Fetal and maternal outcomes after maternal biologic use during conception and pregnancy: a systematic review and meta-analysis.

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Abstract

Background: Biologic medications, specifically the TNF-α inhibitors, have become increasingly prevalent in the treatment of chronic inflammatory disease (CID) in pregnancy. Objective: To determine pregnancy outcomes in women with CID exposed to biologics during pregnancy. Search strategy: PubMed and EMBASE databases were searched through January 1998-July 2021. Selection criteria: Peer reviewed, English language cohort, case-control, cross-sectional studies, and case series which contained original data. Data collection and analysis: Two authors independently conducted data extraction and assessed study quality. A meta-analysis of proportions using a random-effects model was used to pool outcomes. Linear regression analysis was used to compare the mean of proportions of outcomes across exposure groups using the 'treated' group as the reference category. All studies were evaluated using an appropriate quality assessment tool described by McDonald et al. Main Results: 35 studies, 11172 pregnancies, were eligible for inclusion. Analysis showed pooled proportions for congenital malformations: treated 4%(95% CI 0.03-0.4) vs disease matched 4%(0.03-0.05).Preterm delivery treated 12%(0.10-0.14) vs disease matched 10%(0.09-0.12) Severe neonatal infection: treated 5%(0.03-0.07) vs disease matched 5%(0.02-0.07) Low birth weight: treated 10%(0.07-0.12) vs disease matched 8%(0.07-0.09) The pooled Miscarriage: treated 13%(0.10-0.15) vs disease matched 8%(0.04-0.11) Pre-eclampsia; treated 1%(0.01-0.02) vs disease matched 1%(0.00-0.01). No statistical differences in proportions were observed. Conclusion: We demonstrated comparable pregnancy outcomes in pregnancies exposed to biologics, disease matched controls and CID free pregnancies. Overall, women receiving biologics in pregnancy may be reassured regarding their safety.

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Running title: Biologics in pregnancy

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Search strategy: PubMed and EMBASE databases were searched through January 1998-July 2021.

Selection criteria: Peer reviewed, English language cohort, case-control, cross-sectional studies, and case series which contained original data.

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Main Results: 35 studies, 11172 pregnancies, were eligible for inclusion. Analysis showed pooled proportions for congenital malformations: treated 4%(95% CI 0.03-0.4) vs disease matched 4%(0.03-0.05).Preterm delivery treated 12%(0.10-0.14) vs disease matched 10%(0.09-0.12) Severe neonatal infection: treated 5%(0.03-0.07) vs disease matched 5%(0.02-0.07) Low birth weight: treated 10%(0.07-0.12) vs disease matched 8%(0.07-0.09) The pooled Miscarriage: treated 13%(0.10-0.15) vs disease matched 8%(0.04-0.11) Pre-eclampsia; treated 1%(0.01-0.02) vs disease matched 1%(0.00-0.01). No statistical differences in proportions were observed.

Conclusion: We demonstrated comparable pregnancy outcomes in pregnancies exposed to biologics, disease matched controls and CID free pregnancies. Overall, women receiving biologics in pregnancy may be reassured regarding their safety.

Tweetable Abstract:

Meta-analysis of 11172 pregnancies exposed to biologics shows these medications are predominantly safe for the fetus and mother.

Main Text

Introduction:

Chronic inflammatory diseases (CIDs) are a group of autoimmune diseases which affect between 5-7% of the population and include rheumatoid arthritis (RA), psoriatic arthritis and inflammatory bowel disease (IBD).[1,2] Many CIDs have a female preponderance and are often associated with activity during reproductive years.[3–5] They share a similar pathophysiology centring on dysregulation of the systemic immune response mediated by cytokines including tumour necrosis factor (TNF), interleukin 1 (IL-1), and interleukin 6 (IL-6) which are known to affect pregnancy and embryogenesis.[6,7] Modulation of these cytokines with the introduction of biologic agents over two decades ago was a revolution in the care for these patients and are increasingly used to manage chronic autoimmune diseases during pregnancy.

CID activity is inherently associated with an increased risk of a range of adverse pregnancy outcomes.[8–10] Women with active IBD during pregnancy have higher rates of miscarriage, preterm delivery, low birth weight, congenital anomalies and Caesarean section compared to a general population.[8] Likewise, there is a strong correlation with activity in RA and adverse outcomes such as miscarriage, low birth weight, pre-eclampsia and Caesarean section.[9] Disease flares are associated with a greater magnitude of risk for both women and their pregnancy with balancing the risk of disease flare with fears regarding adverse effects of biologic medications.[10]

Randomised control trials on biologic medications during pregnancy are lacking and the majority of data regarding safety in pregnancy arises from case series, population data review and cohort studies. One of the most recent meta-analysis by Tsao et al[11] focused solely on studies that had a disease matched control group thus limiting their review to 24 studies including 10 published as abstracts only. The other most recent meta-analysis by Komaki et al included 13 studies and compared outcomes in the treatment group to the general population only, with no disease matched cohort included.[12]

The primary aim of this systematic review and meta-analysis was to examine a range of maternal and neonatal adverse pregnancy outcomes in pregnant women exposed to biologics for the management of underlying CID compared with disease matched cohorts and women without CID.

Methods

This review was performed according to an *a-priori* -designed protocol recommended for systematic reviews and meta-analysis.[13] Maternal and fetal systematic review protocols were prospectively registered on PROSPERO CRD4201707072 and CRD42020185926. The systematic review was based on the following PICO requirements; Population: Pregnant women with a diagnosis of CID. Intervention/Exposure: Treatment with Biologic medication. Comparison: Pregnant women with a diagnosis of CID without treatment with biologics and a CID free population. Outcomes: fetal outcomes included congenital malformations, preterm delivery, severe neonatal infection, low birth weight and small for gestational age. Maternal outcomes included severe maternal infection, miscarriage and pre-eclampsia.

Search methodology

The search strategy was developed with librarian assistance and was carried out through PubMed and EMBASE search engines to identify peer reviewed published papers relating to the association between biologics use for CID in pregnancy and the risk of maternal and neonatal outcomes. Searches were conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-analysis).[14] PubMed and EMBASE searches were conducted through January 1998 - April 2020 by two reviewers (LOB, SA), and updated again July 2021. Full search terms can be found in the Appendix. Bibliographies of included studies were also searched for additional studies eligible for inclusion. Titles and abstracts of studies retrieved from each database were stored and managed in Endnote reference manager. Three review authors (LOB, SA, AOS) reviewed titles and abstracts, obtaining full text as required.

Study Inclusion and exclusion criteria

English language cohort, case-control, cross-sectional studies and case series with a minimum n=30 were eligible for inclusion. Studies must have been peer-reviewed and contain original data. A diagnosis of a CID requiring treatment with biologics had to be described for women treated during pregnancy/or the three months prior to pregnancy (as early cessation of these medications is common).

Ineligible studies were those who did not specify maternal underlying medical condition or a condition that was not a chronic inflammatory disease e.g.: neoplasia. Studies that were not published in English, those that did not address maternal or fetal outcomes, non-peer reviewed studies, commentaries, reviews, and conference abstracts were excluded.

Data extraction

Three reviewers (LOB, SA, AOS) independently extracted data using a standardised collection form for all eligible studies, including study characteristics and reported outcomes for analysis. Where multiple publications using the same data existed, we included the most recent study, provided the earlier publication did not contain reported information not available in the most recent study. In studies in which adequate data was not reported, an effort was made to contact authors to provide us with additional information to allow us to compute effect estimates. Risk of bias assessment was undertaken by three reviewers (LOB, SA, AOS) using an appropriate quality assessment tool described by McDonald et al[15], with all included studies classified as low to moderate risk of bias.

Statistical analysis

Where data permitted, Stata 14 was used to conduct meta-analyses of proportions using a random-effects model. We analysed the available data from three main population groups. The 'treated' group were women with CID who required treatment with biologic medications throughout their pregnancy. The 'disease matched' group were the group of women with CID not prescribed biologics in pregnancy. The 'disease free' group was a group representative of the general population, (i.e. women who were pregnant and did not have a diagnosis of CID). We modelled data using the program *metaprop* which augments the metan program. This allowed for computation of 95% confidence intervals[16]and pooling of proportions, presenting a weighted sub-group and overall pooled estimates with inverse-variance weights from a random effects model. The primary analysis was performed on all eligible studies, with subgroup analyses by biologic type and by chronic inflammatory disease subtype where appropriate. We used linear regression analysis to compare the mean of proportions of outcomes across exposure groups using the 'treated' group as the reference category.

Results

The search for fetal outcomes produced 1887 titles, after exclusion for duplicates and ineligible studies, 35 studies were eligible and 33 were included in the meta-analysis (Figure S1). The initial search for maternal outcomes produced 2104 results after exclusion for duplicates and ineligible studies, 34 were suitable for inclusion and 25 studies were included in the maternal outcome meta-analysis (Figure S2).

Overall, there were 35 individual observational studies included in the meta-analysis, 24 cohort studies and 11 case series fulfilling the inclusion criteria. This review contains a total of 11172 pregnancies exposed to biologics, 39290 disease matched controls and 2892933 chronic inflammatory disease free pregnancies used for the meta-analysis. The addition of the peer reviewed case series added 2653 women exposed to biologics in this meta-analysis.

Congenital malformations

There were 28 eligible studies in the congenital malformation meta-analysis. There were 1288762 infants in this cohort, (7811 born to women using biologics in pregnancy, 29171 infants born to women with CID who were not treated with biologics in pregnancy and 1251780 infants born to women who were CID free) (Table 1). The proportion of congenital malformations in the treated group was 4% (95% CI 0.03-0.04), the disease matched group was 4% (0.03 to 0.05) and the disease free group 4% (0.03 to 0.05). No differences were observed in proportions between disease matched compared with disease treated women (p=0.238, nor in disease free compared with disease treated women (p=0.579 Figure 1 and Table S1).

Sub analysis by chronic inflammatory disease type did not significantly change results. Those women with IBD treated with biologics had a proportion of congenital malformations of 4% (95% CI 0.02 to 0.05) compared to CID overall having 4% (0.02 to 0.06) and RA alone of 4% (0.02 to 0.05) (Figure S5).

Preterm delivery

There were 26 studies included in the preterm birth (PTB) meta-analysis. This included 7728 pregnancies exposed to biologics and 18574 disease matched controls (Table 1). The proportion of PTB in the treated group was 12% (95% CI 0.10 to 0.14), 10% (0.09 to 0.012) in the disease matched and 6% (0.04 to 0.07) in the disease free group (Figure S4). There was no statistical difference in the treated group vs the disease

matched group (p=0.250), there was a statistical difference when comparing disease free with disease treated women (p= 0.008 Table S1).

Subgroup analysis examining anti-TNF-α only revealed a change in the PTB rate for the treated group to 11% (95% CI 0.09 to 0.13) (Figure 2). Subgroup analysis by disease classification showed anti-TNF-α treated IBD had a PTB rate of 9% (0.07 to 0.11) with the disease matched IBD group having a PTB rate of 9% (0.08 to 0.010) (Figure S5). Only one study focused on anti-TNF-α use and RA[17] with a treated PTB rate of 18% (0.14 to 0.24) and disease matched of 14% (0.12 to 0.15). The remaining studies focused on mixed CID with a preterm birth rate of 12% (0.09 to 0.15).

Neonatal infection

The pooled data on severe neonatal infection included 9 studies with 22368 neonates. This was divided into 7569 neonates born to women with CID, 3554 neonates born to women requiring biologics treatment during pregnancy and 4015 disease matched controls (Table 1).

The proportion of severe neonatal infections requiring hospitalisations in the treated group was 5% (95% CI 0.03 to 0.07), the proportion in the disease matched group was 5% (0.02 to 0.07) and the disease free was 2% (0.02 to 0.02) (Figure S6). No differences were observed in proportions between disease matched compared with disease treated women (p=0.970), nor in disease free compared with disease treated women comparison (p=0.225; Table S1). Subgroup analysis by disease diagnosis revealed no statistical difference between groups (results not shown).

Birth weight

We examined both small for gestational age (SGA) and low birth weight (LBW) because reports on biologics use during pregnancy and neonatal birth weight varied. LBW was defined as less than 2.5kg at birth regardless of gestation while SGA was defined as $<10^{th}$ centile for weight at birth by gestation. In the LBW group there were 17 studies included with a total of 11474 infants, 5112 exposed to maternal biologic use, 3046 disease matched and 3316 CID free pregnancies (Table 1).

The overall proportion of LBW in the treated group was 10% (95% CI 0.07 to 0.12) the disease matched 8% (0.07 to 0.09) and the disease free group 4% (0.01 to 0.08) (Figure S7). No statistical differences were observed between disease matched and disease treated women (p=0.241), nor in disease free (p=0.079; Table S1). Sub group analysis on anti-TNF-α use alone revealed no difference between groups outcomes (results not shown).

The SGA group included seven studies with 1638595 infants, 3342 born to women medicated with biologics during pregnancy and 10720 disease matched controls(Table 1). All of the SGA studies focused on anti-TNF-α biologics only. The proportion of SGA in the treated group was 6% (95% CI 0.02 to 0.10), the disease matched control 7% (0.02 to 0.11) and the disease free population 10% (0.10 to 0.10) (Figure S8). No differences were observed in proportions between disease matched compared with disease treated women (p=0.753), nor in comparison with disease free (p=0.170; Table S1).

Maternal infection

The data available on maternal serious infection requiring hospitalisation included two studies both of which focused on anti-TNF-α use in pregnancy. There was a total of 1685 pregnant women in this cohort.[18,19] There were 916 women who were treated with biologics during their pregnancy (Table 2) and 453 disease matched control. The studies included in this analysis were Chaparro[19] who focused on anti-TNF-α use in IBD and pregnancy and Clowse[18] on certolizumab pegol use in CID in pregnancy.

Overall the pooled analysis showed that the treated group had a proportion of serious infection of 4% (95% CI 0.03 to 0.05), while the disease matched group had a proportion of serious infections of 1% (0.00 to 0.02) (Figure S9). There were only 2 studies included in this analysis with a statistical difference in proportions between disease matched compared with disease treated women (p <0.001.; Table S2).

Miscarriage

The data available on miscarriage included 15 studies with 9368 pregnancies. There were 2708 pregnancies in women treated with biologics in pregnancy (Table 2). The proportion of miscarriage in the biologics treated group was 13% (95% CI 0.10 to 0.15), the proportion of miscarriage in the disease matched group was 8% (0.04 to 0.11) and in the disease free group 11% (0.03 to 0.19) (Figure S10). There was no significant difference in proportions between disease matched compared with disease treated women (p=0.078), or in disease free compared with disease treated women comparison (p=0.631; Table S2). One study was excluded from the analysis, they had no difference in their miscarriage rate across their treated and untreated groups of 3%, but a rate much lower than all other included studies[20]. Subgroup analysis revealed no difference in groups when focusing on anti-TNF-α studies only (results not shown).

Pre-eclampsia:

There were 5 eligible studies for inclusion in the meta-analysis for pre-eclampsia. This included data on 1175 pregnant women treated with biologics and 1017 disease matched controls (Table 2). In the treated group the percentage of pre-eclampsia was 1% (95% CI 0.01 to 0.02) and the disease matched control 1% (0.00 to 0.01) (Figure S11). No differences were observed in proportions between disease matched compared with disease treated women (p=0.193; Table S2).

Discussion

Main findings

We detected no difference in the rates of congenital malformations, neonatal infection, low birth weight, small for gestational age, miscarriage or pre-eclampsia with the use of biologics in pregnancy. The rates of preterm delivery were not statistically different between the treated and the disease matched groups but there was a statistical difference noted between the treated and disease free group, possibly pointing towards the disease process being a factor. Too few studies examined serious maternal infection as an outcome to be concluded upon. These findings may offer significant reassurance to both clinicians and patients alike in continuing these targeted agents during pregnancy.

Strengths and limitations

Studies examining the use of biologics in pregnancy have been limited due to small sample size and the rare outcomes of interest. To our knowledge this is the largest cohort of pregnancies exposed to biologics collated to date. This review was based on a pre-published protocol on PROSPERO and followed the PRISMA guidelines. This review allows areas of future research to be highlighted that are currently lacking, primarily elucidating the links with preterm birth, maternal infection risk as well as exploring likely protective effects of these medications against uncontrolled disease activity. There are several limitations to this study, our search included English only literature. Disparities in the measurement criteria e.g.: birth weight, infection criteria and even the diagnostic criteria for congenital malformation make meta-analysis on this topic difficult with an already small sample being made smaller by misusing the appropriate definition and criteria. Additionally, the recording of concomitant medications, particularly corticosteroids, dosing and pregnancy outcomes which can differ between studies is imprecise at best. Pregnancy outcomes in this population can be influenced by the activity of the underlying disease state peri-conceptually and during pregnancy which can be difficult to accurately collate in these observational studies and difficult to control for by using a "disease matched cohort" when matched by diagnosis only.

We have expanded on the previous reviews by increasing the pool of data to include peer reviewed cohort studies and case series[11,12,21] with statistical analysis of proportions rather than odds ratio. Another novel approach that we have taken was allowing comparisons across three populations; the treated, disease matched and disease free. We also performed sub analysis by biologic type and disease type where appropriate.

Interpretation

We found no evidence to suggest biologics, with the strongest evidence for the TNFα inhibitor class, increase the risk of congenital anomalies. This further expands on the evidence provided from previous meta-analyses that found no difference in congenital anomalies such as reported by Tsao et al (OR 1.18, 95% CI 0.88 to 1.5)[11], Komaki et al[12] and Neilsen[21].This is the largest preterm birth meta-analysis to date, with twenty-six studies included in the preterm birth meta-analysis with 7728 pregnancies exposed to biologics. As expected, a higher rate of PTB was observed in the treated group (12% compared with 6% in the disease-free group (p=0.008), with no difference in the rates observed between the treated and disease matched groups. The disease free group rates of 6% compare with WHO PTB rates for Europe and North America of 9% and 11% respectively.[22] The lower rate of PTB in our disease free population likely reflects the inclusion of a large study by Broms et al[4] which encompasses population registry data from Denmark, Finland and Sweden.

One of the primary factors which may impact PTB rates is disease activity. Geldhof concluded that women with active or flaring disease during pregnancy were at a much higher risk of complications irrespective of exposure to biologics with their exposure group having a PTB rate of 9.2% (n=143) and their corticosteroid group a PTB rate of 14.7% (n=36).[23] Of concern, maternal disease may flare when biologic agents are discontinued and this itself may impact on PTB rates; this was reported with discontinuation of biologics prior to 24 weeks and a higher incidence of preterm delivery in a number of studies included in this analysis.[4,23,24]

Our meta-analysis revealed no statistical difference in severe neonatal infection between groups. This was similar to the findings of two studies which were eligible but could not be included in the metanalysis, Tsao *et al* 2019 (due to a data sharing agreement) and Luu *et al* . Tsao *et al* 2019 found no increased risk of serious infections in the first year postpartum for either the mothers or the neonates[3]. Similarly, Luu *et al* found no difference in community or hospital acquired infections in the biologic treated group compared to a disease matched population.[24] Interestingly studies specifically examining biologic use during the third trimester found no alteration in the neonatal infection rate during the first 12 months of life for the neonate.[19,20,25–27] The only variable associated with an increased incidence of neonatal infection in multiple studies was PTB.[19,20,24]

Our meta-analysis found no statistical difference in birth weight with biologic use. Literature around this topic has been controversial with previous studies highlighting the greater prevalence of growth restriction/low birth weight babies in women with chronic inflammatory conditions[4,17]. Of the eligible studies included in this meta-analysis, Moens had the largest treated group and found no difference between their treated and untreated groups.[28] Tsao *et al* found an OR for the association between biologic exposure and SGA was 0.91 (95% CI 0.46 to 1.78).[29] The PIANO trial found no difference in LBW in those exposed to biologics after controlling for PTB and disease activity[20].

Our analysis included only two studies examining severe maternal infection. The recent large Canadian 10 year retrospective cohort study by Tsao *et al* data could not be obtained.[3]However in published work they reported the occurrence of serious maternal infections to be rare with an incidence of 0-5% which is similar to the proportions found in our meta-analysis. Luu *et al*found no difference in infection rates (community or hospital treated) in women treated with biologic agents in their third trimester but echoing findings above, those who discontinued were more likely to have a flare of their inflammatory disease.[24] There was no greater likelihood of miscarriage for biologic treated patients compared to the comparator populations. This mirrors previous data reported[18,30–32] which did not find an increased risk of miscarriage with biologics. Assimilating the data on pre-eclampsia, which is a less studied outcome of interest, we found no data to suggest that TNF inhibitors increase the risk. This data reflects information obtained from a small number of studies. Notably, no pre-eclampsia cases were reported with CZP use in Clowse et al.[18] Chaparro*et al* found pre-eclampsia equally distributed across both the biologics exposed group and the disease matched cohort.[19] Julsgaard *et al* specifically found no difference in the pre-eclampsia rates between women who ceased their medication prior to 30 weeks' gestation or continued.[33]

Conclusion

With the data that is available in the published literature shows no increased risk with biologics over disease matched cohorts with respect to congenital malformations, preterm delivery, neonatal infection, small for gestational age, low birth weight, miscarriage and pre-eclampsia. There is a suggestion of an increased risk of maternal infections in the treated group but this is likely due to the lack of studies examining this outcome.

With over 11172 pregnancies exposed to biologics, our study shows these medications are predominantly safe for the fetus and the mother. More evidence is required to prove the likely protective effects of these medications from unwanted outcomes that disease flare may cause in CID affected pregnancies. This is important for gastroenterologists, rheumatologists and obstetricians alike when reassuring women regarding continuation of treatment throughout pregnancy and for refractory disease during childbearing years.

Disclosure of interests

None Declared.

Contribution to Authorship

FMcC, AK, GMurphy conceived the study and FMcC, AK, GMurphy, SA, LOB, GMaher designed the protocol. LOB, SA performed the literature search. LOB, SA, AOS selected the studies and extracted the relevant information. LOB, GMaher synthesised the data. LOB wrote the first draft of the paper. FMcC, AK , GMurphy, GMaher critically revised successive drafts of the paper. LOB is the guarantor of the review.

References

1. Maniadakis N, Toth E, Schiff M, et al. A Targeted Literature Review Examining Biologic Therapy Compliance and Persistence in Chronic Inflammatory Diseases to Identify the Associated Unmet Needs, Driving Factors, and Consequences. *Adv Ther* . 2018;35(9):1333-1355. doi:10.1007/s12325-018-0759-0

2. Jacobs P, Bissonnette R, Guenther LC. Socioeconomic burden of immune-mediated inflammatory diseases - Focusing on work productivity and disability. *J Rheumatol* . 2011;38(SUPPL. 88):55-61. doi:10.3899/jrheum.110901

3. Tsao NW, Lynd LD, Sayre EC, Sadatsafavi M, Hanley G, De Vera MA. Use of biologics during pregnancy and risk of serious infections in the mother and baby: A Canadian population-based cohort study. *BMJ Open* . 2019;9(2):1-9. doi:10.1136/bmjopen-2018-023714

4. Bröms G, Kieler H, Ekbom A, et al. Anti-TNF treatment during pregnancy and birth outcomes: Apopulation-based study from Denmark, Finland, and Sweden. *Pharmacoepidemiol Drug Saf* . 2020;(September 2019):1-12. doi:10.1002/pds.4930

5. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: The sex ratio. *Ann N Y Acad Sci* . 2006;1069:212-222. doi:10.1196/annals.1351.019

6. De Lorenzo R, Ramirez GA, Punzo D, et al. Neonatal outcomes of children born to mothers on biological agents during pregnancy: State of the art and perspectives. *Pharmacol Res* . 2020;152(September 2019):104583. doi:10.1016/j.phrs.2019.104583

7. Yockey LJ, Iwasaki A. Interferons and Proinflammatory Cytokines in Pregnancy and Fetal Development. *Immunity* . 2018;49(3):397-412. doi:10.1016/j.immuni.2018.07.017

8. Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* . 2007;56(6):830-837. doi:10.1136/gut.2006.108324

9. Genest G, Spitzer KA, Laskin CA. Maternal and fetal outcomes in a cohort of patients exposed to tumor necrosis factor inhibitors throughout pregnancy. *J Rheumatol* . 2018;45(8):1109-1115. doi:10.3899/jrheum.171152

10. Selinger CP, Nelson-Piercy C, Fraser A, et al. IBD in pregnancy: Recent advances, practical management. *Frontline Gastroenterol* . Published online 2020:1-11. doi:10.1136/flgastro-2019-101371

11. Tsao NW, Rebic N, Lynd LD, De Vera MA. Maternal and neonatal outcomes associated with biologic exposure before and during pregnancy in women with inflammatory systemic diseases: a systematic review and meta-analysis of observational studies. *Rheumatology* . 2020;59(8):1808-1817. doi:10.1093/rheumatology/keaa064

12. Komaki F, Komaki Y, Micic D, Ido A, Sakuraba A. Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor-α use in females with immune mediated diseases; a systematic review and meta-analysis. *J Autoimmun* . 2017;76:38-52. doi:10.1016/j.jaut.2016.11.004

13. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. *Univ York York, UK,* . Published online 2009. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf

14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.*PLoS Med* . 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097

15. McDonald SD, Han Z, Mulla S, Murphy KE, Beyene J, Ohlsson A. Preterm birth and low birth weight among in vitro fertilization singletons: A systematic review and meta-analyses. *Eur J Obstet Gynecol Reprod Biol* . 2009;146(2):138-148. doi:10.1016/j.ejogrb.2009.05.035

16. Nyaga VN, Arbyn M, Aerts M. Metaprop: A Stata command to perform meta-analysis of binomial data. *Arch Public Heal* . 2014;72(1):1-10. doi:10.1186/2049-3258-72-39

17. Carman WJ, Accortt NA, Anthony MS, Iles J, Enger C. Pregnancy and infant outcomes including major congenital malformations among women with chronic inflammatory arthritis or psoriasis, with and without etanercept use. *Pharmacoepidemiol Drug Saf* . 2017;26(9):1109-1118. doi:10.1002/pds.4261

18. Clowse MEB, Scheuerle AE, Chambers C, et al. Pregnancy Outcomes After Exposure to Certolizumab Pegol: Updated Results From a Pharmacovigilance Safety Database. *Arthritis Rheumatol* . 2018;70(9):1399-1407. doi:10.1002/art.40508

19. Chaparro M, Verreth A, Lobaton T, et al. Long-term safety of in utero exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: Results from the multicenter European TEDDY study.*Am J Gastroenterol* . 2018;113(3):396-403. doi:10.1038/ajg.2017.501

20. Mahadevan U, Long MD, Kane S V., et al. Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease. *Gastroenterology* . 2021;160(4):1131-1139. doi:10.1053/j.gastro.2020.11.038

21. Nielsen OH, Gubatan JM, Juhl CB, Streett SE, Maxwell C. Biologics for Inflammatory Bowel Disease and Their Safety in Pregnancy: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* . Published online 2021. doi:10.1016/j.cgh.2020.09.021

22. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Heal* . 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0

23. Geldhof A, Slater J, Clark M, Chandran U, Coppola D. Exposure to In iximab During Pregnancy : Post-Marketing Experience. 2019;(0123456789).

24. Luu M, Benzenine E, Doret M, et al. Continuous Anti-TNFα Use Throughout Pregnancy: Possible Complications For the Mother But Not for the Fetus. A Retrospective Cohort on the French National Health Insurance Database (EVASION). *Am J Gastroenterol* . 2018;113(11):1669-1677. doi:10.1038/s41395-018-0176-7

25. De Lima A, Zelinkova Z, Van Der Ent C, Steegers EAP, Van Der Woude CJ. Tailored anti-TNF therapy during pregnancy in patients with IBD: Maternal and fetal safety. *Gut* . 2016;65(8):1261-1268. doi:10.1136/gutjnl-2015-309321

26. Kanis SL, Modderman S, Escher JC, et al. Health outcomes of 1000 children born to mothers with inflammatory bowel disease in their first 5 years of life. *Gut* . 2021;70(7):1266-1274. doi:10.1136/gutjnl-2019-319129

27. U. M, D.C. B, M.C. D, et al. Pregnancy outcomes in the tofacitinib ulcerative colitis octave studies. *Am J Gastroenterol* . 2017;112:S410-S411. doi:10.1038/ajg.2017.303

28. Moens A, van der Woude CJ, Julsgaard M, et al. Pregnancy outcomes in inflammatory bowel disease patients treated with vedolizumab, anti-TNF or conventional therapy: results of the European CONCEIVE study.*Aliment Pharmacol Ther* . 2020;51(1):129-138. doi:10.1111/apt.15539

29. Tsao NW, Sayre EC, Hanley G, et al. Risk of preterm delivery and small-for-gestational-age births in women with autoimmune disease using biologics before or during pregnancy: A population-based cohort study.*Ann Rheum Dis* . 2018;77(6):869-874. doi:10.1136/annrheumdis-2018-213023

30. Chambers CD, Johnson DL, Xu R, et al. Birth outcomes in women who have taken adalimumab in pregnancy: A prospective cohort study.*PLoS One* . 2019;14(10):1-17. doi:10.1371/journal.pone.0223603

31. Kawai Y, Tsuchiya T, Aoki S. Pregnancy Outcomes of Patients Exposed to Adalimumab in Japan. *Dig Dis* . 2019;37(2):123-130. doi:10.1159/000493462

32. Lichtenstein GR, Feagan BG, Mahadevan U, et al. Pregnancy Outcomes Reported During the 13-Year TREAT Registry: A Descriptive Report.*Am J Gastroenterol* . 2018;113(11):1678-1688. doi:10.1038/s41395-018-0202-9

33. Julsgaard M, Hvas CL, Gearry RB, et al. Anti-TNF Therapy in Pregnant Women with Inflammatory Bowel Disease: Effects of Therapeutic Strategies on Disease Behavior and Birth Outcomes. *Inflamm Bowel Dis* . 2020;26(1):93-102. doi:10.1093/ibd/izz110

Tables and Figures:

Table 1: Fetal outcomes with the use of biologics in pregnancy.

Fetal outcomes	Number of studies	Number of patients	Proportion of event	95% CI
Congenital malformations				
Treated group	28	7811	4%	0.03-0.04
Disease matched	10	29171	4%	0.03-0.05
Disease free	5	1251780	4%	0.03-0.05
Preterm Delivery				
Treated group	26	7728	12%	0.10-0.14
Disease matched	11	18574	10%	0.09-0.12
Disease free	6	1626254	6%	0.04-0.07
General population WHO	-	-	9%	0.09-0.09
Neonatal Infection				
Treated group	9	3554	5%	0.03-0.07
Disease matched	6	4015	5%	0.02-0.07
Disease free	2	14799	2%	0.02-0.02
Low Birth weight				
Treated group	17	5112	10%	0.07-0.12
Disease matched	5	3046	8%	0.07-0.09
Disease free	4	3316	4%	0.01-0.08
Small for Gestational Age				
Treated group	8	3342	6%	0.02-0.10
Disease matched	4	10720	7%	0.02-0.11
Disease free	4	1624533	10%	0.10-0.10

Table 2: Maternal pregnancy outcomes with the use of biologics in pregnancy.

Maternal outcomes	Number of studies	Number of patients	Proportion of event	95% CI
Maternal severe infection				
Treated group	2	916	4%	0.03-0.05
Disease matched	1	453	1%	0.00-0.02
Disease free	0	-	-	-
Miscarriage				
Treated group	16	3348	12%	0.09-0.15
Disease matched	4	3424	6%	0.01-0.11
Disease free	4	3641	11%	0.03-0.19
Pre eclampsia				
Treated group	5	1175	1%	0.01-0.02
Disease matched	2	1017	1%	0.00-0.01
Disease free	0	-	-	-

Figure 1: Metaprop proportions for congenital malformations.

Figure 2: Metaprop proportions of preterm delivery with anti TNF α use only.

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`Figure 1 Metaprop proportions for congenital malformations..docx` available at https://authorea.com/users/430154/articles/533691-fetal-and-maternal-outcomes-after-maternal-biologic-use-during-conception-and-pregnancy-a-systematic-review-and-meta-analysis

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`Figure 2 Metaprop proportions of preterm delivery with anti TNF \selectlanguage{greek} \selectlanguage{` available at https://authorea.com/users/430154/articles/533691-fetal-and-maternal-outcomes-after-maternal-biologic-use-during-conception-and-pregnancy-a-systematic-review-and-meta-analysis