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Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: a prospective multicentre cohort study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- TNF-α inhibitors constitute an important treatment option of autoimmune disorders in women of childbearing age.
- Large studies on TNF-α inhibitors during pregnancy are lacking.
- Selected cases report on malformations in the offspring. However, overall, no increased risk of birth defects has been observed as yet.

WHAT THIS STUDY ADDS

- Prenatal TNF-α inhibitor exposure for maternal chronic inflammatory conditions led to a) A moderately increased risk of birth defects without a distinct pattern of malformations, b) An increased risk of preterm birth and reduced birth weight, c) No increased risk of spontaneous abortion.

AIMS

TNF-α inhibitors are considered relatively safe in pregnancy but experience is still limited. The aim of this study was to evaluate the risk of major birth defects, spontaneous abortion, preterm birth and reduced birth weight after first trimester exposure to TNF-α inhibitors.

METHODS

Pregnancy outcomes of women on adalimumab, infliximab, etanercept, certolizumab pegol or golimumab were evaluated in a prospective observational cohort study and compared with outcomes of a non-exposed random sample. The samples were drawn from pregnancies identified by institutes collaborating in the European Network of Teratology Information Services.

RESULTS

In total, 495 exposed and 1532 comparison pregnancies were contributed from nine countries. The risk of major birth defects was increased in the exposed (5.0%) compared with the non-exposed group (1.5%; adjusted odds ratio (OR_{adj}) 2.2, 95% CI 1.0, 4.8). The risk of preterm birth was increased (17.6%; OR_{adj} 1.69, 95% CI 1.1, 2.5), but not the risk of spontaneous abortion (16.2%; adjusted hazard ratio [HR_{adj}] 1.06, 95% CI 0.7, 1.7). Birth weights adjusted for gestational age and sex were significantly lower in the exposed group compared to the non-exposed cohort ($P = 0.02$). As a diseased comparison group was not possible to ascertain, the influence of disease and treatment on birth weight and preterm birth could not be differentiated.

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CONCLUSIONS

TNF-α inhibitors may carry a risk of adverse pregnancy outcome of moderate clinical relevance. Considering the impact of insufficiently controlled autoimmune disease on the mother and the unborn child, TNF-α inhibitors may nevertheless be a treatment option in women with severe disease refractory to established immunomodulatory drugs.

Introduction

Tumour necrosis factor alpha (TNF-α) inhibitors are approved for the treatment of moderate to severe forms of various chronic inflammatory conditions like inflammatory bowel disease (IBD) or rheumatoid arthritis (RA). The five approved TNF-α inhibitors, adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETA), golimumab (GOL) and infliximab (IFX), are particularly indicated in cases of severe disease or following insufficient response to other disease modifying drugs (DMDs), partly in combination with methotrexate (MTX). Although they are regarded as relatively safe, recommendations remain inconclusive concerning the treatment of pregnant women or patients planning a pregnancy while under therapy [1]. This represents a topic of urgent interest, given that women of childbearing age are one of the main groups affected by IBD [2]. Thus, exposure during either planned or unintended pregnancy is considered a likely occurrence. Possible risks discussed after immunosuppressant therapy during pregnancy include teratogenicity, higher rates of spontaneous abortion, preterm birth, growth retardation and compromised fetal immunity [3, 4].

Since all the approved TNF-α inhibitors are substances of high molecular weight, they are expected to require active transport to cross the human placenta. A similar process is known for IgG antibodies and is generally understood to only occur after the 20th week of gestation. Therefore, placental transfer during the embryonic period is not expected. Clinical experience is limited and varies widely between the five agents. In total, approximately 500 pregnancies exposed to TNF-α inhibitors have been published via registries, pharmacovigilance surveillance, case series [3, 5–8], and cohort studies [9, 10]. Additionally a variety of case reports, abstracts and conference communications are available [1, 11]. While the main body of reports covers IFX, ADA, and ETA, there are only few cases with CZP and with GOL [12]. Though malformations were described in a few pregnancies [5], these were heterogeneous and no distinct pattern was observed. Currently, there is no evidence of an increased malformation risk. This is in line with the preliminary results of the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) study reporting 161 pregnancies exposed to TNF-α inhibitors [13].

A report on a child with VACTERL association (V: vertebral defects; A: anal atresia; C: cardiac anomalies; T: tracheal-oesophageal fistula; E: oesophageal atresia; R: radial and renal problems; L: limb anomalies) following exposure to ETA throughout pregnancy [14] led to considerable discussion [15]. Interestingly, the authors were unable to ascertain additional children with VACTERL syndrome among 22 retrospectively recorded pregnancies with birth defects [7], though, in a somewhat unorthodox approach, they suggested isolated heart defects to be part of an incomplete VACTERL. An evaluation of the EUROCAT database accordingly did not confirm VACTERL to be associated with TNF-α inhibitor exposure [16].

A register evaluation including 71 prospectively recorded pregnancies on TNF-α inhibitors, among them 48 with ETA, nine with IFX and 14 with ADA, revealed a 27% miscarriage rate. Even after exclusion of pregnancies with MTX co-medication, the miscarriage rate remained high. However, the total number of evaluated pregnancies was small and the results have not been confirmed by other studies to date [8]. Furthermore, TNF-α has been suggested to be an important factor in spontaneous abortion aetiology and data are available which have shown that ADA and ETA may prevent (recurrent) miscarriage [17, 18].

After the 20th week of pregnancy there is an increasing placental transfer of monoclonal antibodies through an active process via the neonatal Fc receptor [19]. This applies particularly to the full antibodies ADA and IFX [20, 21]. However, simultaneous measurements in the mother's blood and the cord blood demonstrated that ETA, a TNF receptor-Fc fusion protein, also crosses the placenta [22]. Placental transfer for CZP, a pegylated Fab fragment of a recombinant humanized anti-TNF-α monoclonal antibody, was also shown [20]. The mechanism of transfer is not yet understood since it lacks an Fc portion which is essential for active transfer. There are no human reports on placental transfer for GOL as yet. However transfer can be assumed as it is a complete IgG1 antibody [23].

The aim of this collaborative prospective cohort study was to evaluate the risks of major birth defects and spontaneous abortion after first trimester exposure to TNF-α inhibitors. Secondary objectives were to evaluate the risks of preterm birth and reduced birth weight as well as the rate of electively terminated pregnancies. It was hypothesized that our study would add further evidence for the safety of TNF-α inhibitors during the first trimester of pregnancy.

Methods

The study was a prospective observational multicentre cohort study, i.e. neither the outcome of the pregnancy nor the results of prenatal diagnostic tests were known at the time of subject enrolment. The exposed and comparison cohort consisted of pregnancies enrolled at teratology information services (TIS) between 1998 and 2013. TIS offer risk assessment to health care professionals and pregnant women who spontaneously contact these services for consultation in pregnancy. The study was reported in accordance with the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement adapted to the needs of pregnancy outcome studies [24, 25]. Ethics approval was obtained from the ethics committee of the Charité Universitätsmedizin Berlin (no. EA4/013/13). The study was registered at the German Clinical Trials Register (no. DRKS00005036) and at ENCePP (http://www.encepp.eu/encepp/viewResource.htm?id=6138).

Patients

Data of exposed and comparison women were obtained from pregnancies identified by 11 institutions from nine countries collaborating within the European Network of Teratology Information Services (ENTIS): Australia ($n = 24$), Finland ($n = 47$), France ($n = 580$), Germany ($n = 951$), Italy ($n = 91$), The Netherlands ($n = 196$), Turkey ($n = 12$), Switzerland ($n = 60$) and the United Kingdom ($n = 68$).

The exposed group was defined as pregnant women who had been exposed to more than one dose of one of the five approved TNF-α inhibitors (ADA, CZP, ETA, GOL and IFX) at any time during the first 12 weeks after the last menstrual period (LMP). Exposure may have started earlier and can have continued longer. The comparison group consisted of non-exposed pregnant women identified through spontaneous TIS consultations for other conditions or exposures such as hair-dyeing, urinary tract infection, asthma or depression. Exclusion criteria for both groups were women with malignancies and exposure to known major teratogens or fetotoxicants, namely acitretin, isotretinoin, mycophenolate, thalidomide, valproic acid as well as angiotensin-II receptor blockers and ACE inhibitors, when used during the 2nd and/or 3rd trimester. Low dose MTX was not considered an exclusion criterion.

Each TIS identified pregnancies that met the study criteria. The target sample size to be reached was at least 200 exposed and 600 controls. From the eligible pool within each TIS, pregnancies for the non-exposed comparison group were randomly selected and frequency matched to the exposed cohort on year of ascertainment, aiming at an approximate 3:1 ratio per centre. The same method of ascertainment applied for each TIS. The data were then combined across centres.

Data were collected on exposure and outcome from structured telephone or face-to-face interviews and/or mailed questionnaires obtained from both the mother and/or her physician(s) after oral informed consent. Data were collected on demographics, maternal age, pregnancy history including previous number of children with birth defects, pre-pregnancy body mass index, medications including both prescription and over-the-counter, detailing specific dosages and dates of exposure and smoking and alcohol consumption. Details regarding the course and outcome of pregnancy were obtained 9 weeks after birth and focused on pregnancy complications and birth defects. In addition, details of delivery, pregnancy loss, and gestational age at pregnancy loss or at birth, sex, birth weight, length and head circumference were collected.

Outcomes

The primary endpoints were major birth defects and the risk of spontaneous abortion (SAB). Secondary endpoints included the rate of elective termination as well as an assessment of the reasons provided for terminating a pregnancy, and the risk of preterm birth as well as the infant's birth weight. Fetal abnormalities in pregnancy losses including elective terminations of pregnancy (ETOPs) were considered in the calculation of birth defect rates.

Birth defects were classified as major or minor by two of the authors (CWS and CS) according to the EUROCAT classification system. The classifications were performed independently and blinded to exposure status. In case of disagreement between the two authors, consensus was achieved through discussion.

Concomitant use of MTX or other disease-modifying drugs (DMDs) was taken into account in all analyses.

Weeks of gestation were calculated by ultrasound during first trimester or, if not available, from the LMP. SAB was defined as spontaneous pregnancy loss of a fetus <500 g or if weight not known <23 completed weeks after LMP. Gestational age at delivery and birth weight were measured as continuous variables. Birth weight was adjusted for gestational age at birth and sex.

Statistical analysis

Logistic regression was used to evaluate the risk of major birth defects. Crude birth defect rates were calculated by dividing the number of infants and fetuses with birth defects by the number of all live-born infants plus the number of stillbirths/aborted fetuses with birth defects. Birth defects known to be of genetic aetiology were considered separately. The final analysis involved propensity score adjustment for bias reduction, classifying pregnant women into five strata defined by the quintiles of the propensity score [26]. Propensity score estimation used boosted regression trees [27], including maternal age, alcohol consumption, smoking status, and numbers of previous pregnancies, miscarriages and previous infants

with birth defects as covariates, and was repeated for each analysis. Maternal therapy with other DMDs was used as a covariate directly in the analysis, in addition to propensity score stratification, to account for effects of these concomitant medications. It was differentiated whether MTX was part of the DMDs therapy or not. Adjustment was used as described above in all multivariate analyses.

The cumulative incidences of spontaneous abortion and elective termination were assessed using event history analysis for cause-specific sub-distributions of competing risks while accounting for left truncation due to varying time of gestation at enrolment [28]. Hazard ratios (HRs) were then estimated using Cox proportional hazards models.

The effect on the risk of preterm birth was assessed using logistic regression. For the comparison of birth weights between groups, live births from all centres were classified according to new-born birth weight percentile categories [29]. A score was determined through standardization and included in a linear regression model as the dependent variable.

For all models that included covariates, missing values were addressed through multiple imputation using chained equations, assuming that the data were missing at random [30]. Twenty imputed data sets were generated per outcome. The models of multiple imputations were based on the respective outcomes and the covariates used to estimate the propensity score. For each imputed data set, analyses were performed as described above. Results were then combined using Rubin's rule [31].

Heterogeneity among contributing centres was tested using the Breslow-Day test of homogeneity for dichotomous outcomes and the analysis of variance (ANOVA) *F* test for continuous outcomes. Data from Finland, Australia and Turkey were excluded from heterogeneity analysis due to small numbers. All data analyses were performed at the Berlin Institute using R version 2.15.

Results

Cohort size, exposures and maternal characteristics

The study period comprised the period from 1998 until 2013. Follow-up of pregnancy outcome after maternal first trimester TNF-α inhibitor therapy meeting the study criteria was initiated in 629 cases and completed in 495 (79%). Causes for lost-to-follow-up were diverse such as moving house, changing doctors or simply lack of time or interest. In total, 172 ADA, 168 IFX, 140 ETA, 7 CZP, 3 GOL exposed plus five double exposed (three × ADA + ETA; two × ADA + IFX) pregnancies and 1532 comparison pregnancies were contributed from nine countries.

The most frequent treatment indications for a TNF-α inhibitor therapy were IBD (48.1%) and RA (26.9%) (Table 1). Due to the approved treatment indications, the majority of women with ETA therapy were treated for RA (70%) followed by ankylosing spondylitis (18%) whereas IFX was mainly prescribed for IBD (86%). ADA was given for IBD in over half of the cases and in 47% for rheumatic disorders (RA, ankylosing spondylitis and psoriasis/psoriatic arthritis).

The overall median treatment duration during pregnancy was 6.9 weeks (IQR 4.0–25.0). The median gestational week at time of last drug administration was week 7.4 (IQR 4.0–24.0) for ADA, week 5.0 (IQR 4.0–7.4) for ETA and week 22.6 (IQR 5.0–32.0) for IFX.

For maternal characteristics see Table 2. Low dose MTX exposure occurred in 7.5% of the exposed pregnancies and in 0.1% of the comparison cohort. In total, almost half of the patients in the TNF-α inhibitor group were concomitantly treated with other DMDs, such as MTX ($n = 37$), mesalazine/sulfasalazine ($n = 49$), azathioprine/mercaptopurine ($n = 55$), leflunomide ($n = 5$), hydroxychloroquine ($n = 8$), ciclosporin ($n = 4$) and systemic glucocorticoids ($n = 167$). Therapy with DMDs took place in 5.6% of the patients in the non-exposed comparison cohort.

Birth defects

The proportion of infants with birth defects is shown in Table 3. There was a significantly increased risk of major birth defects (21 of 421 [5 %]) in the TNF-α inhibitor group compared with the non-exposed comparison cohort (21 of 1,385 [1.5%]) (adjusted odds ratio [OR_{adj}] 2.20 [95% CI 1.01, 4.8]). Concomitant maternal therapy with other DMDs including therapy with MTX and/or systemic glucocorticoids did not explain the increased risk of birth defects after TNF-α inhibitor exposure. The number of major birth defects by substance was nine of 150 (6.0%) after intrauterine ADA exposure, seven of 156 (4.5%) after IFX and six of 111 (5.4%) after ETA exposure.

Table 1

Drug treatment indication of TNF-α inhibitor exposed pregnancies (numbers)

Drug treatment indication	Number (%)
Inflammatory bowel disease	238 (48.1)
Ulcerative colitis	36 (7.2)
Crohn's disease	200 (40.4)
IBD (unclassified or unclassifiable)	2 (0.4)
Rheumatoid arthritis	133 (26.9)
Ankylosing spondylitis	68 (13.7)
Psoriasis/psoriatic arthritis	39 (7.9)
Miscellaneous	13 (2.6)
Unknown	4 (0.8)
Total	495

Table 2

Maternal characteristics by cohorts

	TNF-α inhibitor (*n* = 495)	Comparison (*n* = 1532)
Maternal age, *n*	481	1431
Age (years) median (IQR)	30 (27–34)	31 (28–35)
min–max (years)	16–42	14–46
BMI (pre-pregnancy), *n*	291	883
BMI (kg m^{-2}) median (IQR)	22 (20.3–24.9)	22.6 (20.6–25.6)
Smoking, *n*	384	1202
No *n* (%)	311 (81)	1040 (86.5)
<= 5 cigarettes/day *n* (%)	21 (5.5)	59 (4.9)
>5 cigarettes/day *n* (%)	52 (13.5)	103 (8.6)
Alcohol, *n*	366	1147
No *n* (%)	342 (93.4)	1075 (93.7)
<= 1 drink/day *n* (%)	14 (3.8)	55 (4.8)
>1 drink/day *n* (%)	10 (2.7)	17 (1.5)
Mother's years of schooling, *n*	177	576
<= 9 years *n* (%)	14 (7.9)	39 (6.8)
>9 and < = 13.5 years *n* (%)	104 (58.8)	291 (50.5)
Academic degree *n* (%)	59 (33.3)	246 (42.7)
Other DMDs, *n*	495	1532
No *n* (%)	250 (50.5)	1447 (94.5)
Other than MTX *n* (%)	208 (42.0)	84 (5.5)
Including MTX *n* (%)	37 (7.5)	1 (0.1)
Previous pregnancies, *n*	451	1336
0 *n* (%)	217 (48.1)	559 (41.8)
1 *n* (%)	133 (29.5)	421 (31.5)
2 *n* (%)	53 (11.8)	204 (15.3)
3 or more *n* (%)	48 (10.6)	152 (11.4)
Previous deliveries, *n*	449	1327
0 *n* (%)	272 (60.6)	684 (51.5)
1 *n* (%)	120 (26.7)	438 (33.0)
2 *n* (%)	40 (8.9)	139 (10.5)
3 or more *n* (%)	17 (3.8)	66 (5.0)
Previous miscarriages, *n*	434	1295
0 *n* (%)	357 (82.3)	1066 (82.3)
1 *n* (%)	60 (13.8)	164 (12.7)
2 or more *n* (%)	17 (3.9)	65 (5.0)
Previous children with birth defect, *n*	414	1240
0 *n* (%)	405 (97.8)	1218 (98.2)
1 *n* (%)	8 (1.9)	20 (1.6)
2 or more *n* (%)	1 (0.2)	2 (0.2)
Gestational week at first contact, *n*	495	1532
Median gestational week (IQR)	8.1 (6–12.9)	9 (6.3–14.3)

BMI, body mass index; DMDs disease-modifying drugs; IQR, interquartile range.

A detailed description of major birth defects of the TNF-α inhibitor exposed infants/fetuses is shown in Table 4. Of note, there was no distinct pattern of birth defects among the TNF-α inhibitor exposed infants. However, there were more cardiac defects than expected, but in most cases they were associated with other birth defects.

Table 3

Rate of birth defects by cohort

	TNF-α inh. (*n* = 419)	Comparison (*n* = 1383)	OR_{adj} (95% CI)
All birth defects (%)	52/423 (12.3)	87/1393 (6.2)	1.64 (1.1, 2.6)
Major birth defects (%)	21/421 (5.0)	21/1385 (1.5)	2.20 (1.0, 4.8)
Minor birth defects (%)	27/419 (6.4)	55/1383 (4.0)	1.27 (0.7, 2.3)
Genetic anomalies (%)	4/421 (0.9)	11/1391 (0.8)	1.80 (0.5, 6.9)

Varying denominators are due to twin pregnancies and to varying numbers of stillbirths/abortions with malformations in the numerator and denominator.

Pregnancy and neonatal outcome

Table 5 gives a summary of pregnancy outcomes of the exposed and non-exposed cohort. The crude rate of live births was slightly lower in the study cohort compared with the comparison group due to more frequent SABs and ETOPs. Cumulative incidences of live birth, SABs, ETOPs and stillbirths are illustrated in Figure 1. The risk of SAB was not increased in the TNF-α inhibitor cohort (adjusted hazard ratio [HR_{adj}] 1.06, 95% CI 0.7, 1.7) whereas ETOPs occurred more frequently (HR_{adj} 1.69, 95% CI 1.0, 2.9). Concomitant low dose MTX therapy increased the chance of having an elective termination (HR_{adj} 2.15, 95% CI 1.2, 3.9) as well as the risk of spontaneous abortion (HR_{adj} 1.60, 95% CI 1.0, 2.6).

There were significantly more preterm births in the TNF-α inhibitor cohort than in the comparison cohort (OR_{adj} 1.69, 95% CI 1.1, 2.5) and also more infants with low birth weight (Table 6). Although the median birth weight of both cohorts was in the normal range, it was lower in the study group (Table 6). After adjustment for sex and gestational age at birth, the difference between the cohorts remained significant ($P = 0.02$). Infants with birth weights $\leq 50^{th}$ percentile were overrepresented in the exposed cohort (Figure 2). The differences in infants' median birth weight were marginal between ADA (3080 g), ETA (3110 g) and IFX (3200 g). As the median birth weight is influenced by gestational age and by infant's sex, we compared adjusted weight scores between the three compounds. ETA exposed infants had a score of only −0.24 (IQR −1.0, 0.2), IFX of −0.30 (IQR −0.9, 0.6) and ADA of −0.43 (IQR −0.9, 0.3). Excluding twins from the analyses did not result in notably different findings. There were no significant differences between the TIS with regard to any of the study endpoints.

Discussion

This study evaluated a cohort of 495 prospectively ascertained pregnancies exposed to TNF-α inhibitors during at least the first trimester. Based on animal experiments [32] and human data published to date, this study was expected to further confirm the safety of this group of biologic agents. However, our data revealed an

Table 4

Description of major birth defects in the TNF-α inhibitor cohort ($n = 21$)

Substance and exposure time (after LMP)	Treatment indication	Co-medication (trimester or exact gestational period)	Gestational age at birth/elective termination (in weeks after LMP) and birth weight, sex	Birth defects
ADA from before pregnancy until week 5 + 6 days	Psoriatic arthritis	None	Week 38 + 5 days, 2770 g, female	Hexadactyly both feet, atrial septal defect
ADA from before pregnancy until week 38 + 5 days	Crohn's disease	Prednisolone (1–3), ASS low-dose (1–3), omeprazole (1–3), lansoprazole (1), enoxaparin (1–3)	Week 38 + 5 days, 2540 g, male	Oesophageal atresia type IIIb (Vogt) with tracheo-oesophageal fistula; ventricular septal defect, syndactyly D2/3 both feet, peripheral pulmonary stenosis, PFO
ADA from before pregnancy until week 2 + 1 day	Ankylosing spondylitis	Amoxicillin (3), betamethasone (lung maturation, 3)	Week 32 + 3 days, 1840 g, female	Atrial septal defect with left-right shunt and aneurysm, cavum septum pellucidum on both sides, haemangioma at left flank
ADA only once in week 3	Rheumatoid arthritis	Prednisone (1–3), levothyroxine (1–3)	Week 39 + 4 days, 3330 g, female	Ventricular septal defect, hip dysplasia type 2c (Graf)
ADA only once in week 1 + 5 days	Psoriasis	Ciclosporin (1), insulin (3)	Week 39 + 3 days, 3490 g, male	Hexadactyly
ADA from before pregnancy until week 7	Ankylosing spondylitis	Ethinylestradiol/chlormadinone (1)	Week 34 + 3 days, 1990 g, male	Haemangioma right temple, (umbilical hernia)
ADA started during week 12 until week 14 (two injections)	Crohn's disease	Prednisolone (1)	Spontaneous abortion in week 15	Imperforate anus
ADA from before pregnancy until week 40 + 5 days	Ankylosing spondylitis	Sulfasalazine (1), fluoxetine(1), alprazolam (1)	Week 40, 3750 g, male	Amniotic band sequence: talipes and amputation of four fingers of the right hand
ADA and ETA from before pregnancy until week 2 + 2 days	Rheumatoid arthritis	Low dose methotrexate (from before pregnancy until week 2 + 2 days), prednisolone (1–3), omeprazole (1–3), ibuprofen (1–2).	Week 40 + 2 days, 2520 g, male	Cystic adenomatoid malformation of the right lung dorsobasal (multiple cysts of different sizes, totally 2.3 cm x 4.2 cm, surgery done), incomplete right bundle branch block, pericardial effusion, PFO and PDA, slight persistent pulmonary hypertension
ETA from before pregnancy until week 8	Rheumatoid arthritis	Prednisone (1–3), fluconazole (1)	Week 35 + 3 days, 2200 g, male	Hypoplastic left heart, hypospadias glandis
ETA from before pregnancy until week 3 + 5 days	Rheumatoid arthritis	Prednisolone (1–3), thyroxine, ibuprofen (as needed)	Week 37 + 3 days, 2860 g, male	Agenesis of left kidney
ETA from before pregnancy until week 4	Ankylosing spondylitis, Crohn's disease	Prednisolone (1–3)	Week 36, 2920 g, female	WPW-syndrome with heart failure
ETA from before pregnancy until week 5	Rheumatoid arthritis	None	Week 36 + 4 days, 3200 g, male	Bilateral hydronephrosis
ETA from before pregnancy until week 32 + 6 days	Behcet's disease	Dalteparin (1–3)	Week 32 + 6 days, 2260 g, female	Atrial septal defect, (inguinal hernia)
IFX from before pregnancy until week 36 + 4 days	Crohn's disease	None	Week 38; 2450 g, female	Aneurysmatic subaortic ventricular septal defect
IFX from before pregnancy until week 27 + 5 days	Crohn's disease	Prednisolone (1–3), methylprednisolone (2–3), azathioprine (2–3), corticoid for lung maturation (2–3), antibiotics (2–3)	Week 27 + 5 days, 860 g, female	Two rapidly growing facial haemangiomata (propranolol therapy), (left inguinal hernia, PFO spontaneously closed)
IFX from before pregnancy until week 34 + 4 days	Crohn's disease	Azathioprine (1–3), acyclovir (1), anti-D-immunoglobulins, human insulin (2–3), cefuroxime	Week 40 + 4 days, 3950 g, male	Hydronephrosis and obstructive megaureter right at birth. (Later silent kidney right and hypertrophy of left kidney)

(Continues)

Table 4. (Continued)

Substance and exposure time (after LMP)	Treatment indication	Co-medication (trimester or exact gestational period)	Gestational age at birth/elective termination (in weeks after LMP) and birth weight, sex	Birth defects
IFX only once in week 3 + 6 days	Crohn's disease	Low dose methotrexate (from before pregnancy until week 4 + 4 days)	Week 38 + 6 days, 2590 g, male	Pelviureteric junction obstruction (surgery required)
IFX from before pregnancy until week 25 (weeks 1, 9, 17, 25)	Crohn's disease	Hydrocortisone rect. (1–2), azathioprine (1–3), mesalazine (1–3), pantoprazole (1–2), isoniazid and pyridoxine (1–2), betamethasone (lung maturation; 3), ibuprofen (1), citalopram (1)	Week 33 + 4 days, 2400 g, male	Hypospadias glandis, hepatic cyst; small aortic-pulmonary collateral
IFX from before pregnancy until week 5 + 2 days	Crohn's disease	Contraceptive pill (until week 5 + 3 days)	Spontaneous abortion week 13 + 5 days (pericentric inversion of chromosome 9).	Megacystis, bilateral talipes
IFX from before pregnancy until week 23 + 5 days	Ulcerative colitis	None	Week 33 + 1 day, 1985 g, male (twin pregnancy, other twin healthy)	Facial haemangioma (cryo-therapy)

LMP last menstrual period; PFO persistent foramen ovale; PDA persistent ductus arteriosus; WPW-syndrome:Wolf Parkinson White syndrome

Table 5

Pregnancy outcomes by cohort

	TNF-inhibitor	Comparison
Pregnancies *n*	**495**	**1532**
SAB *n* (% after excl. of ETOPs)	**43** (9.3)	**116** * (7.9)
Stillbirth *n*	**5**	**7** *
ETOP *n* (%)	**34** (6.9)	**57** (3.7)
voluntary	28	44
maternal disease	4	3
fetal reasons	1	9
unknown reason	1	1
Live birth *n* (%)	**413** (83.4)	**1355** (88.4)
Live-born children *n*	**419** †	**1383**†

SAB, spontaneous abortion; ETOP, elective termination of pregnancy *including twin pregnancies with one live born infant and one fetal loss/stillbirth †including live born infants from twin pregnancies

increased rate of birth defects, a significantly lower birth weight and a higher rate of preterm births in the TNF-α inhibitor exposed cohort.

Birth defects

The significant increase in the number of major birth defects is the most striking result of our study. However, the lower limit of the confidence interval was 1.01. The co-medication does not explain this finding. Although low dose MTX was shown to increase the risk of birth defects [33], the therapy with low dose MTX or other immunomodulatory drugs in this study could not account for the higher number of birth defects in exposed pregnancies. Furthermore, among the 21 infants with major birth defects, only two were prenatally exposed to low dose MTX. In both cases these exposures occurred in very early pregnancy and before the vulnerable time window. Pregnancies exposed to other established teratogens were excluded from both cohorts.

We did not observe a distinct pattern of malformations which would be expected for typical teratogens. Likewise, the previously reported suspicion that TNF-α inhibitors may cause a VACTERL association [7, 14] could not be confirmed by our study. Indeed, in one infant exposed to ADA throughout pregnancy a VACTERL association could be debated (#2, Table 6). The child had oesophageal atresia with tracheo-oesophageal fistula, a ventricular septal defect and syndactyly of both second and third toes. The only core feature of a VACTERL association is the tracheo-oesophageal fistula [34]. The muscular ventricular septal defect was mild and might have closed later. 2/3 syndactyly of the toes occurs frequently and is most often inherited [35]. Since the presence of at least three typical malformations is required to make the diagnosis [34], we do not consider this to be a true case of VACTERL association.

Due to the lack of active placental IgG transport mechanisms during early pregnancy it is assumed that

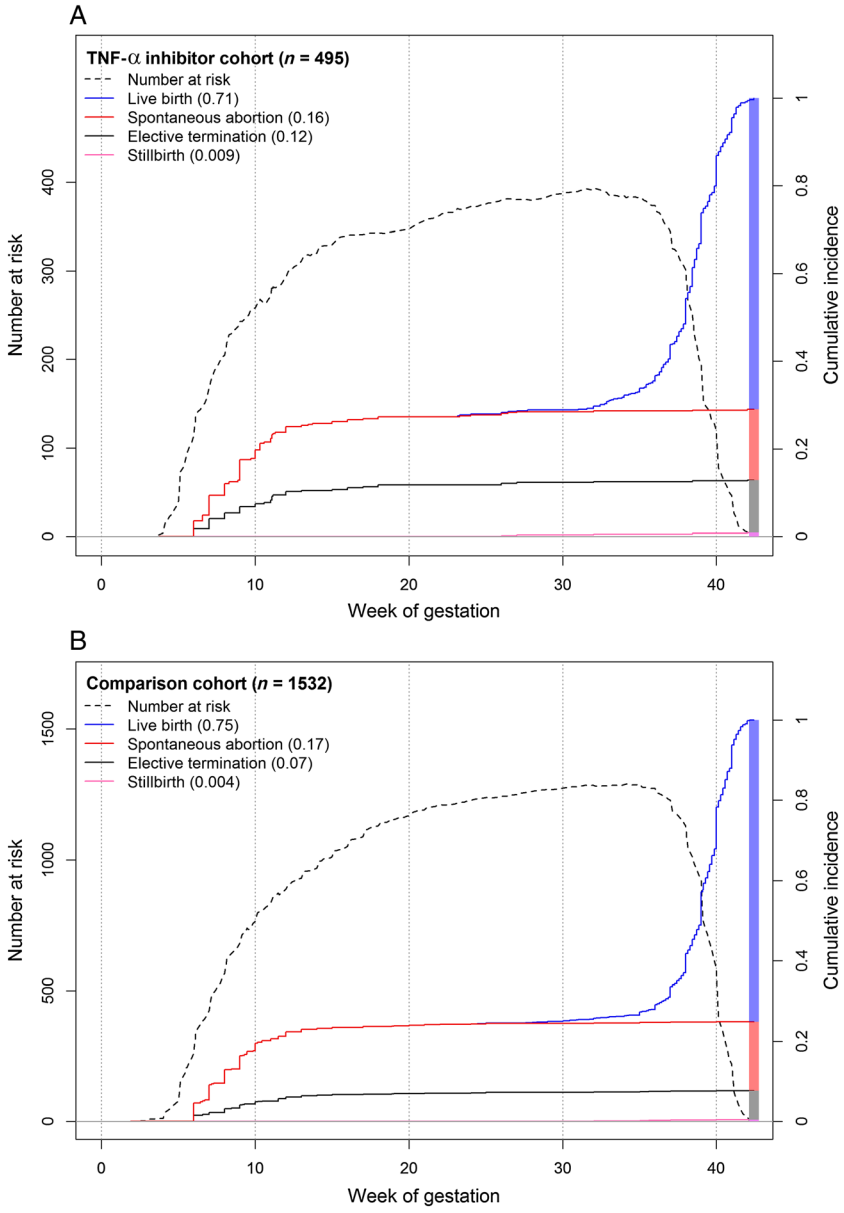

Figure 1

Cumulative incidence rates of fetal loss and live births by cohort. Cumulative incidences of pregnancy outcomes of the TNF-α inhibitor cohort (A) and of the comparison cohort (B) are plotted one above the other. Cumulative incidences for live births are drawn in blue, for spontaneous abortions in red, for elective terminations in black and for stillbirth in pink (y-axis labelling on the right). Of note, the final cumulative incidences add up to 1 covering all possible outcomes. The dotted line represents the number at risk over time (y-axis labelling on the left)

embryonic exposure to TNF-α inhibitors is minimal during the first trimester, making direct teratogenic effects unlikely. However, an indirect effect on the normal embryonic development is debatable. Animal experiments suggest that TNF-α plays a dual role in embryogenesis in activating some defence mechanism on the one hand and inducing embryonic death in cases of developmental damage on the other hand. All this could contribute to the prevention of birth defects in live-births [36]. TNF-α inhibitors may disturb these processes to a certain extent.

One could speculate that a detection bias contributed to the higher rate of birth defects in the study group, a phenomenon discussed also in relation to other drugs suspected to be teratogens [37]. More careful prenatal and postnatal screenings result in higher detection rates of fetal birth defects. However, the malformations reported in our study are heterogeneous and not specifically dependent on extended (ultrasound) diagnostics.

The rate of 1.5% major birth defects in the comparison cohort is lower than the prevalence of all non-chromosomal anomalies of 2.2% recorded by EUROCAT

Table 6

Child characteristics by cohort

	TNF-α inhibitor (*n* = 419/407)*	Comparison (*n* = 1383/1324)
Gestational week (GW) at birth, *n*	403/391	1373/1314
GW, including twins median (IQR)	38.71 (37.4–40)	39.43 (38.3–40.3)
GW, excluding twins median (IQR)	38.86 (37.6–40)	39.57 (38.4–40.4)
Preterm birth (<37 weeks), *n*	403/391	1373/1314
Preterm, including twins *n* (%)	71 (17.6)	123 (9.0)
Preterm, excluding twins *n* (%)	63 (16.1)	93 (7.1)
Infant's weight, *n*	409/399	1357/1299
Weight in g, including twins median (IQR)	3125 (2745–3450)	3350 (3020–3660)
Weight in g, excluding twins median (IQR)	3130 (2797.5–3460)	3374 (3080–3680)
Infants with LBW (excluding twins) *n* (%)	51 (12.8)	14 (1.1)

LBW low birth weight (<2500 g) according to the WHO definition (http://www.who.int/maternal_child_adolescent/documents/9789241548366.pdf). IQR, interquartile range.*numbers with and without twins

for the years 2008-2012 [38]. Therefore, it could be discussed whether a selection bias has contributed to the increased malformation risk. Taking into account differences in maternal characteristics between cohorts, adjustment reduced the crude OR of 3.5 to 2.2 (95% CI 1.0, 4.8), which at least in part removed a potential selection bias.

Not all women received TNF-α inhibitors during the entire period of organogenesis. It is, therefore, debatable whether the exposed cohort is informative for all organ specific vulnerable windows within the first trimester. To answer this question, treatment duration and half-lives of individual TNF-α inhibitors need to be taken into account. The latter refers to the fact that halting of TNF-α inhibitor therapy does not coincide with the end of fetal exposure. Of the IFX exposed women 66.5% received their last infusion after gestational week 10, whereas 26.5% stopped therapy before week 6 (Figure 3). Considering that IFX has a half-life of 8 to 12.3 days and is detectable in maternal blood for up to 8 to 12 weeks after the last dosage, we can be confident that the vast majority of women had detectable IFX concentrations during all sensitive organ-specific periods. ETA in contrast, has a far shorter half-life of 70 h and is usually administered twice weekly. The median week of the last ETA injection was week 5. Therefore it is assumed that only a minority of women had detectable ETA concentrations during the entire first trimester (Figure 3). Considering ADA's half-life of 14 days in women receiving injections every other week, it seems likely that 50% of the exposed women had significant ADA serum concentrations up to week 11 and 42% up to week 13 (Figure 3).

Birth weight and preterm birth

The lower birth weights of exposed infants could either be due to drug toxicity during pregnancy or to the underlying disease and its activity. The tendency towards lower birth weight was most prominent in ADA-exposed infants (SDS -0.43) and least in ETA-exposed infants (SDS -0.24).

Studies on pregnancy outcome in women with IBD have revealed an increased risk of low birth weight, small-for-gestational age and preterm birth, particularly when there were disease flares during pregnancy [39]. Maternal RA seems to have a less pronounced influence on an infant's birth weight [40] which is consistent with the results of our ETA subgroup, since the majority of women with ETA therapy were treated for RA. However, an association between higher disease activity of

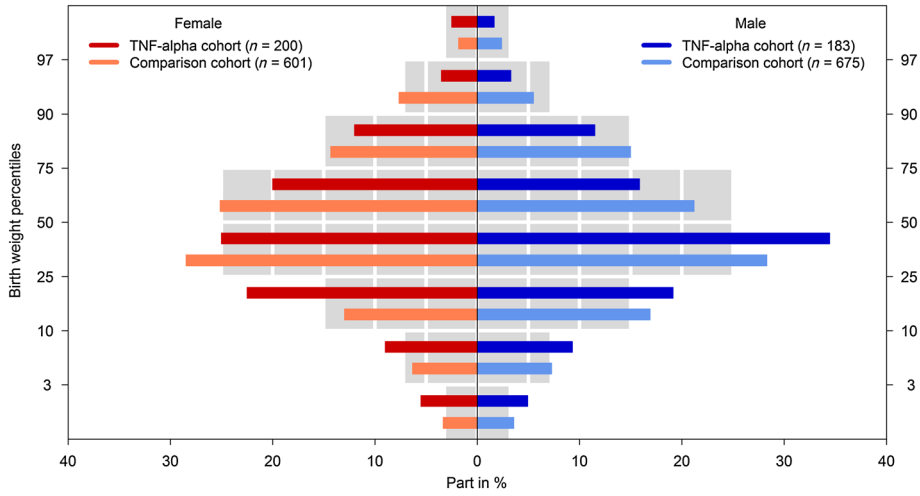

Figure 2

Birth weights according to centile categories and sex by cohort. Coloured bars give the proportions of singletons of both study cohorts according to centile categories. Grey bars represent the proportion of new-borns from the German perinatal survey [29]. (The differences in numbers of infants compared with Table 4 are due to missing values in the gestational week at delivery, sex of the infant or birth weight)

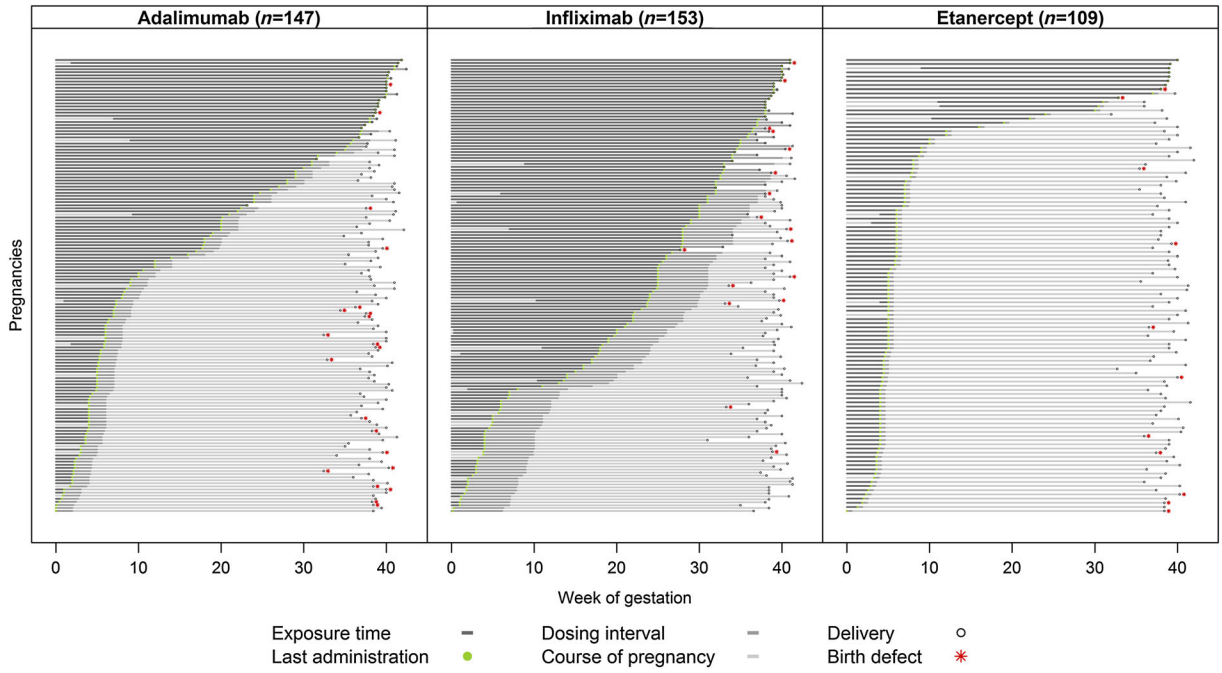

Figure 3

Duration of prenatal ADA, IFX or ETA exposure in live-born infants. Each pregnancy is represented by a single line, showing assumed fetal exposure times, i.e. treatment duration plus 1 dosing interval. The differences in exposure times among the three TNF-α-inhibitors are obvious

maternal RA during pregnancy and lower birth weight could also be shown [41]. Following this, cessation of maternal TNF-α inhibitor therapy might have led to an increased number of flares, to higher disease activity with increased inflammatory processes and, in consequence, to compromised fetal growth.

The higher rate of preterm births may be due to toxicity of the compounds or inadequate disease control. IFX has the lowest rate with 16.0% (24/150), followed by ADA with 17.4% (25/144) and ETA with 17.9% (19/106). A higher rate of preterm birth among pregnant women with IBD [39] and with RA [40] has been discussed in relation to higher disease activity [39, 41] and discontinuation of medication [42].

Strengths and limitations

Strengths of the TIS studies include the prospective approach, the possibility to evaluate a range of pregnancy outcomes and to control for a variety of potential confounders. Drug exposure is documented in real time, and the lost-to-follow-up rate is relatively small. Exposed and unexposed women are ascertained with similar procedures over the same time period. Thus, comparison is made between the average TIS population with and without exposure to the studied TNF-α inhibitors [43].

One limitation is that exposed pregnancies were only compared with a general comparison cohort. Usually, TNF-α inhibitors are used only in cases of severe disease and after failure of classical DMDs. TIS data on disease activity are incomplete due to the focus on drug toxicity. Therefore, an appropriate diseased comparison group could not be provided. This limitation is unlikely to confound the evaluation of teratogenicity because neither Crohn's disease [44, 45] nor rheumatoid arthritis are suspected to increase the risk of birth defects [40]. However, high disease activity and flares during pregnancy might have an influence on pregnancy outcome in terms of preterm birth and other complications [39, 41, 46]. The design of this study does not allow differentiating the influence of the underlying disease and treatment on birth weight and preterm birth. It is likely that disease activity, the mother's medication as well as the interaction of these factors influence the outcome of pregnancy.

Strengths and limitations of prospective observational pregnancy outcome studies have been discussed in detail in other papers [25]. Using pregnancies from the respective TIS population as controls has the advantage of similar procedures of ascertainment across cohorts and contributing centres. Women assigned to the control cohort have contacted the TIS because of fear of embryotoxicity of agents that proved to be of no risk during consultation. Therefore, the control group does not necessarily represent the general pregnant population but rather a subset of particularly concerned and/or health-oriented patients with non-teratogenic drug exposure. A recent publication demonstrated that this approach does not substantially bias the results of pregnancy outcome studies [47].

Although this is the largest study published to date on pregnancy outcomes following administration of

TNF-α inhibitors during pregnancy, the sample size is still limited in power particularly with regard to individual agents. However, the prospective approach and similar procedures of ascertainment across cohorts makes substantial bias in the assessment of exposure and the outcome data unlikely.

In conclusion TNF-α inhibitors may carry a risk of adverse pregnancy outcome of moderate clinical relevance. Given the results of our study and elsewhere published data on first trimester exposure, IFX is the TNF-α inhibitor with the largest evidence for safety in pregnancy. In contrast, GOL and CZP should only be used with special consideration of the still limited experience. Considering the impact of insufficiently controlled autoimmune disease on the mother and the unborn child, TNF-α inhibitors may nevertheless be a treatment option in women with severe disease refractory to established immunomodulatory drugs. Above all effective disease control resulting in low disease activity is an important prerequisite for a favourable pregnancy outcome.

Competing Interests

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Contributors

Conception and design of the study: C.W-S., M.O., E.W., R. M., and C.S.; collection of data: C.W-S, M.O., N.B., D.B., B. C-M., J.L.R., L.E.R., A.P., H.M., G.E., D.K., M.KD.; analysis and interpretation of data: C.W-S., M.O., E.W., R.M., and C.S.; drafting of the manuscript: C.W-S; M.O.; reviewing and approving the submitted version of the manuscript: C.W-S., M.O., E.W. N.B., D.B., B.C-M., J.L.R., L.E.R., A.P., H.M., G.E., D.K., M.KD, R.M., and C.S.

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