerland, however, mesalazine is still an option for CD patients who refuse repeated steroids or who do not want to start immunosuppressives or biologics [12].

Most medications used to treat IBD are generally considered safe to continue during pregnancy [14], with for example the exception of methotrexate [17]. Guidelines agree that women on ASA, thiopurine, anti-TNF monotherapy for maintenance should continue treatment during pregnancy. Anti-TNF usually begin crossing the placenta around 14 weeks of gestation, when the crucial period of organogenesis is complete. There is currently no evidence of harm if treatment is continued during pregnancy and stopped to allow its elimination before delivery when the disease is quiescent. When continued until delivery, neonates are considered immunosuppressed for two to six months after the last maternal administration, as some anti-TNF inhibitors have been measured at high levels in neonatal blood such as infliximab [15]. Finally, the BSG highlights the lack of data on the newest biologics including vedolizumab, ustekinumab, or tofacitinib during pregnancy [17] and emphasizes the importance of pre-conception counselling for these women [15].

Despite reassuring data, previous reports have highlighted women's negative perception of IBD medications and related fear [18, 19], which often lead to poor adherence [20]. Data on how IBD is treated before and during pregnancy in Switzerland are lacking.

We aimed to study the exposure prevalence and patterns of use of different IBD medications before and during pregnancy in Switzerland over time, using representative Swiss claims data.

2. Methods

2.1 Study design

This study was conducted within the MAMA cohort [21]. This cohort consists of data of the Chrétienne sociale suisse (CSS) health insurance among women who had a delivery in Switzerland between January 2012 and December 2019.[1]

2.2 Setting

In Switzerland, citizens must have a health insurance and approximately 17% of the Swiss population is covered by CSS [22]. The CSS Datawarehouse provides anonymized information regarding inpatient and outpatient services and prescribed medications in the outpatient setting. Records were extracted for every woman with at least one delivery between January 2012 and December 2019 and continuously covered by CSS from 9 months before her estimated last menstrual period to 9 months after the delivery code for each retraced pregnancy.

2.3 MAMA cohort

2.3.1 Identification of pregnancies

Pregnancies were recorded through codes from both SwissDRG (Diagnosis Related Groups) and TARMED (Swiss medical services tariffication system). Supplementary Table 1 lists the codes used to identify a delivery, which could include stillbirths and livebirth. Pregnancies ending with a miscarriage, or an elective medical abortion were excluded because the study also aims to analyze longitudinal patterns of medication use.

2.3.2 Identification of delivery dates

Delivery codes registered within a 30-day window of each other were regarded as related to the same pregnancy [23]. The date of delivery was defined as the first recorded code during this period, except when both DRG and TARMED codes were available. In such cases, DRG codes were prioritized to set the delivery date. Different delivery dates for the same woman had to be recorded at least 300 days apart. DRG delivery codes registered between 30 and 300 days after the initial delivery date were excluded from consideration except when the initial delivery date had been identified through a sequence of a TARMED code followed by a DRG code, then the delivery data was adjusted to the DRG code date.

2.3.4 Identification of the beginning of pregnancy and pre-pregnancy period

Neither gestational age nor the date of the beginning of pregnancy are recorded in Swiss health insurance data. Thus, the beginning of pregnancy was estimated using an algorithm validated in US claims data [24] and already implemented in a Swiss pregnancy cohort using another claims database [23, 25, 26]. The beginning of pregnancy was set at 270 days before the delivery date for pregnancies ending in a term delivery (determined based on DRG codes) and 245 days for pregnancies with a preterm delivery code (see Supplementary Table 2). Each pregnancy trimester (Trimester 1 (T1), Trimester 2 (T2) and

Trimester 3 (T3)) was defined as a 90-day period. In case of preterm delivery, T3 was shortened to a 65-day period. A pre-pregnancy period of 252 days (9 months) before the last menstrual period was also observed.

2.4. Study population

The final study population consisted of pregnancies of women who had a pharmaceutical cost group (PCG) code indicating an IBD during pre-pregnancy and who were prescribed at least one medication commonly used to treat IBD (see 2.5) in the pre-pregnancy period (excluding corticosteroids, which are commonly used to treat flares but are not specific to IBD).

PCG codes are a system used to classify medical conditions based on distinct combinations and dosages of prescribed medications. They are primarily designed for administrative and financial purposes rather than clinical diagnosis. Medications within the same PCG code may be used to treat different conditions, and conversely, medications for the same condition may fall under different PCG codes. Treatment of IBD includes medications that can be used for other conditions, such as rheumatoid arthritis (RA) or psoriasis. However, it is essential to emphasize that the assignment of PCG codes for one condition (i.e., IBD) requires distinct combinations and dosages of these medications compared to the assignment of another condition (i.e., RA), which we believe contributes to a reasonably high level of accuracy. Nevertheless, some women may have both conditions (IBD and RA) at the same time (see Flowchart 1).

In our cohort, among pregnancies with a PCG code indicating IBD and a prescription for IBD in the pre-pregnancy period, we further defined three groups of users («continuers», «switchers», «discontinuers»).

2.4.1 Continuers

We defined a group of «continuers», that included pregnancies with a dispensation in pre-pregnancy and the same dispensation in or after T2.

2.4.2 Switchers

We defined a group of «switchers» that included pregnancies with a dispensation in pre-pregnancy and a different dispensation in or after T2. If a pregnant woman had multiple treatments during pre-pregnancy and only partially continued these treatments, she was considered a switcher for the stopped treatments and a continuer for the continued treatments.

2.4.3 Discontinuers

We defined a group of «discontinuers» that included pregnancies with a dispensation in pre-pregnancy and no dispensation in or after T2.

2.5 Exposure

We recorded exposure to any group of medication and individual medication commonly used to treat IBD based on recorded Anatomical Therapeutic Classification (ATC) codes: Aminosalicylates (including suppositories and enemas [A07EC]): sulfasalazine (A07EC01), mesalazine (A07EC02); Traditional immunosuppressants: azathioprine (L04AX01), mercaptopurine (L01BB02), methotrexate (L04AX03), ciclosporin (L04AD01), tacrolimus (L04AD02), tofacitinib (L04AA29); Biologics: infliximab (L04AB02), adalimumab (L04AB04), golimumab (L04AB06), certolizumab (L04AB05), vedolizumab (L04AA33), ustekinumab (L04AC05). We also recorded exposure to systemic and topic corticosteroids used in the treatment of IBD flares: systemic corticosteroids (betamethasone (H02AB01), methylprednisolone (H02AB04), prednisolone (H02AB06), prednisone (H02AB07); topical corticosteroids (budesonide, A07EA06). Exposure was defined as at least one outpatient dispensation of the above-mentioned medications during the periods of interest (i.e., pre-pregnancy, in or after T2). The "in or after T2" period was chosen to more accurately capture women who were continuously treated during pregnancy. Relying solely on treatment records from T1 would not be accurate, as women may have stopped or switched medications in T2 or T3. Relying solely on T3 treatment records may have missed some women who were prescribed their medication in T2, but who were also treated in the T3 period, depending on the medication package and dose.

2.6 Demographic information

Demographic information was extracted for each pregnancy, including year of delivery and maternal age at delivery.

2.7. Statistical methods

We quantified the prevalence of pregnancies with treated IBD during pre-pregnancy (i.e., with a PCG code for IBD and exposure to at least one IBD medication during pre-pregnancy). We also quantified the prevalence of «continuers», «switchers», and «discontinuers» among these pregnancies.

For each medication group (i.e., aminosalicylates, traditional immunosuppressants, biologics) and individual substances within groups, we quantified the prevalence of pregnancies exposed during pre-pregnancy, and the prevalence of «continuers», «switchers», and «discontinuers» among these pregnancies. Finally, we quantified the prevalence of exposure to corticosteroids, including systemic and topic corticosteroids, during or after trimester 2 among «continuers», «switchers», and «discontinuers».

Exposure prevalence was calculated for the entire study period and by calendar year.

Exposure prevalence was defined as the proportion of pregnancies during which at least one prescription was filled for the respective active substance, divided by the total number of enrolled pregnancies during the respective period. Results are presented as absolute numbers divided by 10,000 with 95% confidence intervals (CI). Time series analyses were used to assess whether the prevalence of exposure followed a linear trend over time, using a linear regression model with bootstrapped standard errors.

All analyses were performed using the statistical software R version (3.6.1) and R Studio version (1.2.5001).

3. Results

We identified 104,098 deliveries from 80,320 women. The mean maternal age at delivery in our cohort was 31.7 years. Overall, 31.9% of all deliveries were caesarean sections (see Table 1).

Table 1
Description of the MAMA cohort [21]

	MAMA Cohort			**Swiss Statistics (BfS) [27, 28]**		
Year	N of deliveries	Mean maternal age at delivery (years (min-max))	Caesarean section[1]	N of deliveries[2]	Mean maternal age at delivery (years)	Caesarean section
2012*	10,639	31.3 (14.5–46.4)	3,431 (32.2)	81,274	31.5	27,115 (33.4)
2013	11,484	31.4 (14.2–47.3)	3,742 (32.6)	81,951	31.6	27,310 (33.3)
2014	12,306	31.6 (15.5–48.5)	3,940 (32.0)	84,014	31.7	23,337 (33.3)
2015	12,917	31.6 (15.7–48.9)	4,243 (32.8)	85,421	31.8	28,483 (33.3)
2016	13,780	31.8 (15.1–50.3)	4,460 (32.4)	86,787	31.8	28,778 (33.2)
2017	13,803	31.9 (15.7–51.4)	4,303 (31.2)	85,990	31.9	27,814 (32.3)
2018	14,525	32.0 (15.9–50.7)	4,574 (31.5)	86,411	32.0	27,754 (32.1)
2019	14,644	32.2 (16.2–51.8)	4,558 (31.1)	85,128	32.1	27,246 (32.0)
2012–2019	104,098	31.7 (14.2–51.8)	33,247 (31.9)	676,976	31.8	217,837 (32.1)

[1] A total of 14 deliveries were recorded as neonatal deaths without a code indicating the mode of delivery.

[2] Includes liveborn infants only.

** Before 01.01.2012, recorded SwissDRG and TARMED codes did not correspond to the codes we used to identify deliveries (example of codes which were recorded before 2012 but were not counted as deliveries*

"O64A", "O64B","O61Z").

Pregnancies with treated IBD during pre-pregnancy between 2012 and 2019 in the MAMA cohort.

Figure 1 shows the number of pregnancies with treated IBD during pre-pregnancy between 2012 and 2019, and those treated with aminosalicylates, biologics or traditional immunosuppressants. «continuers», «switchers», and «discontinuers» within each group are shown.

Prevalence and time trends of IBD medication exposure during pre-pregnancy.

In total, 92.6/10,000 pregnancies were assigned a PCG code for IBD, among which 29.8/10,000 were dispensed at least one medication used to treat IBD in the 9 months prior to pregnancy between 2012 and 2019. This prevalence remained stable throughout the study period, as no significant linear trend (b = 1.09, 95% CI -0.25; 2.43, p = 0.109) was observed over the period. Figure 2 shows the proportion of pregnancies exposed to at least one aminosalicylate, biologic or traditional immunosuppressant during pre-pregnancy over the study period. Supplementary Table 3 shows the proportion of pregnancies exposed to at least one IBD medication overall, per class and per individual substance during pre-pregnancy between 2012 and 2019.

Aminosalicylates

The most prescribed group of medication to treat IBD during pre-pregnancy between 2012 and 2019 were aminosalicylates (19.0/10,000, 19/35.3[2], 53.8%), including mesalazine (14.7/10,000) and sulfasalazine (4.3/10,000) (see Supplementary Table 3). The proportion of pregnancies treated with aminosalicylates during pre-pregnancy remained stable throughout the study period, as no significant linear trend was observed (b = 0.29, 95% CI -0.9; 1.49, p = 0.629). Among ASAs, the proportion of mesalazine and sulfasalazine prescriptions remained stable ([mesalazine linear trend: b = 0.24, 95% CI -0.8; 1.3, p = 0.648]; [sulfasalazine linear trend: b=-0.1, 95% CI -0.5; 0.6, p = 0.839]).

Biologics

Biologics were the second most prescribed group of medication to treat IBD between 2012 and 2019 (10.4/10,000, 10.4/35.3, 29.5%), mostly represented by TNF-alpha inhibitors (9.9/10,000), including infliximab (4.5/10,000) and certolizumab (3.5/10,000) (see Supplementary Table 3).

The proportion of pregnancies during which biologics were prescribed increased over the study period, with a significant linear trend (b = 1.18, 95% CI 0.2; 2.2, p = 0.022).

Among biologics, the proportion of infliximab prescriptions decreased, with a significant linear trend (b=-0.5, 95% CI -0.95; 0.04, p = 0.033), while that of certolizumab increased (b = 0.8, 95% CI 0.6; 1.0, p < 0.001).

Traditional immunosuppressants

Traditional immunosuppressants were prescribed in 5.9/10,000 (5.9/35.3, 16.7%) pregnancies, most frequently azathioprine (4.8/10,000) and mercaptopurine (0.6/10,000) (see Supplementary Table 3). The proportion of pregnancies during which traditional immunosuppressants were prescribed remained stable throughout the study period, as no significant linear trend (b=-0.5, 95% CI -1.2; 0.1, p = 0.103) was observed. Among traditional immunosuppressants, the proportion of azathioprine prescriptions remained stable (b=-0.6, 95% CI -1.3; 0.2, p = 0.122) and that of mercaptopurine decreased, with a significant linear trend (b=-0.2, 95% CI -0.3; -0.1, p = 0.002). Methotrexate was prescribed in less than 4.8/10,000 pregnancies over the entire study period; all prescriptions were limited to the pre-pregnancy period.

Patterns of use among pregnancies exposed to at least one IBD medication during pre-pregnancy.

Figure 3 show*s* the proportion of *"continuers", "switchers", and "discontinuers" among pregnancies with at least one IBD medication during pre-pregnancy over the study period.* Supplementary Table 4 shows the proportion of «continuers», «switchers», and «discontinuers» among pregnancies exposed to at least one IBD medication during pre-pregnancy between 2012 and 2019.

Among pregnancies with at least one prescription for IBD medication during pre-pregnancy between 2012 and 2019, (29.8/10,000), 20.0/10,000 (20.0/29.8, 67.1%) were «continuers», 1.2/10,000 (1.2/29.8, 4.0%) were «switchers», and 8.6/10,000 (8.6/29.8, 28.9%) were «discontinuers» (see Supplementary Table 4). The proportion of «continuers», «switchers», and «discontinuers» remained stable, as no significant linear trends were observed ([continuers: b = 1.1, 95% CI -0.1; 2.3, p = 0.076] ; [«switchers» : b = 0.3, 95% CI -0.2; 0.7, p = 0.222]; [«discontinuers» : b= -0.3, 95% CI -0.9; 0.3, p = 0.393]).

Patterns of use among pregnancies with prescriptions for aminosalicylates, biologics, and traditional immunosuppressants during pre-pregnancy.

Supplementary Table 5 shows the proportion of «continuers», «switchers», and «discontinuers» among pregnancies with each medication class during pre-pregnancy between 2012 and 2019. Supplementary Table 6 shows the proportion of «continuers», «switchers», and «discontinuers» among each individual substance within each medication class.

Aminosalicylates

Among pregnancies with a prescription for ASA during pre-pregnancy (19.0/10,000), 12.6/10,000 were «continuers» (12.6/19.0, 66.3%), 1.4/10,000 (1.4/19.0, 7.4%) were «switchers», and 5.0/10,000 (5.0/19.0, 26.3%) were «discontinuers» (see Supplementary Table 5). The proportions of ASA «continuers», «switchers», and «discontinuers» remained stable, as no significant linear trends were observed ([«continuers»: b = 0.6, 95% CI -0.3; 1.6, p = 0.194]; [«switchers»: b=-0.1, 95% CI -0.6; 0.4, p = 0.674]; [«discontinuers»: b=-0.2, 95% CI -0.8; 0.3, p = 0.343]).

Biologics

Among pregnancies with a prescription for biologics during pre-pregnancy (10.4/10,000), 6.5/10,000 were «continuers» (6.5/10.4, 62.5%), 1.0/10,000 (1.0/10.4, 9.6%) were «switchers», and 2.9/10,000 (2.9/10.4, 27.9%) were «discontinuers». The proportion of biologic «continuers» increased, with a significant linear trend (b = 1.4, 95% CI 0.7; 2.0, p < 0.001), while the proportion of «switchers» decreased, with a significant linear trend (b=-0.23, 95% CI -0.5; -0.0001, p = 0.015). The proportion of «discontinuers» remained stable (b = 0.05, 95% CI -0.5; 0.6, p = 0.862).

Traditional immunosuppressants

Among pregnancies with a prescription for traditional immunosuppressants during pre-pregnancy (5.9/10,000), 3.4/10,000 were «continuers» (3.4/5.9, 57.6%), 1.1/10,000 (1.1/5.9, 18.6%) were «switchers», and 1.4/10,000 (1.4/5.9, 23.7%) were «discontinuers». The proportion of traditional immunosuppressants «continuers» increased, with a significant linear trend (b = 1.4, 95% CI 0.7; 2.0, p < 0.001), while that of «switchers» decreased, with a marginally significant linear trend (b=-0.23, 95% CI -0.5; 0.03, p = 0.083). The proportion of «discontinuers» remained stable (b = 0.05, 95% CI -0.6; 0.7, p = 0.879).

Figure 4, 5, 6 show the proportion of «continuers», «switchers», and «discontinuers» among pregnancies with at least one aminosalicylate, one biologic, or one immunosuppressant during pre-pregnancy between 2012 and 2019.

Prevalence and type of corticosteroid use during or after trimester 2 among «continuers», «switchers», and «discontinuers» (who were prescribed at least one IBD medication during pre-pregnancy) between 2012 and 2019.

Supplementary Table 7 shows the proportion of pregnancies with at least one corticosteroid prescribed during or after trimester 2 among «continuers», «switchers», and «discontinuers» between 2012 and 2019. Respectively 0.5/10,000, 0.0/10,000 and 0.1/10,000 pregnancies among «continuers», «switchers», and «discontinuers» received a systemic corticosteroid within the 7 days before the delivery.

Between 2012 and 2019, at least one corticosteroid was prescribed during or after T2 in 5.3 (5.3/20.0, 26.5%) pregnancies among «continuers» (20.0/10,000). This was the case in 0.2/10.000 (0.2/1.2, 16.7%) pregnancies among «switchers» and 1.2/10.000 (1.2/8.6, 14.0%) among «discontinuers».

Supplementary Table 8 shows the proportion of pregnancies with at least one systemic or topic corticosteroid prescribed among «continuers», «switchers», and «discontinuers» with at least one corticosteroid prescribed during or after T2.

Within each group of «continuers», «switchers», and «discontinuers», the most used corticosteroids were systemic corticosteroids, mostly prednisone and prednisolone, followed by topic corticosteroids (budesonide).

Discussion

This study aimed to determine the exposure prevalence and patterns of use of prescribed medications for the treatment of IBD in pregnant women before and during pregnancy between 2012 and 2019 in Switzerland using the MAMA cohort. We identified a study population of 104,087 completed pregnancies with a mean maternal age at delivery of 31.7 years and 31.9% of caesarean sections, which was comparable to the total population of Swiss pregnant women.

Overall, 29.8/10,000 (0.3%) pregnancies had a PCG code for IBD with a dispensation for at least one IBD medication during pre-pregnancy between 2012 and 2019. This likely reflects the prevalence of pregnancies with pharmacologically treated IBD in our cohort, which remained stable over the study period. A similar prevalence (0.3%) has been reported across North America, Western Europe, and Australia in a systematic review which included 147 studies [5].

More than half of pregnancies with a dispensation of IBD medication before pregnancy were exposed to at least one ASA, and this proportion remained stable over time. The efficacy of ASA as first-line treatment for UC is widely accepted, but evidence in CD is lacking. Already in 2010, the European evidence-based Consensus on the diagnosis and management of Crohn's disease in the general population did not recommend ASA for maintaining remission in CD [16]. The 2015 Toronto Consensus Statement on management of IBD during pregnancy [17] did not mention the role of ASA in the treatment of Crohn's disease. However, their treatment algorithm for induction therapy in CD during pregnancy only suggests TNF-alpha inhibitors or corticosteroids. Guidelines that have been published after our study period, emphasize the lack of evidence to support the use of ASA in the treatment of Crohn's disease [15, 29]. We cannot distinguish between UC and CD in our cohort, but a previous Swiss study from the canton of Vaud reported a ratio of 1:1 of UC and CD in the general population in Switzerland (51% CD cases; 49% UC cases) [30]. It seems unlikely that all women with UC in our study group would have been prescribed ASA, as some of them may not have responded well to this treatment and may have required other medications such as thiopurines or biologics. As a result, a non-negligible number of pregnancies that were exposed to ASA may have involved women with Crohn's disease, for which ASA is actually not recommended due to a lack of evidence of effectiveness. A possible explanation for this is that Swiss healthcare providers may have a different approach, as evidenced by their guidelines, in which mesalazine may still be considered an option for patients who are unwilling to progress to immunosuppressants or biologics.

Studies in the general population have shown much lower numbers of ASA prescriptions with declining rates over time. For example, in a Chinese cohort study of patients diagnosed with CD or UC between 1999 and 2019, the use of ASA in CD decreased from 39.6% in 2009 to 5.5% in 2020 while it remained stable in UC [31]. Declining rates have also been reported in the US and Denmark in the general population [32, 33] and in pregnant women in a study analyzing the use of IBD medications in two cohorts in the US (2001–2013) and in Sweden (2006–2015) [34]. In all three cohorts, the prescription rates of ASA decreased over time. We have considered three potential explanations for the lack of decline

in the prescriptions of ASA in our cohort. First, our data are more recent than the other reports and it is possible that a decline occurred earlier and was therefore not be observed in our data. However, in a Swiss cohort of patients diagnosed with IBD between 2006 and 2012 (prior to our data), only a slight decrease in new and continued ASA prescriptions was observed [35]. The authors have already pointed out the gap between the widespread clinical use of ASA and the very weak evidence supporting its use in CD. Second, despite our hypothesis of a 1:1 ratio of UC and CD cases in our cohort based on Swiss numbers, many reports have suggested a higher prevalence of UC cases than CD cases [36]. This would explain the high proportion of ASA/sulfasalazine treatment, but not the absence of decline. Finally, the traditional gap between the publication of new evidence/guidelines and their implementation in clinical practice [37] is likely reinforced in the pregnant population. Indeed, guidelines for pregnant women are usually adapted from those for the general population and hence, are published later. In addition, changing prescribing habits in this population usually takes more time because data on new(er) medications are rarer and caution prevails in that area. It is likely that prescribers consider ASA safer as long-term data is available on this class of medication.

In parallel to the absence of decline in ASA prescriptions, the proportion of pregnancies exposed to biologics showed an increasing trend over the study period (b = 1.18, 95% CI 0.2; 2.2, p = 0.022), while immunosuppressants remained stable. This increase in biologics appeared to be largely due to certolizumab, which has a low placental transfer during the third trimester and is the only TNF-alpha inhibitor approved for use in pregnancy in the European Union and Switzerland [38, 39]. This observation is consistent with observations from the US and Swedish pregnancy cohorts as well as observations in the general population [32, 33]. However, it may be questionable whether women who successfully managed their condition with other TNF inhibitors, for which long-term safety data are available, should be switched to this treatment during pregnancy. In our cohort, among pregnancies exposed to a biologic treatment during pre-pregnancy and switched to a different treatment during or after the second trimester, 0.1/10,000 pregnancies were switched from adalimumab to golimumab and the rest were switched to certolizumab (0.3/0.8 pregnancies from infliximab to certolizumab, 0.1/0.3 from adalimumab, 0.1/0.3 from golimumab and 0.1/0.2 from vedolizumab) or to a non-biologic treatment.

Prescriptions for the newest biologics (i.e., ustekinumab, vedolizumab) were very low reflecting the limited data available for these drugs during the study period. The very small numbers observed for each substance among immunosuppressants prevent us from drawing conclusions about a pattern over the years. Prescriptions for methotrexate were very small (4.8/10,000) and all pregnancies exposed to methotrexate during pre-pregnancy had either switched or discontinued medication before or during the first trimester.

Finally, we observed that almost one third of pregnancies exposed to an IBD medication during pre-pregnancy had no record of an IBD prescription in or after the second trimester. This rate remained stable throughout the study period. It is unclear from the data whether women who discontinued their treatment did so because they had a quiescent disease or because they/their prescriber had concerns about the potential harm of continuing their medication. However, since we only followed women who were treated

for IBD before pregnancy (excluding those with untreated IBD), our cohort likely reflects a subgroup of women with more severe disease, who probably should have continued their treatment during pregnancy, as this is essential to ensure the best possible outcomes. In parallel, the overall rate of pregnancies exposed to any treatment both before pregnancy and in or after T2 ("continuers" and «switchers») remained stable over time.

Still, when patterns of use within each medication group (exposure to ASA, to biologics, or to traditional immunosuppressants) were examined more closely, the rate of «continuers» among pregnancies exposed to biologics and to traditional immunosuppressants showed an increasing trend over the study period, while the rate of «switchers» showed a decreasing trend. Again, this may be due to the increasing data available on these medications and the evolution of the guidelines recommending against their discontinuation except in very specific cases [15, 17].

Methodological considerations

This study is, to our knowledge, the first to examine prescription of IBD medications before and during pregnancy over time at the population level in Switzerland. Our results are based on a large administrative claims database covering 17% of the Swiss population in 2021. Maternal age and caesarean section numbers were consistent with those reported by the Swiss Federal Statistical Office for the total population of women giving birth in Switzerland [27, 28]. However, due to the lack of information on the socio-demographic characteristics of the included women, we cannot rule out that these women may not be fully representative of all pregnant women in Switzerland. Approximately one third of our cohort was assigned both a PCG code for both IBD and RA. It is likely that the PCG code for RA includes women treated for both RA and IBD-related arthritis, which has been reported in as frequently as 16–30% of IBD cases [40]. Thus, it is possible that some of the medications used in our cohort were intended to treat RA or IBD-related arthritis rather than IBD itself.

One of our study's strengths was that information on medication dispensations was automatically recorded during outpatient care, which minimizes maternal volunteer or recall bias. However, we cannot confirm whether the medications were actually taken by the women and whether they were taken close to the time of dispensation. In addition, our algorithm for calculating gestational age and trimester has only been validated in US claims data, so exposure misclassification might have occurred. However, because our study focused on relatively long periods of interest, such as the entire pregnancies or semesters, rather than specific trimesters, this risk should have been minimized.

Our study only included information on outpatient medication dispensations and did not include inpatient medication dispensation. While this may have reduced the proportion of pregnancies exposed to specific groups of medications or substances, it is unlikely to have affected the overall proportion of pregnancies exposed to at least one IBD medication. Finally, we did not include pregnancies that ended in a miscarriage or abortion because our aim was to examine longitudinal patterns of medication use. However, we believe that the inclusion of these pregnancies would not have affected our prevalence of IBD exposure, as IBD medications are not known to have an abortifacient effect except for methotrexate.

Conclusion

The dispensation of medications to treat inflammatory bowel disease (IBD) among pregnant women in the MAMA cohort in Switzerland remained stable over time and was consistent with other reports. Aminosalicylates were the most commonly prescribed medication to treat IBD, with a stable rate over time. Thus, it appears that a non-negligible proportion of women with Crohn's disease might still being treated with these medications, despite the lack of evidence to support their use as first-line therapy. The prescription rate of traditional immunosuppressants decreased over the study period, while biologics' prescriptions increased, reflecting the growing evidence on the safety of the latter medicines during pregnancy. One in three women discontinued all treatment during pregnancy, with a stable proportion over time. It is not known whether women discontinued treatment due to quiescent disease or concerns about medication harm. If the latter, these women should be identified and counseled, preferably during the pre-conception period, about the risks and benefits of disease and treatment.

Abbreviations

Inflammatory bowel diseases (IBD), Crohn's disease (CD) , Ulcerative colitis (UC), Aminosalicylates (ASAs), British Society of Gastroenterology (BSG), Chrétienne sociale Suisse Assurance (CSS), SwissDRG (Diagnosis Related Groups), fTARMED (Swiss medical services tariffication system), Trimester 1 (T1), Trimester 2 (T2), Trimester 3 (T3), pharmaceutical cost group (PCG), rheumatoid arthritis (RA), Anatomical Therapeutic Classification (ATC).

Declarations

Ethics approval and consent to participate: Since the data used was anonymous, ethical review and approval were not required for this study.

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of the data provider.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: EG, AP designed the study. EG, MD, SB analyzed the data. EG drafted the manuscript. EG, MD, SB, BO, SK, GF, EM, UW, CS, HL, MC, DB, JS, AP reviewed and edited the manuscript. All authors approved the final version of the article, including the authorship list.

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Footnotes

1. To avoid any potential confounding effects of COVID-19, we decided not to include data beyond 2019 in our analysis. Any data collected after that time will be reserved for a future publication.
2. 35.3/10,000 corresponds to the sum of pregnancies exposed to at least one aminosalicylate, at least one biologic and at least one traditional immunosuppressant during pre-pregnancy between 2012–2019. One pregnancy may have been exposed to multiple groups during pre-pregnancy and therefore the medication groups are not mutually exclusive. Thus, the denominator is superior to the total of pregnancies exposed to at least one IBD medication during pre-pregnancy (29.8/10,000).

Figures

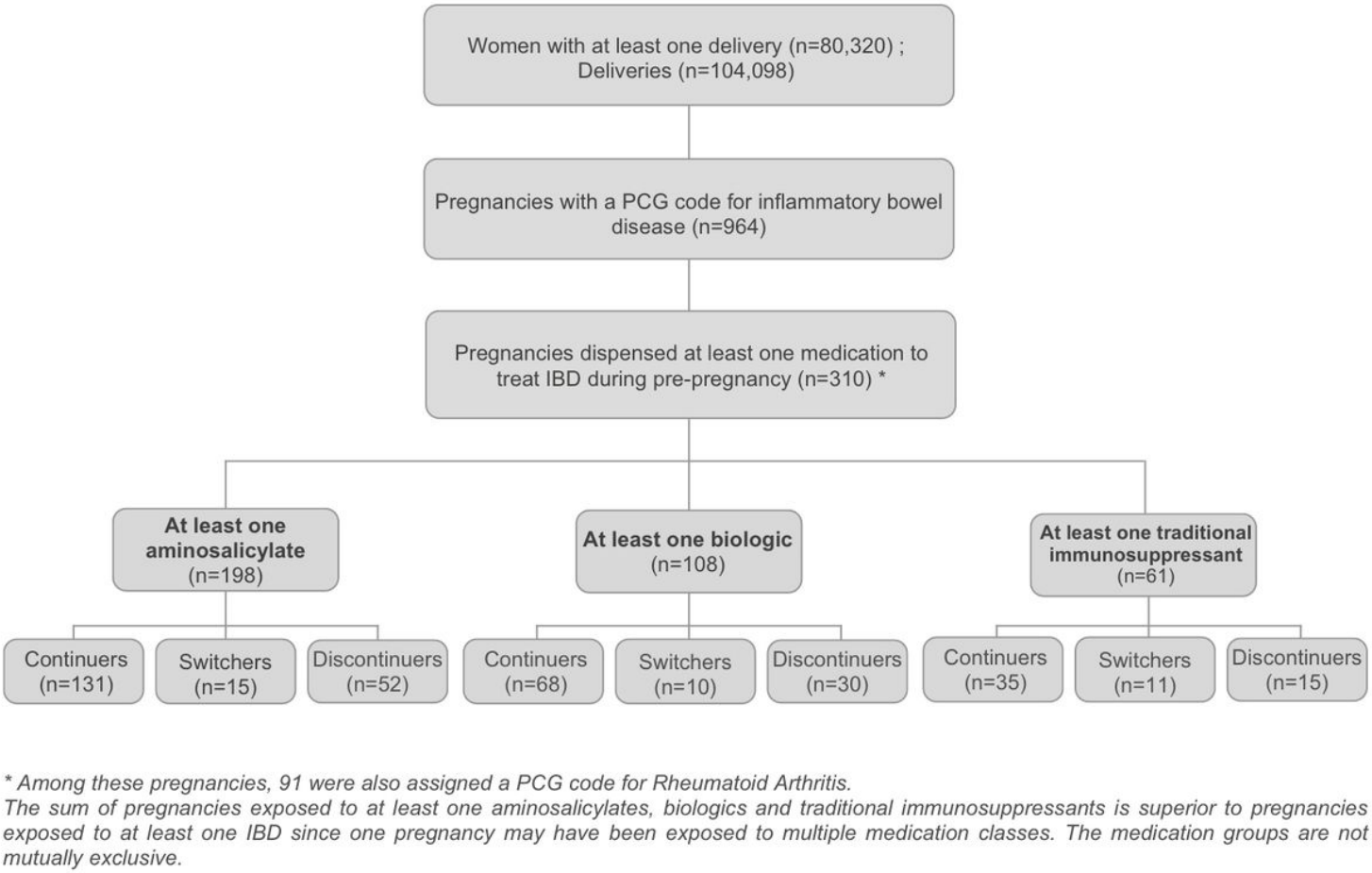
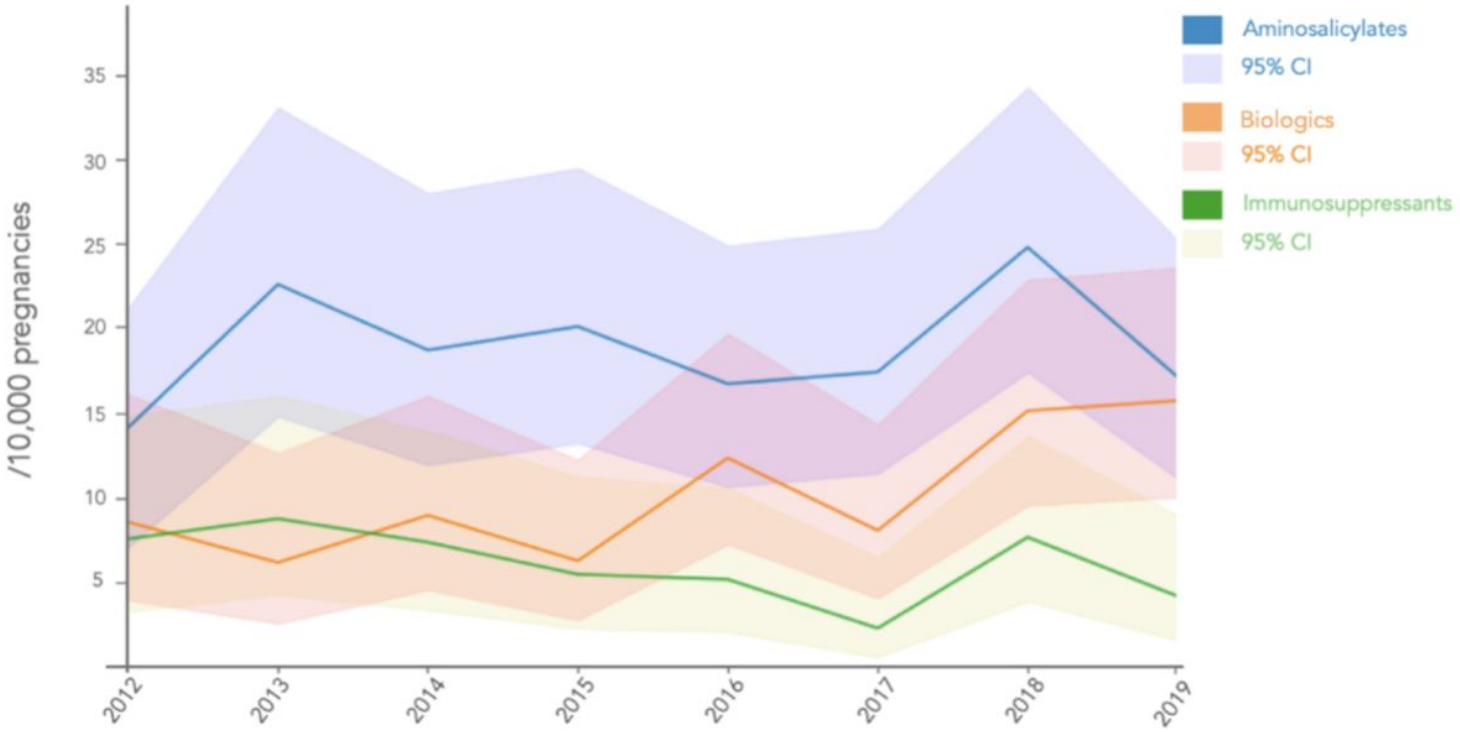


Figure 1

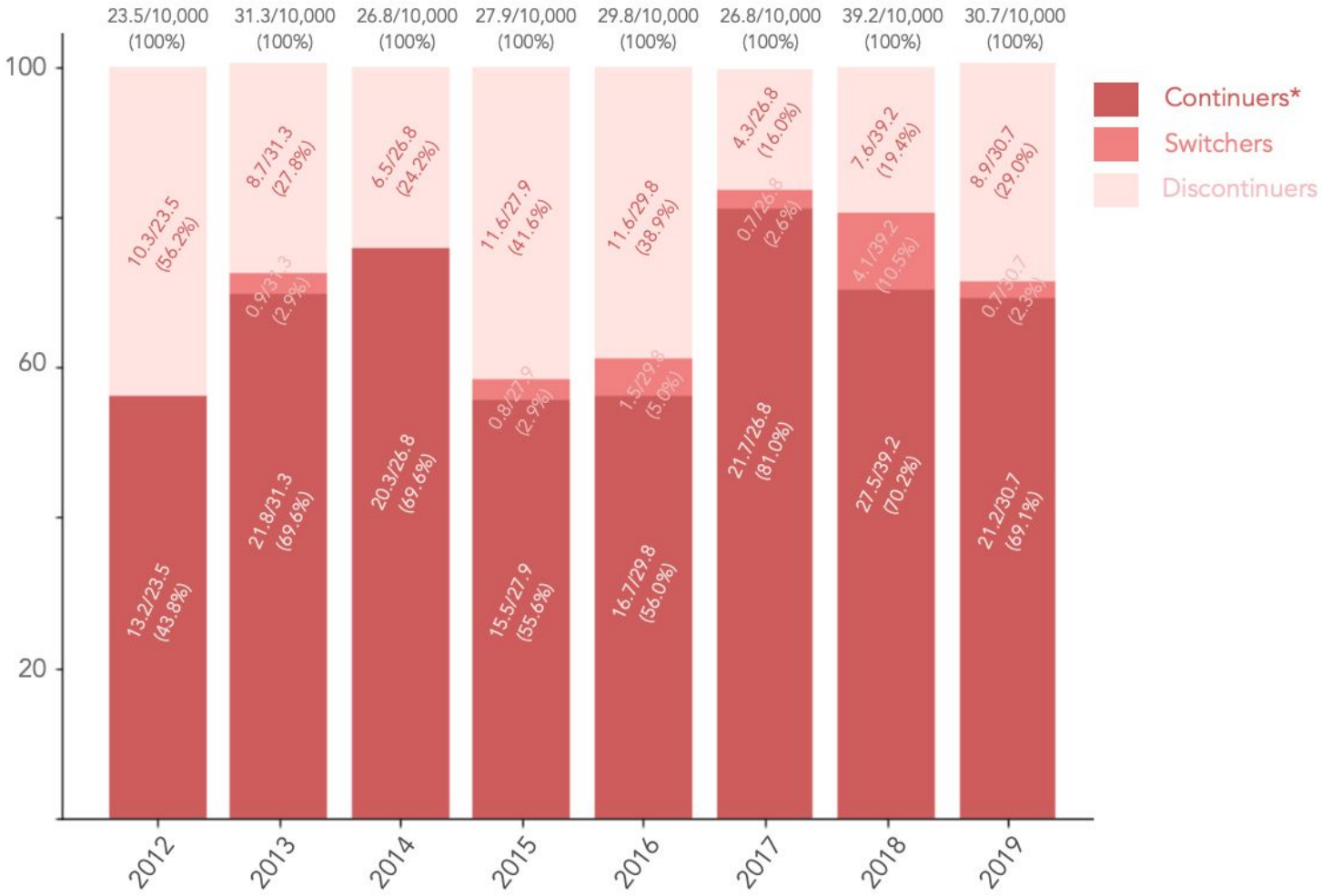
Flowchart of pregnancies with treated IBD during pre-pregnancy between 2012 and 2019 in the MAMA cohort.



** The sum of pregnancies exposed to at least one aminosalicylates, biologics and traditional immunosuppressants is superior to pregnancies exposed to at least one IBD since one pregnancy may have been exposed to multiple medication classes. The medication groups are not mutually exclusive.*

Figure 2

Proportion of pregnancies exposed to at least one aminosalicylate, biologic, or traditional immunosuppressant during pre-pregnancy between 2012 and 2019.



*When a pregnancy is prescribed multiple medication classes/substances during pre-pregnancy, it will be counted as a continuer for the medication class that is continued during or after T2 and as a switcher for the medication that is not continued during or after T2.

Figure 3

Proportion of «continuers», «switchers», and «discontinuers» among pregnancies with at least one IBD medication during pre-pregnancy between 2012 and 2019.

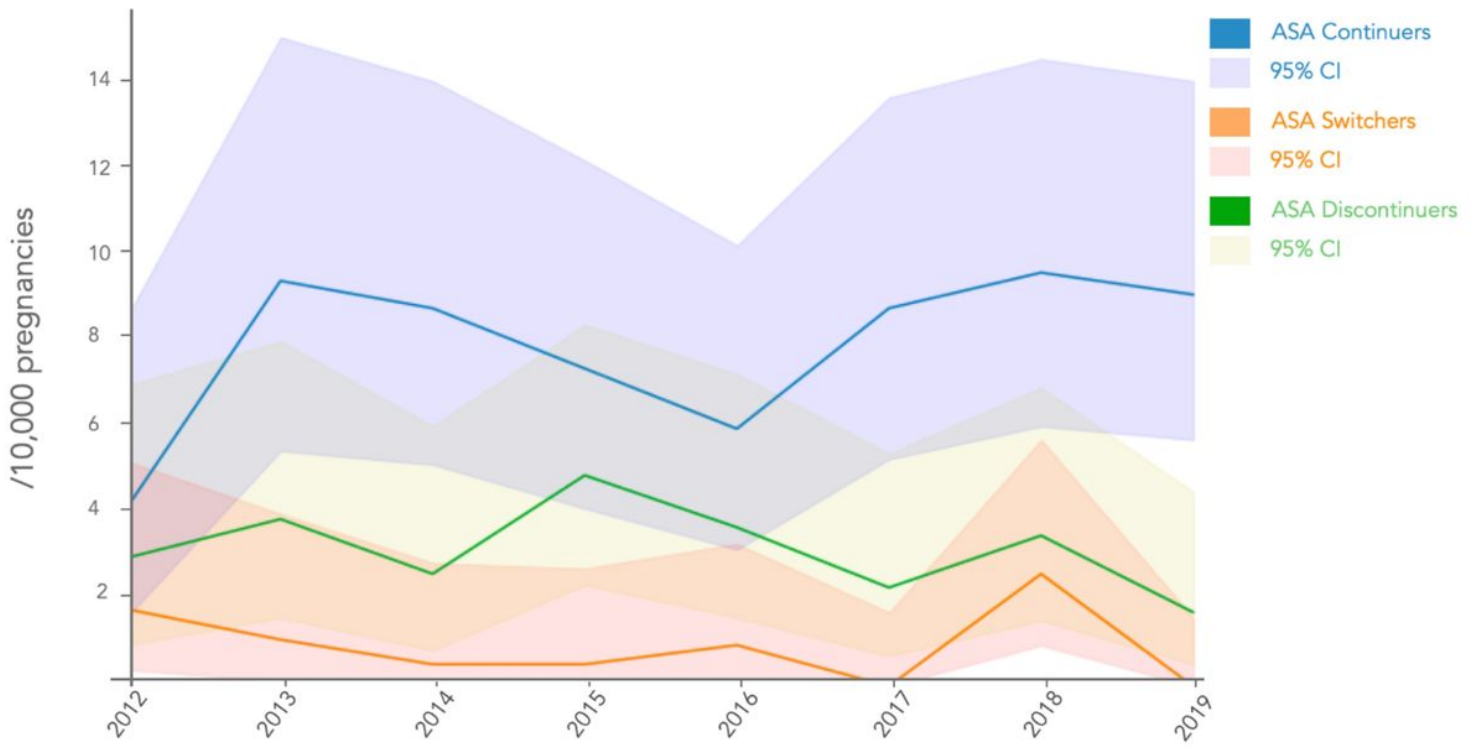


Figure 4

Proportion of «continuers», «switchers», and «discontinuers» among pregnancies with at least one aminosalicylate prescription during pre-pregnancy between 2012 and 2019.

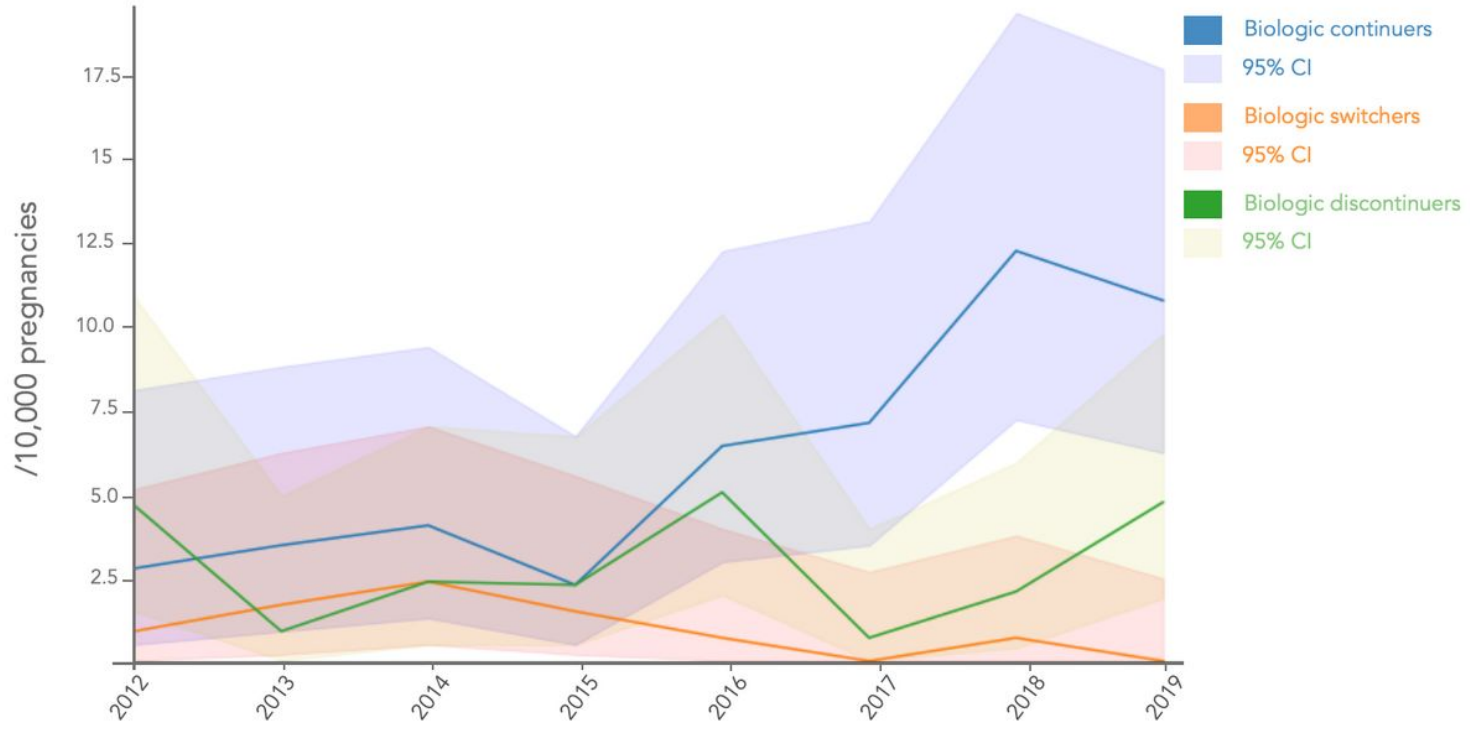


Figure 5

Proportion of «continuers», «switchers», and «discontinuers» among pregnancies with at least one biologic prescribed during pre-pregnancy between 2012 and 2019.

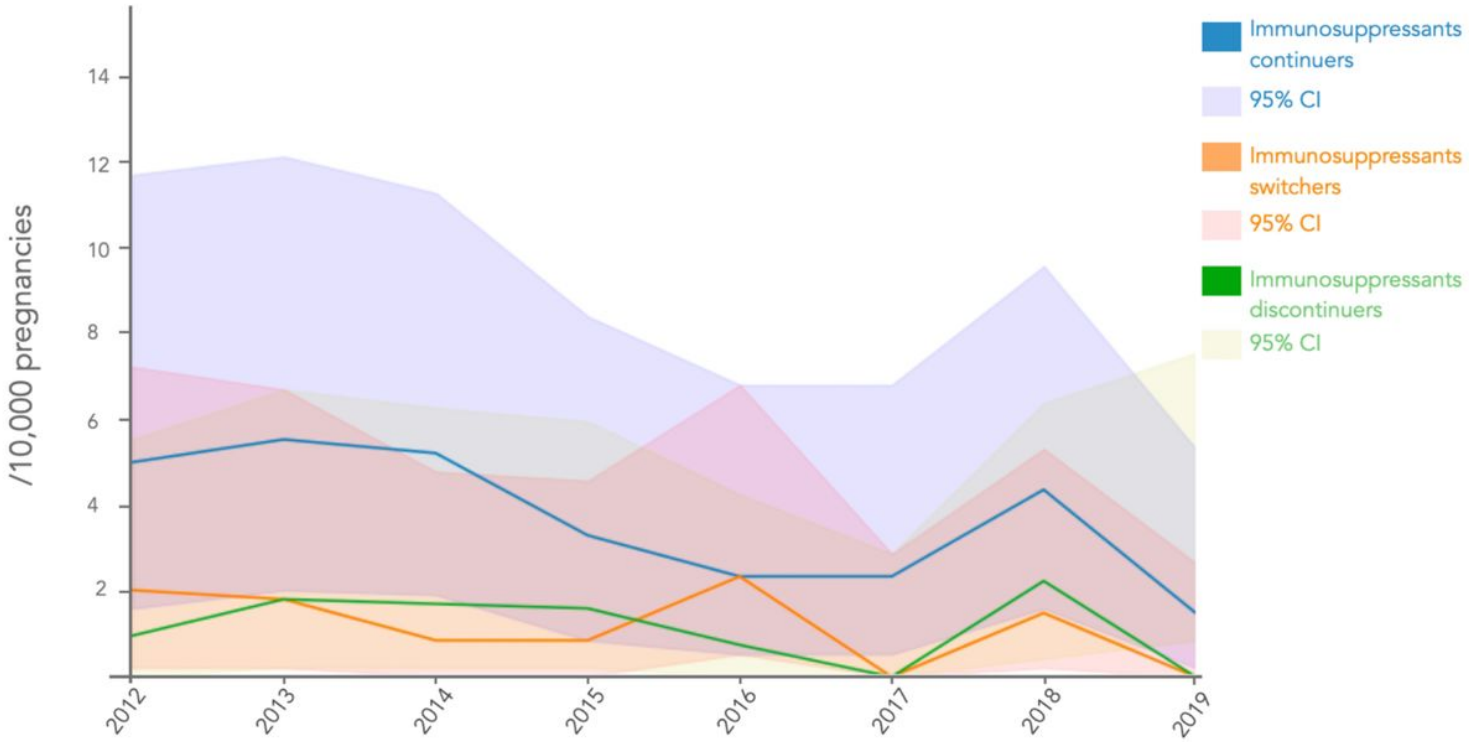


Figure 6

Proportion of «continuers», «switchers», and «discontinuers» among pregnancies with at least one traditional immunosuppressant prescribed during pre-pregnancy between 2012 and 2019.

Supplementary Files

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- Supplementarymaterials211123.docx