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PREGNANCY OUTCOMES AFTER EXPOSURE TO TNF-α INHIBITORS FOR THE TREATMENT OF ARTHRITIC DISEASES: A META-ANALYSIS OF OBSERVATIONAL STUDIES

TNF-α Inhibitors and Pregnancy Outcomes in Arthritic Diseases

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ABSTRACT

Background

Autoimmune arthritic diseases affect many women of child-bearing age. Tumour necrosis factor (TNF)-α inhibitors are currently used for the treatment of various immune-mediated diseases during pregnancy. However, there has been no evaluation of safety in the treatment of arthritic diseases during gestation.

Objective

To analyze the risk of adverse pregnancy and neonatal outcomes after treatment of arthritic diseases with TNF-α inhibitors.

Methods

Major databases including Ovid MEDLINE, Embase, and Web of Science, were searched inclusive to April 2016. Observational prospective cohort studies evaluating pregnancy outcomes (birth defects, Spontaneous abortion, therapeutic abortion, birth weight, preterm birth, live birth) after exposure to TNF-α inhibitors for the treatment of arthritic diseases during pregnancy were included. Data on pregnancy and neonatal outcomes was extracted from all included studies. A meta-analysis was performed using inverse-variance random effect with a 95% confidence interval (95%CI) and $p<0.05$.

Results

Eight prospective studies with comparison groups were included in the meta-analysis. TNF-α inhibitors were associated with significantly higher risks of low birth weight (odds ratio (OR), 1.43; 95%CI, 1.00–2.04) and significantly lower rates of live birth (OR, 0.61; 95%CI, 0.38–0.98). However, birth defects, therapeutic abortion, spontaneous abortion, and preterm birth were not significantly different between the 2 groups.

Conclusion

Treatment of arthritic diseases with TNF-α inhibitors during pregnancy increases the risk of lower birth weight and decreases the rate of live birth in this population. While duration of treatment and gestational age at exposure may play a role in these outcomes, evaluation of risk versus benefit is crucial in this patient population.

Autoimmune arthritic diseases affect many women in their reproductive years. According to a Canadian Population Health Longitudinal Survey 1994–2006, women are at 10% higher risk of developing arthritis in Canada.[1] According to Statistics Canada approximately 300,000 women between the ages of 12 and 44 are affected by arthritic diseases.[2] Systemic release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) associated with arthritic diseases, can affect tissues and organs such as the liver, intestines, kidneys, and placenta.[3,4] Several studies have reported pregnancy complications and adverse outcomes with arthritic diseases including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis.[4-6] Reed et al. reported that women with rheumatoid arthritis are at increased risk for cesarean delivery, premature birth (PB), and longer hospitalization at birth.[7] Increased risk of pre-eclampsia, severe maternal morbidity, and neonatal complications requiring intensive care in women with juvenile idiopathic arthritis and rheumatoid arthritis has also been documented.[8,9] Therefore, proper disease management is crucial to address pregnancy and neonatal outcomes. Disease-modifying anti-rheumatic drugs (DMARDs) and biologics are commonly prescribed for autoimmune inflammatory conditions in the general adult patient population. Among biologics, TNF-α inhibitors are considered safer options during pregnancy for their low placental transfer.[10] TNF-α inhibitors are large-molecule monoclonal antibodies that bind to the TNF-α receptor, stabilize with the Fc fragment of human immunoglobulin G (IgG), and thus suppress inflammation.[8,11] While these drugs cross the placenta and are detectable in the serum of infants until a few months after birth,[8] current literature indicates a lower risk for adverse pregnancy outcomes compared with small-molecule DMARDs.[12] On the other hand, a causal relationship between the use of TNF-α inhibitors and VACTREL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) has been reported.[12,13] Increased risk of lower birth weight and spontaneous abortion have also been seen in infants born to mothers treated with TNF-α inhibitors during pregnancy.[5,14–17]

While many have investigated the safety of TNF-α inhibitors for the management of various auto-immune diseases during pregnancy,[18,19] no definitive safety profile has been drawn for this class of medications in women of child-bearing age with arthritis. To date, the interaction between TNF-α inhibitors and arthritic diseases in pregnancy, and their effect on neonatal outcomes is still unclear. Arthritic diseases negatively impact the quality of life of many pregnant women and can contribute to several maternal and neonatal complications. Therefore, the objective of this meta-analysis was to assess the combined effects of TNF-α inhibitors and arthritic diseases on neonatal outcomes.

MATERIALS AND METHODS

Study Design

A systematic review and meta-analysis was conducted and documented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[20] Pregnant women treated with TNF-α inhibitors were compared with pregnant women who were either treated with DMARDs or were not on any treatment. There is no published protocol for this work, and it is not registered in any database.

Search Strategy and Study Collection

Using a systematic search strategy using structured and key words (appendix 1), we searched 3 major electronic databases including: (1) Ovid MEDLINE(R) (1946 to 2016 Week 19) using daily update, in-process and non-indexed citations, (2) Embase Classic+Embase (1947 to 2016 Week 19), and 3) Web of Science. Reference lists of review articles and relevant articles were also searched. Where needed, principal investigators were contacted for additional study data. The complete search strategy is shown in Supplementary Appendix S1. Studies were eligible if: (1) they included participants with arthritic diseases that were treated with a TNF-α inhibitor during pregnancy, (2) the comparison group was comprised of pregnant women with arthritis who were either treated with DMARDs, or were not on treatment, (3) they were published in English, (4) they reported individual pregnancy outcomes in different groups. While prospective studies either in full text or abstract were included, retrospective, case control, case series, and case reports were excluded.

Studies that did not include a comparison group were also excluded.

Pregnancy and neonatal outcomes referred to birth defects (BD), spontaneous abortion (SA), therapeutic abortion (TA), PB, low birth weight (LBW), and live birth (LB). SA was characterized by loss of pregnancy prior to 20 weeks of gestation.

After retrieving potentially eligible articles from database searches, all titles and abstracts were screened by 2 reviewers independently (KM and TS) according to the pre-defined inclusion criteria. Full texts were screened where eligibility was not clear from the abstract. Eligible articles were then screened in full text by the 2 independent reviewers. Disagreement was presented to a third independent reviewer to resolve (MPM).

Data extraction

Raw data was extracted by the 2 independent reviewers (KM and TS) from all included studies using a data collection form. Data collection included study and patient characteristics, pregnancy, and neonatal outcomes (BD, SA, TA, LB, PB, and BW). Risk of bias at the study and outcome level was assessed by an independent reviewer (RV), who was not involved in the process of analysis and was blinded to study authors and funding sources.

Statistical Analysis

All individual patient data was entered into Co-chrane Review Manager 5.3 software. Meta-analysis was conducted using inverse-variance random effects. A 95% confidence interval and p<0.05 were considered significant. I^2 statistics was used to determine heterogeneity. A low value of I^2 indicates low heterogeneity, whereas a high value shows heterogeneity.[21] The Summary of Findings Table was created using Cochrane GRADEpro software.[22]

RESULTS

Characteristics of Studies Included

Our objective was to compare pregnancy and neonatal outcomes in 2 groups. One group was pregnant women who were treated with TNF-α inhibitors. The comparison group included women who were either on treatment with DMARDs (no TNF-α inhibitors), or no treatment. In the majority of studies (6/8), the comparison group included both women who were untreated (no treatment) or those receiving just disease-modifying agents (DMARD). This information is shown in Table 1.

Of the 2324 records identified through the database search and other sources, 584 were duplicat[21]es. A total of 1549 records were excluded after first title and abstract screening, and 191 articles were determined to be eligible for full text screening. Of those, 183 studies were excluded for reasons including inadequate data report, study design, and cases where data of pregnant women with arthritis could not be extracted from other autoimmune diseases. Eight prospective studies were included in the meta-analysis. Flow chart of the study selection process was made based on PRISMA statement (Figure 1).[20] In the TNF-α inhibitors users group, there were 692 women with rheumatoid arthritis (RA), 82 with psoriasis (Ps), 45 with psoriatic arthritis (PsA), 52 with ankylosing spondylitis (AS), and 6 with juvenile idiopathic arthritis (JIA). There were 665 exposures to etanercept (ETN), 143 to adalimumab (ADA), 38 to infliximab (INF), 6 to certolizumab (CTZ), and 5 to golimumab (GOL). Confounding factors included concomitant drug use with DMARDs in the first group. There were no significant differences between characteristics of the included women in those studies which provided demographic information (data not shown). In the comparison group (non-TNF-α inhibitors users), there were 4953 pregnancies with RA, 6472 with Ps, 915 with PsA, 780 with AS, 6 with JIA, and one patient with Still's disease. DMARDs exposure is shown in Table 1, where applicable. In the majority of studies in the comparison group patients are either on DMARDs treatment or no treatment. In 2 studies, DMARDs use included category 'X' drugs such as methotrexate or leflunomide.[17,22–26] The majority of exposures to TNF-α inhibitors were limited to the first trimester. The age range of women was 25–40 years. The characteristics of the included studies and patient population are shown in Table 1. New-Castle Ottawa scale was used to assess the quality of the included studies.[26] Studies receiving a star grade of 6 or more were considered high quality.
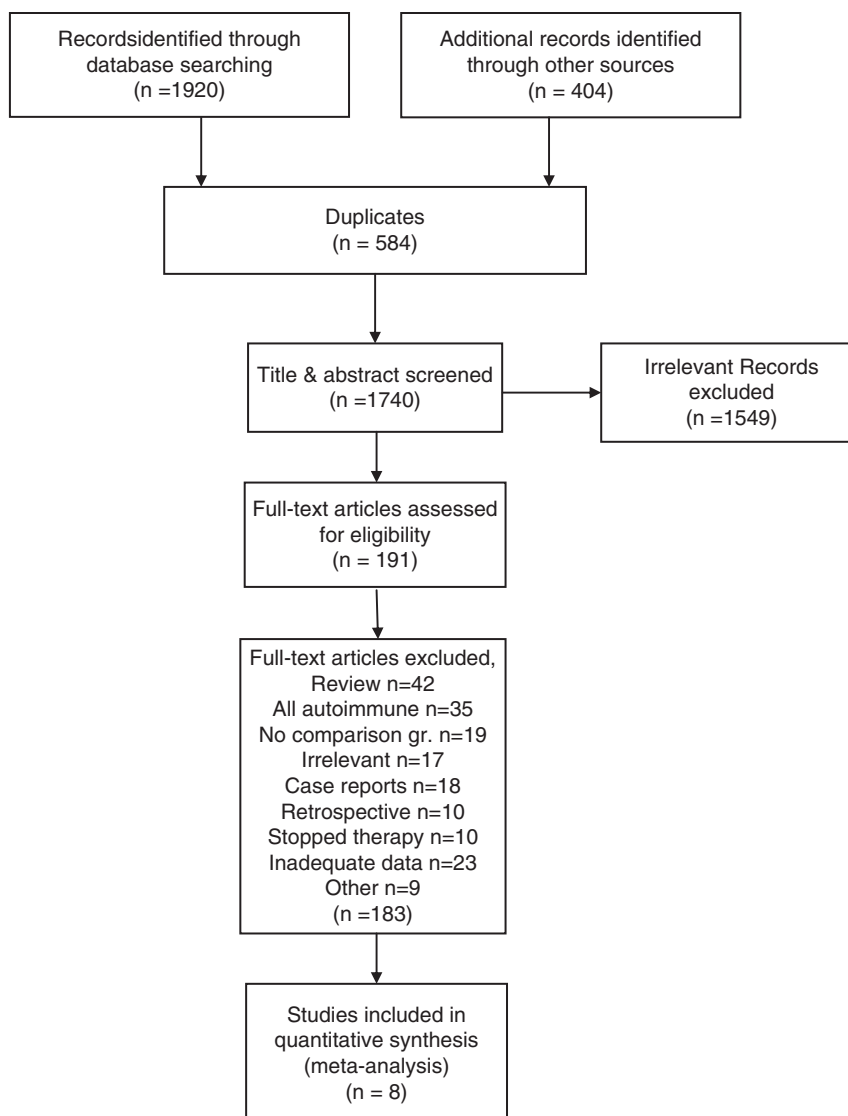
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│ database searching       │    │ identified through       │
│ (n =1920)                │    │ other sources            │
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   │ (n =1740)                │        │ excluded                 │
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   │ Full-text articles       │
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   │ Full-text articles       │
   │ excluded,                │
   │ Review n=42              │
   │ All autoimmune n=35      │
   │ No comparison gr. n=19   │
   │ Irrelevant n=17          │
   │ Case reports n=18        │
   │ Retrospective n=10       │
   │ Stopped therapy n=10     │
   │ Inadequate data n=23     │
   │ Other n=9                │
   │ (n =183)                 │
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   │ Studies included in      │
   │ quantitative synthesis   │
   │ (meta-analysis)          │
   │ (n = 8)                  │
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FIG. 1 Flow chart of the process of study assessment and selection, Format adapted from PRISMA Statement.

Neonatal Outcomes

A statistically significant increased risk of infant LBW was seen in patients treated with TNF-α inhibitors (OR, 1.43; 95%CI, 1.00–2.04) as compared to non-TNF-α inhibitor-exposed group (Figure 2). In addition, the rate of LB was significantly lower in the TNF-α inhibitors treated group, (OR, 0.61; 95%CI, 0.38–0.98). The rate of BD was slightly higher in the infants of patients treated with TNF-α inhibitors but did not reach statistical significance (OR, 1.23;

95%CI, 0.87–1.73). No heterogeneity and risk of bias were seen in any of the outcomes.

Pregnancy Outcomes

No significant differences were found in the number of TAs (OR, 0.95; 95%CI, 0.21–4.41) (Figure 3). While SA was slightly increased in the TNF-α inhibitors group, this did not reach significance (OR, 1.28; 95%CI, 0.61–2.70). Heterogeneity (I^2) was 46% and 30% for TA and SA respectively. PB was not significantly different between the groups (OR, 1.23;
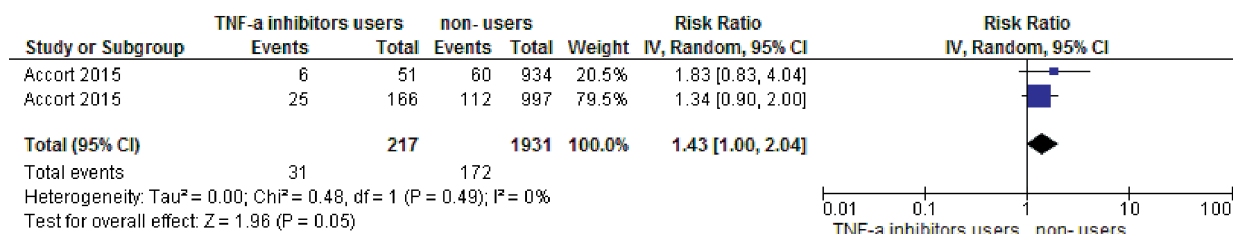
TABLE 1 Characteristics of Studies Evaluating Pregnancy Outcomes after Use of TNF-A Inhibitors for the Treatment of Rheumatic and Arthritic Diseases

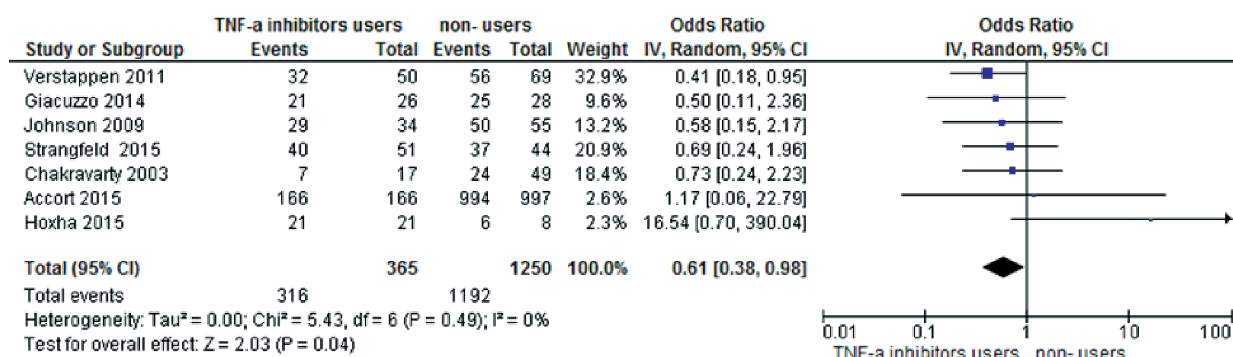| Author	Year	Study Design	Anti-TNF-α Exposed Diseases (N)	Anti-TNF-α Exposure (N)	Anti-TNF-a Exposed Concomitant Medications(N)	Comparison Group Diseases (N)	Comparison Group DMARDs (N)
Strangfeld et al[16]	2015	Prospective, RABBIT registry	RA (57)	ETN (29) ADA (11) TCZ (5) CTZ (4) RTX (3) ABA (3) INF (1) GOL (1)	PDN (15)	RA (4(9))	PDN (9)
Hoxha et. al.[37]	2016	Prospective	RA (16) AS (6) PsA (2)	ETN (17)) ADA (5) CTZ (2)	PDN (11) CYSP (1) SSZ (1) HCQ (8)	RA (8) AS (2) PsA (1)	PDN (8) SSZ (1) HCQ (3)
Giacuzzo et. al.[23]	2014	Prospective	RA (10) AS (5) PsA (3) uSpA (3)	ETN (13) ADA (6) INF (3) RTX (4)	SSZ (2) MTX (1)	RA (12) uSpA (9) JIA (2) PsA (2)	SSZ (7) HCQ (7) CYSP (1) PDN (15)
Verstappen et. al.[24]	2010	pregnancy registry (BSRBR)	RA (52) PsA (3) JIA (6) AS (2) Still's (1)	ETN (36) ADA (10) INF (4)	MTX (13) LEF (3) SSZ (1) AZA (1) IM-gold (1)	RA (56) PsA (1) JIA (4) AS (1) Still's (1) SLE (1)	SSZ (7) HCQ (1) AZA (2) IM-gold (1) Combo (28) Any DMARD (4)
Accort et. al.[5]	2015	population-based prospective	Inflm Arthritis (166) Ps (51)	ETN (217)	(0)	Inflam Arth (997) Ps (943)	(0)
Broms et. al.[17]	2016	Population-based health register	RA (340) PsA (37) AS (39) Ps (31)	ETN (338)** ADA (77) IFX (28) GOL (4)	MTX (20)*	RA (3727)** PSA (911) AS (777) Ps (5529)	MTX (53)*
Johnson et. al.[38]	2009	Prospective (OTIS)	RA (34)	ADA (34)	(0)	RA (55)	(0)
Chakravarty et al.[39]	2003	Physician Survey	RA (17)	ETN (15) INF (2)	N/A	RA (49)	MTX (39) LEF (10)

ABA = abatacept; AD = adalimumab; AS = ankylosing spondylitis; AZA = azathioprine; CTZ = certolizumab; CYSP = cyclosporine; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; INF = infliximab; JIA = juvenile idiopathic arthritis; LEF = leflunomide; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drugs; PDN = prednisone; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RTX = rituximab; SA = spondyloarthropathies; SLE = systemic lupus erythematosus; SS = sulfasalazine; TCZ = tocilizumab; USpA = undifferentiated spondyloarthropathy.

*exposure to MTX in arthritic and rheumatic diseases are not reported. Results are reported in combination with IBD **Obtained data through personal communication with authors.

2a: Low birth weight

Study or Subgroup	TNF-a inhibitors users Events	Total	non- users Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Accort 2015	6	51	60	934	20.5%	1.83 [0.83, 4.04]
Accort 2015	25	166	112	997	79.5%	1.34 [0.90, 2.00]
Total (95% CI)		**217**		**1931**	**100.0%**	**1.43 [1.00, 2.04]**
Total events	31		172			

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)

Risk Ratio IV, Random, 95% CI

2b: Live birth

Study or Subgroup	TNF-a inhibitors users Events	Total	non- users Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Verstappen 2011	32	50	56	69	32.9%	0.41 [0.18, 0.95]
Giacuzzo 2014	21	26	25	28	9.6%	0.50 [0.11, 2.36]
Johnson 2009	29	34	50	55	13.2%	0.58 [0.15, 2.17]
Strangfeld 2015	40	51	37	44	20.9%	0.69 [0.24, 1.96]
Chakravarty 2003	7	17	24	49	18.4%	0.73 [0.24, 2.23]
Accort 2015	166	166	994	997	2.6%	1.17 [0.06, 22.79]
Hoxha 2015	21	21	6	8	2.3%	16.54 [0.70, 390.04]
Total (95% CI)		**365**		**1250**	**100.0%**	**0.61 [0.38, 0.98]**
Total events	316		1192			

Heterogeneity: Tau² = 0.00; Chi² = 5.43, df = 6 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)

Odds Ratio IV, Random, 95% CI

2c : Birth defects

Study or Subgroup	TNF-a inhibitors users Events	Total	non- users Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Hoxha 2015	1	21	0	10	1.1%	1.54 [0.06, 41.08]
Chakravarty 2003	0	17	3	49	1.3%	0.38 [0.02, 7.73]
Accort 2015	0	24	12	943	1.4%	1.52 [0.09, 26.42]
Strangfeld 2015	1	40	3	37	2.2%	0.29 [0.03, 2.93]
Accort 2015	5	72	17	418	10.9%	1.76 [0.63, 4.93]
Broms 2016	31	447	624	10944	83.1%	1.23 [0.85, 1.79]
Total (95% CI)		**621**		**12401**	**100.0%**	**1.23 [0.87, 1.73]**
Total events	38		659			

Heterogeneity: Tau² = 0.00; Chi² = 2.59, df = 5 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)
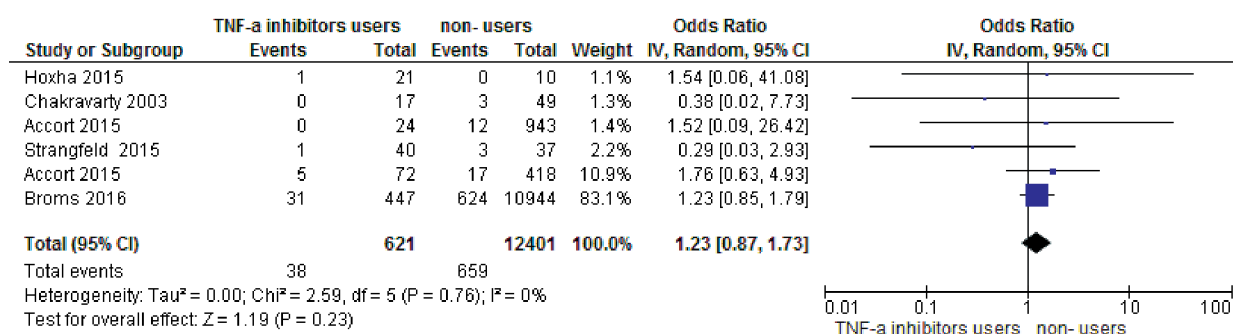
Odds Ratio IV, Random, 95% CI

FIG. 2A-C Forest plots of neonatal outcomes comparing TNF-a inhibitors users and non-users. A: outcome: BD. B: outcome: LBW.C: LB. Significant increased risk of infant LBW in patients treated with TNF-α inhibitors (OR, 1.43; 95%CI, 1.00–2.04) as compared to non-TNF-α inhibitor-exposed group. Significant lower rate of LBs in the TNF-α inhibitors treated group, (OR, 0.61; 95%CI, 0.38–0.98). The rate of BD was slightly higher in the infants of patients treated with TNF-α inhibitors but did not reach statistical significance (OR, 1.23; 95%CI, 0.87–1.73).

95%CI, 0.87–1.72). There was no heterogeneity in PB. Risk of bias was not significant in the outcomes. Complete findings from each study are summarized in Table 1.

DISCUSSION

The objective of this meta-analysis was to demonstrate how the interaction between TNF-α inhibitors

Table 2: Summary of findings table was built in GRADE PRO. Quality of evidence was assessed by independent reviewers.
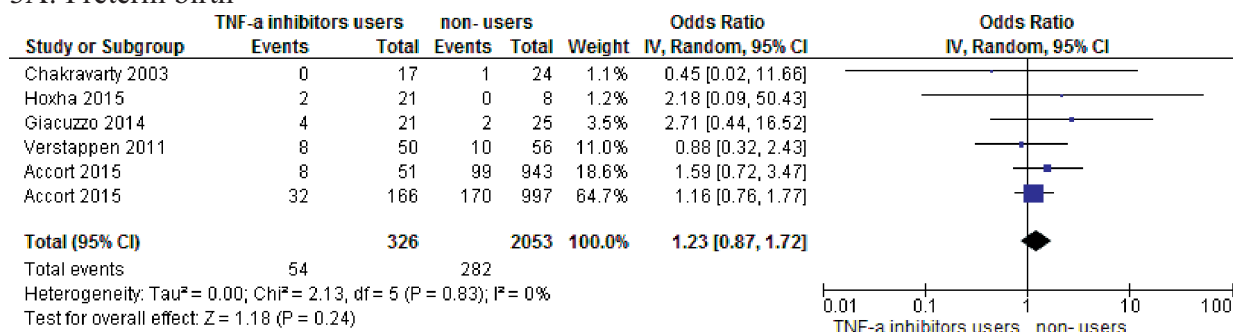
TNF-a inhibitors users compared to non-users for arthritic disease in pregnancy						
Patient or population: Arthritic diseases in Pregnancy **Intervention:** TNF-a inhibitors users **Comparison:** non-users						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Risk with non-users	**Risk with TNF-a inhibitors users**				
Birth Defects (BD)	5 per 100	6 per 100 (5 to 9)	OR 1.23 (0.87 to 1.73)	13022 (6 observational studies)	⊕⊕⊕⊕ HIGH	
Spontaneous Abortion (SA)	12 per 100	15 per 100 (8 to 27)	OR 1.28 (0.61 to 2.70)	452 (6 observational studies)	⊕⊕○○ LOW [a]	
Low Birth Weight (LBW)	9 per 100	13 per 100 (9 to 18)	RR 1.43 (1.00 to 2.04)	2148 (1 observational study)	⊕⊕⊕⊕ HIGH	
Preterm Birth (PB)	14 per 100	16 per 100 (12 to 21)	OR 1.23 (0.87 to 1.72)	2379 (6 observational studies)	⊕⊕⊕○ MODERATE	
Therapeutic Abortion (TA)	8 per 100	8 per 100 (2 to 27)	OR 0.95 (0.21 to 4.41)	334 (4 observational studies)	⊕⊕○○ LOW [b]	
Live Birth (LB)	95 per 100	93 per 100 (89 to 95)	OR 0.61 (0.38 to 0.98)	1615 (7 observational studies)	⊕⊕⊕○ MODERATE	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
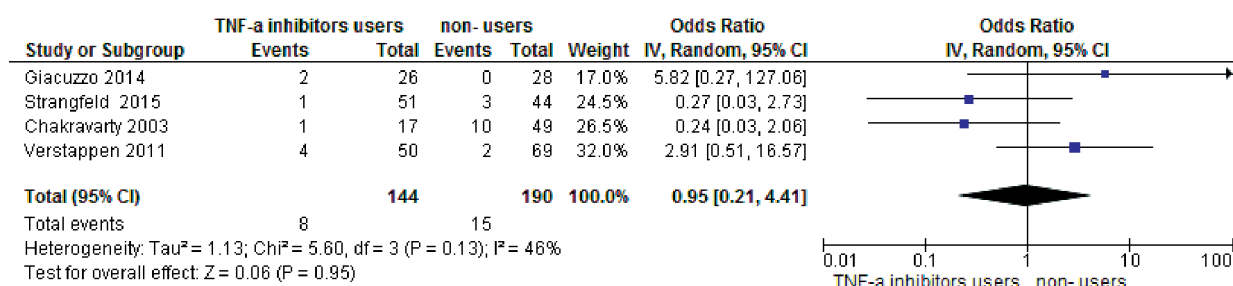
Explanations
a. I2=30%
b. I2=46%

3A: Preterm birth

Study or Subgroup	TNF-a inhibitors users Events	Total	non- users Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Chakravarty 2003	0	17	1	24	1.1%	0.45 [0.02, 11.66]
Hoxha 2015	2	21	0	8	1.2%	2.18 [0.09, 50.43]
Giacuzzo 2014	4	21	2	25	3.5%	2.71 [0.44, 16.52]
Verstappen 2011	8	50	10	56	11.0%	0.88 [0.32, 2.43]
Accort 2015	8	51	99	943	18.6%	1.59 [0.72, 3.47]
Accort 2015	32	166	170	997	64.7%	1.16 [0.76, 1.77]
Total (95% CI)		**326**		**2053**	**100.0%**	**1.23 [0.87, 1.72]**
Total events	54		282			

Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 5 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)

3B: Therapeutic abortion

Study or Subgroup	TNF-a inhibitors users Events	Total	non- users Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Giacuzzo 2014	2	26	0	28	17.0%	5.82 [0.27, 127.06]
Strangfeld 2015	1	51	3	44	24.5%	0.27 [0.03, 2.73]
Chakravarty 2003	1	17	10	49	26.5%	0.24 [0.03, 2.06]
Verstappen 2011	4	50	2	69	32.0%	2.91 [0.51, 16.57]
Total (95% CI)		**144**		**190**	**100.0%**	**0.95 [0.21, 4.41]**
Total events	8		15			

Heterogeneity: Tau² = 1.13; Chi² = 5.60, df = 3 (P = 0.13); I² = 46%
Test for overall effect: Z = 0.06 (P = 0.95)

3C: SPontaneous abortion

Study or Subgroup	TNF-a inhibitors users Events	Total	non- users Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Hoxha 2015	1	21	2	8	7.4%	0.15 [0.01, 1.96]
Chakravarty 2003	1	17	8	49	9.9%	0.32 [0.04, 2.77]
Giacuzzo 2014	2	26	3	28	12.4%	0.69 [0.11, 4.53]
Johnson 2009	5	34	3	55	17.3%	2.99 [0.67, 13.42]
Strangfeld 2015	10	51	4	44	22.2%	2.44 [0.71, 8.42]
Verstappen 2011	12	50	11	69	30.8%	1.67 [0.67, 4.16]
Total (95% CI)		**199**		**253**	**100.0%**	**1.28 [0.61, 2.70]**
Total events	31		31			

Heterogeneity: Tau² = 0.25; Chi² = 7.12, df = 5 (P = 0.21); I² = 30%
Test for overall effect: Z = 0.65 (P = 0.52)

FIG. 3A–C Forest plots of pregnancy outcomes comparing TNF-a inhibitors users and non-users; A: Preterm Birth, B: TA, C: Spontaneous Abortion. Preterm birth was not significantly different between the groups (OR, 1.23; 95%CI, 0.87–1.72). No significant differences in the number of TAs between the 2 groups (OR, 0.95; 95%CI, 0.21–4.41). Slightly increased rate of SA but not significant in the TNF-α inhibitors group (OR, 1.28; 95%CI, 0.61–2.70).

and arthritic diseases affects pregnancy and neonatal outcomes. While the effect of these drugs on pregnancy outcomes has been previously reported in patients with other autoimmune conditions,[27–29] this was the first study to specifically examine these outcomes in pregnant women with arthritis. TNF-α inhibitors are commonly used in treating various autoimmune diseases during pregnancy owing to their low risk

profile as compared to DMARDs. Our findings show a higher incidence of LBW and lower rate of LB in infants of women with arthritis treated with TNF-α inhibitors. The significantly increased risk for LBW (OR, 1.43) is consistent with the meta-analysis by Komaki et. al., which detected a significantly higher risk of LBW (OR, 5.95) in patients receiving TNF-α inhibitors for a variety of autoimmune diseases.[30] The Significantly reduced rate of LB with TNF-α inhibitors (OR, 0.61) we observed is also comparable to results reported by Komaki et. al. (OR, 0.69; 95%CI, 0.39–1.22). However, their findings did not reach significance. The observed discrepancy could be due to differences in patient and study inclusion. The analysis by Komaki et. al. included a variety of unrelated autoimmune diseases. Nevertheless, based on the similar OR values obtained in both studies, the extent of risk appears comparable.

The etiology responsible for the increased neonatal LBW and decreased LB in women on anti-TNF-α therapy is unknown. However, underlying pathophysiological-mediated changes in the maternal system may play a role. It is believed that high circulating levels of the pro-inflammatory cytokines in active disease can adversely affect placental function, nutrient availability and fetus neurodevelopment, potentially leading to decreased fetal growth and LBW.[31] Furthermore, using TNF-α inhibitor use during pregnancy increases the risk of infection post-natally.[32] It is possible that higher disease severity is associated with the need for anti-TNF-α therapy and this increased inflammatory state could impact neonatal outcomes.

While Komaki et. al. also found a significantly increased risk of PB (OR, 2.62) and SA (OR, 4.08), we did not detect any significant associations between TNF-α inhibitor exposure and these outcomes. Again, this divergence between the studies could stem from differences in disease states, disease activity, and concomitant drug use. The observed heterogeneity among the studies may also explain the divergence between our results. While, an increased risk of VACTREL with TNF-α inhibitors has been reported in the newborns of pregnant women with arthritis,[10] our study did not find such an association. Overall, we did not observe any increased risk of BD above the general pregnant population risk of 3–5% [33] in

TNF-α inhibitor exposed group. This finding is in line with the systematic review of Panchal et. al., where there was no indication of increased risks for major congenital malformations or SA.[34]

STRENGTHS AND LIMITATIONS

To our knowledge, this was the first meta-analysis investigating adverse pregnancy and neonatal outcomes in pregnant women with arthritis, treated with TNF-α inhibitors. Outcomes from drug therapy are often unique in different disease populations. Overall, the qualities of the evidences were in a range of high, moderate, and low, and the risk of bias in the included studies was low. As we were only able to retrieve a limited number of studies from the literature search, sensitivity analysis was not performed. Heterogeneity among the results of included studies might have also affected the final results but it was not significant. Among the included studies, most exposures to TNF-α inhibitors occurred in the first trimester, therefore we have limited data on the effects in the third trimester.[35,36] The effect of individual anti-TNF-α biologics could not be examined since outcomes were not reported separately for each drug and disease. Concomitant use of other immunosuppressive agents including category "X" drugs such as methotrexate and leflunomide could also have confounding effects on pregnancy outcomes and the final results of this study.

CONCLUSION

The findings of our meta-analysis have several implications for practice. As arthritic diseases are prevalent in the reproductive years of women, they place a burden on the maternal quality of life during gestation and neonatal complications. It is known that different diseases can influence pregnancy outcomes to a dissimilar extent and this may impact the risk-to-benefit ratios of therapeutic interventions. The results of our analysis indicate that treatment with TNF-α inhibitors could be a contributing factor in the increased rate of LBW and reduced rate of LB in pregnant women with arthritis. A higher rate of LBW and reduced rate of LB that we found in our study may be an indication that these drugs are able to exert adverse effects in the late stages of pregnancy. TNF-α inhibitors are known to cross the placenta in

the third trimester, thus it is frequently recommended to discontinue use in the third trimester. Our work did not identify significant increases in the rate of BD, SA, TA, and PB in TNF-α inhibitor treated patients. In light of these findings, TNF-α inhibitors may still be considered the preferred treatment option for arthritic diseases during gestation compared with conventional DMARDs. However, larger scale studies are recommended to further rule out the risk of adverse outcomes associated with both the underlying condition or treatment with TNF-α inhibitors.

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AUTHOR CONTRIBUTIONS

Participated in research design: KM, MPM.
Conducted literature search and study selection: KM, TS.
Performed data analysis: KM.
Independent reviewer: RV.
Wrote or contributed to the writing of the manuscript: KM, MPM, MP, TS.

CONFLICT OF INTEREST

None to disclose.

ETHICS APPROVAL

No ethics approval was required for this work.

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APPENDIX

Appendix 1 Complete search strategy used in Ovid MEDLINE, EmBase, and Web of Science for the identification of studies to assess risk of pregnancy outcomes with the use of TNF-α inhibitors in patients with arthritic diseases

Ovid Medline	May 12, 2016	220
Embase	May 12, 2016	1529
Web of Science	May 12, 2016	171

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 11, 2016>
Search Strategy:

1   Adalimumab/ (3332)
2   Certolizumab Pegol/ (341)
3   Etanercept/ (4637)
4   Infliximab/ (7806)
5   (adalimumab or avakine or certolizumab or cimzia or cimzias or embrel or enbrel or etanercept or golimumab or humira or inflectra or infliximab or remicade or remsima or revellex or simponi or trudexa).mp. (16684)
6   (anti-tnf* or anti-tumor necrosis factor* or anti-tumour necrosis factor*).mp. (11085)
7   ((tnf* or tumor necrosis factor* or tumour necrosis factor*) adj3 inhibitor*).mp. (5758)
8   1 or 2 or 3 or 4 or 5 or 6 or 7 (26829)
9   exp "congenital, hereditary, and neonatal diseases and abnormalities"/ (1057164)
10 prenatal injuries/ or prenatal exposure delayed effects/ (23308)
11 exp "Embryonic and Fetal Development"/ (232857)
12 exp Embryonic Structures/ (394978)
13 exp Teratogens/ (24998)
14 Teratogenesis/ (231)
15 exp Pregnancy/ (790169)
16 exp Pregnancy Complications/ (371928)
17 Maternal Exposure/ (6314)
18 (pregnan* or prenatal* or pre-natal*).mp. (892514)
19 (teratogen* or embryo* or foetus* or fetus* or foetal or fetal).mp. (712863)
20 gestation*.mp. (199305)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (2383325)
22 8 and 21 (1681)
23 arthritis, juvenile/ or arthritis, psoriatic/ or exp arthritis, rheumatoid/ (110453)
24 ((psoria* or rheumatoid) adj3 (arthriti* or arthropath*)).mp. (119306)
25 23 or 24 (135348)
26 22 and 25 (230)
27 26 not (exp animals/ not humans/) (220)

Database: Embase Classic+Embase <1947 to 2016 Week 19>
Search Strategy:

1   adalimumab/ (20129)
2   certolizumab pegol/ (3724)
3   etanercept/ (22652)
4   infliximab/ (35350)
5   golimumab/ (3339)
6   (adalimumab or avakine or certolizumab or cimzia or cimzias or embrel or enbrel or etanercept or golimumab or humira or inflectra or infliximab or remicade or remsima or revellex or simponi or trudexa).mp. (51118)
7   tumor necrosis factor inhibitor/ (6790)
8   (anti-tnf* or anti-tumor necrosis factor* or anti-tumour necrosis factor*).mp. (20255)
9   ((tnf* or tumor necrosis factor* or tumour necrosis factor*) adj3 inhibitor*).mp. (18187)
10   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (68136)
11   exp congenital disorder/ (1242527)
12   prenatal drug exposure/ or prenatal exposure/ (27481)
13   exp prenatal development/ (209752)
14   exp embryonic structures/ (119645)
15   exp teratogenesis/ or exp teratogenic agent/ (27229)
16   teratogenicity/ (16296)
17   exp pregnancy/ (701782)
18   exp prenatal disorder/ (108396)
19   prenatal period/ (8129)
20   (pregnan* or prenatal* or pre-natal*).mp. (1024173)
21   (teratogen* or embryo* or foetus* or fetus* or foetal or fetal).mp. (947926)
22   gestation*.mp. (259576)
23   11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (2820275)
24   10 and 23 (4605)
25   exp rheumatoid arthritis/ (181821)
26   psoriatic arthritis/ (14380)
27   ((psoria* or rheumatoid) adj3 (arthriti* or arthropath*)).mp. (205962)
28   25 or 26 or 27 (208026)
29   24 and 28 (1540)
30   29 not ((exp animal/ or nonhuman/) not exp human/) (1529)

Search History: Web of Science

Set	Results	
# 11	171	#10 AND #9 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 10	144,480	TS=((psoria* or rheumatoid) NEAR/3 (arthriti* or arthropath*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 9	741	#8 AND #4 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 8	980,292	#7 OR #6 OR #5 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 7	143,083	TS=gestation* *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 6	617,561	TS=(teratogen* or embryo* or foetus* or fetus* or foetal or fetal) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*

# 5	447,191	TS=(pregnan* or prenatal* or pre-natal*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 4	39,071	#3 OR #2 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 3	8,119	TS=((tnf* or "tumor necrosis factor*" or "tumour necrosis factor*") NEAR/3 inhibitor*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 2	13,266	TS=("anti-tnf*" or "anti-tumor necrosis factor*" or "anti-tumour necrosis factor*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 1	25,150	TS= (adalimumab or avakine or certolizumab or cimzia or cimzias or embrel or enbrel or etanercept or golimumab or humira or inflectra or infliximab or remicade or remsima or revellex or simponi or trudexa) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*

Appendix S1: Complete search strategy used with Ovid MEDLINE, EmBase, and Web of Science for the identification of studies to assess risk of pregnancy outcomes with the use of TNF-α inhibitors in patients with arthritic diseases.