

SYSTEMATIC REVIEW

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

Laura J. O'Byrne^{1,2}  | Safi G. Alqatari³ | Gillian M. Maher^{1,4} | Aoife M. O'Sullivan³ |
Ali S. Khashan^{1,4} | Grainne P. Murphy³ | Fergus P. McCarthy^{1,2}

¹INFANT Research Centre, University College Cork, Cork, Ireland

²Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, Cork, Ireland

³Department of Rheumatology, Cork University Hospital, Cork, Ireland

⁴School of Public Health, Western Gateway Building, University College Cork, Cork, Ireland

Correspondence

Laura O'Byrne, Department of Obstetrics and Gynaecology, 5th Floor, Cork University Maternity Hospital, Wilton, Cork, Ireland.
Email: lobyrne@ucc.ie

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Abstract

Background: Biologic medications, specifically tumour necrosis factor- α (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 that contained original data.

Data collection and analysis: Two authors independently conducted data extraction. 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. The GRADE approach was used to assess the overall certainty of evidence.

Main results: Thirty-five studies, describing 11 172 pregnancies, were eligible for inclusion. Analysis showed pooled proportions for congenital malformations as follows: treated 0.04 (95% CI 0.03–0.04; $I^2 = 77$) versus disease-matched 0.04 (95% CI 0.03–0.05; $I^2 = 86$; $p = 0.238$); preterm delivery treated 0.04 (95% CI 0.10–0.14; $I^2 = 88$) versus disease-matched 0.10 (95% CI 0.09–0.12; $I^2 = 87$; $p = 0.250$); severe neonatal infection: treated 0.05 (95% CI 0.03–0.07; $I^2 = 88$) versus disease-matched 0.05 (95% CI 0.02–0.07; $I^2 = 94$; $p = 0.970$); low birthweight: treated 0.10 (95% CI 0.07–0.12; $I^2 = 93$) versus disease-matched 0.08 (95% CI 0.07–0.09; $I^2 = 0$; $p = 0.241$); pooled miscarriage: treated 0.13 (95% CI 0.10–0.15; $I^2 = 77$) versus disease-matched 0.08 (95% CI 0.04–0.11; $I^2 = 5$; $p = 0.078$); pre-eclampsia: treated 0.01 (95% CI 0.01–0.02; $I^2 = 0$) versus disease-matched 0.01 (95% CI 0.00–0.01; $I^2 = 0$; $p = 0.193$). No statistical differences in proportions were observed. GRADE certainty of findings was low to very low.

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Grainne P. Murphy and Fergus P. McCarthy contributed equally.

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Conclusion: We demonstrated comparable pregnancy outcomes in pregnancies exposed to biologics, disease-matched controls and CID-free pregnancies using the GRADE approach.

KEY WORDS

medical disorders in pregnancy, systematic reviews

Tweetable abstract:

Meta-analysis of 11 172 pregnancies exposed to biologic medications shows no evidence of harm for the fetus or the mother.

1 | INTRODUCTION

Chronic inflammatory diseases (CIDs) are a group of autoimmune diseases that affect between 5 and 7% of the population and include rheumatoid arthritis, 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 and interleukin-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 of these patients and biologics are increasingly used to manage chronic autoimmune diseases during pregnancy.

Activity of CID 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 birthweight, congenital anomalies and caesarean section compared with a general population.⁸ Likewise, there is a strong correlation with activity in rheumatoid arthritis and adverse outcomes such as miscarriage, low birthweight, 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 arise from case series, population data review and cohort studies. As biologics are capable of passing through the placental interface, concerns regarding safety are at the forefront of patients' and clinicians' minds.¹¹ The most recent meta-analysis by Tsao et al¹² focused solely on studies that had a disease-matched control group, thus limiting their review to 24 studies including ten published as abstracts only. The other most recent meta-analyses by Komaki and Nielsen and their colleagues compare outcomes in the treatment group with the general population only, with no disease-matched cohort included.^{13,14}

The aim of this systematic review and meta-analysis was to evaluate and pool the available evidence with regards to maternal and neonatal adverse pregnancy outcomes across three groups, pregnant women exposed to biologics for the management of underlying CID, a disease-matched cohort and a disease-free comparator group.

2 | METHODS

This review was performed according to an a-priori-designed protocol recommended for systematic reviews and meta-analyses.¹⁵ Maternal and fetal systematic review protocols were prospectively registered on PROSPERO CRD4201707072 and CRD42020185926.

2.1 | 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 use of biologics for CID in pregnancy and the risk of maternal and neonatal outcomes. We also conducted a post hoc search of Web of Science. Searches were conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-analysis).¹⁶ PubMed and EMBASE searches were conducted through January 1998–April 2020 by two reviewers (LOB, SA) and updated July 2021. Full search terms can be found in Appendix S1. 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.

2.2 | Study inclusion and exclusion criteria

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 (<37 weeks), severe neonatal infection requiring hospitalisation, low birthweight (<2.5 kg) and small for gestational age (<10th centile). Maternal outcomes included severe maternal infection requiring hospitalisation, miscarriage and pre-eclampsia.

English language randomised controlled trials, 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 3 months before pregnancy (as early cessation of these medications is common).

Ineligible studies were those that did not specify maternal underlying medical condition or a condition that was not a CID, 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.

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.

2.3 | Data extraction

Three reviewers (LOB, SA, AOS) independently extracted data using a standardised collection form for all eligible studies, including study characteristics (study design, country of data collection, data source, type of biologic studies, exposure pre-pregnancy, throughout pregnancy, gestation of cessation, inclusion and exclusion criteria, what confounders were adjusted for) and reported outcomes (congenital malformations, preterm delivery, neonatal infection, low birthweight, small for gestational age, maternal infection, miscarriage and pre-eclampsia) for analysis. In studies in which adequate data were 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.¹⁷ which examined six types of bias; selection, exposure, outcome, confounding, analytical and attrition. Studies were then rated as minimal, low, moderate or high levels of bias. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to rate the certainty of findings. In the GRADE approach, observational studies start as low-quality evidence. Five factors (risk of bias, imprecision, inconsistency, indirectness and publication bias) may lead to rating down the quality of evidence and three factors (large effect, dose response and if residual confounding

is likely to decrease rather than increase the magnitude of effect) may lead to rating up.¹⁸

2.4 | Statistical analysis

Where data permitted, STATA 14 (StataCorp, College Station, TX, USA) 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 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% CI¹⁹ 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. A sensitivity analysis by disease diagnosis, drug type, risk of bias and study design was performed where heterogeneity was high.

3 | RESULTS

The search for fetal outcomes produced 1887 titles; after exclusion of duplicates and ineligible studies, 35^{4,9,11,20-51} 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 35 studies with 11 172 pregnancies exposed to biologics, 17 studies with 39 290 disease-matched controls and nine studies with 2 892 933 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.

Risk of bias assessment was undertaken using an appropriate tool,¹⁷ all studies included had a low to moderate grading (Table S3). Sensitivity analysis was performed across all outcomes in the meta-analysis with available numbers by disease diagnosis of participants, drug type, risk of bias and study type. Overall, the heterogeneity is likely to be due to a combination of factors including disease diagnosis grouping, study type and drug type. The

sensitivity analysis did not change the prevalence estimates among the subgroups. All results are included in Tables S4–S9. GRADE certainty of findings was low to very low (Table S10).

3.1 | Congenital malformations

There were 28 eligible studies in the congenital malformation meta-analysis. There were 1 288 762 infants in this cohort (7811 born to women using biologics in pregnancy, 29 171 infants born to women with CID who were not treated with biologics in pregnancy and 1 251 780 infants born to women who were CID free) (Table 1). The proportion of congenital malformations in the treated group was 0.04 (95% CI 0.03–0.04), in the disease-matched group was 0.04 (95% CI 0.03–0.05) and in the disease-free group was 0.04 (95% CI 0.03–0.05). 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. Pregnancies in women with IBD treated with biologics had a proportion of congenital malformations of 0.04 (95% CI 0.02–0.05) compared with CID overall having 0.04 (95% CI 0.02–0.06) and rheumatoid arthritis alone 0.04 (95% CI 0.02–0.05) (Figure S5).

3.2 | Preterm delivery

There were 26 studies included in the preterm birth (PTB) meta-analysis. This included 7728 pregnancies exposed to biologics and 18 574 disease-matched controls (Table 1). The proportion of PTB was 0.12 (95% CI 0.10–0.14) in the treated group, 0.10 (95% CI 0.09–0.12) in the disease-matched group and 0.06 (95% CI 0.04–0.07) in the disease-free group (Figure S4). There was no statistical difference in the treated group versus the disease-matched group ($p = 0.250$), but 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 0.11 (95% CI 0.09–0.13) (Figure 2). Subgroup analysis by disease classification showed anti-TNF- α -treated IBD had a PTB rate of 0.09 (95% CI 0.07–0.11) with the disease-matched IBD group having a PTB rate of 0.09 (95% CI 0.08–0.10) (Figure S5). Only one study focused on anti-TNF- α use and rheumatoid arthritis²⁰ with a treated PTB rate of 0.18 (95% CI 0.14–0.24) and disease-matched PTB rate of 0.14 (95% CI 0.12–0.15). The remaining studies focused on mixed CID with a preterm birth rate of 0.12 (95% CI 0.09–0.15).

3.3 | Neonatal infection

The pooled data on severe neonatal infection included nine studies with 22 368 neonates. This was divided into 7569

TABLE 1 Fetal outcomes with the use of biologics in pregnancy

Fetal outcomes	Number of studies	Number of patients	Proportion of event	95% CI	$I^2\%$
Congenital malformations					
Treated group	28	7811	0.04	0.03–0.04	77.3
Disease-matched	10	29 171	0.04	0.03–0.05	86.8
Disease-free	5	1 251 780	0.04	0.03–0.05	46.3
Preterm delivery					
Treated group	26	7728	0.12	0.10–0.14	88.4
Disease-matched	11	18 574	0.10	0.09–0.12	87.3
Disease-free	6	1 626 254	0.06	0.04–0.07	85.9
General population WHO	–	–	9%	0.09–0.09	–
Neonatal infection					
Treated group	9	3554	0.05	0.03–0.07	88.3
Disease-matched	6	4015	0.05	0.02–0.07	94.0
Disease-free	2	14 799	0.02	0.02–0.02	0.0
Low birthweight					
Treated group	17	5112	0.10	0.07–0.12	92.5
Disease-matched	5	3046	0.08	0.07–0.09	0.0
Disease-free	4	3316	0.04	0.01–0.08	95.4
Small for gestational age					
Treated group	8	3342	0.06	0.02–0.10	96.1
Disease-matched	4	10 720	0.07	0.02–0.11	97.3
Disease-free	4	1 624 533	0.10	0.10–0.10	0.00

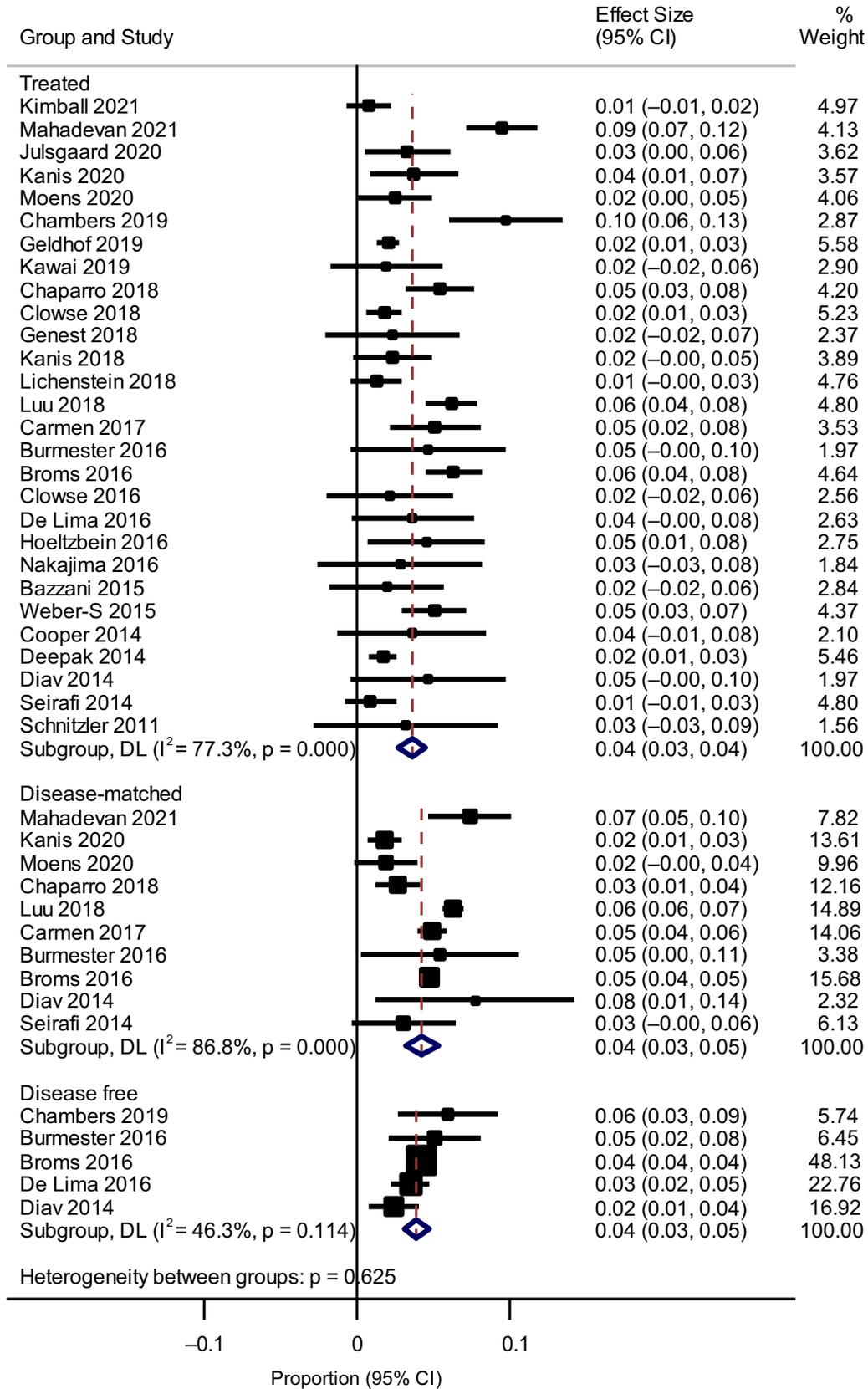


FIGURE 1 Metaprop proportions for congenital malformations

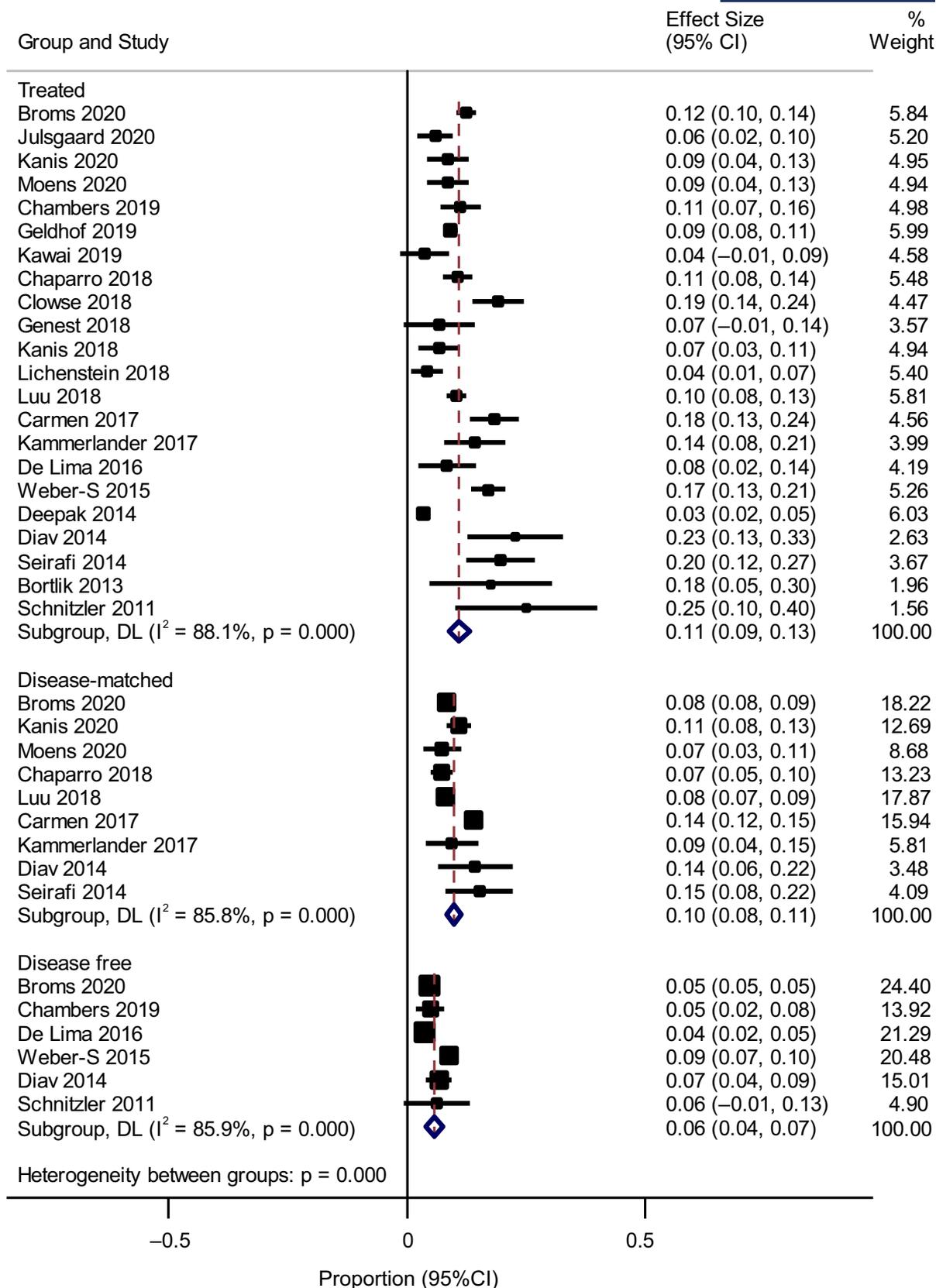


FIGURE 2 Metaprop proportions of preterm delivery with anti-tumour necrosis factor- α (TNF- α) use only

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 0.05 (95% CI 0.03–0.07), the proportion in the disease-matched group was 0.05 (95% CI 0.02–0.07) and in the disease-free group was 0.02 (95% CI 0.02–0.02) (Figure S6). No differences were observed in proportions between disease-matched and disease-treated women ($p = 0.970$), nor in disease-free compared with disease-treated women ($p = 0.225$; Table S1). Subgroup analysis by disease diagnosis revealed no statistical difference between groups (results not shown).

3.4 | Birthweight

In the low-birthweight group there were 17 studies included with a total of 11 474 infants, 5112 exposed to maternal biologic use, 3046 disease-matched and 3316 CID-free pregnancies (Table 1).

The overall proportion of low birthweight in the treated group was 0.10 (95% CI 0.07–0.12), in the disease-matched group was 0.08 (95% CI 0.07–0.09) and in the disease-free group was 0.04 (95% CI 0.01–0.08) (Figure S7). No statistical differences were observed between disease-matched and disease-treated women ($p = 0.241$), nor in disease-free women ($p = 0.079$; Table S1). Sub-group analysis on anti-TNF- α use alone revealed no difference between group outcomes (results not shown).

The small-for gestational-age group included seven studies with 1 638 595 infants, 3342 born to women medicated with biologics during pregnancy and 10 720 disease-matched controls (Table 1). All of the small-for gestational-age studies focused on anti-TNF- α biologics only. The proportion of small-for gestational-age infants in the treated group was 0.06 (95% CI 0.02–0.10), in the disease-matched control group was 0.07 (95% CI 0.02–0.11) and in the disease-free population was 0.10 (95% CI 0.10–0.10; 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 women ($p = 0.170$; Table S1).

3.5 | 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.^{21,22} There were 916 women who were treated with biologics during their pregnancy (Table 2) and 453 disease-matched control women. The studies included in this analysis were Chaparro et al.,²¹ who focused on anti-TNF- α use in IBD and pregnancy, and Clowse et al.,²² who investigated certolizumab pegol use in CID in pregnancy.

Only two studies were included in this analysis with a statistical difference in proportions between disease-matched compared with disease-treated women ($p < 0.001$; Table S2). Overall, the pooled analysis showed that the treated group had a proportion of serious infection of 0.04 (95% CI 0.03–0.05), whereas the disease-matched group had a proportion of serious infections of 0.01 (95% CI 0.00–0.02; Figure S9).

3.6 | 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 0.13 (95% CI 0.10–0.15), the proportion of miscarriage in the disease-matched group was 0.08 (95% CI 0.04–0.11) and in the disease-free group was 0.11 (95% CI 0.03–0.19) (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

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	I^2
Maternal severe infection					
Treated group	2	916	0.04	0.03–0.05	0.0
Disease-matched	1	453	0.01	0.00–0.02	0.0
Disease-free	0	–	–	–	–
Miscarriage					
Treated group	16	3348	0.13	0.10–0.15	76.9
Disease-matched	4	3424	0.08	0.04–0.11	74.5
Disease-free	4	3641	0.11	0.03–0.19	98.2
Pre-eclampsia					
Treated group	5	1175	0.01	0.01–0.02	0.0
Disease-matched	2	1017	0.01	0.00–0.01	0.0
Disease-free	0	–	–	–	–

disease-treated women ($p = 0.631$; Table S2). One study was excluded from the analysis; it had no difference in miscarriage rate across the treated and untreated groups of 3%, but the rate was much lower than all other included studies.¹¹ Subgroup analysis revealed no difference in groups when focusing on anti-TNF- α studies only (results not shown).

3.7 | Pre-eclampsia

There were five eligible studies for inclusion in the meta-analysis for pre-eclampsia. They 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 0.01 (95% CI 0.01–0.02) and of disease-matched controls was 0.01 (95% CI 0.00–0.01; Figure S11). No differences were observed in proportions between disease-matched women and disease-treated women ($p = 0.193$; Table S2).

4 | DISCUSSION

4.1 | Main findings

We have expanded on the previous reviews by increasing the pool of data to include peer-reviewed cohort studies and case series^{12–14} with statistical analysis of proportions rather than odds ratio. Another novel approach that we have taken was allowing comparisons across three populations: treated, disease-matched and disease-free. We also performed sub-analysis by biologic type and disease type where appropriate.

We detected no difference in the rates of congenital malformations, neonatal infection, low birthweight, 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 groups, possibly pointing towards the disease process being a factor. Too few studies examined serious maternal infection as an outcome to be concluded upon. These treatments are possibly safe, but their use in each woman must be individualised and include a thorough evaluation of the benefit–risk profile.

4.2 | Strengths and limitations

Studies examining the use of biologics in pregnancy have been limited by observational studies with small sample size. 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 and maternal infection risk, as well as exploring likely protective effects

of these medications against uncontrolled disease activity. There are several limitations to this study; first, our search included English-only literature, The full search strategy only included two databases; therefore, we conducted a post-hoc search of Web of Science. However, no new studies were identified in the process. Second, disparities in the measurement criteria, e.g. birthweight, 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. Studies included in this systematic review also contain some limitations. For example, although the majority of studies were classified as minimal or low risk of bias, GRADE certainty of findings was low to very low. Third, the recording of concomitant medications, particularly corticosteroids, dosing and pregnancy outcomes, which can differ between studies, is imprecise at best. Fourth, 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. Finally, the available studies for inclusion in this systematic review were observational in nature (i.e. cohort studies and case series studies only) as there are no randomised controlled trials examining the potential impact of biologics in pregnancy on fetal and maternal outcomes. Using proportions rather than measures of association such as odds ratios increased the total number of women substantially but may have introduced a higher risk of bias and residual confounding. Therefore, the results should be interpreted with caution. Furthermore, although our disease-matched control group was drawn from a highly selected population of women with the same disease diagnosis as the treated group, confounding by indication is of concern.

4.3 | Interpretation

We found no evidence to suggest that biologics, with the strongest evidence for the TNF- α 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.¹² (OR 1.18, 95% CI 0.88–1.5), Komaki et al.¹³ and Nielsen et al.¹⁴. This is the largest preterm birth meta-analysis to date, with 26 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.

Comparing our findings with those of previous meta-analyses, Tsao et al.¹² found the risk of PTB in treated versus disease-matched women to be (adjusted hazard ratio 1.09, 95% CI 0.70–1.69), Komaki et al.¹³ reported a 2.62-fold higher rate of PTB in the treated group in comparison to the general

population and Nielsen et al.¹⁴ found the overall pooled prevalence of PTB to be 9% (95% CI 7–11%; $I^2 = 89$) with biologics use in pregnancy, comparable with a rate of preterm birth of 10% in a cohort of 1960 women with IBD including active disease and 11% in the background population.

The disease-free group rates of 6% compare with WHO PTB rates for Europe and North America of 9% and 11%, respectively.⁵² The lower rate of PTB in our disease-free population likely reflects the inclusion of a large study by Bröms et al.⁴ which encompasses population registry data from Denmark, Finland and Sweden.

One of the primary factors that may impact PTB rates is disease activity. Geldhof et al. 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 before 24 weeks of gestation 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. The only previous meta-analysis to review neonatal infection was Tsao et al.¹², there were four studies included ($n = 1669$) and no association between biologic exposure in utero and the risk of serious infections requiring hospitalisation in infants' first year of life (adjusted odds ratio 1.09, 95% CI 0.82–1.47).

This was similar to the findings of two large studies that were eligible but could not be included in the meta-analysis, Tsao et al. (2019)³ (because of a data-sharing agreement) and Luu et al.²⁴ Tsao et al. in 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-acquired or hospital-acquired infections in the biologic-treated group compared with a disease-matched population.²⁴ 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.^{11,21,25,26,31} The only variable associated with an increased incidence of neonatal infection in multiple studies was PTB.^{11,21,24}

Our meta-analysis found no statistical difference in birthweight with biologic use. Literature around this topic has been controversial with previous individual studies highlighting the greater prevalence of growth-restricted/low-birthweight babies in women with chronic inflammatory conditions.^{4,20}

Previous meta-analysis by Nielsen et al.¹⁴ found the overall pooled prevalence of low birthweight to be 8% (95% CI 5–10%) with biologics. Komaki et al.¹³ found 5.95-fold higher rate of low birthweight compared with the general population but no difference with users and non-users 1.33 ($p = 0.31$, 95% CI 0.77–2.30). Tsao et al.¹² found the odds ratio for low birthweight was 1.68 (95% CI 1.21–2.31) in pregnancies exposed to a biologic compared with unexposed pregnancies.

Of the eligible studies included in this meta-analysis, Moens et al. had the largest treated group and found no difference between their treated and untreated groups.²⁷ Tsao et al. found an odds ratio for the association between biologic exposure and SGA was 0.91 (95% CI 0.46–1.78).²⁸ The PIANO trial found no difference in LBW in those exposed to biologics after controlling for PTB and disease activity.¹¹

Our analysis included only two studies examining severe maternal infection. Data from the recent large Canadian 10-year retrospective cohort study by Tsao et al. 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 This topic was either not reported on in previous meta-analyses or could not be analysed.^{12–14}

There was no greater likelihood of miscarriage for biologic-treated patients compared with the comparator populations. This mirrors previous data reported,^{22,29–31} 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. These data reflect information obtained from a small number of studies. Notably, no pre-eclampsia cases were reported with certolizumab pegol use in Clowse et al.²² Chaparro et al. found pre-eclampsia equally distributed across both the biologics-exposed group and the disease-matched cohort.²¹ Julsgaard et al. specifically found no difference in the pre-eclampsia rates between women who ceased their medication before 30 weeks of gestation or continued.³²

5 | CONCLUSION

The available data in the published literature show no increased risk with biologic use during pregnancy over disease-matched cohorts with respect to congenital malformations, preterm delivery, neonatal infection, small for gestational age, low birthweight, miscarriage and pre-eclampsia. There is a suggestion of an increased risk of maternal infections in the treated group but this is probably due to the lack of studies examining this outcome. It should be noted that the GRADE certainty of findings was low to very low.

With over 11 172 pregnancies exposed to biologic medications, our study shows no evidence of harm for the fetus or 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.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

ORCID

Laura J. O'Byrne  <https://orcid.org/0000-0002-1916-2347>

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