Report
Exposure to ENBREL® (etanercept) during Pregnancy
Non-Interventional Study

Centre for Pharmacoepidemiology

Karolinska institutet

Stockholm, Sweden

Report
Exposure to ENBREL® (etanercept) during Pregnancy
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PASS information

Title	An observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland
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Active substance	Etanercept ATC code: L04AB01
Medicinal product	Enbrel
Product reference	EU MA Numbers: Enbrel 25 mg powder and solvent for solution for injection (EU/1/99/126/003); Enbrel 25 mg and 50 mg solution for injection in pre-filled syringe (EU/1/99/126/013; EU/1/99/126/017); Enbrel 50 mg solution for injection in pre-filled pen (EU/1/99/126/020).
Procedure number	EMEA/H/C/000262/MEA/167
Marketing Authorisation Holder (MAH)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT13 9NJ United Kingdom
Joint PASS	No

Research question and objectives	To compare the risk of adverse pregnancy outcomes, including major birth defects, in infants born to women with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis (PsO) or juvenile idiopathic arthritis (JIA) who have been treated with etanercept during pregnancy with a similar population with the same diseases who were treated with non-biologic systemic drugs but without etanercept or other biologic therapies during pregnancy.
Countries of study	Sweden, Denmark and Finland
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1. ABSTRACT

Title: An observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland.

Date: July 2, 2018

Principal Investigator: Helle Kieler, MD, PhD; Professor, Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Keywords: Etanercept, pregnancy, birth defects, infant health, birth outcomes

Rationale and background

The introduction of tumor necrosis factor (TNF) inhibitor, or anti-TNF, drugs has greatly improved the treatment of patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. To date, there are limited data from large population-based studies on the risk of adverse pregnancy outcomes in women exposed to anti-TNF therapy in general, and etanercept specifically. The existing data does not suggest that exposure to anti-TNF therapy during pregnancy increases the risk of adverse pregnancy outcomes (Chambers & Johnson, 2012). In a cohort study using data from the national registers in Denmark and Sweden, including more than 22,000 women with chronic inflammatory disease, there were 344 live-born infants to women with a recorded treatment of etanercept in early pregnancy (Broms et al., 2016). When compared to those with no treatment of a TNF inhibitor, 24 (7.0 %) vs 1019 (4.7 %) infants had a major birth defect, corresponding to adjusted odds ratio (OR) of 1.49 (95% confidence interval (CI): 0.92-2.28). However, some studies have indicated an increased risk of birth defects after exposure to anti-TNF agents in early pregnancy. Weber-Schoendorfer's prospective, observational study of 495 exposed children, who had been referred for teratological evaluation, reported a moderately increased risk, adjusted OR 2.20 (95% CI: 1.01-4.8) (Weber-Schoendorfer et al., 2015). The Organization of Teratology Information Specialists (OTIS) reported an adjusted OR of 2.77 (95% CI: 1.04-7.35). In STORK (Systematic Tracking of Real Kids), a retrospective cohort study using a large insurance database affiliated with OptumInsight (Optum), there were no notable differences in the proportion of claims-identified or chart-identified major birth defects across the chronic inflammatory arthritis and psoriasis cohorts when comparing pregnancy outcomes among women with chronic inflammatory arthritis (cIA) and PsO who were treated with etanercept during pregnancy with women with cIA and PsO who were not treated with etanercept or any anti-TNF during pregnancy.

To follow up on the results of the existing studies, the Marketing Authorisation Holder (MAH) proposed to use merged pregnancy outcome data from linked registers in Sweden, Finland and Denmark, and described the approximate size of the etanercept and comparison cohorts that could be provided by such sources.

To further investigate the relationship between etanercept exposure and the outcome of major birth defects, it was proposed to conduct an observational cohort study by using merged pregnancy outcome data for etanercept in Sweden, Denmark and Finland, where it is possible to link information from national registers including patient registers, medical birth registers,

prescribed drug registers and disease-specific quality registers. This non-interventional study was designated as a post-authorisation safety study (PASS) and is a commitment to the EMA.

Research question and objectives

1. The **primary** objective is to compare the prevalence of major birth defects in infants born to women with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and juvenile idiopathic arthritis who were treated with etanercept during the first trimester of pregnancy with a similar population with the same diseases who were treated with non-biologic systemic drugs but without etanercept or other biologic therapies during pregnancy in Sweden, Denmark and Finland.

The **secondary** objectives of this study are to:

2. Compare the prevalence of all birth defects and minor birth defects in infants born to women with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and juvenile idiopathic arthritis who were treated with etanercept during the first trimester of pregnancy with a similar population with the same diseases treated with non-biologic systemic drugs during pregnancy in Sweden, Denmark and Finland

3. Compare the risk of other adverse pregnancy outcomes including preterm birth, low birth weight, small for gestational age (SGA) and stillbirth in women with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and juvenile idiopathic arthritis treated with etanercept during pregnancy with a similar population with the same diseases treated with non-biologic systemic drugs in pregnancy in Sweden, Denmark and Finland.

4. Compare the risk of serious and opportunistic infections in the first year of life among infants born to women with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and juvenile idiopathic arthritis treated with etanercept during pregnancy with a similar population with the same disease treated with non-biologic systemic drugs during pregnancy in Sweden, Denmark and Finland.

Study design

This study is a population-based, multi-country, observational and non-interventional study using merged pregnancy outcome data from registers in Sweden, Denmark and Finland. Three comparison cohorts of women and their infants were established, and the exposure of the infant was determined by their mother's exposure in pregnancy as 1) etanercept exposed, including infants born to women exposed to etanercept at any time during pregnancy or within 90 days before last menstrual period (LMP); 2) non-biologic systemic treatment, including infants born to women exposed to systemic treatment other than anti-TNF therapy or other biologic treatment at any time during pregnancy or within 90 days before LMP; and 3) general population, including infants born to women with no record of the diseases of interest and no exposure to biologic or non-biologic systemic treatment.

Setting

The included women and infants were treated at the discretion of their treating physician. Data were obtained from national health registers in Sweden, Denmark and Finland. All three countries have public health care, which is free of charge. Reporting to the national registers is mandatory and resulting in high register coverage.

Study population

The study population comprises all women and infants identified in the Swedish Medical Birth Register (SMBR), the Danish Medical Birth Register (DMBR) and the Finnish Medical Birth Register (FMBR) between July 1st 2006 and December 31st 2013. All infants were followed up to one year of age.

Variables

The main exposure variable was maternal etanercept treatment and exposure was defined as at least one filled prescription with etanercept or a recorded administration of the drug during the period of interest as described below. In the primary analysis of major birth defects, and the secondary analyses of all birth defects and minor birth defects, the period of interest was exposure during the first trimester, i.e from first day of LMP to 90 days of pregnancy. For Finland, data was only available for major birth defects, and not for minor birth defects, which prevented the analysis of minor birth defects as an outcome as well as of all birth defects as a composite of major and minor birth defects.

In the secondary analyses of birth outcomes and infant infections in the first year of life, the period of interest was defined as exposure occurring during the period starting from within 90 days before LMP and until delivery. The outcome variables included information on all births, such as birth defects, stillbirth, preterm birth, low birth weight and SGA. Infants were followed up concerning occurrence of infections during the first year of life. In addition, data on patients' demographic and clinical characteristics including maternal comorbidities, maternal body mass index (BMI) and smoking in early pregnancy were presented.

Data sources

This register study utilized data on pregnancy outcomes available from the Swedish Medical Birth Register (SMBR), the Danish Medical Birth Register (DMBR), and the Finnish Medical Birth Register (FMBR). In addition, data on drug exposure and diseases were obtained from national patient registers and registers on prescribed drugs in Sweden, Denmark and Finland, including the Swedish Patient Register (SNPR), the Danish National Register of Patients (DNRP), the Finnish National Care Register (HILMO), Swedish Cause of Death Register, Danish Register of Causes of Death, Finnish Cause of Death Register, Swedish Prescribed Drug Register (SPDR), Danish Register of Medicinal Product Statistics (DPDR), Finnish Register on Prescribed Medicine (FPDR), and the quality registers ARTIS (Antirheumatic treatment in Sweden) and ROB-FIN (National register for biologic treatment in rheumatic diseases, Finland).

Data analysis

The primary comparison of risk was between the etanercept group and the non-biologic systemic treatment group. The general population group was included as a point of reference, but not included in formal comparison analyses. Descriptive statistics, such as mean, median and standard deviation for continuous variables, and count and percentage for categorical variables, were used to summarize the data and were presented for all three groups. Data from all countries were presented as pooled counts and estimates. Univariate and multivariate logistic regression were used to estimate the crude and adjusted OR and 95% CIs when comparing the risk of adverse pregnancy outcomes between the two groups. Results were presented with step-wise adjustments. In the primary model, adjustments were made for the potential confounders country (Sweden, Denmark or Finland), parity, maternal age and smoking. In the next step, additional adjustments were made for history of prosthethic surgery, hospitalization during pregnancy and corticosteroid treatment during pregnancy in a sensitivity analysis.

Results

A total of 1,680,204 births were included, 522 in the etanercept group, 3508 in the non-biologic systemic treatment group and 1,676,174 in the general population. Of the 522 pregnancies in women exposed to etanercept within 90 days before LMP until delivery, 425 were exposed during the first 90 days of pregnancy, which was the exposure definition in the primary outcome analysis. The comparison group, of women with the diseases of interest and non-biologic systemic treatment at anytime within 90 days before LMP until delivery, contributed with 3,508 pregnancies.

Most of the included women had rheumatoid arthritis (58.4% in the etanercept exposed cohort and 52.8% in non-biologic systemic cohort), while others had either juvenile idiopathic arthritis (20.1% in the etanercept exposed cohort and 13.8% in the non-biologic systemic cohort), ankylosing spondylitis (9.4% in the etanercept exposed cohort and 15.0% in the non-biologic systemic cohort), psoriatic arthritis (8.2% in the etanercept exposed cohort and 9.1% in the non-biologic systemic cohort), or psoriasis (3.8% in the etanercept exposed cohort and 9.3% in the non-biologic systemic cohort).

In the primary analysis comparing the rates of any major birth defect among women treated with etanercept in the first trimester and women exposed to non-biologic systemic treatment during pregnancy, the crude OR was 1.22 (95% CI: 0.79-1.90) and the corresponding OR adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy was 0.96 (95% CI: 0.58-1.60).

In the secondary analyses of any birth defect, major or minor, which only included Danish and Swedish births, the crude OR was 1.22 (95% CI: 0.83-1.81) and the adjusted OR was 1.08 (95% CI:0.70-1.69). For minor birth defects, the crude OR was 0.94 (95% CI: 0.53-1.68) and the adjusted OR was 0.92 (95% CI: 0.50-1.72). Adjustments were made for country, maternal disease, parity, maternal age and smoking in early pregnancy and further adjustment for history of prosthethic surgery, hospitalization during pregnancy, and corticosteroid treatment using the Danish and Swedish data, did not change the results.

In adjusted analyses, taking into consideration country, maternal disease, parity, maternal age and smoking in early pregnancy, the risk of preterm birth, SGA and low birth weight were compared

among the offspring of women treated with etanercept at any time during pregnancy to the offspring of women exposed to non-biologic systemic treatment during pregnancy.The adjusted OR for preterm birth was 1.16 (95% CI: 0.84-1.61), the adjusted OR for SGA was 1.32 (95% CI: 0.80-2.16) and the adjusted OR for low birth weight was 1.38 (95% CI: 0.98-1.93), respectively. In sensitivity analyses, treatment with etanercept in the second and third trimesters was associated with a significantly increased risk of SGA, the adjusted ORs were 2.40 (95% CI: 1.11-5.18) and 2.96 (95% CI: 1.23-7.17), respectively. Possible explanations to these findings, such as confounding by indication and difference in disease activity could not be ruled out. There were no cases of stillbirth in the etanercept exposed group, precluding any further analysis. The adjusted ORs for serious infections and opportunistic infections in the first year of life were 1.00 (95% CI: 0.80-1.25) and 1.36 (95% CI: 0.67-2.78), respectively.

Limitations

Although the Swedish, Danish and Finnish national health registers are of high validity and coverage, using register data as a proxy for the definition of the main exposure and the main outcomes, rather than collecting information on actual intake, may introduce misclassification bias. Only pregnancies leading to birth are included in the registers, which may result in selection bias of healthier fetuses. Such biases would affect both comparison groups. In addition, the analyses may be confounded by the indication for treatment, as women who have been prescribed etanercept may represent a patient group with more severe disease and activity. To address bias in disease severity, women treated with non-biologic systemic treatment with the same diseases as those exposed to etanercept were included for comparisons. However, we lacked sufficient information to completely control for disease activity.

Conclusion

In this population-based cohort study which evaluated the safety of etanercept during pregnancy using national health register data from Sweden, Denmark and Finland, there were no observed increased risks of birth defects, preterm birth, SGA, low birth weight, or infections in the infant's first year of life in the primary analyses, when comparing offspring of women treated with etanercept and offspring of women with similar chronic inflammatory diagnoses but treated with non-biologic systemic treatment during pregnancy. Treatment with etanercept in pregnancy may be associated with SGA, and a slightly increased risk of low birth weight, according to the sensitivity analyses by treatment timing. However, the associations may also be attributed to small numbers of exposed patients in the sensitivity analyses and residual confounding by indication since women who were treated with etanercept may have more severe disease.

2. LIST OF ABBREVIATIONS

ARTIS	AntiRheumatic Therapies In Sweden
AS	Ankylosing spondylitis
ATC	Anatomic Therapeutic Chemical classification
BMI	Body mass index
BSRBR	The British Society for Rheumatology Biologics Register
CI	Confidence interval
cIA	Chronic inflammatory arthritis
DMARD	Disease-modifying anti-rheumatic drugs
DMBR	Danish Medical Birth Register
DNRP	Danish National Register of Patients
DPDR	Danish Register of Medicinal Product Statistics
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FMBR	Finnish Medical Birth Register
FPDR	Finnish Register on Prescribed Medicine
GEE	Generalized estimating equation
HILMO	Finnish National Care Register for Health Care Institutions
ICD	International Classification of Diseases
JIA	Juvenile idiopathic arthritis
LEF	Leflunomide
LMP	Last menstrual period
MAH	Marketing Authorisation Holder
MTX	Methotrexate
OR	Odds ratio
OTIS	The Organization of Teratology Information Specialists

2. LIST OF ABBREVIATIONS

SNPR	Swedish Patient Register
PASS	Post-authorisation safety study
PIN	Personal identification number
PL	Package Leaflet
PsA	Psoriatic arthritis
PsO	Psoriasis
RA	Rheumatoid arthritis
RMP	Risk Management Plan
ROB-FIN	Finnish quality register of biological treatment in patients with rheumatological conditions
SGA	Small for gestational age
SMBR	Swedish Medical Birth Register
SmPC	Summary Product Characteristics
SPDR	Swedish Prescribed Drug Register
STORK	Systematic Tracking of Real Kids
TNF	Tumour necrosis factor

3. NAMES AND AFFILIATIONS OF INVESTIGATORS

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4. MILESTONES

Milestones	
Milestone	**Planned date**
Start of data collection	July 1st 2006
End of data collection	December 31st 2014
Registration in the EU PAS register	August 1st 2017
Final report of the study results	February 28th 2018

5. RATIONALE AND BACKGROUND

Etanercept and birth defects

Etanercept is a tumour necrosis factor (TNF) inhibitor. It is a bioengineered fusion protein incorporating TNF receptor p75 and the crystallisable fragment (Fc) component of immunoglobulin G1 (IgG1), which binds specifically to TNF and lymphotoxin, inhibiting their interaction with cell surface receptors. In the European Union (EU), etanercept is indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis and non-radiographic axial spondyloarthritis (AS), plaque psoriasis (PsO) and psoriatic arthritis (PsA).

Etanercept would appear to have a low probability of crossing the placenta during the first trimester, owing to its molecular size, making potential adverse effects on early fetal viability or organogenesis unlikely. Significant fetal effects, such as preterm delivery or fetal growth restriction, would more reasonably be expected to manifest either later in pregnancy, when active transplacental transport of similar antibody molecules has been documented, or following delivery. In the current EU Summary Product Characteristics (SmPC) for etanercept there is a recommendation that women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during therapy, and for three weeks after discontinuation. The SmPC (section 4.6) also states that "Etanercept is not recommended during pregnancy".

Adverse pregnancy outcomes are listed as an important potential risk in the current etanercept risk management plan (RMP). Additional pharmacovigilance activities for this safety concern, include observational studies, notably the Rheumatic Diseases and Psoriasis Pregnancy Register study conducted by the Organization of Teratology Information Specialists (OTIS) and the STORK (Systematic Tracking of Real Kids) study, a retrospective study to evaluate pregnancy outcomes associated with and without etanercept treatment among pregnant women with chronic inflammatory arthritis or psoriasis.

Birth defects in connection with disease severity and other systemic treatment

The prevalence of birth defects among infants of women with RA has been reported to be between 0 to 4.3% in Sweden and Denmark (Norgaard et al., 2010). When compared with infants of women without the disease, a non-statistically significant association was observed for the incidence of birth defects among women with RA, odds ratio (OR) 1.32 (95% confidence interval (CI): 0.98-1.79). Women who were seropositive for rheumatoid factor (OR 1.66 (95% CI: 1.15-2.40)) or had at least one previous hospital admission associated with RA (OR 1.43 (95% CI: 1.00-2.05)), respectively, were shown to have an increased risk of giving birth to infants with birth defects than those without RA. When stratified by period of birth, the risk for birth defects decreased from 2.57 (95% CI: 1.59-4.16) in 1994 - 1997 to 1.00 (95% CI: 0.64-1.56) in 2002 – 2006 (Norgaard et al., 2010). Disease activity, seropositivity for rheumatoid factor, severity of disease (measured by surgery performed and/or hospitalization), and medication use seem to play an important role in pregnancy outcomes among patients with RA. However, limited information is available regarding adjustment for disease severity or use of medications during pregnancy in most of the studies referenced (Norgaard et al., 2010).

Methotrexate (MTX), designated pregnancy category X by the US Food and Drug Administration (FDA) and category D in Europe, can cause fetal death or teratogenic effects when administered

to pregnant women. The use of methotrexate in the first trimester has been associated with a specific pattern of birth defects, including malformations of the infant's head, face, and bones. There is a recognized association between high-dose methotrexate and spontaneous abortion. A systemic review found that 23% of pregnancies exposed to methotrexate in the first trimester resulted in spontaneous abortion and 5% of pregnancies resulted in reported minor birth defects (Martinez Lopez, Loza, & Carmona, 2009).

Leflunomide (LEF) is also designated pregnancy category X by the FDA and category D in Europe. Women should not conceive for 2 years after the last dose of leflunomide or undergo cholestyramine washout. Among 45 women who took leflunomide while pregnant, 2 infants of women exposed to leflunomide during the first trimester of pregnancy had major structural defects (12.5%) (Cassina et al., 2012).

Isolated cleft palate among infants born to women exposed to any corticosteroid therapy during the first trimester of pregnancy has been reported with a prevalence of 0.54 per 1,000 live births (Pradat et al., 2003). A non-statistically significant increased risk of septal cardiac defects after exposure to multiple NSAIDs has also been reported, OR 3.9 (95% CI: 0.9-15.7) (van Gelder, Roeleveld, & Nordeng, 2011). In a prospective study from Sweden, the total malformation rate was similar to the expected rate, OR 1.04 (95% CI: 0.84-1.29), however, the risk for cardiac defects was higher than expected, OR 1.86 (95% CI: 1.32-2.62) (Adams, Bombardier, & van der Heijde, 2012; Ericson & Kallen, 2001). In addition, the risk for orofacial cleft defects was also increased, OR 2.61 (95% CI: 1.01-6.78).

There are limited data on the risk of adverse pregnancy outcomes in etanercept exposed patients from large population-based studies. Hyrich et al summarized the information available with regard to the use of biologic therapies during conception, pregnancy and breastfeeding. The collective evidence suggested that exposure to anti-TNF therapy in inflammatory arthritis and inflammatory bowel disease at the time of conception or during the first trimester does not result in increased risks of adverse pregnancy and fetal outcomes (Hyrich & Verstappen, 2014). The British Society for Rheumatology Biologics Register (BSRBR) collected data on 130 pregnancies in 118 patients with RA, who received anti-TNF therapy (etanercept, infliximab or adalimumab) (Verstappen et al., 2011). The pregnancy outcomes in the anti-TNF exposed patients were compared with those in RA patients who received non-biologic disease-modifying anti-rheumatic drugs (DMARDs). There were 2 (2/32=6.25%) reports of birth defects (congenital dislocation of the hip and pyloric stenosis) in patients exposed to anti-TNF therapy (without MTX or LEF) at conception, and 2 (2/46=4.35%) (winking jaw syndrome and strawberry birth mark) in patients exposed to anti-TNF therapy before conception.

In a recent prospective, observational, cohort study, Weber-Schoendorfer et al compared pregnancy outcomes of 495 women treated with anti-TNF therapy (including adalimumab, infliximab, etanercept, certolizumab pegol or golimumab) with 1532 women unexposed to anti-TNF therapy who were referred for teratological evaluation between 1998 and 2013 (Weber-Schoendorfer et al., 2015). It was reported that there may be a moderately increased risk of birth defects associated with prenatal anti-TNF exposure for maternal chronic inflammatory conditions, adjusted OR 2.20 (95% CI: 1.01-4.80), without a distinct pattern of birth defects. There may be an increased risk of preterm birth and reduced birth weight, but no increased risk of spontaneous abortion. One of the limitations of this study is that exposed pregnancies with chronic inflammatory conditions were only compared with a general comparison cohort, which may leave open the possibility of confounding by indication.

In a cohort using data from the national registers in Denmark and Sweden and including more than 22,000 women with chronic inflammatory disease there were 344 live-born infants to women with a recorded treatment of etanercept in early pregnancy. When compared to those with no anti-TNF treatment, 24 (7.0 %) vs 1019 (4.7 %) infants had any major birth defect, corresponding to an adjusted OR of 1.49 (95% CI: 0.92 - 2.28) (Broms et al., 2016).

In the OTIS pregnancy register in North America, which was a prospective, observational, cohort study to evaluate pregnancy outcomes in women with RA (including JIA), PsO, PsA or AS, it was found that any major birth defect was prevalent in 30 of 319 (9.4%) etanercept-exposed live-born subjects compared with 5 of 144 (3.5%) unexposed live-born infants, resulting in an adjusted OR 2.77 (95%, CI: 1.04-7.35). A higher rate of major birth defects was also observed when comparing all pregnancies exposed to etanercept during the first trimester, with all pregnancies not exposed to etanercept or other anti-TNF agents, adjusted OR 2.37 (95% CI: 1.02-5.52). When four of the 30 live-born exposed malformed subjects with chromosomal or genetic anomalies were excluded, the proportion of major birth defects in the first trimester exposed group decreased to 8.3%, reducing the adjusted OR to 2.49 (95% CI: 0.92-6.68). However, no pattern of major birth defects was observed among the exposed subjects. Other adverse pregnancy outcomes such as spontaneous abortion, preterm birth, stillbirth and serious or opportunistic infections were not increased in the etanercept-exposed group.

The STORK study, a retrospective cohort study using a large insurance database affiliated with OptumInsight (Optum), compared pregnancy outcomes among women with chronic inflammatory arthritis (cIA) and PsO who were treated with etanercept during pregnancy with women with cIA and PsO who were not treated with etanercept or any anti-TNF during pregnancy. Thirty-one (18.7%) of 166 live born infants whose mothers had cIA and exposed to etanercept had claims for major birth defects while one hundred ninety (19.1%) had at least one claim for major birth defects among 997 live born infants whose mothers had cIA but without exposure to etanercept or other anti-TNFs. Eight (15.7%) of 51 live born infants whose mothers had claims for PsO and were exposed to etanercept had claims for major birth defects, while one hundred thirty-seven (14.5%) had at least one claim for major birth defects among 943 live born infants whose mothers had psoriasis but without exposure to etanercept or other anti-TNFs. In summary, the STORK study examined 6 mutually exclusive cohorts of pregnant women defined by claims-based evidence of cIA, PsO and etanercept exposure. There were no notable differences in the proportion of claims-identified or chart-identified major birth defects across the 3 cIA cohorts (women with cIA and exposed to etanercept, women with cIA and unexposed to etanercept or any anti-TNF during pregnancy, and those without cIA and unexposed to etanercept or other anti-TNFs). The proportion of enrolled infants with low birth weight was highest in the etanercept-exposed cIA cohort and lowest in the non-diseased/non-exposed comparator cohort. Proportions of preterm birth were higher in both etanercept exposed and unexposed cIA disease cohorts than in the comparator cohort. There were no notable differences in the proportion of most outcomes between the PsO cohorts, however the numbers were insufficient to draw reliable conclusions.

On the basis of the information summarised above from the OTIS and STORK studies and the results from other studies, the Marketing Authorisation Holder (MAH) proposed to use merged pregnancy outcome data from linked registers in Sweden, Denmark and Finland, and described the approximate size of the etanercept and comparison cohorts that could be provided by such

sources. An estimate of the likely timelines to obtain an analysis and overall feasibility of such an investigation was also provided.

To further investigate the relationship between etanercept exposure and the outcome of major birth defects, the MAH proposed to conduct an observational cohort study by using merged pregnancy outcome data from three Nordic countries (Sweden, Denmark and Finland), where various national registers are linked, by collaborating with the investigators from the ARTIS (AntiRheumatic Therapies In Sweden) register and the Centre for Pharmacoepidemiology at Karolinska Institute (CPE). CPE has been in charge of the previous/ongoing assessments of pregnancy outcomes following immunomodulator treatments. This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

6. RESEARCH QUESTION AND OBJECTIVES

1. The **primary** objective is to compare the prevalence of major birth defects in infants born to women with RA, PsA, AS, PsO or JIA who were treated with etanercept during the first trimester of pregnancy with a similar population with the same diseases who were treated with non-biologic systemic drugs but without etanercept or other biologic therapies during pregnancy in Sweden, Denmark and Finland.

The **secondary** objectives of this study are to:

2. Compare the prevalence of all birth defects and minor birth defects in infants born to women with RA, PsA, AS, PsO or JIA who were treated with etanercept during the first trimester of pregnancy with a similar population with the same diseases treated with non-biologic systemic drugs but without etanercept or other biologic treatment during pregnancy in Sweden, Denmark and Finland.

3. Compare the risk of other adverse pregnancy outcomes including preterm birth, low birth weight, small for gestational age (SGA) and stillbirth in women with RA, PsA, AS, PsO or JIA treated with etanercept during pregnancy with a similar population with the same diseases treated with non-biologic systemic drugs in pregnancy in Sweden, Denmark and Finland.

4. Compare the risk of serious and opportunistic infections in the first year of life among infants born to women with RA, PsA, AS, PsO or JIA treated with etanercept during pregnancy with a similar population with the same disease treated with non-biologic systemic drugs during pregnancy in Sweden, Denmark and Finland.

7. AMENDMENTS AND UPDATES

None.

8. RESEARCH METHODS

8.1. Study Design

This study is a population-based, multi-country, observational register study of pregnancy outcomes and 1-year follow-up health status in infants born to women with RA, PsA, AS, PsO and JIA with exposure to etanercept from 90 days before LMP through birth, in the clinical setting. Women with the diseases of interest, who had non-biologic systemic treatment, but without exposure to biologic therapy, and their infants, served as the comparison. Women without the diseases of interest and without biologic or non-biologic treatment were included to serve as a reference to the general population.

Data was obtained from national medical birth registers, patient registers, and registers on prescribed drugs in Sweden, Denmark and Finland. Additional information on drug treatment was obtained from the ARTIS in Sweden and the ROB-FIN in Finland. Data in these registers in each country can be linked using the unique Personal Identification Number (PIN) assigned at birth or upon immigration to all residents of Sweden, Denmark and Finland.

8.2. Setting

The national medical birth registers were used to identify all women who gave birth from July 1st 2006 to December 31st 2013 in Sweden, Denmark and Finland. The registers have collected nationwide information on births for several decades with almost complete coverage. Midwives and physicians record information about the pregnancy, the delivery, and the neonatal period using structured forms (Cnattingius, Ericson, Gunnarskog, & Kallen, 1990; Knudsen & Olsen, 1998; Langhoff-Roos et al., 2014). The information is collected prospectively, but not entered into the respective register database until the time of maternal hospital discharge following delivery. Maternal characteristics including medical history of the diseases of interest, etanercept or other anti-TNF treatment during pregnancy (or within 90 days before last menstrual period (LMP)), pregnancy outcomes information, and neonatal diagnoses were collected from the Swedish Medical Birth Register (SMBR), the Danish Medical Birth Register (DMBR) and the Finnish Medical Birth Register (FMBR). The LMP was estimated from the routine ultrasound examination in early pregnancy, which is offered to all women in the three countries. For women who were not recorded with an LMP by ultrasound (≈ 1%), an estimated LMP was imputed, 278 days before the date of delivery.

In addition, information concerning maternal diseases, including chronic inflammatory diseases, other diseases and dispensed and prescribed drugs, were collected from other national and disease-specific or quality registers in Sweden, Denmark and Finland.

The medical birth registers link the PIN of the women to the PIN of their infants and the infant's PIN can be used to link information on the infant's health from other registers. Infants were followed for one year after birth concerning records of birth defect diagnoses and infections as defined by diagnosis codes in the patient registers and filled prescriptions of antibiotics in the prescribed drug registers. Follow-up information was collected until December 2014, to correspond to the first year of life following birth up to December 2013.

Data from Sweden, Denmark and Finland were obtained and analysed with the collaboration and assistance of Dr Helle Kieler and co-workers at Karolinska institutet in Stockholm, Sweden, where data were subsequently validated and analysed in collaboration with Dr Henrik Toft

Sorensen of Aarhus University Hospital in Aarhus, Denmark and Dr Mika Gissler at THL (National Institute for Health and Welfare) in Finland and their designees.

To perform the study, the data from the relevant registers in each of the three countries were requested by the country-PI from the register holders and national datasets were then created. After merging of national data at each register holder, the PINs were replaced by a random number to secure the individual integrity and the anonymised data were then delivered to CPE at Karolinska institutet for performance of analyses. CPE may only present aggregate data to the sponsor.

Table 1 Register information included in the report

Name of Register	Date Initiated	Data Reporting Period [a]
Sweden		
Swedish Medical Birth Register (SMBR)	Established in 1973	July 1st 2006-December 31st 2013
Swedish National Prescribed Drug Register (SPDR))	Established July 1st 2005	July 1st 2005-December 31st 2014
Swedish Hospital Discharge Register[b]	Established in the 1964. In 1987 reporting was made compulsory	January 1st 2000-December 31st 2014
Swedish National Patient Register Ambulatory Care Visits [b]	Almost complete reporting from 2001	January 1st 2001-December 31st 2014
Swedish Cause of Death Register	Established in 1952	January 1st 2000-December 31st 2014
Anti-Rheumatic Therapies in Sweden (ARTIS)	Established in 1999	January 1st 2000-December 31st 2013
Denmark		
Danish Medical Birth Register (DMBR)	Established in 1968 (computerized since 1973)	July 1st 2006-December 31st 2013
Danish Register of Medicinal Product Statistics (DPDR)	Established in 1994	July 1st 2005-December 31st 2014
Danish National Patient Register (DNRP)	Established in 1977; since 1995 data on outpatients and emergency patients has been submitted	January 1st 2000-December 31st 2014
Danish Cause of Death Register	Established in 1970	January 1st 2000-December 31st 2014
Finland		
Finnish Medical Birth Register (FMBR)	Established in 1987	July 1st 2006-December 31st 2013
Finnish Register on Prescribed Medicine (FPDR)	Prescribed medicines since 1995 and special refunded medicine since 1964	July 1st 2005-December 31st 2014
Finnish National Care Register for Health Care Institutions	Established in 1967; includes all surgical procedures since 1996 (all hospitals) and all hospital outpatient visits since 1998 (public hospitals only)	January 1st 2000-December 31st 2014
Finnish Register on Congenital Malformations	Established in 1963	July 1st 2006-December 31st 2014
Finnish Society for Rheumatology Register of Biological Treatment (ROB-FIN)	Established in 1999	January 1st 2000-December 31st 2013

[a] In order to obtain 1-year follow-up information for infants born to women exposed to anti-TNFα therapy, the data accrual period to identify these infants was 2006 to 2013, while the follow-up information for these infants was collected through 2014.

[b] These registers have since 2001 been combined into the Swedish National Patient Register (SNPR).

8.3. Subjects

8.3.1. Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Have a diagnosis of RA, PsA, AS, PsO or JIA at any time before pregnancy

2. For the etanercept treated cohort, have had any treatment with etanercept within 90 days before the first day of the LMP or any time during pregnancy.

3. For the main comparison group, have had any treatment with a systemic non-biologic treatment, without any biologic treatment, within 90 days before the first day of the LMP or any time during pregnancy.

4. In addition, and for the general population group without the diseases of interest and without biologic or non-biologic treatment, have a birth recorded in the respective national birth register between July 1st 2006 – December 31st 2013.

8.3.2. Exclusion criteria

No exclusion criteria were applied in the main analyses.

Patients exposed to the following drugs/drug classes were excluded in the sensitivity analyses due to their known teratogenicity:

Exposure to acitretin, mycophenylate mofetil, methotrexate, leflunomide or anti-epileptics (Attachment A1) within 90 days before the first day of LMP or during pregnancy as recorded in the registers providing the information will disqualify a women from inclusion in the study due to the known teratogenicity of these medications and/or the extremely long half-life of these medications (Lammer, 1988; Lofberg, Reiners, Spielmann, & Nau, 1990).

8.4. Variables

The following data were available for the analysis. Study variables, their roles and operational definitions are described in Table 2.

8.4.1. Exposure and cohort requirements

To determine the diagnosis/indication that led to initiation of etanercept/non-biologic treatment, information on the diseases as International Classification of Diseases, 10th revision (ICD-10), codes recorded at any time before or during pregnancy has been obtained from the patient registers, ARTIS and the medical birth registers from 1998 and onward (ICD-10 codes: M05–M06 for RA; L405, M070–M073, M090 for PsA; M45 for AS, M08 for JIA, L40 for PsO). For patients diagnosed with more than one disease, the latest diagnosis of a chronic inflammatory disease was used.

Qualification for the etanercept exposed cohort required a combination of relevant ICD-10 diagnoses of RA, PsA, AS, PsO or JIA at any time before or during pregnancy, from year 2000 and onwards, and treatment with etanercept as identified by at least one filled prescription with the Anatomic Therapeutic Chemical classification (ATC) code of L04AB01 or a treatment code

of BOHJ18A2 in the DNRP as illustrated in Table 2. Timing of exposure to etanercept during pregnancy (from 90 days before the first day of LMP until delivery) is mainly based on data from the filled prescriptions as recorded in the SPDR. For the Swedish cohort, additional data such as dates when starting or stopping treatment for specific anti-rheumatic drugs has been obtained from the ARTIS register and for Finland, the ROB-FIN provided similar information.

For the primary objective, that is to compare the prevalence of major birth defects in infants born to women who have received etanercept during pregnancy with a similar population with the same diseases who have not received etanercept or other biologic therapies, the exposure period for the primary analysis is during the first trimester (from the first day of LMP until 90 days after LMP). In sensitivity analyses, various other exposure periods (from 90 days before the first day of LMP until 90 days after LMP and from 30 days before LMP until 90 days after LMP) were assessed.

For the secondary objective, comparing the prevalence of all birth defects in infants born to women in the etanercept exposed cohort with a similar population with the same diseases in the non-biologic systemic cohort in Sweden, Denmark and Finland, similar approaches as when addressing the primary objective concerning definition of exposure periods were used.

For the other secondary objectives, i.e. adverse pregnancy outcomes other than birth defects, the exposure period was from 90 days before the first day of LMP until birth. Since prescriptions are generally written to last for three months of treatment, and thus renewed every three months, exposure from 90 days before the first day of LMP was chosen. In sensitivity analyses various other exposure periods (from 90 days before the first day of LMP to LMP, and during each trimester) were also assessed.

Qualification for the non-biologic systemic cohort required a combination of relevant ICD-10 of RA, PsA, AS, PsO or JIA and at least one prescription of treatment with non-biologic systemic therapy (such as azathioprine, ciclosporin, cyclophosphamide, chloroquine, hydroxychloroquine and sulfalsalazine, etc.). The non-biologic cohort had no indication on use of etanercept or any other biologics in the period 90 days before the first day of LMP to delivery. (ATC codes shown in Attachment A1). Women in the etanercept group could also have these treatments in addition to etanercept.

8.4.2. Birth outcomes

The primary outcome for this study was major birth defects as defined according to the EUROCAT classification and based on ICD-codes (as shown in Attachment A2). The secondary outcomes were all birth defects, minor birth defects, stillbirth, preterm birth, low birth weight, small for gestational age, and infections during infancy (Table 2).

Occurrence of birth defects, in general and by organ system–specific subgroups, and hospital visits in infants up to 1 year of age were ascertained from ICD-10 codes in the medical birth registers and in the patient registers (see Attachment A2), except for the birth defects in Finland, where the ICD-9 code was used (specific definitions for each outcome are shown in Table 2).

The Swedish Medical Birth Register includes data on all births in Sweden, including stillbirths after gestational week 22 from 2008 and onwards. Before that, only live births and stillbirths occurring after gestational week 28 were recorded. Information is forwarded electronically to the

register through standardized and generally used antenatal, obstetrical and paediatric records. Information includes delivery hospital, maternal socio-demographic characteristics and data on pregnancy, delivery and the neonatal period including birth defects until the woman and infant are discharged from the hospital. In Sweden birth defects are also recorded in the Patient Register and information on birth defects until one year of age can be obtained.

The Danish Medical Birth Register is part of the Danish National Patient Register and includes data on live births, stillbirths of foetuses with a gestational age of at least 22 weeks and data on the mothers. Birth defects are reported to the register until one year of age.

The Finnish Medical Birth Register includes data on live births and stillbirths of foetuses with a birth weight of at least 500 grams or with a gestational age of at least 22 weeks, as well as data on the mothers. A data collection form is completed for each new-born in the maternity hospital, at the latest seven days after the delivery, which is sent to the register. Birth defects are identified through the Register on Congenital Malformations, which was started in 1963 and is run by THL. The data is collected from multiple sources, such as mandatory notifications by hospitals and physicians, other registers, and the Cause-of-Death Register. This register contains information on all observed malformations in spite of the type of pregnancy endpoint (miscarriage, induced abortion, still birth, and live birth), and it includes the personal identification numbers of the mother and the live new-borns. Information on malformations in the register is completed over the first year of life. The register also includes diagnoses according to ICD-9 codes, as well as all exposures and risk factors related to the malformation. The data on all congenital malformations is collected; however, reporting is done on major congenital malformations only. Minor anomalies are excluded according to the exclusion list of European Registration of Congenital Anomalies (EUROCAT).

Infant infections and antibiotic treatment were used as markers for infant health status (attachment A3). Most manifestations of immunodeficiency result from frequent infections, usually beginning with recurrent respiratory infections (though many immunologically normal infants have 6 to 8 respiratory infections per year, particularly when exposed to older siblings or other children), and most patients with immunodeficiency eventually develop one or more severe bacterial infections that persist, recur, or lead to complications (e.g., sinusitis, chronic otitis and bronchitis following repeated upper respiratory infections) (Merck Manual of Diagnosis and Therapy, Seventeenth Edition [on-line]). Infections with opportunistic organisms and infections of the skin and mucous membranes may also occur, and malabsorption, failure to thrive and diarrhea are also common. Information concerning antibiotic usage and hospitalization has been used previously in the evaluation of infant health status and immune function (Celedon, Fuhlbrigge, Rifas-Shiman, Weiss, & Finkelstein, 2004; Rutstein et al., 2005; Viani, Araneta, Deville, & Spector, 2004).

8.4.3. Covariates

The following covariates were considered: infant’s year of birth, country of birth, maternal age, maternal parity, maternal BMI, maternal diagnosis and indication for treatment, maternal smoking in early pregnancy, maternal comorbidity as defined by diabetes and hypertension, previous preterm delivery, previous children with birth defects, history of prosthetic surgery, hospitalization during pregnancy (for Sweden and Denmark) and corticosteroid treatment during pregnancy.

Table 2 Study variables, their roles and operational definitions

Variable	Role	Time frame	Operational definition	Data Source		
				Sweden	Denmark	Finland
Exposure variables						
Etanercept use (Yes/No)	Main exposure	90 days before LMP to delivery	Filled prescription with ATC code L04AB01 Treatment code BOHJ18A2 in the DNRP Recorded in ARTIS by start/stop date	SPDR ARTIS SNPR	DPDR DNRP	FPDR ROB-FIN
RA (Yes/No)		From year 2000 until day of delivery	ICD-10 codes: M05–M06	SNPR SMBR	DNRP DMBR	HILMO FMBR
PsA (Yes/No)			ICD-10 codes: L405, M070–M073, M090	SNPR SMBR	DNRP DMBR	HILMO FMBR
AS (Yes/No)			ICD-10 codes: M45	SNPR SMBR	DNRP DMBR	HILMO FMBR
PsO (Yes/No)			ICD-10 codes: L40 (not L405)	SNPR SMBR	DNRP DMBR	HILMO FMBR
JIA (Yes/No)			ICD-10 codes: M08	SNPR SMBR	DNRP DMBR	HILMO FMBR
Gestational age at the time of exposure to etanercept	Main exposure	90 days before LMP to delivery	All prescriptions filled during the period from 90 days before LMP to date of birth were identified in the national prescription registers. Based on the number of syringes prescribed and their strength (25/50 mg) exposure was assigned to four periods: LMP-90 days to LMP; and trimesters 1 to 3. Assignment in the four periods was based on the assumption of weekly administration irrespective of the strength.	SMBR	DMBR	FMBR
Etanercept treatment dose	Main exposure		Treatment dose in the four periods was calculated as the cumulative dose in mg in each period and assuming weekly administrations irrespective of strength.	SPDR ARTIS SNPR	DPDR DNRP	FPDR ROB-FIN
Other treatments received during pregnancy	Other exposure		Attachment A1	SPDR	DPDR	FPDR
Outcome variables						
Major birth defects	Primary outcome	From delivery until end of infant's first year	According to EUROCAT (Attachment A2)	SMBR SNPR	DMBR DNRP	FMBR HILMO
All birth defects	Secondary outcome		ICD-10:Q-chapter and D215, D821, D1810, P350,P351,P371	SMBR SNPR	DMBR DNRP	FMBR HILMO
Minor birth defects	Secondary outcome		All birth defects not defined as major (according to Attachment A2)	SMBR SNPR	DMBR DNRP	N/A Data not available
Stillbirth	Secondary outcome	Delivery	Country specific indicator variable in national medical birth registers	SMBR	DMBR	FMBR
Preterm birth	Secondary outcome	Delivery	Preterm: Born before gestational week 37 Very Preterm: Born before gestational week 32	SMBR	DMBR	FMBR
Birth weight	Secondary outcome	Delivery	Low birth weight: ≤ 2500 grams Very low birth weight: ≤ 1500 grams	SMBR	DMBR	FMBR

SGA	Secondary outcome	Delivery	Small for gestational age, 2SD below, according to Marsal (Marsal et al., 1996)	SMBR	DMBR	FMBR
Serious infections (Yes/No, type of infection) in the first year of life	Secondary outcome	From delivery until end of infant's first year	Attachment A3	SNPR	DNRP	HILMO
Opportunistic infections (Yes/No, type of infection) in the first year of life	Secondary outcome		Tuberculosis, pneumonia requiring antibiotic treatment and/or hospitalization, neonatal sepsis, meningitis invasive fungal infection pneumocystis, septic arthritis, osteomyelitis, abscess (deep tissue) (Attachment A3 for ICD-10 codes))	SNPR	DNRP	HILMO
Covariates						
Demographics (age, country, parity, infant's year of birth)	Baseline characteristics	Delivery	Country specific variable in national medical birth registers	SMBR	DMBR	FMBR
Maternal indications	Baseline characteristics	From year 2000 until day of delivery	Attachment A4 (ICD-10 codes for TNF-indication)	SMBR SNPR	DMBR DNRP	FMBR HILMO
Smoking in early pregnancy	Baseline characteristics	Self-report at first prenatal care visit	Country specific variable in national medical birth registers (yes/no/missing)	SMBR	DMBR	FMBR
BMI	Baseline characteristics		From country specific variables of weight and height in national medical birth registers. BMI = weight/height^2	SMBR	DMBR	FMBR
Previous preterm delivery	Baseline characteristics		Linkage to previous pregnancies identified in national medical birth registers (nullipara/ multipara without previous preterm birth/multipara with previous preterm birth)	SMBR	DMBR	FMBR
Any previous child (-ren) with birth defect (-s)	Baseline characteristics		Linkage to previous pregnancies identified in national medical birth registers (nullipara/ multipara without previous child with birth defect/multipara with previous child with birth defects)	SMBR	DMBR	FMBR
Maternal comorbidities	Baseline characteristics	From year 2000 until day of delivery	Diagnosis of hypertension or diabetes, antihypertensive treatment, antidiabetic treatment (Attachment A5 for ICD-10 codes)	SMBR SNPR	DMBR DNRP	FMBR HILMO
Prosthetic surgery	Baseline characteristics		Surgery code for prosthetic joint surgery before pregnancy (Attachment A6 for procedure codes)	SNPR	DNRP	-
Maternal hospitalization during pregnancy	Other exposure	90 days before LMP to delivery	ICD code for RA, PSA, AS, PsO, JIA during pregnancy	SNPR	DNRP	-
Prednisone and/or systemic oral corticosteroid	Other exposure		Filled prescription with ATC code H02AB Dosing was not assessed. Corticosteroids were divided into subgroups (prednisone/others). Gestational age at exposure was based on the date of filling the prescription.	SPDR	DPDR	FPDR

8.5. Data sources

Medical Birth Registers

The SMBR is a comprehensive pregnancy outcome database established in 1973 for the purpose of compiling information on pre- and perinatal risk factors and their significance for infant health. Statistics from SMBR data have formed the basis for more than 300 published scientific studies during the past decade. The EMA "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data" (EMA/CHMP/313666/2005, p. 8) specifically endorses the use of information from the SMBR for European register studies.

The SMBR is administered by the Swedish National Board of Health and Welfare, whose responsibilities include maintenance of high quality epidemiologic registers, production of national reports on public health and social conditions, and coordination of statistics within the areas of health and social services. Women whose pregnancy outcome information is contained in the SMBR are identified by the unique personal identification number (PIN) assigned to every legal resident of Sweden, which makes it possible to establish links between data contained in different Swedish national health registers. The PIN of an infant is also included in the Medical Birth Register and is linked with the mother's PIN. The register includes information on all live births and still births from gestational week 22. Before July 1st 2008 the cut-off for inclusion of still births was gestational week 28. Like in the Danish and Finish mecidal birth registers, data includes maternal, gestational and neonatal data, prospectively recording maternal age, weight, height, diagnoses before and developed during pregnancy, gestational age, birth weight, delivery complications and neonatal care.

The DMBR comprises information on all live births and stillbirths by women who are permanent residents of Denmark. Established in 1968 and computerized since 1973, the DMBR was originally intended to provide a means of monitoring infant health and the quality of pre- and perinatal care services, but has also come to be used extensively for epidemiologic research. As for the Swedish national health registers, the unique PINs of mothers and infants make possible the linkage of DMBR data with those available in other Danish health information databanks.

The FMBR, established in 1987 and administered by the National Institute for Health and Welfare (http://www.THL.fi/en_US/web/en), is a register that includes data on all live births and stillbirths of fetuses weighing at least 500 grams or having a gestational age of at least 22 weeks. Social and medical information about the mother is also included in the FMBR. The purpose of the FMBR is to provide data for statistical research on the development of maternity, obstetrical, and neonatal care in Finland. The FMBR collects baseline data on care and interventions for the mother during pregnancy and delivery and on infant outcome through the first 7 days. Data for less than 1% of the infant population is missing from the FMBR, and information on those cases is routinely obtained from the Central Population Register and the Cause-of-Death Register.

Patient registers

Apart from information on maternal diagnoses found in the medical birth registers, information on each health-care visit is captured in the national patient registers, including the Swedish National Patient Register (SNPR), the Danish National Register of Patients (DNRP) and the Finnish National Care Register for Health Care Institutions (HILMO). HILMO records diagnoses assigned at in- and outpatient visits to specialised care according to ICD-codes. Procedures

including prostethic surgery is also recorded by procedure codes and data were available for this report from the SNPR and the DNRP.

Prescribed drug registers

The Danish Register of Medicinal Product Statistics (DPDR) was set up in 1994 and includes data on all filled precriptions by each individual by substance, date, amount and preparation. The Swedish Prescribed Drug Register (SPDR) and the Finnish Register on Prescribed Medicine (FPDR) provide similar information. Specific prescribed dose for the individual is, however, generally not recorded, and calculations for duration of treatment is based on the collected amount of drugs.

Disease specific registers

For the Swedish and Finnish cohorts, additional information on use of biologics can be obtained from the quality register of AntiRheumatic Therapies In Sweden (ARTIS) and the national register for biologic treatment in rheumatic diseases in Finland (ROB-FIN), respectively. These registers were set up upon the introduction of biologic treatment in the early 2000's to monitor the utilization and complications of biologic treatment. The data includes substance, date of initiation and discontinuation of treatment.

Linking the data

Distinct advantages of this study design are the comprehensive nature of the prenatal and pregnancy outcomes data that are available from the birth registers for both women and infants, and the potential to obtain additional maternal information as well as reasonably robust infant follow-up information due to the linkages between maternal and infant PIN numbers and among the several Swedish, Danish, and Finnish national registers. To ensure good coverage of data, information on some variables were obtained from several data sources (Table 2). For maternal disease during pregnancy information was obtained from both the national birth registers and the patient registers. Similarly, information on systemic treatment for chronic inflammatory diseases was obtained from the drug registers and for certain treatments also from the patient registers or the disease specific registers (ARTIS and ROB-FIN). All available information to define exposures and in assessment of outcomes was obtained from the various data sources.

8.6. Bias

Bias may be present in observational studies when non-comparable information is obtained from different sources. Bias can be described and assessed by identifying sources of selection bias, information bias and confounding respectively.

Identification and information on study participants, women and their infants, was obtained from the national health registers in Sweden, Denmark and Finland. Virtually all births, health care visits, drug prescriptions and deaths are recorded, limiting selection bias in the inclusion of the study population. Reporting to the registers is mandatory and the study participants could not agree nor refute to participate in the study.

This study used prospectively collected data from the national health registers, limiting information bias due to differential recall that might occur when information is obtained retrospectively. However, misclassification may occur during data collection, recording and coding or in the measurement of exposure of interest, study outcomes and covariates. In this study, filled prescriptions of etanercept were used as the main source of data to define exposure

to this drug, and filled prescriptions of other systemic treatment defined the comparison group. The filling of prescriptions may not necessarily be equivalent to actual drug exposure, in part or entirely, since the administration of the drug is not recorded in the drug registers. Due to the prospective and routine collection of all data, the possible errors are, however, most likely to be independent of the subsequently recorded outcomes. As a result, non-differential misclassification may yield weaker observed associations.

In observational studies, where exposure is not randomized there is a risk of confounding. To minimize such risks, the characteristics of the study participants were taken into consideration in the design and through adjustments in the analyses.. The analyses were adjusted step-wise for pre-defined confounders such as country, maternal disease, parity, smoking and other medical treatments. However, some potentially confounding variables were not captured in the study. In particular, there was no explicit measure of disease activity, but proxies for disease activity in the form of history of prostethic surgery, hospitalization during pregnancy and corticosterod treatment during pregnancy were used to adjust for these potential confounders. It may be that women with greater risk for adverse outcomes, associated with their underlying disease activity, were more often exposed to etanercept than women with no anti-TNF treatment. Such bias would in this study, if anything, overestimate the adverse effects of etanercept.We used SGA as a proxy for intrauterine growth restriction and the most important factors that are associated with SGA, such as birth defects, maternal diseases and smoking were taken into consideration in the design or the analyses.

8.7. Study size

We included 522 women with RA, JIA, PsA, AS or PsO treated with etanercept in the period between 90 days before LMP until delivery. Of these, 425 women were treated with etanercept between LMP and 90 days after LMP. For the comparison group, 3,508 women with RA, JIA, PsA, AS or PsO and non-biologic systemic treatment in the period between 90 days before LMP until delivery were included.

Power calculation prior to the conduct of the present study were based on the number of exposed children in the pooled dataset with information from Sweden, Denmark and Finland until December 2012. There were 435 in the etanercept group vs 2588 in the non-biologic systemic group with treatment within 90 days prior to LMP until delivery, and the prevalence of major birth defects of 4.5% in the non-biologic systemic cohort. We estimated by power analyses that a 1.78-times higher frequency of major birth defect could be detected in the etanercept exposed cohort compared to the non-biologic systemic treatment cohort with 80% power at a 5% significance level (2-sided test).

An alternative calculation, conservatively addressing the potential dependence between children with the same mother, assumes that each woman only contributes with one child (378 in the etanercept cohort vs 2149 in the non-biologic systemic cohort) yielded a corresponding detectable relative increase of 1.84. When restricting exposure to etanercept within 90 days before LMP or during the 1st trimester of pregnancy (240 exposed children), a power calculation suggested a detectable relative risk of 2.04.

Table 3 Power calculations

Given 80% power at a 5% significance level (2-sided test)

Non-biologic vs. Etanercept	Background Rate	Detectable Event Rate Increase
All 2588 vs. 435	4.5%	1.78-fold
	3%	2.00-fold
	1%	3.00-fold
	0.5%	4.00-fold
One infant per woman 2149 vs. 378	4.5%	1.84-fold
	3%	2.07-fold
	1%	3.10-fold
	0.5%	4.40-fold
Exposure within 90 days before LMP to 90 days after LMP 2588 vs. 240	4.5%	2.04-fold
	3%	2.33-fold
	1%	3.70-fold
	0.5%	5.40-fold

8.8. Statistical methods

All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC).

8.8.1. Main summary measures

Descriptive statistics such as mean, median, standard deviations, and range for continuous variables; counts and percentages for categorical variables were used to summarize data. The percentages were calculated based on available data for each specific characteristic.

Descriptive statistics were summarized for the overall population and by country for the following: maternal characteristics and diagnoses, birth outcomes and infants' outcomes. Summary tables were also provided for type of anti-TNF exposure during pregnancy as well as trimester of exposure. In addition, summaries were provided for birth defects and the type of infections in the first year of life.

8.8.2. Main statistical methods

Modeling analyses were performed to evaluate the risk of etanercept exposure during pregnancy, compared with the group with systemic non-biological treatment, regarding birth defects, serious infections, opportunistic infections and birth outcomes. The general population group was included as a point of reference, but not included in formal comparison analyses. The dichotomized endpoints were analyzed by exact logistic regression. In the analyses, five different OR comparison models were performed. The potential confounders were selected based on earlier studies published in peer-reviewed literature (Norgaard et al., 2010).

- OR1: Unadjusted comparison
- OR2: Adjusted for country (Sweden, Denmark, Finland)
- OR3: Adjusted for country and maternal disease (RA, PsA, AS, PsO, JIA)
- OR4: Adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy
- OR5: Adjusted for country, maternal disease, parity, maternal age, smoking in early pregnancy, history of prosthetic surgery, hospitalization during pregnancy, and corticosteroid treatment

In the analyses of birth defects and infections in the first year of life, only live-births were included. The analyses of birth outcomes included live-births and stillbirths.

8.8.3. Missing values

Since missing data are minimal in the data sets, observed data was used in the analysis without imputation, apart from LMP. The total population was used to calculate the proportion of patients who had missing data. Missing values for LMP were imputed by subtracting 278 days from delivery date.

8.8.4. Sensitivity analyses

In the sensitivity analyses, women with potentially teratogenic drugs during pregnancy (Attachment A1) were excluded from the analyses. In additional analyses, chromosomal defects were excluded from the analyses of birth defects, given their presumed different mechanism of occurrence before implantation. Exposure in different time periods were assessed in separate sensitivity analyses, by changing the time period for the etanercept exposed cohort (Table 4).

Exposure in the same defined different time periods were also assessed in separate analyses, by changing the time period for both the etanercept exposed cohort and the non-biologic systemic cohort. Since some women contributed with more than one birth during the study period, adjustments were made by generalized estimating equation (GEE) methods in sensitivity analyses, where possible.

Table 4. Time windows for sensitivity analyses

	Primary analysis	Sensitivity analyses
Major birth defects	1st trimester, i.e. LMP to 90 days after LMP	1. 90 days before LMP to 90 days after LMP 2. 30 days before LMP to 90 days after LMP
All birth defects, minor birth defects	1st trimester, i.e. LMP to 90 days after LMP	1. 90 days before LMP to 90 days after LMP 2. 30 days before LMP to 90 days after LMP
Other birth outcomes, and infections	90 days before LMP to birth	1. 90 days before LMP to 90 days after LMP 2. LMP to 90 days after LMP 3. 91 days after LMP to 180 days after LMP 4. 181 days after LMP to delivery

8.9. Quality control

The study was conducted in accordance with legal and regulatory requirements, and follows generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology, and the Guidelines for Good Pharmacovigilance Practice (GVP), issued by the EMA. Data were managed and analyzed in accordance with the current version of the Quality manual 3.0 at CPE, Karolinska Institutet, Sweden.

8.10. Protection of human subjects

While there are no assigned interventions in this register study, the study was performed following the required approval by the Regional Ethical Review Board of Karolinska Institutet in Stockholm, Sweden and Aarhus University in Aarhus, Denmark, and the THL (National Institute for Health and Welfare) in Finland, and as required by any relevant government agencies, and was conducted in conformance with all applicable Swedish, Danish, and Finnish regulatory safeguards of patient confidentiality. In the event of a health authority audit, Karolinska Institutet would make available the de-identified analytic datasets. The health authority would request approval from the Swedish, Danish, and Finnish National Boards of Health and Welfare to audit patient identified data.

De-identified pregnancy outcome information were obtained from the Swedish, Danish, and Finnish Medical Birth Registers for all women with the indications of interest who have and who have not been exposed to etanercept during pregnancy during the specified study time period. De-identified information were obtained from Swedish, Danish, and Finnish national hospitalization and prescription pharmacy registers concerning the health status of the infants of these women during their first year of life. Information from all of these sources was obtained with the collaboration and assistance of Dr. Helle Kieler of the Karolinska Institutet in Stockholm, Sweden, Dr. Henrik Toft-Sorensen of Aarhus University Hospital in Aarhus, Denmark, and Dr. Mika Gissler (or designees) at THL (National Institute for Health and Welfare) in Finland.

8.11. Patient information and consent

Not Applicable.

8.12. Patient withdrawal

Not Applicable.

8.13. Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

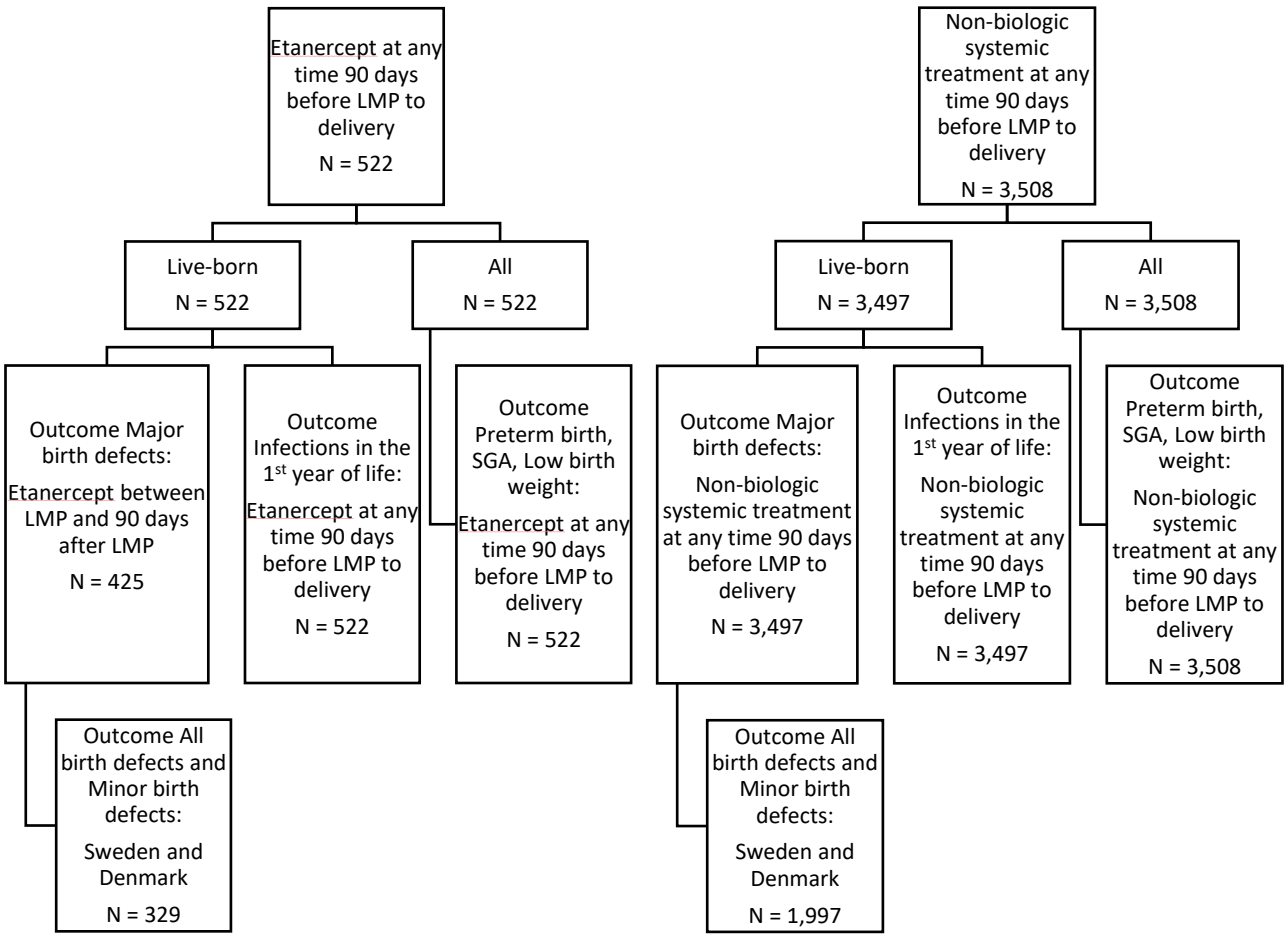
The study was conducted according to the approval from the Regional Ethical Review Board in Stockholm, registration number 2009/1250-31/4 and amendment 4-2178/2017.

9. RESULTS

9.1. Participants

This study included 522 pregnancies in women exposed to etanercept within 90 days before LMP until delivery. Of these, 425 were exposed during the first 90 days of pregnancy, which was the exposure definition in the primary outcome analysis. The comparison group, of women with the diseases of interest and other non-biologic systemic treatment, contributed with 3,508 pregnancies. For the general population without the diseases of interest and without biologic or non-biologic treatment, a total of 1,676,174 birth were included. For the analyses on birth defects and infections in the first year of life, only live-born infants were included. For all and minor birth defects, only data from Sweden and Denmark were included. All births, live- and stillborn, were included in the analyses of birth outcomes. A flowchart of participants in each group of analyses is presented in Figure 1.

Figure 1. Flowchart of participants in each group of analyses.



9.2. Descriptive data

Descriptive statistics are presented in Table 5. Considering the year of birth, the number of women exposed to etanercept during pregnancy increased yearly in the first years of the study period, with 10 exposed from July 1st to December 31st 2006, 34 in 2007, 72 in 2009 and 95 in 2013. The non-biological systemic treatment remained at the similar level over the years. The majority of the women exposed to etanercept were from the Swedish population, 71.1%.

Most of the included women had RA (58.4% in the etanercept exposed cohort and 52.8% in non-biologic systemic cohort), while others had either JIA (20.1% in the etanercept exposed cohort and 13.8% in the non-biologic systemic cohort), AS (9.4% in the etanercept exposed cohort and 15.0% in the non-biologic systemic cohort), PsA (8.2% in the etanercept exposed cohort and 9.1% in the non-biologic systemic cohort), or PsO (3.8% in the etanercept exposed cohort and 9.3% in the non-biologic systemic cohort).

Table 5. Descriptive statistics of study population

		Etanercept N = 522		Non-bio Systemic N = 3,508		General population N = 1,676,174	
Variable	**Category**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total		522	100.0	3508	100.0	1676174	100.0
Year of birth	**2006**	10	1.9	179	5.1	110131	6.6
	2007	34	6.5	392	11.2	221874	13.2
	2008	51	9.8	420	12.0	225843	13.5
	2009	72	13.8	472	13.5	225432	13.4
	2010	73	14.0	530	15.1	231360	13.8
	2011	95	18.2	489	13.9	222032	13.2
	2012	92	17.6	513	14.6	221231	13.2
	2013	95	18.2	513	14.6	218271	13.0
Country	**Denmark**	48	9.2	554	15.8	453758	27.1
	Finland	103	19.7	1505	42.9	434172	25.9
	Sweden	371	71.1	1449	41.3	788244	47.0
Maternal age	**<=12**	.	.	.	.	3	0.0
	13-19	3	0.6	26	0.7	28553	1.7
	20-24	26	5.0	263	7.5	219211	13.1
	25-29	110	21.1	879	25.1	504323	30.1
	30-34	205	39.3	1341	38.2	576435	34.4
	>=35	178	34.1	999	28.5	347638	20.7
	Missing	.	.	.	.	11	0.0
Parity (categorical) [a]	**0**	251	48.1	1551	44.2	730032	43.6
	>0	268	51.3	1953	55.7	937700	55.9
	Missing	3	0.6	4	0.1	8442	0.5

Table 5. Descriptive statistics of study population

		Etanercept N = 522		Non-bio Systemic N = 3,508		General population N = 1,676,174	
Variable	**Category**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
BMI	**11.0-19.9**	33	6.3	298	8.5	145906	8.7
	20.0-24.9	264	50.6	1633	46.6	818471	48.8
	25.0-29.9	136	26.1	872	24.9	409272	24.4
	30+	59	11.3	540	15.4	209110	12.5
	Missing	30	5.7	165	4.7	93415	5.6
Maternal disease	**Rheumatoid arthritis**	305	58.4	1851	52.8	Not applicable[b]	
	Juvenile idiopathic arthritis	105	20.1	485	13.8		
	Ankylosing spondylitis	49	9.4	527	15.0		
	Psoriatic arthritis	43	8.2	320	9.1		
	Psoriasis	20	3.8	325	9.3		
Smoking	**No**	474	90.8	3063	87.3	1448832	86.4
	Yes	36	6.9	332	9.5	172747	10.3
	Missing	12	2.3	113	3.2	54595	3.3
Any birth defect in previous pregnancies	**Nullipara**	251	48.1	1551	44.2	730032	43.6
	Multipara without history	261	50.0	1843	52.5	895888	53.4
	Multipara with history	10	1.9	114	3.2	50254	3.0
Any previous preterm delivery	**Nullipara**	251	48.1	1551	44.2	730032	43.6
	Multipara without history	238	45.6	1773	50.5	879988	52.5
	Multipara with history	33	6.3	184	5.2	66154	3.9
Maternal comorbidity[c]	**Yes**	51	9.8	165	4.7	49183	2.9
History of prostethic surgery[d]	**Yes**	70	13.4	120	3.4	5387	0.3
Hospitalization during pregnancy[d]	**Yes**	12	2.3	31	0.9	Not applicable[b]	
Prednisone	**Yes**	17	3.3	126	3.6	Not applicable[b]	
Corticosteroids other than prednisone	**Yes**	330	63.2	1863	53.1	Not applicable[b]	
Treatment timing	90 days before LMP to birth	522	100.0	3508	100.0	Not applicable[b]	
	90 days before LMP to LMP	476	91.2	2692	76.7		
	LMP to 90 days after LMP	425	81.4	2705	77.1		
	91 days after LMP to 180 days after LMP	98	18.8	2238	63.8		
	181 days after LMP to birth	69	13.2	2074	59.1		

[a]Parity: the number of times a woman has given birth to an infant with a gestational age of 24 weeks or more, regardless of whether the infant was born alive or was an intrauterine death.

[b] Not applicable. The population control cohort does not include women with the diseases or treatment of interest.

[c]Treatment for or diagnosis of diabetes or hypertension at baseline

[d]Available for Sweden and Denmark

Women with the diseases of interest, regardless of which exposure among those treated, were less often below 25 years of age, compared with the general population, for etanercept 5.6%, for the non-biologic systemic group 8.2% and for the general population 14.8%. Median maternal age was 33.0 for the women with etanercept treatment and 32.0 for the women in the non-biologic systemic treatment group, compared to 30.0 in the general population (Table 6). Multiparity was similar across treatment groups. In each group, most women had a pre-pregnancy BMI within the normal range of 20.0 to 24.9 kg/m^2, and the median BMI was 23.4, 23.6 and 23.3 in the three groups, respectively.

Table 6. Descriptive statistics of study population, continuous variables

	Etanercept				Non-bio Systemic				General population			
Variable	N	mean	median	std	N	mean	median	std	N	mean	median	std
Maternal age (yr) [a]	522	32.5	33.0	4.8	3508	31.6	32.0	4.9	1676163	30.2	30.0	5.2
BMI [a]	492	24.3	23.4	4.3	3343	24.8	23.6	5.0	1582759	24.4	23.3	4.8

[a]N lower due to missing values

9.3. Outcome data

A descriptive summary of infant health outcomes and birth outcomes are provided in Table 7. The results of the different analyses are discussed for each individual outcome of interest in the sections that follow. N in the table describes the included participants in each group of analyses, according to the flowchart in Figure 1.

Table 7. Outcome data

	Etanercept			Non-bio Systemic			General population		
Outcome	**N**	**Events**	**Rate (%)**	**N**	**Events**	**Rate (%)**	**N**	**Events**	**Rate (%)**
Birth defects[a]									
Any major birth defect	425	24	5.65	3497	163	4.66	1670082	71666	4.29
All birth defects[b]	329	33	10.03	1997	167	8.36	1237196	89059	7.20
Minor birth defects[b]	329	14	4.26	1997	90	4.51	1237196	44693	3.61
Birth outcomes[c]									
Preterm birth (<37 weeks)	522	60	11.49	3508	347	9.89	1676174	106239	6.34
Very preterm birth (<32 weeks)	522	5	0.96	3508	48	1.37	1676174	22465	1.34
Small for gestational age	522	26	4.98	3508	118	3.36	1676174	36376	2.17
Low birth weight (<=2500 g)	522	55	10.54	3508	286	8.15	1676174	85420	5.10
Very low birth weight (<=1500 g)	522	6	1.15	3508	45	1.28	1676174	22489	1.34
Stillbirth	522	0	0.00	3508	11	0.31	1676174	6092	0.36
Infant infections[d]									
Infectious pathogens in first year of life	522	162	31.03	3497	910	26.02	1670082	391007	23.41
Opportunistic infections pathogens in first year of life	522	14	2.68	3497	72	2.06	1670082	30689	1.84

[a] Only live-born infants included in the analyses.
[b] Women and infants from Finland not included in the analyses.
[c] All live-born and still-born included in the analyses.

[d] Only live-born infants included in the analyses.

9.4. Main results

Unadjusted rates and the results of modelled analyses are presented for all study birth outcomes and infant outcomes.

- OR1: Unadjusted comparison
- OR2: Adjusted for country (Sweden, Denmark, Finland)
- OR3: Adjusted for country and maternal disease (RA, PsA, AS, PsO, JIA)
- OR4: Adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy
- OR5: Adjusted for country, maternal disease, parity, maternal age, smoking in early pregnancy, history of prosthetic surgery, hospitalization during pregnancy, and corticosteroid treatment

9.4.1. Birth defects

The proportion of infants diagnosed with any major birth defect was 5.65% for etanercept and 4.66% for the non-biologic systemic therapy group (Table 8). In the primary analysis comparing the rates of any major birth defect among women treated with etanercept in the first trimester and women exposed to non-biologic systemic treatment during pregnancy, the crude OR was 1.22 (95% CI: 0.79-1.90), and the corresponding OR adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy was 0.96 (95% CI: 0.58-1.60).

Table 8. Any major birth defect: Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	1.22	0.79	1.90	0.3683
OR2	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	1.21	0.77	1.90	0.4009
OR3	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	1.21	0.77	1.90	0.4206
OR4	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	0.96	0.58	1.60	0.8810
OR5	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	0.92	0.55	1.53	0.7388

The proportion of infants diagnosed with any birth defect, major or minor, was 10.03% for etanercept and 8.36% for the non-biologic systemic therapy group (Table 9). In the secondary

analyses of any birth defect, major or minor, which only included Danish and Swedish births, the crude OR was 1.22 (95% CI: 0.83-1.81) and the adjusted OR was 1.08 (95% CI:0.70-1.69).

For minor birth defects, the corresponding numbers were 4.26% and 4.51%, respectively (Table 10). The crude OR was 0.94 (95% CI: 0.53-1.68) and the adjusted OR was 0.92 (95% CI: 0.50-1.72). There were no patterns in the types of major or minor birth defects for etanercept when examined by organ system or by individual events (Appendix table 1).

Across the analyses of any major birth defect, any birth defect and any minor birth defect, there was no increased risk for these events following exposure to etanercept relative to the non-biologic systemic therapy group (Tables 8-10).

Table 9. Any birth defect, major or minor: Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.22	0.83	1.81	0.3179
OR2	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.24	0.83	1.85	0.2929
OR3	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.23	0.82	1.84	0.3221
OR4	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.08	0.70	1.69	0.7189
OR5	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.01	0.64	1.58	0.9710

Table 10. Any minor birth defect: Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.94	0.53	1.68	0.8380
OR2	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.95	0.53	1.71	0.8706
OR3	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.93	0.52	1.68	0.8149
OR4	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.92	0.50	1.72	0.7956
OR5	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.91	0.49	1.70	0.7649

9.4.1.1. Sensitivity analyses

We performed sensitivity analyses in which women who had filled prescriptions of potentially teratogenic drugs (according to list in Attachment A1) during pregnancy were excluded. In separate analyses, chromosomal anomalies were not counted as a type of major birth defect. Neither of these actions changed the results for any major birth defect, any birth defect or any minor birth defect (Appendix tables 2-6). Considering the timing of exposure, changing the definition of etanercept exposure to range from 90 days before LMP to 90 days after LMP, and from 30 days before LMP to 90 days after LMP did not change the results (Appendix tables 7-9). The results after changing the definition of the exposure window for the non-biologic systemic group to align with the exposure window for etanercept exposed group, from LMP to 90 days after LMP, are presented in tables 25-27 in Appendix. The ORs adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy were 0.97 (95% CI: 0.58-1.64) for any major birth defect, 1.06 (95% CI: 0.67-1.68) for any birth defect (major or minor), and 0.89 (95% CI: 0.47-1.69) for any minor birth defect. Performing GEE analyses did not change OR1-OR3, or the point estimates for OR4-OR5. For OR4-OR5 the Hessian matrix was not positively definite so CIs and p-values could not be reported (Appendix tables 39-41).

9.4.2. Birth outcomes

9.4.2.1. Preterm birth

The proportion of infants delivered preterm (<37 gestational weeks) was as follows: Etanercept (11.49%), non-biologic systemic therapy (9.89%). There was no association between etanercept treatment during pregnancy and preterm birth (Table 11), or very preterm birth (Table 12) in the primary comparison with the non-biologic systemic therapy group. For preterm birth, the crude OR was 1.18 (95% CI: 0.88-1.58) and the corresponding OR adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy was 1.16 (95% CI: 0.84-1.61).

Table 11. Preterm birth (<37 weeks): Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.18	0.88	1.58	0.2573
OR2	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.14	0.85	1.54	0.3847
OR3	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.12	0.83	1.51	0.4786
OR4	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.16	0.84	1.61	0.3606
OR5	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.15	0.83	1.59	0.4140

Table 12. Very preterm birth (<32 weeks): Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.70	0.28	1.76	0.4449
OR2	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.66	0.26	1.68	0.3771
OR3	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.66	0.25	1.70	0.3835
OR4	Non-biologic systemic therapy	3508	48	1.37	1.000	.	.	.
	Etanercept	522	5	0.96	0.72	0.27	1.90	0.5090
OR5	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.75	0.28	1.99	0.5591

9.4.2.2. Birth size

9.4.2.2.1. Low birth weight

The proportion of infants with low birth weight (≤2500 grams) was as follows: Etanercept (10.54%), non-biologic systemic therapy group (8.15%). The logistic regression analyses indicated a slightly increased risk estimate concerning exposure to etanercept and low birth weight, which, however, was not statistically significant (Table 13). The crude OR was 1.33 (95% CI: 0.98-1.80) and the corresponding OR adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy was 1.38 (95% CI: 0.98-1.93). There was no association between etanercept treatment and very low birth weight (≤1500 grams) (Table 14).

Table 13. Low birth weight (<=2500 g): Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.33	0.98	1.80	0.0684
OR2	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.29	0.94	1.76	0.1097
OR3	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.29	0.94	1.76	0.1191
OR4	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.38	0.98	1.93	0.0663
OR5	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.35	0.96	1.90	0.0822

Table 14. Very low birth weight (<=1500 g): Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.90	0.38	2.11	0.7994
OR2	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.85	0.35	2.03	0.7094
OR3	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.86	0.35	2.08	0.7334
OR4	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.94	0.38	2.33	0.8912
OR5	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.97	0.39	2.42	0.9438

9.4.2.2.2. Small for Gestational Age

The proportion of infants born SGA was 4.98% in the etanercept group, 3.36% in the non-biologic systemic therapy group. Although there was no statistically significant increase in observed risks in the comparison of the etanercept group and the non-biologic systemic therapy group in the adjusted model OR4, the risk estimate was slightly elevated (Table 15) The crude OR was 1.51 (95% CI: 0.98-2.33) and the corresponding OR adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy was 1.32 (95% CI: 0.80-2.16).

Table 15. Small for gestational age: Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.51	0.98	2.33	0.0650
OR2	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.57	1.00	2.45	0.0484
OR3	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.51	0.96	2.38	0.0759
OR4	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.32	0.80	2.16	0.2755
OR5	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.27	0.77	2.08	0.3540

9.4.2.3. Stillbirth

There were no cases of stillbirth in the etanercept group and few in the non-biologic systemic therapy group. Formal analyses could therefore not be performed.

9.4.2.4. Sensitivity analyses

When women treated with potentially teratogenic drugs (Attachment A1) were excluded, no increased risks were observed for preterm birth, very preterm birth, SGA, low birth weight or very low birth weight (Appendix tables 10-14).

Analyses of risks of preterm birth and SGA for treatment with etanercept in different time periods: 90 days before LMP to 90 days after LMP, LMP to 90 days after LMP, 91 days after LMP to 180 days after LMP, 181 days after LMP to birth for OR4, and adjusted for country, maternal disease, parity, maternal age and smoking in early pregnancy are presented in Table 16. OR1-OR5 are presented in Appendix tables 15-19. Looking at the size of the exposed group in these analyses reveals that treatment was clearly the most common in early pregnancy: 522 women were treated at some point from 90 days before LMP to delivery, 425 in the first trimester, and only 98 in the second trimester and 69 in the third trimester.

There was a significant increase in risk estimates observed for SGA when exposure was in the second trimester, OR4 2.40 (95% CI: 1.11-5.18) or in the third trimester, OR4 2.96 (95% CI: 1.23-7.17) (Table 16). Further adjustment for history of prostethic surgery, hospitalization during pregnancy, and corticosteroid treatment revealed similar results (Appendix table 17). In sensitivity analyses, changing the time window for both cohorts, the risk estimates for SGA in the second trimester, OR4 2.06 (95% CI:0.94-4.54) and in the third trimester, OR4 2.75 (95% CI: 1.11-6.77), were slightly attenuated (Appendix table 28). Performing GEE analyses did not change the results. For preterm birth, very preterm birth and very low birth weight, OR4-OR5 the Hessian matrix was not positively definite so CIs and p-values could not be reported for OR4-OR5 (Appendix tables 42-46).

A slightly increased risk of low birth weight was observed. Looking at treatment with etanercept in the first trimester, the OR was 1.53 (95% CI: 1.08 -2.18), looking at treatment with etanercept in the second trimester, the OR was 1.63 (95% CI: 0.85-3.13), and looking at treatment with etanercept in the third trimester, the OR was 1.34 (95% CI: 0.57-3.18), when adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy (Table 16). Changing the time period to the first trimester for both cohorts, the adjusted OR was 1.39 (95% CI: 0.97-1.99), which was slightly attenuated (Appendix table 28).

Table 16. Birth outcomes (Preterm birth, Low Birth Weight, Small for Gestational Age): Results of sensitivity analysis of different time windows. OR4.

Time window	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
Pretem birth (<37 weeks)								
90 days before LMP to 90 days after LMP	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	517	60	11.61	1.17	0.85	1.62	0.3449
LMP to 90 days after LMP	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.

Table 16. Birth outcomes (Preterm birth, Low Birth Weight, Small for Gestational Age): Results of sensitivity analysis of different time windows. OR4.

Time window	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
	Etanercept	425	53	12.47	1.33	0.95	1.85	0.0987
91 days after LMP to 180 days after LMP	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	98	11	11.22	1.30	0.68	2.50	0.4287
181 days after LMP to birth	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	69	4	5.80	0.51	0.16	1.66	0.2660
Low birth weight (≤2500 g)								
90 days before LMP to 90 days after LMP	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	517	55	10.64	1.38	0.98	1.94	0.0617
LMP to 90 days after LMP	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	425	47	11.06	**1.53**	**1.08**	**2.18**	**0.0175**
91 days after LMP to 180 days after LMP	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	98	11	11.22	1.63	0.85	3.13	0.1445
181 days after LMP to birth	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	69	7	10.14	1.34	0.57	3.18	0.4997
SGA								
90 days before LMP to 90 days after LMP	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	517	26	5.03	1.33	0.81	2.18	0.2662
LMP to 90 days after LMP	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	425	17	4.00	1.19	0.69	2.06	0.5303
91 days after LMP to 180 days after LMP	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	98	8	8.16	**2.40**	**1.11**	**5.18**	**0.0256**
181 days after LMP to birth	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	69	7	10.14	**2.96**	**1.23**	**7.17**	**0.0159**

9.4.3. Infant infections

9.4.3.1. Serious infections

The proportion of infants diagnosed with an infection in the first year of life was 31.03% for etanercept and 26.02% for the non-biologic systemic treatment (Table 17). In the crude logistic regression analysis (OR1), the risk estimate was 1.28 (95% CI: 1.05-1.56). After adjusting for further potential confounders in OR2 to OR5, no significantly increased risk of infections following exposure to etanercept remained.

Table 17. Infections in the first year of life: Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.28	1.05	1.56	0.0159
OR2	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.05	0.86	1.29	0.6408
OR3	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.06	0.86	1.30	0.5932
OR4	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.00	0.80	1.25	0.9891
OR5	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	0.99	0.79	1.24	0.9473

9.4.3.2. Opportunistic infections

The proportion of infants diagnosed with an opportunistic infection in the first year of life was 2.68% for etanercept and 2.06% for the non-biologic systemically treated group (Table 18). The risk estimate after adjustment for country, maternal disease, parity, maternal age and smoking (OR4), was 1.36 (95% CI: 0.67-2.78), signifying no observed association between etanercept and opportunistic infections in the infant's first year of life.

Table 18. Opportunistic infections in the first year of life: Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.31	0.73	2.34	0.3595
OR2	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.69	0.93	3.07	0.0865
OR3	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.56	0.85	2.85	0.1526
OR4	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.36	0.67	2.78	0.3972
OR5	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.28	0.63	2.63	0.4962

9.4.3.3. Sensitivity analyses

Excluding women treated with potentially teratogenic drugs (Attachment A1), revealed similar results, OR4 was 1.00 (95% CI: 0.80-1.25) for infections (Appendix table 20) and 1.30 (95% CI: 0.62-2.75) for opportunistic infections (Appendix table 21). Considering treatment with etanercept in different time periods: 90 days before LMP to 90 days after LMP, LMP to 90 days after LMP, 91 days after LMP to 180 days after LMP, 181 days after LMP to birth revealed no significant associations with serious infections or opportunistic infections. The risk estimate for treatment 91 days after LMP to 180 days after LMP, i.e. the second trimester was elevated, 2.58 (95% CI: 0.90-7.42) (Appendix table 22-23). Performing GEE analyses did not change the results (Appendix tables 47-48).

10. DISCUSSION

10.1. Key results

This study consisted of 522 pregnant women exposed to etanercept before delivery. The main comparison group was women exposed to non-biologic systemic therapy for the same diseases as the etanercept exposed, and included data for 3508 pregnancies.

Of note is that the disease distribution differed between the groups. While RA was the most common for both those exposed to etanercept and the comparison group of non-biologic systemic therapy, AS and PsO were more common in the non-biologic systemic therapy group, and JIA was more common in the etanercept group.

Several outcomes were assessed in this report, for both infant outcomes and birth outcomes. In the primary analyses of major birth defects, there was no association with etanercept exposure when comparing with the non-biologic systemic therapy group. The secondary analyses of all birth defects, minor births defects, preterm birth, low birth weight, SGA and stillbirth revealed no association with etanercept exposure. Sensitivity analyses in which the timing of exposure was considered, there was an increased risk of SGA for etanercept exposure in late pregnancy, and a slightly increased risk of low birth weight with etanercept treatment in the first 90 days after LMP. However, as the numbers included in these analyses were small, the results should be interpreted with caution. In addition, as several analyses were performed, the findings of increased risks found in some analyses may be attributed to chance findings and simply due to multiple testing. Also, confounding by disease activity cannot be ruled out as those prescribed etanercept may be more severely ill and with more active disease than their comparators.

10.1.1. Birth defects

The cumulative prevalence of major birth defects was comparable between the etanercept group (5.65%), the non-biologic systemic therapy group (4.66%) and the general population (4.29%), as it was for all birth defects and minor birth defects. Most etanercept exposures occurred in the 90 days before LMP and during the first trimester, suggesting that treatment was discontinued before or at the time point, when pregnancy was confirmed. Generally, and in most of the analyses, there was no difference in the risk of birth defects (major or minor), or in birth defects after exclusion of chromosomal defects for etanercept exposure compared with the non-biologic systemic treatment. The primary analysis defined exposure as occurring in the first trimester, and the results were comparable in sensitivity analyses with different timing of exposure. These findings

are in line with the current literature (Diav-Citrin, Otcheretianski-Volodarsky, Shechtman, & Ornoy, 2014; Marchioni & Lichtenstein, 2013; Schnitzler et al., 2011), (Broms et al., 2016), though it should be noted that the finding reported in the paper by Broms et al included partly the same data as in the current report.

In contrast, Weber-Schoendorfer (Weber-Schoendorfer et al., 2015) found an increased rate of birth defects among infants to women exposed to anti-TNF therapy during pregnancy. However, the exposed group was compared to the general population with a lower rate of birth defects than that observed in the comparison group included in the present study and there was no disease matching in the comparisons.

10.1.2. Birth outcomes

In the primary analyses, in which etanercept treatment was defined as exposure at any time in the 90 days before LMP and/or during pregnancy until birth, there was no significantly increased risk of preterm birth, very preterm birth, low birth weight, very low birth weight or SGA. The risk of stillbirth could not be assessed due to no stillbirths among the etanercept exposed group. In the sensitivity analyses, where different time windows of exposure were considered, there was an observed significantly increased risk estimate for SGA concerning exposure in the second and third trimester, and suggesting an association with etanercept exposure in late pregnancy. The analyses included 98 and 69 exposed women, respectively, and yielded broad CIs, OR4 2.40 (95% CI: 1.11-5.18) and 2.96 (95% CI: 1.23-7.17), respectively. Both estimates were attenuated in the sensitivity analyses where treatment exposure was required in the corresponding trimester for both cohorts. Further adjustments, which included previous prostethic surgery, hospitalization during pregnancy and use of corticosteroids as proxies for disease activity had no effect on these results. The indication of a slightly increased risk concerning exposure to etanercept and low birth weight, was further analyzed in the sensitivity analyses. In one instance a statistically significant estimate was observed with etanercept exposure during the first trimester, where the OR was 1.53 (95% CI: 1.08 -2.18) when adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy. The risk estimates for the other trimesters were similar, but not statistically significant. Thus an association between exposure to etanercept in pregnancy and low birth weight cannot be ruled out.

10.1.3. Infant infections

There was no association observed for exposure to etanercept in pregnancy and serious infections, including opportunistic infections, in the infant's first year of life.

10.2. Limitations

The Swedish, Danish, and Finnish registers have nationwide routine data collection on prescribed drugs, births, and health outcomes linked on an individual patient level, and thus provide a unique opportunity to study the safety of drug use during pregnancy. All pharmacy, maternal, and perinatal data in the registers is obtained prospectively, thereby precluding recall bias.

However, there were a number of limitations related to the data collected in this study.

- No information for pregnancies that may have ended before week 22 of gestation was available, and nothing can be concluded about drug exposure and pregnancies that may

have ended before week 22. For Swedish data before July 1st 2008, this is also true for stillbirths before week 28 of gestation, prior to a change in the collection of data was made to align with the rest of the data included. Data for early spontaneous pregnancy loss or voluntary termination of pregnancy is not available.

- No data were available for alcohol or recreational drug use.
- Data were limited for disease severity or concomitant medication use, and the only available proxies for disease severity in the adjusted analyses called OR5 were history of prosthethic surgery, hospitalization during pregnancy and corticosteroid treatment. Adjusting for these proxies may not have sufficiently controlled for differences in disease activity.
- Drug exposure may be misclassified since filled prescriptions were used as a proxy for actual drug intake.
- The detection of birth defects and infections is subject to misclassification. There may be detection bias, in that women with etanercept treatment and their infants may be followed more closely than women with non-biologic systemic treatment. However, this would likely bias results away from the null, and since no association between etanercept exposure and birth defects was observed, this is unlikely.
- It was not possible to evaluate with any certainty the strength of dose of etanercept administered at each record of exposure.
- Information on maternal infections and exposure to antibiotics during pregnancy was not included. The most frequent infections are likely to be treated in primary care, which is not covered in the patient registers.
- There was no information available on folic acid intake.

10.3. Interpretation

In this study evaluating the safety of etanercept during pregnancy in the Swedish, Danish and Finnish birth registers, no increased risk of birth defects, infections in the first year of life, preterm birth, low birth weight or SGA were observed in the main analyses. There was an association with SGA when looking at treatment in the second and third trimesters, respectively, and with low birth weight when looking at treatment in the first trimester. There were no cases of stillbirth among those exposed to etanercept, and no formal analyses were performed to assess the association.

10.4. Generalizability

The Nordic registers provide a unique opportunity to study the safety of medications during pregnancy since the registers are population-based and include data on virtually all births, health care visits, prescribed drugs and deaths. However, the study findings may or may not be applicable to other settings where the health care systems and local practices differ.

11. CONCLUSION

In this population-based register study set in Sweden, Denmark and Finland, there were no observed increased risks of birth defects, infections in the first year of life, preterm birth, low birth weight, SGA or stillbirth for infants born to women with etanercept treatment during pregnancy in general in the primary analyses. Treatment with etanercept in pregnancy may be associated with SGA, and a slightly increased risk of low birth weight was observed for treatment with etanercept during pregnancy in sensitivity analyses by treatment timing. However, the associations may also be attributed to small numbers of exposed patients in the sensitivity analyses and residual confounding by indication since women who were treated with etanercept may have more severe disease.

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Attachment A3 **ICD-10 codes for infections**

Attachment A4 **ICD-10 codes for maternal chronic inflammatory disease**

Attachment A5 **ICD-10 codes for maternal comorbidities**

Attachment A6 **ICD-10 codes for prosthetic surgery**

Attachment 1 **Study protocol**

Attachment 2 **Appendix, sensitivity analyses**

ATTACHMENT A1: ATC CODES IDENTIFYING TREATMENT

ETANERCEPT COHORT	
Etanercept	L04AB01

NON-BIOLOGIC SYSTEMIC THERAPY COMPARISON COHORT	
Azathioprine	L01BB01
Azathioprine	L04AX01
Mercaptopurine	L01BB02
Corticosteroids for systemic use	H02xxxx
Ciclosporin	L04AD01
Ciclosporin	L04AA01
Cyclophosphamide	L01AA01
Tacrolimus	L04AA05
Tacrolimus	L04AD02
Hydroxycarbamide/Hydrea	L01XX05
Alitretinoin	D11AH04
Tioguanin/Lanvis	L01BB03
Phototherapy, PUVA, oral	DQ010
Phototherapy, PUVA, bath	DQ011
Chloroquine	P01BA01
Hydroxychloroquine	P01BA02
Sulfalsalazine	A07EC

ATC CODES FOR EXCLUSION IN SENSITIVITY ANALYSES	
Methotrexate	L01BA01
Methotrexate	L04AX03
Leflunomide	L04AA13
Acitretin	D05B
Mycophenolic acid	L04AA06
Anti-epileptics*	N03A
*Barbiturates, phenytoin, clonazepam, carbamazepine, valproate, levetiracetam, lamotrigine, topiramate, gabapentin	
OTHER BIOLOGIC THERAPIES	
Anakinra	L04AC03
Tocilizumab	L04AC07
Rituximab	L01XC02
Abatacept	L04AA24
Efalizumab	L04AA21
Ustekinumab	L04AC05
Alefacept	L04AA15
Infliximab	L04AB02
Adalimumab	L04AB04
Certolizumab pegol	L04AB05
Golimumab	L04AB06
COMORBIDITY THERAPIES	
Antihypertensives	C02-C09
Antidiabetics	A10

ATTACHMENT A2: ICD-10 CODES IDENTIFYING MAJOR BIRTH DEFECTS

EUROCAT SUBGROUPS OF MAJOR BIRTH DEFECTS[a]		
		Exclusion diagnoses
Nervous system	Q00-Q07	
Eye, Ear, face and neck	Q11-Q16, Q100, Q104, Q106, Q107, Q178, Q183, Q187, Q188	Q135
Congenital heart defects	Q20-Q26	Q250
Respiratory	Q30-Q34	Q314, Q320
Oro-facial clefts	Q35-Q37	
Digestive system	Q41-Q45, Q402-Q409, Q38, Q39, Q790, Q792, Q793, Q795	Q381, Q382, Q3850, Q4021, Q430, Q4320, Q4381, Q4382
Urinary	Q60-Q64, Q794	Q627, Q633
Genital organs	Q50, Q51, Q52, Q54, Q55, Q56	Q523, Q525
Limb	Q69-Q74, Q650, Q651, Q652, Q658, Q659, Q660, Q681, Q682, Q688	Q6821
Musculoskeletal system	Q750, Q751, Q754, Q755, Q756, Q757, Q758, Q759, Q761, Q762, Q763, Q764, Q766, Q767, Q768, Q769, Q77, Q78, Q796, Q797, Q798, Q799	
Chromosomal abnormalities	Q90, Q91, Q92, Q93, Q96, Q97, Q98, Q99	Q936
Others	Q80-Q87, Q27, Q28, Q89, Q936	Q270, Q825, Q8280, Q833, Q845, Q899

[a] For Finnish data, type of malformation is already grouped by the EUROCAT

ATTACHMENT A3: ICD-10 CODES FOR INFECTIONS

INFECTIOUS PATHOGENS IN FIRST YEAR OF LIFE (ICD-10 code)	
Intestinal infectious diseases	A00-A09
Tuberculosis	A15-A19
Certain zoonotic bacterial diseases	A20-A28
Infection due to other mycobacteria	A31
Listeriosis	A32
Tetanus neonatorum	A33
Other tetanus	A35
Diphtheria	A36
Whooping cough	A37
Scarlet fever	A38
Meningococcal infection	A39
Streptococcal sepsis	A40
Other sepsis	A41
Actinomycosis	A42
Nocardiosis	A43
Bartonellosis	A44
Erysipelas	A46
Other bacterial diseases, not elsewhere classified	A48
Bacterial infection of unspecified site	A49
Congenital syphilis	A50
Early syphilis	A51
Late syphilis	A52
Other and unspecified syphilis	A53

Gonococcal infection	A54
Acute poliomyelitis	A80
Atypical virus infections of central nervous system	A81
Mosquito-borne viral encephalitis	A83
Tick-borne viral encephalitis	A84
Other viral encephalitis, not elsewhere classified	A85
Unspecified viral encephalitis	A86
Viral meningitis	A87
Other viral infections of central nervous system, not elsewhere classified	A88
Unspecified viral infection of central nervous system	A89
Herpesviral [herpes simplex] infections	B00
Varicella [chickenpox]	B01
Zoster [herpes zoster]	B02
Measles	B05
Rubella [German measles]	B06
Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified	B08
Unspecified viral infection characterized by skin and mucous membrane lesions	B09
Viral hepatitis	B15-B19
Human immunodeficiency virus [HIV] disease	B20-B24
Cytomegaloviral disease	B25
Mumps	B26
Infectious mononucleosis	B27
Other viral diseases, not elsewhere classified	B33
Viral infection of unspecified site	B34

Mycoses	B35-B49
Toxoplasmosis	B58
Pneumocystosis	B59+
Sequelae of infectious and parasitic diseases	B90-B94
Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95
Other specified bacterial agents as the cause of diseases classified to other chapters	B96
Viral agents as the cause of diseases classified to other chapters	B97
Other specified infectious agents as the cause of diseases classified to other chapters	B98
Other and unspecified infectious diseases	B99
Inflammatory diseases of the central nervous system	G00-G09
Polyneuropathy in infectious and parasitic diseases classified elsewhere	G630
Myopathy in infectious and parasitic diseases classified elsewhere	G734
Other disorders of brain in diseases classified elsewhere	G940
Abscess of external ear	H600
Cellulitis of external ear	H601
Malignant otitis externa	H602
Other infective otitis externa	H603
Disorders of external ear in diseases classified elsewhere	H62
Suppurative and unspecified otitis media	H66
Otitis media in diseases classified elsewhere	H67
Mastoiditis and related conditions	H70
Infective pericarditis	I301
Acute and subacute infective endocarditis	I330
Infective myocarditis	I400

Myocarditis in bacterial diseases classified elsewhere	I410
Myocarditis in other infectious and parasitic diseases classified elsewhere	I412
Cardiomyopathy in infectious and parasitic diseases classified elsewhere	I430
Other heart disorders in bacterial diseases classified elsewhere	I520
Other heart disorders in other infectious and parasitic diseases classified elsewhere	I521
Acute upper respiratory infections	J00-J06
Influenza and pneumonia	J09-J18
Other acute lower respiratory infections	J20-J22
Chronic sinusitis	J32
Peritonsillar abscess	J36
Other abscess of pharynx	J391
Other diseases of pharynx	J392
Suppurative and necrotic conditions of lower respiratory tract	J85-J86
Pulpitis	K040
Acute apical periodontitis of pulpal origin	K044
Periapical abscess without sinus	K047
Acute gingivitis	K050
Acute periodontitis	K052
Abscess of salivary gland	K113
Cellulitis and abscess of mouth	K122
Acute appendicitis	K35
Other appendicitis	K36
Unspecified appendicitis	K37
Abscess of anal and rectal regions	K61
Infections of the skin and subcutaneous tissue	L00-L08

Pyogenic arthritis	M00
Direct infections of joint in infectious and parasitic diseases classified elsewhere	M01
Reactive arthropathies	M02
Osteomyelitis of vertebra	M462
Infection of intervertebral disc (pyogenic)	M463
Other infective spondylopathies	M465
Spondylopathy in other infectious and parasitic diseases classified elsewhere	M493
Myositis in bacterial diseases classified elsewhere	M630
Myositis in other infectious diseases classified elsewhere	M632
Necrotizing fasciitis	M726
Osteomyelitis	M86
Acute tubulo-interstitial nephritis	N10
Tubulo-interstitial nephritis, not specified as acute or chronic	N12
Pyonephrosis	N136
Acute cystitis	N300
Urinary tract infection, site not specified	N390
Salpingitis and oophoritis	N70
Other inflammation of vagina and vulva	N76
Infections specific to the perinatal period	P35-P39

OPPORTUNISTIC INFECTIONS PATHOGENS IN FIRST YEAR OF LIFE (ICD-10 code)	
Tuberculosis	A15-A19
Meningococcal infection	A39
Streptococcal sepsis	A40
Other sepsis	A41

Other mycoses	B48, B49
Pneumocystosis	B59+
Bacterial meningitis	G00
Meningitis in bacterial diseases elsewhere	G01
Pneumonia due to streptococcus pneumoniae	J13 (in-patient) +/- ATC J01, J02[b]
Pneumonia due to Haemophilus influenza	J14 (in-patient) +/- ATC J01, J02 [b]
Bacterial pneumonia	J15 (in-patient) +/- ATC J01, J02 [b]
Pyogenic arthritis	M00
Osteomyelitis of vertebra	M462
Infection of intervertebral disc (pyogenic)	M463
Myositis in bacterial diseases classified elsewhere	M630
Myositis in other infectious diseases classified elsewhere	M632
Necrotizing fasciitis	M726
Osteomyelitis	M86
Bacterial sepsis of newborn	P36

[b]Pneumonia with antibiotic treatment

ATTACHMENT A4: ICD-10 CODES FOR MATERNAL CHRONIC INFLAMMATORY DISEASES

Disease State	ICD-10 Code
Rheumatoid arthritis	M05, M06
Juvenile rheumatoid arthritis	M08
Ankylosing spondylitis	M45
Arthropathic psoriasis	L40.5, M07.0, M07.1, M07.2, M07.3, M09.0
Psoriasis	L40

ATTACHMENT A5: ICD-10 CODES FOR MATERNAL COMORBIDITIES

Disease State	ICD-10 Code
Hypertension	I10-I13
Diabetes	E10-E14

ATTACHMENT A6: SURGERY CODES FOR PROSTHETIC SURGERY

History of prosthetic surgery	NOMESCO [a] Codes
Knee prosthesis	NGB
Hip prosthesis	NFB
Shoulder prosthesis	NBB
Foot surgery	NHB, NHC, NHE, NHF, NHG
Hand surgery	NDB, NDC, NDE, NDF, NDG

[a] The Nordic Medico Classification of Surgical Procedures