SYSTEMATIC REVIEW

Intrauterine Exposure to Biologics in Inflammatory Autoimmune Diseases: A Systematic Review

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Abstract

Background Inflammatory autoimmune diseases are chronic diseases that often affect women of childbearing age. Therefore, detailed knowledge of the safety profile of medications used for management of inflammatory autoimmune diseases during pregnancy is important. However, in many cases the potential harmful effects of medications (especially biologics) during pregnancy (and lactation) on mother and child have not been fully identified.

Objective Our aim was to update the data on the occurrence of miscarriages and (major) congenital malformations when using biologics during pregnancy based on newly published articles. Additionally, we selected several different secondary outcomes that may be of interest for clinicians, especially information on adverse events in the use of a specific biologic during pregnancy.

Material and Methods A search was conducted from 1 January 2015 until 4 July 2019 in Embase.com, Medline Ovid, Web of Science, Cochrane CENTRAL, and Google Scholar with specific search terms for each database. Selection of publications was based on title/abstract and followed by full text (double blinded, two researchers). An overview was made based on outcomes of interest. References of the included publications were reviewed to include and minimize the missing publications.

Results A total of 143 publications were included. The total number of cases ranged from nine for canakinumab to 4276 for infliximab. The rates of miscarriages and major congenital malformations did not show relevant differences from those rates in the general population.

Conclusion Despite limitations to our study, no major safety issues were reported and no trend could be identified in the reported malformations.

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Key Points

The rates of miscarriages and major congenital malformations after exposure to biologics during pregnancy do not deviate from these rates in the general population.

It is likely that use of adalimumab, certolizumab pegol, and etanercept is safe during pregnancy.

Data on risks of using abatacept, anakinra, canakinumab, golimumab, rituximab, tocilizumab, ustekinumab, and vedolizumab are scarce.

Adis

1 Introduction

Chronic inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), and psoriasis, are common in women of childbearing age [1–3].

Active disease may not only be harmful for the mother, but also carries a risk for the fetus. There is an overlap between biologics used for the management of rheumatic, gastroenteric, and dermatologic autoimmune diseases. Even though biologics have shown efficacy in keeping the disease under control, their safety profile in pregnant women is still uncertain. Based on the mode of action, biologics are classified into tumor necrosis factor (TNF)-α inhibitors and non-TNF biologics. At present, pregnancy registry data have become available for only four TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, and infliximab) [4–7]. For other biologics (non-TNF-α inhibitors) and biosimilars used during pregnancy in autoimmune diseases there is still insufficient information on the occurrence of adverse events such as congenital malformations (CMs). As a precaution, the use of such medications during pregnancy is discouraged before acquisition of reassuring results from a pregnancy registry. In addition, unintentional exposure to medication(s) may also occur in cases of unplanned pregnancies. Accordingly, knowledge on the safety of medication during pregnancy is of great importance [8–10].

In the pre-authorization period, pregnant women are excluded from randomized clinical trials (RCTs) for ethical reasons. After authorization, the main available data are collected prospectively by different registries or retrospectively from healthcare databases, and in some circumstances published as case reports. Summarizing the available data in a systematic review can be helpful to gain a better perspective on the use of different biologics during pregnancy and lactation.

The European League Against Rheumatism (EULAR) have published a systematic review on this topic (search period 2008–2015) [8]. However, it is important to provide up-to-date knowledge based on published data after this period. In this regard, a meta-analysis that included data from 24 studies was published by Tsao et al., in which the authors pooled the available evidence to assess the impact of biologic therapy during pregnancy [11]. This current systematic review aimed to update the data on the impact of maternal exposure to biological therapy by focusing specifically on miscarriages and (major) CMs. Furthermore, in this systematic review, each biologic is considered separately and the pattern of reported CMs is documented. Other clinically

relevant outcomes such as vaccination response, detectable drug levels during different stages of pregnancy, infections, and stillbirths are also investigated.

Thus the aim of this systematic review was to update the data on miscarriages and (major) CMs separately for each biologic used in inflammatory autoimmune diseases, based on newly published articles since 2015. Due to overlap in indications of biologics between rheumatic diseases, IBD, and psoriasis, studies on the use of biologics in IBD and psoriasis were also included.

2 Materials and Methods

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [11] guideline was followed in the design of this study.

2.1 Protocol and Registration

This systematic review was registered retrospectively at PROSPERO under the code CRD42019135316. The recorded protocol was not provided prospectively in PROSPERO [12].

2.2 Information Sources and Search Strategy

A systematic search was conducted in the following databases: Embase.com, Medline Ovid, Web of Science, Cochrane CENTRAL, and Google Scholar. The search strategy was designed and conducted by an experienced librarian with input from the study's main investigator (NG). The Medical Subject Heading (MeSH) terms used for each database are detailed in the Electronic Supplementary Material (ESM). The search only included articles published from 1 January 2015 until 4 July 2019.

2.3 Study Selection and Data Collection Process

All relevant citations were saved in a bibliographic reference manager (Endnote × 9 version, Thomson Reuters, Philadelphia, PA, USA) and duplicates were removed. Titles and abstracts were analyzed according to inclusion and exclusion criteria (see Box 1). Additional citations were identified from the reference list of all previously selected articles. The selection process was conducted by two researchers (NG and IC) with a medical background, by reviewing the titles and the abstracts, independently. Discrepancies were resolved through discussions at consensus meetings.

Box 1. Inclusion and exclusion criteria

Following publications were included:
- Cohort studies, case-control studies, case reports, registry studies, pharmacological signaling studies and abstracts (RCTs are not included in this study, as all the investigated biologics are registered before 01/01/2015)
- Full text in English, German, Dutch, French, Spanish or any other languages, provided that an English abstract was available
- Publications published after 01/01/2015

Following publications were excluded:
- Duplicate articles
- Meta-analysis, literature review articles, editorial articles, animal/in-vitro studies, comments, research letters
- Articles without an English abstract
- Studies on diseases other than rheumatoid, gastroenterological and dermatologic autoimmune diseases
- Articles that do not provide information about the outcome of the pregnancies exposed to biologics
- Studies with same population source as another included article (the most recent article was chosen to be included in these situations)
- Only Paternal exposure

2.4 Data Items, Outcomes, and Prioritization

Primary outcomes were defined as:

1. *Miscarriages* Spontaneous loss of pregnancy before 24 weeks of gestation, also known as spontaneous abortion [13];
2. *Major CMs* Conditions caused by failure of a particular body site or body system to develop correctly during the antenatal period, which had medical implications, required surgical repair, or were life threatening. (The list of malformations considered as major can be found in Supplementary Table 1) [14].

Other variables for which data were sought were categorized in two groups:

1. Maternal-related outcomes:

   (a) *Ectopic pregnancies* Any condition characterized by implantation of the embryo outside the endometrium and endometrial cavity during pregnancy;
   (b) *Induced abortions* The removal of an embryo or fetus from the uterus at a stage of pregnancy when it is deemed incapable of independent survival; at any time between conception and the 24th week of gestation (GW);
   (c) *Pregnancy-related hypertension* Gestational hypertension, pre-eclampsia, and eclampsia;
   (d) *Premature rupture of membranes* Spontaneous rupture of fetal membranes before the onset of labor;
   (e) *Emergent caesarian sections* Unplanned caesarian section (C-section) due to maternal/fetal condition; other types/uncategorized C-sections were not considered in the results;

   (f) *Flare-up during pregnancy/post-partum* Active disease during pregnancy/during 6 months after delivery;
   (g) *Detectable drug concentration in breast milk*

2. Child-related outcomes:

   (a) *Minor CMs* Conditions caused by failure of a particular body site or body system to develop correctly during the antenatal period, which pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual, were considered minor CMs;
   (b) *Live births* The complete expulsion or extraction from the mother of a baby, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life;
   (c) *Still birth* A baby born with no signs of life at or after 24 weeks of gestation;
   (d) *Neonatal death* Death during the first 28 days of life;
   (e) *Low birth weight* When the infant was born weighing less than 2500 g;
   (f) *Pre-term birth* When the infant was born before 37 weeks of gestation;
   (g) *Small for gestation age (SGA)* When birth weight was below − 2 standard deviations of the mean or below the 10th percentile according to local intrauterine growth charts;
   (h) *Adequate vaccination response* Measured by laboratory findings on immune response after vaccination;

   (i) *Adverse drug reactions (ADRs) related to vaccinations*;
       (j) *Allergies*;

(k) *Eczema*;

(l) *Serious/opportunistic infections* Infections that required medical intervention/hospitalization;

(m) *Anti-drug antibodies at birth in the newborn*;

(n) *Detectable drug levels*

    (i) *in cord blood*
    (ii) *in infant's blood at birth*
    (iii) *during first 6, 9, and 12 months of life*;

(o) *Abnormal development* Physical/psychological developmental delay in children.

ther variables for which data were sought were categorized in two groups.

Data that did not meet mentioned definitions were not considered in the final results.

2.5 Risk of Bias in Individual Studies

The quality of the studies was scored by awarding points in each domain following the guidelines of the Newcastle–Ottawa Scale (NOS) for either cohort studies or case–control studies. The NOS assigns up to a maximum of nine points for the least risk of bias in three domains: (1) selection of study groups (four points); (2) comparability of groups (two points); and (3) exposure or outcome (three points) for case–control and cohort studies (see Supplementary Table 2, ESM) [15].

2.5.1 Summary Measures

Numbers of cases occurred for each specific outcome and with exposure to each specific biologic were extracted from each article and entered into the chart.

2.5.2 Risk of Bias Across Studies

Due to heterogeneity of the data the calculated percentages are up to clinical interpretations and comparison of the outcomes should be performed with caution.

2.5.3 Data Synthesis

All included articles were considered in data synthesis if they had reported at least one outcome for a specific biologic. Percentage of occurrence for each outcome was calculated as cumulative number of cases divided by the

population, for which that specific outcome was reported in the included publications.

2.5.4 Confidence in Cumulative Evidence

The cumulative evidence of the studies was assessed by GRADE scoring (The Grading of Recommendations Assessment, Development and Evaluation Working Group; [retrieved 17 September 2019]) and the score of the Oxford Centre for Evidence-Based Medicine (CEBM) [retrieved 17 September 2019] [16–18].

The GRADE approach results in an assessment of the quality of evidence on four levels: (1) high (++++), (2) moderate (+++), (3) low (++), and (4) very low (+) based on all publications and their limitations. First a primary ranking of 'high' or 'low' was assigned to RCTs or observational studies (if included for the specific group of publications for one specific biologic). Then the initial ranking was downgraded or upgraded based on among others risk of bias, inconsistency, imprecision, indirectness, confounding in cumulative evidence based on all included publications for the specific biologic. It should be mentioned that the final score is not an average of individual scores, but a cumulative assessment for all the publications together, as explained above [16, 18].

The strength of cumulative evidence was graded using a 1–5 ordinal scale for CEBM, in which the lower the risk of confounding (bias), the further to the left the type of evidence will lie in the scale. Steps were taken as for GRADE score and final score was assigned to the cumulative evidence from all publications included for one biologic at a time [17].

For both the GRADE scoring and the CEBM calculations the included studies and case reports were weighted considering case–control studies are recommended studies for identifying congenital anomalies [19] followed by cohort studies and case reports, as they have the lowest weight. Abstracts scored lower than full articles, because the methods section often does not sufficiently describe the control group and the adjusting for confounders. The GRADE and CEBM scores based on these considerations are presented in Table 1.

3 Results

3.1 Study Selection

A total of 4823 articles were primarily extracted from the mentioned databases up to 4 July 2019. Selection of publications was based on title/abstract and followed by full text (double blinded, two researchers). 151 articles were excluded after reading the full text based on the following

reasons: duplicate articles (including abstracts/posters that had published full texts) ($n = 69$), information on the outcome of the pregnancies exposed to biologics not provided ($n = 64$), studies with the same population source as another included article ($n = 13$), in vitro studies ($n = 3$), only paternal exposure was investigated ($n = 1$), studies on diseases other than intended for this article ($n = 1$). References of the included articles were screened for additional inclusion. Nine additional articles were added to the dataset sheets based on reference-screening of included articles. A total of 143 articles were included. The steps taken are shown in Fig. 1.

3.2 Study Characteristics

In total 143 publications were included. The number of publications for each biologic ranged from two (canakinumab) to 59 (infliximab). The references, type of publications, and GRADE and Oxford CEBM scores for each biologic are presented in Table 1.

3.3 Risk of Bias Within the Studies

The authors acknowledge the risk of information bias in some studies that evaluated pooled data on several biologics, without reporting the numbers of outcomes for each biologic separately. The results of these studies, however, are described in this article as two additional categories under the subtitles of "TNF alpha blocker (in general, not specified in the full text)" and "Biologics (in general, not specified in the full text)".

3.4 Results of Individual Studies and Synthesis of the Results

The key outcomes for each biologic are discussed below. To gain a better perspective regarding overall possible confounders, data on maternal characteristics such as disease type, co-morbidities, concomitant medication exposure, presence of anti-drug antibodies in maternal serum, exposure during the first and all three trimesters, and rate of breastfeeding after delivery were calculated, if possible (Table 2). Outcome measures are presented in Tables 3 and 4 for maternal- and child-related outcomes, respectively. It
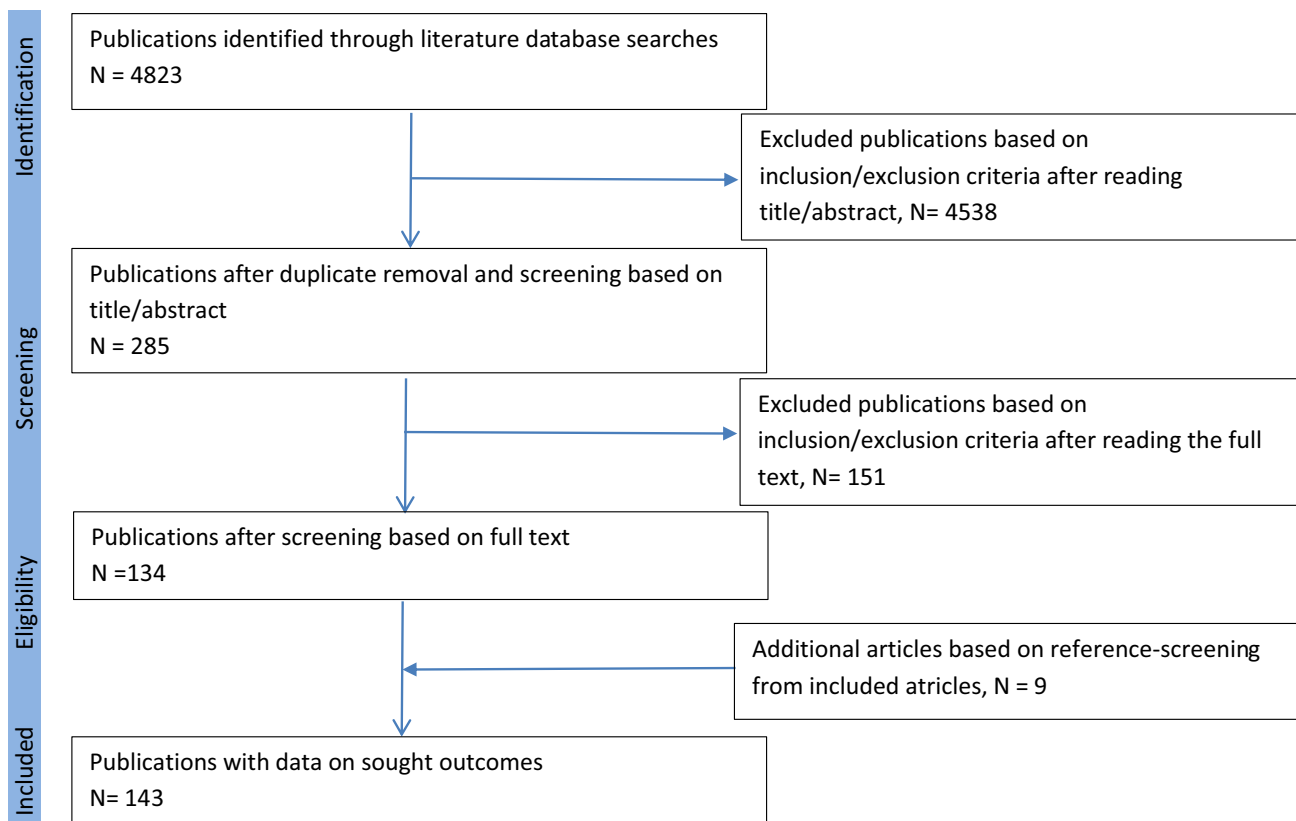

Fig. 1 Flow diagram of databases searched according to the PRISMA guidelines

Table 1 Summary of the references and GRADE scores (confidence in cumulative evidence)

Drug	Number and type of publications	References	GRADE	CEBM
Abatacept	1 cohort, 2 register data (2 abstracts), 2 case reports/series (1 abstracts)	[9, 20–23]	++	3–4
Adalimumab	19 cohorts (9 abstract), 14 register data (6 abstract), 6 case controls (1 abstract), 11 case reports/series (3 abstract)	[1, 20–69]	+++	3
Anakinra	4 cohorts (1 abstract), 2 case reports/series	[20, 57, 70–73]	+	4
Canakinumab	1 cohort, 1 case report (1 abstract)	[72, 74]	+	4
Certolizumab pegol	14 cohorts (6 abstract), 10 register data (1 abstract), 4 case controls (1 abstract), 4 case reports/series (3 abstract)	[1, 20, 22, 23, 31, 33, 37, 39, 40, 42, 44, 48, 54, 55, 57, 58, 63, 64, 66, 68, 75–88]	++	3–4
Etanercept	12 cohorts (5 abstract), 6 register data (2 abstract), 2 case controls (1 abstract), 6 case reports/series (2 abstract)	[1, 20–23, 27, 33, 35, 40, 41, 44, 45, 47, 53–57, 60, 63, 66, 68, 87, 89–91]	+++	3
Golimumab	9 cohorts (2 abstract), 3 register data (1 abstract), 2 case controls (1 abstract), 2 case reports/series (1 abstract)	[20, 22, 23, 33, 35, 40, 44, 48, 53–55, 58, 64, 66, 68, 80]	+	4
Infliximab	23 cohorts (11 abstract), 13 register data (2 abstract), 3 case controls, 20 case reports/series (10 abstract)	[1, 20–25, 28, 31, 34–38, 40, 42–44, 46–48, 51, 53, 55, 57, 58, 60–62, 64–68, 76, 77, 79, 80, 92–112]	++	3–4
Rituximab	5 cohorts (2 abstract), 3 register data (2 abstract), 1 case reports/series (1 abstract)	[20, 22, 44, 45, 56, 57, 63, 66, 113]	+	4
Tocilizumab	1 cohort, 1 register data (1 abstract), 8 case reports/series (3 abstract)	[22, 23, 41, 45, 114–119]	++	3–4
Ustekinumab	4 cohorts, 3 register data (2 abstract), 15 case reports/series (3 abstract)	[27, 37, 44, 53, 59, 60, 64, 66, 67, 77, 80, 120–130]	+	4
Vedolizumab	2 cohorts (1 abstract), 1 register data, 2 case controls (1 abstract), 2 case reports/series (1 abstract)	[64, 77, 131–135]	+	4

should be noted that due to heterogeneity of the data the calculated percentages cannot be compared.

3.4.1 Abatacept

In total 157 maternal pregnancies were investigated in five articles. Outcomes regarding miscarriages were investigated for 153 of these pregnancies, in which 40 miscarriages were reported (26.1%).

Seven major CMs were reported in 88 pregnancies (7.9%), which included:

1. Cleft palate ($n = 1$)
2. Congenital aortic-anomaly ($n = 1$)
3. Meningocele ($n = 1$)
4. Pyloric stenosis ($n = 1$)
5. Skull malformation (unspecified) ($n = 1$)
6. Ventricular septal defect (VSD) ($n = 1$)
7. Congenital arterial malformation ($n = 1$) [9].

The percentage and variety of co-medication use (including methotrexate (MTX) exposure) could not be extracted for the reported miscarriages from the presented data.

3.4.2 Adalimumab

A total of 2027 maternal pregnancies were described in 50 articles. Outcomes regarding miscarriages were reported for 180 pregnancies, in which 16 miscarriages occurred (8.9%). Forty-six ($n = 46$) major CMs were reported in 1008 pregnancies (4.6%). Thirteen major CMs were described as follows (the other cases did not describe explicitly the major CM or the major CM could not be linked to this specific biologic):

1. Cleft palate ($n = 1$).
2. Cleft palate, micrognathia, myopia, glaucoma and esophageal motility disorder ($n = 1$).
3. Congenital diaphragmatic hernia and obstructive mega ureter ($n = 1$).
4. Polydactyly ($n = 1$).
5. Hexadactyly ($n = 1$).
6. Hexadactyly both feet and atrial septal defect (ASD) ($n = 1$).
7. Esophageal atresia with tracheo-esophageal fistula, VSD, syndactyly in both feet, peripheral pulmonary stenosis, persistent foramen ovale (PFO) ($n = 1$).

Table 2 Maternal characteristics of pregnancies exposed to different biologic drugs

Drug	Abatacept	Adalimumab	Anakinra	Canakinumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Ustekinumab	Vedolizumab
Indications												
Rheumatoid diseases	4/157 (2.5)	118/2,027 (5.8)	7/35 (20)	9/9 (100)*	318/883 (36)	458/1145 (40)	9/31 (29)	34/4276 (0.8)	42/42 (100)	340/373 (91.2)	1/54 (1.9)	–
Inflammatory bowel disease	–	1182/2027 (58.3)	–	–	328/883 (37.2)	–	5/31 (16.1)	2539/4276 (59.4)	–	–	23/54 (42.6)	147/147 (100)
Psoriasis	–	12/2027 (0.6)	3/35 (8.6)	–	–	97/1145 (8.5)	–	10/4276 (0.2)	–	–	26/54 (48.1)	–
Not defined/other	153/157 (97.4)	715/2027 (35.2)	25/35 (71.4)	–	237/883 (26.8)	591/1145 (51.6)	17/31 (54.8)	1693/4276 (39.6)	–	33/373 (8.8)	5/54 (9.3)	–
Pre-pregnancy existing co-morbidities												
APS	0/1 (0)	0/19 (0)	0/1 (0)	–	1/12 (8.3)	0/74 (0)	0/4 (0)	0/20 (0)	0/2 (0)	–	–	–
Diabetes	5/151 (3.3)	–	–	–	–	36/337 (10.7)	–	–	–	–	–	–
Hospitalization/surgery	–	1/5 (20)	–	–	–	–	–	34/260 (13.1)	–	–	–	1/5 (20)
Hypertension†	–	–	1/5 (20)	–	–	74/337 (22)	–	2/16 (12.5)	–	1/16 (6.2)	–	–
Mental disorders	–	–	–	–	–	126/337 (37.4)	–	0/14 (0)	–	1/16 (6.2)	–	–
Smoker	–	8/63 (12.7)	1/5 (20)	–	0/6 (0)	–	–	53/333 (15.9)	–	1/14 (7.1)	–	–
Alcohol	–	–	1/5 (20)	–	–	–	–	0/16 (0)	–	0/14 (0)	–	–
Previous miscarriages	–	0/4 (0)	1/4 (25)	1/8 (12.5)	–	–	–	3/19 (15.8)	–	33/304 (10.9)	–	–
Previous unfertility	–	5/58 (8.6)	1/5 (20)	–	–	–	–	3/73 (4.1)	–	–	–	–
Perianal complications	–	12/58 (20.6)	–	–	2/27 (7.4)	–	–	3/115 (26.1)	–	–	–	6/39 (15.4)
Thyroid disfunction	–	–	–	–	–	38/337 (11.3)	–	0/14 (0)	–	1/16 (6.2)	–	–
Other	–	–	–	–	–	–	–	–	–	1/16 (6.2)+	–	1/20 (5)++
Concomitant exposure (any)	–	71/278 (25.5)	4/5 (80)	–	402/553 (72.7)	70/353 (19.8)	–	85/461 (42.9)	5/23 (21.7)	54/210 (25.7)	–	6/34 (17.6)
Corticosteroid	–	11/61 (18.1)	–	–	14/30 (46.7)	–	–	90/450 (20)	2/23 (8.7)	15/27 (55.6)	0/2 (0)	3/35 (8.6)
Cyclosporine	–	–	–	–	0/4 (0)	0/5 (0)	–	2/228 (0.9)	2/23 (8.7)	–	1/2 (50)	–

Table 2 (continued)

Drug	Abatacept	Adalimumab	Anakinra	Canakinumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Ustekinumab	Vedolizumab
Hydroxychloroquine	–	–	–	–	6/21 (28.6)	–	–	–	3/22 (13.6)	1/16 (6.2)	–	–
Leflunomide	–	1/9 (11.1)	–	–	0/6 (0)	0/31 (0)	–	–	4/23 (17.4)	2/17 (11.7)	–	–
Mesalazine	–	5/58 (8.6)	–	–	0/3 (0)	–	–	124/348 (35.6)	–	–	–	4/9 (44.4)
MTX	–	6/80 (7.5)	0/5 (0)	–	0/25 (0)	59/343 (17.2)	–	36/221 (16.3)	5/23 (21.7)	40/208 (25.6)	–	0/10 (0)
NSAID	–	–	1/5 (20)	–	5/13 (38.5)	–	–	–	–	–	–	–
Sulfasalazine	–	–	–	–	5/21 (23.8)	–	–	–	5/22 (22.7)	1/16 (6.2)	–	1/24 (4.2)
Thiopurines	–	33/136 (24.3)	–	–	–	–	–	116/296 (39.2)	2/22 (9.1)	–	–	2/10 (20)
Any non-biologic DMARDs	–	–	–	–	–	23/337 (6.9)	–	5/57 (8.8)	–	–	–	–
Another biologic	–	23/803 (2.9)	–	2/8 (25)	3/17 (17.6)	23/337 (6.8)	–	21/819 (2.6)	2/22 (9.1)	1/4 (25)	–	–
Other	–	–	1/4 (25) Colchicine	–	394/541 (72.8) Any drugs	46/337 (13.6) Teratogenic DMARDs	–	63/83 (75.9) Folic acid	–	–	–	–
Anti-drug antibodies	–	2/16 (12.5)	–	–	0/21 (0)	–	–	0/2 (0)	–	–	–	–
Exposure period												
First trimester	–	529/534 (99)	29/34 (85.3)	9/9 (100)	424/528 (80.3)	252/268 (94)	10/10 (100)	510/675 (75.6)	9/25 (36)	341/355 (96.1)	22/25 (88)	38/47 (80.8)
All three trimesters	0/2 (0)	19/78 (24.3)	25/33 (75.8)	4/9 (44.4)	9/41 (21.9)	19/256 (7.4)	0/10 (0)	20/94 (21.3)	3/25 (12)	10/355 (2.8)	12/31 (38.7)	35/47 (74.4)
Breastfeeding	–	19/78 (24.3)	14/25 (56)	–	9/41 (21.9)	5/27 (18.5)	–	20/94 (21.3)	–	5/39 (12.8)	1/4 (25)	12/75 (16)

Values are given as number (%)

NSAID non-steroidal anti-inflammatory drugs, *MTX* methotrexate, *HCQ* hydroxychloroquine, *ADRs* adverse drug reactions, *RA* rheumatoid arthritis, *JIA* juvenile rheumatoid arthritis, *AS* ankylosing spondylitis, *PsA* psoriatic arthritis, *FMF* familial Mediterranean fever, *APS* anti-phospholipid syndrome, *DMARDs* disease-modifying antirheumatic drugs

† Not related to pregnancy

*4/9 CAPS (cryopyrin-associated periodic fever syndromes), 1/9 Cogan syndrome, and 1/9 not defined

+ Previous pregnancy complications

++ Obesity

8. ASD with left–right shunt and aneurysm, cavum septum pellucidum on both sides, hemangioma at left flank ($n=1$).
9. VSD and hip dysplasia ($n=1$).
10. Hemangioma right temple, umbilical hernia ($n=1$).
11. Imperforate anus ($n=1$).
12. Amniotic band sequence: talipes and amputation of four fingers of the right hand ($n=1$).
13. Cystic adenomatoid malformation of the right lung, incomplete right bundle branch block, pericardial effusion, PFO, persistent ductus arteriosus (PDA) and slight persistent pulmonary hypertension (co-medication: etanercept) ($n=1$) [1, 20, 68].

Data on overall concomitant medication was available for 278 cases. Use of one or more co-medications was reported for 71 of these patients (25.5%). Data on exposure to MTX were available for 80 cases, of which six patients (7.5%) were exposed to MTX.

Growth was investigated in 61 children exposed to adalimumab during pregnancy, of which only one primary growth failure due to cystic fibrosis was reported (1.6%) [43].

Adalimumab was detectable in breast milk of two patients from the total 21 investigated cases (9.5%), with a maximum concentration of 0.71 µg/mL seen between 12 and 24 h after injection. In seven cases breast milk was examined after 7 days from the injection and it was not detectable in any of these cases [80].

3.4.3 Anakinra

In total 35 maternal pregnancies were investigated in six articles. Outcomes regarding miscarriages were investigated for 33 of these pregnancies, in which only one miscarriage was reported (3.1%, concomitant therapy was not reported in this case) [72]. One major CM was reported (2.9%, unilateral renal agenesis and ectopic neurohypophysis, which also had abnormal growth due to growth hormone deficiency) [72]. One minor CM (a case of tied tongue after exposure to anakinra during pregnancy [73]) was reported among nine cases that were investigated for such an outcome. Data on overall concomitant medication was available for five cases. Use of one or more co-medications was reported for four of these patients (80.0%). MTX exposure was not reported for any of these patients.

Emergent C-sections were reported in two cases. One case because of a pathological cardiotocography (CTG) and premature rupture of the membranes and umbilical cord entanglement. The other case was a secondary emergent C-section due to uterine rupture under spontaneous delivery [70].

3.4.4 Canakinumab

In total nine pregnancies were investigated in two articles [72, 74]. Outcomes regarding miscarriages were investigated for all of these pregnancies, in which only one miscarriage was reported (11.1%, at 6 weeks of pregnancy to a mother with refractory Cogan syndrome). Concomitant medication was not reported in this case [72]. No CMs were reported in eight live births. Data on overall concomitant medication (including MTX exposure) were not available.

3.4.5 Certolizumab Pegol

In total 883 maternal pregnancies were investigated in 32 articles. Outcomes regarding miscarriages were investigated for 679 of these pregnancies, in which 78 miscarriages were reported (11.5%). Ten major CMs were reported from a total of 535 investigated cases (1.9%). In the article by Broms et al. the described major CMs were not categorized based on the kind of biologic used during pregnancy. Therefore, the one reported case of major CM for certolizumab pegol in this study could not be associated with the described cases [40]. Nine described cases in other articles could be linked to certolizumab pegol and were as follows (the rest of the cases were not described explicitly or could not be linked to this specific biologic):

1. Clubfeet and Hirschsprung's disease ($n=1$)
2. Anal fistula ($n=1$)
3. Talipes ($n=1$)
4. Vesicoureteric reflux ($n=1$)
5. Cerebral ventricle dilatation ($n=1$)
6. Hydronephrosis ($n=1$)
7. Congenital heart disease ($n=1$)
8. Accessory auricle ($n=1$)
9. Polydactyly ($n=1$) [75, 78].

Data on overall concomitant medication were available for 553 cases. Use of one or more co-medications was reported for 402 of these patients (72.7%). Data on exposure to MTX were available for 25 cases, of which none were exposed to MTX.

From the two reported cases of early membrane ruptures, one was due to infection [75]. The other one occurred at the 35th week in a mother exposed to certolizumab pegol during the first trimester [1].

Reported infections in mothers were mainly urinary tract infections and upper respiratory tract infections. In one case pyelonephritis with septicemia at 30th GW was reported in a patient who was on certolizumab pegol combination therapy with hydroxychloroquine, sulfasalazine, and prednisone [75].

Table 3 Outcomes of pregnancy exposure related to different biologic drugs

Drug	Abatacept	Adalimumab	Anakinra	Canaki-numab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Ustekinumab	Vedolizumab
Number of pregnancies	157	2027	35	9	883	1145	31	4276	42	368	54	147
Prospective	99 (63.1)	898 (44.3)	8 (22.9)	1 (11.1)	641 (72.6)	657 (57.4)	15 (48.4)	2453 (57.4)	35 (83.3)	204 (55.4)	36 (66.7)	58 (39.5)
Retrospective	58 (36.9)	1129 (55.7)	27 (77.1)	8 (88.9)	242 (27.4)	488 (42.6)	16 (51.6)	1823 (42.6)	7 (16.7)	164 (44.6)	18 (33.3)	89 (60.5)
Pregnancy related outcomes												
Misscarriages (total)	40/153 (26.1)	16/180 (8.9)	1/33 (3.1)	1/9 (11.1)	78/679 (11.5)	69/359 (19.2)	–	170/1584 (10.7)	1/24 (4.2)	84/361 (23.3)	3/27 (11.1)	19/72 (26.4)
Prospective	17/70 (24.3)	11/121 (9.1)	1/27 (3.70)	0/1 (0)	47/556 (8.5)	0/4 (0)	–	169/1551 (10.9)	1/19 (5.3)	43/199 (21.6)	1/17 (5.9)	9/57 (15.8)
Retrospective	23/83 (27.7)€	5/59 (8.4)	0/6 (0)	1/8 (12.5)	31/123 (25.2)	69/355 (19.4)	–	1/33 (3)	0/5 (0)	41/162 (25.3)	2/10 (20)	10/15 (66.7)
Ectopic pregnancy	–	–	0/6 (0)	–	0/3 (0)	–	–	9/1363 (0.7)	–	0/16 (0)	–	–
Induced abortion	20/153 (13.1)	3/86 (3.5)	0/5 (0)	–	37/679 (5.4)	30/338 (8.9)	–	90/1552 (5.8)	1/19 (5.3)	6/69 (8.7)	1/26 (3.8)	7/57 (12.3)
Diseases during pregnancy												
Placental abnormalities	–	0/6 (0)	–	–	1/23 (4.3)	–	–	1/6 (16.7)	–	–	–	2/4 (50)
Pregnancy-related hypertension	–	1/5 (20)	–	–	5/454 (1.1)	74/362 (20.4)	–	–	1/19 (5.3)	1/20 (5)	–	1/21 (4.8)
Gestational diabetes	5/148 (3.4)	1/53 (1.8)	–	–	6/468 (1.3)	–	–	–	–	–	–	–
Serious infections	–	1/6 (16.6)	1/9 (11.1)	–	25/543 (4.6)	33/363 (9.1)	–	2/8 (25)	–	–	–	–
Other	–	–	–	–	–	40/337 (11.9)∞	–	–	–	–	–	–
Delivery												
Early membrane rupture	1/86 (1.2)	0/5 (0)	1/5 (20)	–	2/17 (11.8)	1/25 (4)	–	1/7 (14.3)	–	53/288 (18.4)	–	–
Emergent C-section	1/86 (1.2)	0/4 (0)	2/4 (50)	–	1/16 (6.2)	–	–	6/1372 (0.4)	–	2/5 (40)	–	2/33 (6.1)

Table 3 (continued)

Drug	Abatacept	Adalimumab	Anakinra	Canaki-numab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Ustekinumab	Vedolizumab
Dose range $(N)^\dagger$	–	40 mg/2w (14), 40 mg/w (6)	50 mgD (2), 100 mgD (21), 200–300 mgD (1)	120 mg once (1), 150 mg/8w (4), 300 mg/8w (1), 150 mg/4w (2)	200 mg/2w (36), 400 mg/4w (3)	–	–	5 mg/kg/8w (37)††, 5 mg/kg/6w (14), 7.5 mg/kg/8w (1), 5 mg/kg/4w (8), 10 mg/kg/8w (2), 10 mg/kg/6w (4), 10 mg/kg/4w (1)	–	4 mg/kg/4w (13), 8 mg/kg/4w (147)	45 mg/12w (5), 90 mg/12w (3), 90 mg/8w (1), 45 mg/2w (1), 90 mg/4w (1)	300 mg/8w (13)
Detectable in breast milk	–	2/21 (9.5)	–	–	13/25 (52)	–	0/1 (0)	19/29 (65.5)	–	4/4 (100)	4/6 (66.7)	5/5 (100)

Values are given as number (%)

W week, *D* daily

†Data on dose were not retractable in all the cases, the number of patients, for whom dose was reported, is mentioned in bracket instead of percentages. Doses are mentioned from lowest to the highest in order

††In two cases infliximab was used at dose of 5 mg/kg one to three times during the third trimester, the rest of the cases were administered during all the trimesters

€The rest of the prospective and retrospective data were not distinguished

∞Hemorrhage

Table 4 Child-related outcomes of pregnancy exposure related to different biologic drugs

Drug	Abatacept	Adalimumab	Anakinra	Canakinumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Ustekinumab	Vedolizumab
Birth-related outcomes												
Live birth	88/152 (57.8)	200/222 (90.0)	32/33 (96.9)	8/9 (88.9)	582/702 (82.9)	270/372 (72.6)	6/6 (100)	1740/2017 (86.3)	19/24 (79.2)	218/362 (60.2)	26/30 (86.7)	39/69 (56.5)
Major CMs (total)	7/88 (7.9)	46/1008 (4.6)	1/34 (2.9)	0/8 (0)	10/535 (1.9)	47/815 (5.8)	0/13 (0)	51/1222 (4.2)	0/20 (0)	11/345 (3.2)	0/28 (0)	2/110 (1.8)
Prospective	0/36 (0.0)	25/543 (4.6)	1/27 (3.7)	0/1 (0)	10/507 (2)	30/466 (6.4)	0/8 (0)	28/751 (3.7)	0/20 (0)	8/194 (4.1)	0/18 (0)	2/40 (5)
Retrospective	7/52 (13.4)[€]	21/465 (4.5)	0/7 (0)	0/7 (0)	0/28 (0)	17/349 (4.9)	0/5 (0)	23/471 (4.9)	–	3/151 (2)	0/10 (0)	0/70 (0)
Minor CMs	–	2/68 (2.9)	1/9 (11.1)	–	–	0/20 (0)	0/2 (0)	2/94 (2.1)	–	0/4 (0)	0/19 (0)	1/5 (20)
Low birth weight (<2500 g)	0/1 (0)	11/123 (8.9)	6/19 (31.6)	0/6 (0)	25/243 (10.3)	31/253 (12.2)	0/2 (0)	65/584 (11.1)	0/6 (0)	27/118 (22.9)	2/24 (8.3)	1/9 (11.1)
Pre-term births (<37 weeks)	–	4/146 (2.7)	6/28 (21.4)	0/8 (0)	42/380 (11.1)	40/269 (14.9)	0/2 (0)	104/1,754 (5.9)	0/19 (0)	32/177 (18.1)	3/20 (15)	16/94 (17)
SGA	–	1/87 (1.1)	–	–	5/463 (1.1)	0/48 (0)	0/5 (0)	3/106 (2.8)	0/6 (0)	3/39 (7.7)	–	–
Still birth/intrauterine death (≥20 weeks)	4/151 (2.6)	2/258 (0.8)	0/32 (0)	–	5/570 (0.9)	0/30 (0)	–	2/2,146 (0.1)	2/30 (6.7)	1/202 (0.5)	0/23 (0)	1/28 (3.6)
Neonatal death	–	–	0/32 (0)	–	2/543 (0.4)	0/29 (0)	–	0/435 (0)	0/30 (0)	0/3 (0)	0/14 (0)	–
Immune system-related outcomes												
Adequate vaccination response	–	17/17 (100)	–	–	9/9 (100)	25/26 (96.2)	2/2 (100)	12/12 (100)	–	–	1/1 (100)	–
ADRs related to vaccination	–	1/102 (0.9)	–	–	0/26 (0)	0/12[δ] (0)	–	6/197 (3)	–	–	0/3 (0)	0/1 (0)
Allergies	–	5/103 (4.9)	–	–	–	–	–	8/183 (4.4)	–	–	–	–
Eczema	–	6/44 (13.6)	–	–	–	–	–	15/61 (24.6)	–	–	–	–
(Serious/opportunistic) infections[Ψ]	0/17 (0)	13/229 (5.7)	0/30 (0)	0/8 (0)	2/41 (4.9)	0/62 (0)	0/4 (0)	212/786 (27)	0/13 (0)	0/3 (0)	0/7 (0)	5/110 (4.6)
Drug-related outcomes												
Anti-drug antibodies at birth	–	–	–	–	0/16 (0)	–	–	4/51 (7.8)	–	–	–	–
Detectable drug levels												
Cord blood	–	50/50 (100)	–	–	6/26 (23.1)	–	–	–	–	–	–	–
At birth	–	28/36 (77.8)	–	–	1/14 (7.1)	–	–	51/99 (51.5)	–	–	–	–
During first 6 months	–	–	–	–	0/14 (0)	–	–	–	–	–	–	0/5 (0)

Table 4 (continued)

Drug	Abatacept	Adalimumab	Anakinra	Canakinumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Ustekinumab	Vedolizumab
At 9 months of age	–	1/37 (27)	–	–	–	–	–	7/46 (15.2)	–	–	–	–
At 12 months of age	–	0/36 (0)	–	–	–	–	–	3/46 (6.5)	–	–	–	–
Abnormal development	–	1/61 (1.6)	1/32 (3.1)	0/8 (0)	0/8 (0)	–	–	33/533 (6.2)	–	0/3 (0)	0/4 (0)	0/5 (0)

Values are given as number (%)

SGA (small for gestational age): below 10th centile for weight at birth, *CM* congenital malformation.

Ψ Serious infections defined as antibiotic therapy or hospitalization because of the infection

δ Vaccinations including polio, hepatitis B, diphtheria, pertussis, tetanus, Haemophilus influenza, and pneumococcus vaccines at 3, 6, and 12 months

Two cases of neonatal deaths occurred in a twin pregnancy; one of the twins was born at 25th GW with brain damage and pneumo-peritoneum, the other twin was born at 27th GW with heart defects and passed away due to a gastrointestinal infection at the 8th week of age [78].

Concentration in breast milk was investigated in 13 cases. Certolizumab pegol was detectable in three of these cases with a maximum concentration of 0.29 µg/mL peak. In two cases breast milk was examined after 7 days following the injection, and it was not detectable in either case [80].

3.4.6 Etanercept

In total 1145 maternal pregnancies were investigated in 26 articles. Outcomes regarding miscarriages were investigated for 359 of these pregnancies, in which 69 miscarriages were reported (19.2%). From 815 exposed cases during pregnancy, 47 major CMs were reported (5.8%). Six described cases are as follows (the rest of the cases were not described explicitly or could not be linked to this specific biologic):

1. Hypoplastic left heart and hypospadias ($n = 1$)
2. Agenesis of left kidney ($n = 1$)
3. Bilateral hydronephrosis ($n = 1$)
4. ASD ($n = 1$)
5. Wolf–Parkinson–White syndrome with heart failure ($n = 1$)
6. Omphalocele ($n = 1$) [55, 68].

Data on overall concomitant medication were available for 353 cases. Use of one or more co-medications was reported for 70 of these patients (19.8%). Data on exposure to MTX were available for 343 cases, in which 59 patients (17.2%) were exposed to MTX.

3.4.7 Golimumab

In total 31 maternal pregnancies were investigated in 16 publications. No data regarding miscarriages could be extracted from the presented information in these articles. No major CMs were reported in 13 exposures during pregnancy for golimumab. Data on overall concomitant therapy (including MTX exposure) were not available.

3.4.8 Infliximab

In total 4276 maternal pregnancies were investigated in 59 articles. The largest amount of prospective data was reported from a Janssen biologics database, which reported pregnancy results of 1362 reported spontaneous cases, clinical studies, and registries [101]. Outcomes regarding miscarriages were investigated for 1584 of these pregnancies, in which 170 miscarriages were reported (10.7%).

In total 51 major CMs were reported in 1222 pregnancies (4.2%). Fourteen described major CMs are as follows (the rest of the cases were not described explicitly or could not be linked to this specific biologic):

1–3. VSD ($n=3$).
4, 5. Cleft palate ($n=2$).
6, 7. Facial hemangiomata ($n=2$).
8. ASD ($n=1$)
9. Ectrodactyly ($n=1$)
10. Polydactyly ($n=1$)
11. Hydronephrosis and obstructive megaureter ($n=1$)
12. Pelviureteric junction obstruction ($n=1$)
13. Small aortic-pulmonary collateral, hypospadias, hepatic cyst ($n=1$)
14. Megacystis plus bilateral talipes ($n=1$) [43, 68, 107–109].

Two cases of minor CMs were reported in 94 patients (2.1%). This included one case of duplex kidney and one case of aberrant subclavian artery [136]. Data on overall concomitant medication were available for 461 cases. Use of one or more co-medications was reported for 85 of these patients (42.9%). Data on exposure to MTX were available for 221 cases, of which 36 patients (16.3%) were exposed to MTX.

Five hundred and forty-seven patients from a total of 1939 (28.2%) were exposed to infliximab during the entire pregnancy (all three trimesters). The data on elimination of infliximab during pregnancy were available only from a pharmacokinetics (PK) study, which compared drug levels and its clearance during different trimesters in 22 pregnancies. It was reported in this study that infliximab clearance decreased by 12% in the second and third trimesters [112].

The median ratio of infliximab in cord blood to maternal level was 2.63 (95% confidence interval (CI), 1.67–4.03) in 52 patients [median duration of therapy until 23 GW (range 21–32)] [43] and 3.25 in two patients in another study (therapy continued until last week of gestation) [28]. In one case report in a patient under infliximab treatment with the dose of 10 mg/kg every 6 weeks until the 32th GW, the cord blood concentration was 110.1 μg/mL. Plasma infliximab level in the mother at the time of delivery was 59.7 μg/mL [93]. The median ratio of infant to maternal drug concentration at birth was 1.97 (95% CI 1.50–2.43) in 44 patients (18 patients and 26 patients received last infusion before and after the 30th GW, respectively) [136]. In another study the median concentration was 7.8 μg/mL in patients who used infliximab until the 18th–36th weeks of gestation [51].

Infliximab was detectable in 19 patients' breast milk out of a total of 29 patients, with a maximum range of 0.15–0.74 μg/mL 24 h after infusion, detectable in 17 samples from a total of 29 after 48 h, and detectable in five samples from a total of eight after 168 h (no concentrations were reported for samples in the last two groups). Weight-adjusted dose was not calculated in this study [80].

Six cases from a total of 1372 (0.4%) required emergency C-section. One of these cases had undergone an emergency C-section because of placental dysfunction, in which a very low-birth-weight preterm infant was born [99].

There was a case report of an infant diagnosed with vertical transmission of disseminated histoplasmosis from mother at the time of delivery and through the placenta (authors' conclusion: probable involvement of the central nervous system). The mother was taking infliximab (IBD indication) until the 32th GW (delivery at 35th GW) [93].

A follow-up of 533 children exposed to infliximab showed abnormal development in 33 of these children (6.2%). Descriptions of abnormal development were provided in three of these cases: two cases reported deviations in weight or height percentiles and one case of late gross motor function development, which was resolved by 20 months of age [43, 94, 109].

Regarding vaccination (one or more vaccinations with Bacillus Calmette-Guérin (BCG), rotavirus, *Haemophilus influenzae* type b (Hib), tetanus, or hepatitis B), in total 197 cases were investigated in different publications [1, 43, 51, 58, 62, 77, 94, 100, 109, 137]. Twenty-nine cases were investigated regarding response to tetanus and hepatitis B vaccination, of which 28 had adequate response [28, 51, 62, 77, 100]. Adverse drug reactions were reported in six cases with mild reactions to rotavirus vaccination (fever, $n=5$ and diarrhea, $n=1$) in children exposed to infliximab during pregnancy [77].

3.4.9 Rituximab

In total 42 maternal pregnancies were investigated in nine articles. Outcomes regarding miscarriages were investigated for 24 of these pregnancies, of which only one (4.2%) miscarriage was reported at 12th GW in a case exposed to rituximab 1 month prior to conception and MTX at the time of conception [113].

No major CMs were reported for 20 pregnancy cases expose to rituximab. Data on exposure to MTX were available for 23 cases. It was reported for five of these patients (21.7%).

Two cases of stillbirth were reported, which occurred in the same patient, with rituximab exposure at 9 and 18 months prior to conception [113].

3.4.9.1 Tocilizumab In total 368 maternal pregnancies were investigated in ten articles. Outcomes regarding miscarriages were investigated for 361 of these pregnancies, in which 84 miscarriages were reported (23.3%). Data on con-

comitant exposure to MTX for reported miscarriages were not available.

Eleven major CMs were reported in a total of 345 investigated pregnancies with tocilizumab (3.2%). Eight of these cases were described as follows:

1. Pyelectasia ($n = 1$)
2. Multicystic dysplasia of right kidney ($n = 1$)
3. Esophageal fistula ($n = 1$)
4. Coarctation of the aorta, VSD, and inguinal hernia ($n = 1$)
5. Absence of one cardiac cavity ($n = 1$)
6. Bilateral hip dysplasia ($n = 1$)
7. Polydactyly ($n = 1$)
8. Marked thoracic scoliosis, myelomeningocele, missing sacrum (caudal regression syndrome) ($n = 1$) [117].

Data on overall concomitant medication were available for 210 cases. Use of one or more co-medications was reported for 54 of these patients (25.7%). Data on exposure to MTX were available for 203 cases, in which 40 patients (19.7%) were exposed to MTX. The results of these pregnancies were reported for just two cases (both live births, in one of them tocilizumab, MTX, and hydroxychloroquine till the sixth week of gestation). One case of stillbirth occurred in a pregnancy also exposed to MTX.

Concentration in breast milk was investigated in one study, in which drug concentrations of between 6 and 60,000 ng/mL were measured up to 28 days after administration of 400 mg tocilizumab, with a peak concentration before day 7. The time taken to reach the maximum concentration (Tmax) in breast milk was calculated as 3.2 days. Milk to serum concentration ratios were: 0.0015, 0.00082 and 0.0014 for three patients [119].

3.4.10 Ustekinumab

In total 54 maternal pregnancies were investigated in 22 articles. Outcomes regarding miscarriages were investigated for 27 of these pregnancies, in which three miscarriages were reported (11.1%). In one case of miscarriages the treatment dose of ustekinumab was higher than average due to refractory Crohn's disease [122, 124].

In 28 pregnancies investigated with regard to CMs, no cases were reported. Data on overall concomitant medication (including MTX exposure) were not available.

In one case with the last administered dose at 33 GW, concentration in cord blood at birth was measured (8 µg/mL), which was higher than the drug concentration in the mother's blood at the same point (4.3 µg/mL) [123].

Concentrations in breast milk were detectable in four cases from a total of six samples. Peak concentrations were between 12 and 72 h after injection (range 0.72–1.57 µg/mL). In three cases from four samples ustekinumab was still detectable 48 h after injection [80].

3.4.11 Vedolizumab

In total 147 maternal pregnancies were investigated in seven articles. Outcomes regarding miscarriages were investigated for 72 of these pregnancies, in which 19 miscarriages were reported (26.4%).

From 110 pregnancies investigated for major CMs, two cases were reported (1.8%). The descriptions of these CMs were as follows:

1. One congenital central nervous system anomaly caused by agenesis of the corpus callosum and left frontal polymicrogyria. Estimated time of conception was 79 days after the vedolizumab infusion [132]
2. One case of congenital hypothyroidism [135].

One minor CM of hip dysplasia was also reported [131]. Data on overall concomitant medication were available for 34 cases. Use of one or more co-medications was reported for six of these patients (17.6%). Data on exposure to MTX were available for ten cases, of which none were exposed to MTX.

From a total of 28 investigated cases regarding stillbirth, one case was reported to the Organization of Teratology Information Services (OTIS) due to fetal growth restriction and decreased amniotic fluid volume-induced labor (26th week) [132].

Drug concentrations were measured in mothers' serum and breast milk in the study by Lehat et al. [133]. No statistically significant correlation was found in five patients with a serum concentration range of 4200–18,000 ng/mL and milk concentration range of 22–216 ng/mL ($p = 0.11$). Vedolizumab levels peaked at 3–4 days following infusion to a maximum of 480 ng/mL, and then slowly decreased [133]. Maternal and infants' serum concentrations of vedolizumab were also measured in five patients [131]. The range of drug concentrations was 1.10–14.40 µg/mL in mothers and 1.00–8.70 µg/mL in infants at the time of delivery [131] (weight-adjusted doses were not reported).

One case of a preterm born child, who developed Kawasaki disease with eosinophilia at 3 months, treated with corticosteroids was reported [138]. In one study in 70 children exposed to vedolizumab during pregnancy there were no malignancies reported during the first year of life [134].

3.4.12 Other Biologics

The general conclusions of the articles, which could not be included in the above-mentioned subcategories, are discussed in this section.

3.4.12.1 Secukinumab
Only three case reports/series were found in the search between 1 January 2015 until 4 July 2019. In total five patients in these articles were reported, therefore this is not included in the results tables. Three of these cases reported spontaneous abortions and two resulted in live births. No information on CMs could be found [60, 139, 140]. One retrospective research in a Novartis global safety database was found on this subject; however, it was excluded from the final results as this was a research letter. Two congenital malformations from 54 total live births and 26 spontaneous abortions from 238 maternal pregnancies are reported. The type of CMs in maternal exposure was not specified with paternal exposure [141].

3.4.12.2 Belimumab
There were two case reports on using belimumab during pregnancy, which were excluded as they were published as research letters. Therefore, this is not discussed in the results tables. One Ebstein anomaly, one miscarriage, and one healthy birth were reported in a patient with systemic lupus erythematosus who was under belimumab treatment during three pregnancies. The mother was 41 years old at the time of the miscarriage [142]. The other case report was of a healthy birth after exposure to belimumab up to the 26th week of gestation. However, marked B-cell depletion and reduced T-cell subsets were reported in the baby at birth. B cells were in the normal range at 4 months of age. Rotavirus vaccination 6 weeks after birth and diphtheria–tetanus–pertussis, haemophilus, and pneumococcus vaccinations at 3 and 5 months of age resulted in satisfactory responses [143].

3.4.12.3 TNFα Blocker (in General, Not Specified)
Some of the publications discussed TNF-α blockers in general and did not mention separate data for each biologic. As the outcomes could not be related to one specific biologic with reported data, they were not discussed in the above subcategories [144–154]. In general, these studies have shown a higher chance of flare in patients who discontinue TNF-α blockers during pregnancy [144, 146]. Furthermore, a higher risk of pregnancy complications and severe acute respiratory infections in the first year of life in intrauterine-exposed infants were seen (specially in combination therapy with thiopurines and the chronic use of conventional steroids) [150].

Demyelinating disorders in children exposed to TNF-α blockers during pregnancy were investigated in a nested case–control study in 399 rheumatoid arthritis patients, which did not report any cases of demyelinating disorders in these children during the follow-up period [152].

3.4.12.4 Biologics (in General, Not Specified)
In some of the included publications the type of biologic used was not specified for the outcomes. In general, these studies did not show any abnormal outcomes in children exposed to biologics during pregnancy/lactation [155–167].

3.5 Risk of Bias Across Studies

The authors acknowledge that the risk of bias in total is high as the data are heterogenic and confounding factors could not be retrieved in all of the cases and from all of the studies. Biologics used in different dosages and with different protocols for different indications were considered together in this article. However, it should be remembered that this will not affect the recognition of causality—if any—for CMs and miscarriages (aims of this study).

3.6 Additional Analysis

Additional data to the above-mentioned information have been acquired. As different publications had different primary and secondary outcomes and because this additional information is scarce but still of importance, the authors see the necessity to summarize and present this data.

These further details for each biologic can be found in Tables 2, 3, and 4.

Comparison of the results regarding the rates of major CMs from this study with the rates in the systematic review of EULAR, are provided in ESM, Table 3.

4 Discussion

Available data extracted from the most recent published literature shows that the rates of miscarriages and major CMs in investigated biologics do not differ drastically from those rates in the general population (estimated as 10–20% and 2–5.5%, respectively). In some cases the information on other outcomes (such as ADRs related to vaccination, preterm births, etc.) was not available. Despite this fact and the heterogeneity of the data, no new safety concerns were identified from a total of 143 investigated publications regarding the use of biologics during pregnancy.

Regarding the association of CMs, preterm birth, and birth weight with biologic use during pregnancy, a recent

meta-analysis by Tsao et al. also showed no increased odds ratios [11]. Nonetheless, it should be considered that the methods in the two studies are different. We have investigated a broader range of studies and have summed up data on miscarriages (co-primary outcome) and additional secondary outcomes such as vaccination response and detectable drug levels during different periods. We have also described the pattern of reported CMs. In our systematic review, each biologic was considered separately. This can be of additional value if one specific biologic is the matter of interest. The study of Tsao et al. showed that the underlying conditions are important factors to be considered as a potential confounder for the pregnancy outcomes. In accordance with this conclusion, we provided detailed information on maternal disease baseline characteristics.

According to EMA guidelines, in order to exclude a ten- or twofold risk of congenital malformations for medicine use during pregnancy there is a need for at least 300 or 1000 prospectively collected sets of data on pregnancies, respectively. This information should be collected from exposed pregnancies to that particular pharmaceutical product during at least the first trimester [168, 169]. Based on summed up data in our study combined with the data from the EULAR study, it can be concluded that the use of adalimumab, certolizumab pegol, and infliximab during pregnancy does not carry a twofold increased risk of combined major CMs for the offspring, compared to this risk in the general population (estimated as 2–5.5%) [170]. The rates of major CMs from this study were comparable with the rates in the systematic review of EULAR for most of the investigated biologics, with some minor differences [8]. The use of adalimumab, certolizumab pegol, infliximab, and etanercept during pregnancy has been conditionally approved by the EMA recently, based on the results of their pregnancy registries conducted by pharmaceutical companies [4–7].

For several reasons the impact of medication on the incidence rate of miscarriages is difficult to determine. Often in prospective studies women are only included when they are pregnant and not in the pre-conception period. In these studies early miscarriages are missed. In retrospective studies there is a chance of publication bias, as only women with an abnormal pregnancy are reported. Reliable data would only be available from prospective studies if women are included from the moment they actively try to become pregnant. Furthermore, confounding by indication (some diseases cause more miscarriages) and confounding by concomitant medication (like MTX) can also affect the results. The results on miscarriages and malformations are comparable for adalimumab, certolizumab, and etanercept, although the transplacental passage of adalimumab is extremely high.

In our study, only abatacept, tocilizumab, and vedolizumab show slightly higher rates for miscarriage compared to the incidence rate of miscarriages in the general population (estimated as 10–20%) [90]. It should be considered that the numbers of pregnancies investigated for miscarriages are limited for abatacept [153] and vedolizumab [72]. Due to limited numbers, it cannot be concluded that there is a causal relationship between a slightly higher rate of miscarriages and the use of abatacept or vedolizumab. Regarding tocilizumab, high percentages of miscarriages can be due to publication bias, as this percentage is higher in retrospective data compared to prospective data. For tocilizumab, the high rate of MTX use compared to other biologics can also explain the higher total rate of miscarriages. Comparing the results of miscarriages from this study with the systematic review of EULAR, the rates were comparable for most of the investigated biologics, with some minor differences as follows: rates of miscarriages for anakinra and rituximab were lower in our study versus the EULAR study (1/33 (3.1%) vs. 4/40 (10.0%) and 1/24 (4.2%) vs. 48/210 (22.9%), respectively). However, because of the small number of cases, these findings remain inconclusive [8].

From the secondary outcomes with acceptable reported sample sizes, the results were often as expected. Still there were some increased incidences detected, such as early membrane rupture, low birth weight, and preterm birth rates with tocilizumab therapy during pregnancy. Increased risk of all these three events have been described with the use of corticosteroids [171–173]. It should be noted that the rate of exposure to corticosteroids in the reviewed publications for tocilizumab was high (Table 2).

Further, serious infections rates in children exposed to infliximab during pregnancy were higher than expected (212/786 (27%)). This highlights the need for continuing research evaluating the safety of infliximab on various maternal infections and infections in offspring. Different studies have shown that combination therapy with anti-TNF α and thiopurines during pregnancy is associated with a higher rate of infections in offspring when compared to monotherapy with anti-TNF α [42, 136]. The overall rate of exposure to thiopurines for infliximab in our systematic review was 39.2%, higher than other biologics, which can explain the higher rates of serious infections in this group. Additionally, most of the reported infections were from the study by Truta et al., which reported acute respiratory infections, without differentiating the serious infections from non-serious infections. In this study, data acquisition was done retrospectively, which increases the chance of publication bias. Furthermore, in most of the pregnancies in this study infliximab was discontinued 90 days or less before delivery, therefore it is more likely that an immunoglobulin with a high affinity for the

neonatal Fc receptor (in this case infliximab) transfers through the placenta and reaches the fetus [111, 174].

From the available data on other secondary outcomes some subcategories may give the impression of an increased incidence compared to the normal population such as placental abnormality rate for infliximab and vedolizumab (1/6 (16.7%) and 2/4 (50.0%), respectively), low birth-weight rate for anakinra (6/19 (31.6%)), anti-drug antibodies at birth (4/51 (7.8%)), and detectable drug levels at the 9th (7/46 (15.2%)) and 12th months of age (3/46 (6.5%)), in children exposed to infliximab during pregnancy. However, conclusions should be drawn with caution regarding the above-mentioned increased incidences.

4.1 Limitations

The protocol of this study was recorded retrospectively in PROSPERO (after conducting the first search in the databases). Another limitation of this study is that the small sample sizes and small numbers of reports involved in some outcomes (especially secondary outcomes) make interpretations based on acquired results uncertain. Furthermore, type of disease, disease activity during pregnancy, extent of systemic inflammation, and organ involvement, co-morbidities, and concomitant drug therapy could also have contributed to negative outcomes. In this study all types of rheumatologic, gastroenteric, and dermatologic biologics were considered together as the types of biologics used in the management of these diseases overlap. All the increased incidences should be further investigated and confirmed in future studies, aiming to collect prospective data.

5 Conclusions

Based on the results of our study it is likely that adalimumab, certolizumab pegol, and etanercept conceivably can be prescribed safely during pregnancy, especially considering the negative effects of active disease on mothers, pregnancy outcomes, and the children. Regarding infliximab, high rates of infections in children have been detected, mainly from one study [111], and a more conservative approach, especially in combination therapy with thiopurines, is recommended. Discontinuation before the third trimester may decrease the chance of infections in offspring. Further, the risks of using abatacept, anakinra, canakinumab, golimumab, rituximab, tocilizumab, ustekinumab, and vedolizumab are not well known and available data are scarce in this regard. This study confirms the previous literature reviews carried out on use of biologics during pregnancy in autoimmune diseases.

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