A Safety Assessment of Tumor Necrosis Factor Antagonists During Pregnancy: A Review of the Food and Drug Administration Database

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ABSTRACT. ***Objective.*** To present any congenital anomalies with respect to tumor necrosis factor (TNF) antagonists reported to the US Food and Drug Administration (FDA) to determine if there are common findings.

Methods. A review of the FDA database of reported adverse events with etanercept, infliximab, and adalimumab from 1999 through December of 2005 was performed. Key words for congenital anomalies were employed as search tools. Duplicate reports were eliminated. Any concomitant medicines were recorded.

Results. Our review of > 120,000 adverse events revealed a total of 61 congenital anomalies in 41 children born to mothers taking a TNF antagonist. Of these mothers, 22 took etanercept and 19 took infliximab. There were no reports in women taking adalimumab. The most common reported congenital anomaly was some form of heart defect. Twenty-four of the 41 (59%) children had one or more congenital anomalies that are part of vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limp abnormalities (VACTERL) association. There were 34 specific types of congenital anomalies in total, and 19 (56%) of those are part of the VACTERL spectrum. Nine of these 19 (47%) types of VACTERL anomalies were observed statistically significantly more than historical controls ($p < 0.01$); in 4 of these 9 the p value was ≤ 0.0001. Thirteen (32%) of the children had more than one congenital anomaly; 7 of these 13 children had 2 defects that are part of the VACTERL spectrum. However, only 1 child was diagnosed with VACTERL. In 24/41 cases (59%) the mother was taking no other concomitant medications.

Conclusion. A seemingly high number of congenital anomalies that are part of the VACTERL spectrum have been reported. These congenital anomalies are occurring at a rate higher than historical controls. This commonality raises concerns of a possible causative effect of the TNF antagonists. (First Release Dec 15 2008; J Rheumatol 2009;36:635–41; doi:10.3899/jrheum.080545)

Key Indexing Terms:
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Autoimmune conditions that may require the use of a tumor necrosis factor-α (TNF-α) antagonist often involve women of childbearing age. TNF-α antagonists are rated "category B" and are presumed to be safe in pregnancy based on animal data. However, animal reproductive studies are not always predictive of human response. For obvious reasons, this has never been formally studied in prospective trials involving humans.

Efforts have been made to form pregnancy registries to assess the safety of TNF-α antagonists and other drugs. However, few patients have been documented to take these medications throughout the entire first trimester and even fewer throughout their entire pregnancy. One such registry, the Organization of Teratology Information Specialists (OTIS), prospectively follows women with autoimmune diseases monitoring the potential effects of treatment on the developing embryo or fetus. The number of patients followed in these registries is still rather small, yet birth defects have been observed[1-3].

We previously reported a case of VACTERL (VATER) association in a child of a mother taking etanercept throughout her pregnancy[4]. Recently, we had another case of a child with tracheal stenosis, bronchomalacia, patent ductus arteriosis, and a skeletal disorder (defects part of VACTERL; possible VACTERL association) born to a mother who took adalimumab through her first trimester. VACTERL is a nonrandom association of birth defects that occurs in ~1.6/10,000 live births[5]. The acronym VACTERL is used to describe the association of Vertebral defects, Anal atresia or imperforate anus, Cardiac abnormalities (most commonly

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atrial septal defect, ventricular septal defect, and tetralogy of Fallot), Tracheoesophageal fistula or tracheal atresia/stenosis, Esophageal atresia, Renal and/or Radial abnormalities, and pre-axial Limb abnormalities. In order to be diagnosed with definite VACTERL a child must have at least 3 of the associated congenital anomalies. There are about 300 cases of VACTERL reported in the literature. All of the birth defects that are part of VACTERL are linked, but the exact etiology is unknown.

Interestingly, other drugs that inhibit TNF-α have been linked with similar congenital defects that are part of VACTERL. Thalidomide is known to cause a variety of limb abnormalities[6]. Thalidomide also works, at least in part, through its ability to inhibit TNF-α[7]. Valproic acid has been associated with vertebral body defects in humans[8,9]. It is also known that valproic acid inhibits TNF-α[10].

After publication of our proband case with VACTERL[4], we decided to further analyze the congenital anomalies associated with the TNF-α antagonists. We requested the complete lists of all reported adverse events for all 3 TNF-α antagonists (etanercept, infliximab, and adalimumab) from the US Food and Drug Administration (FDA). Our aim was to determine if there were any common findings.

MATERIALS AND METHODS

Data collection. A written request for the complete lists of all the reported adverse events for all 3 of the commercially available TNF-α antagonists (infliximab, etanercept, and adalimumab) was submitted to the FDA. These data are available through the Freedom of Information Act. After approximately 4 months, we received 3 compact discs from the FDA with the requested data. The database was complete from the time that TNF antagonists were first commercially available through December of 2005.

In order to search for all of the reported congenital anomalies for each drug, the keywords "congenital anomaly," "congenital anomalies," "birth defect," and "birth defects" were employed as search tools. Each adverse event has a unique report number. Any duplicate reports were eliminated so that each event was counted only once.

Each adverse event listed includes the following information: a unique report number, the date of the report, the adverse event(s), the report source (e.g., health professional, consumer), the medication and all concomitant medications, and the medication that is the primary suspect for the adverse event listed (as determined by the reporter). All of these data were recorded.

Statistical analysis. The specific congenital anomalies in the FDA database were compared to historical controls. In order to create a direct comparison for the FDA database, we had to change the historical incidences per live births to incidences per child born with a birth defect. Knowing that congenital anomalies encompass 3%–5% of live births, we divided the historical incidences per live birth by 0.04. A Poisson probability and cumulative Poisson probability were performed on each congenital anomaly in the database. A Poisson probability refers to the probability of getting exactly n occurrences and a cumulative Poisson probability refers to the probability of getting at most n occurrences. P values were determined from the Z-score using the equation Z = n – lambda/(square root of lambda). Because we analyzed multiple p values, there is an increased chance of Type 1 error. Therefore, we considered p values to be significant only if they are < 0.001. In order to prevent bias of including the congenital anomalies from our proband case, this child's birth defects were excluded from the statistical analysis.

RESULTS

This database review totaled over 120,000 adverse events. A total of 41 children with 61 congenital anomalies born to 40 mothers taking a TNF antagonist have been reported to the FDA through December 2005 (Table 1). Twenty-two of these mothers took etanercept at some point during their pregnancy and 19 were taking infliximab. There were no reports in women taking adalimumab. In all 41 cases the TNF-α antagonist was considered the "primary suspect" as the cause of the birth defect. Thirteen (32%) of the children had more than 1 congenital anomaly.

The congenital anomalies from our proband case with VACTERL (Table 1; Subject 19) were excluded from the statistical analysis, leaving 54 reported congenital anomalies in 40 children (Table 2). Our second case of a child born with probable VACTERL association occurred after 2005, and was therefore not included in this database either. The most common reported congenital anomaly was some form of heart defect (n = 11) [4 congenital heart disease, 2 ventricular septal defect (VSD), 2 atrial septal defect (ASD), 1 great vessel malformation, 1 tetralogy of Fallot, and 1 ventricular hypokinesia]. Other anomalies reported more than once were cystic kidney (3), pulmonary malformation (3), teratoma (3), tracheal stenosis (2), hypospadias (2), trisomy 21 (2), and hydrocele (2). Five of the congenital anomalies were not specified.

Regarding the specific congenital anomalies in the FDA database (excluding our proband case), there were 34 different types of birth defects (Table 2). Nineteen of 34 (56%) anomalies are those that are part of the VACTERL spectrum. In order to correct for multiple comparisons (n = 31), we considered a p value as significant only if it was < 0.001. Using this strict criterion, 4/19 (21%) were statistically significantly increased compared to historical controls, with a very low chance of Type 1 error (3.05%). Nine of 19 (47%) of these VACTERL-type defects occurred more than historical controls, with a p value of < 0.01. It is also important to note that there are several congenital heart defects in Table 2 that are not included in the heading "congenital heart disease" (e.g., VSD). If all of these heart defects are included in the heading "congenital heart disease," then congenital heart defects also occurred significantly more compared to historical controls (p = 0.007).

Twenty-four of 41 (59%) children had 1 or more congenital anomalies that are part of VACTERL; 7 had 2 or more (Table 1). However, only 1 was diagnosed with VACTERL (Subject 19 in Table 1). Of all the reported congenital anomalies, 37/61 (61%) are consistent with the birth defects that encompass VACTERL. If the proband case is not included, 30/54 (56%) of the congenital anomalies are consistent with those seen in VACTERL. In spite of the fact that anal atresia and esophageal atresia are part of the VACTERL spectrum, there were none observed in this database (excluding the proband case).

Table 1. Children with congenital anomalies.

Subject	Congenital Anomalies	TNF-x Antagonist	Concomitant Medications	Report Source
1*	Cystic kidney	Etanercept	MTX, PRED, NAP, diazepam	C
2*	Atrial septal defect Ventricular septal defect	Etanercept	PRED, IBU, omeperazole, carabasalate, chlorophenamine, dextropropoxyphene	HP
3*	Cystic kidney furuncle	Etanercept	PRED, IBU, amlodopine, hctz/triamterene	C
4	Duane's syndrome	Etanercept	None	HP
5	Not specified	Etanercept	None	NS
6*	Tracheal stenosis	Etanercept	None	HP
7*	Talipes	Etanercept	None	HP
8	Cystic hygroma	Etanercept	None	HP
9*	Aneurysm Atrial septal defect Ventricular hypokinesia	Etanercept	Leflunomide, lansoprazole, aspirin, lorazepam, gebapentin, propoxyphene, rofecoxib, estropipate, glyburide, oxycodone	
10*	Congenital heart disease Pulmonary malformation	Etanercept	None	NS
11*	Congenital heart disease Pulmonary malformation	Etanercept	None	NS
12	Cleft palate	Etanercept	None	NS
13	Not specified	Etanercept	None	NS
14*	Trisomy 18	Etanercept	None	NS
15*	Lung malformation	Etanercept	None	NS
16	Not specified	Etanercept	None	NS
17	Trisomy 21	Etanercept	None	NS
18*	Limb malformation	Etanercept	None	NS
19**	Tracheal atresia Tracheoesophageal fistula Esophageal atresia Imperforate anus Hypospadias Vertebral body abnormality Patent foramen ovale	etanercept	None	HP
20	Not specified	Etanercept	None	NS
21	Anencephaly	Etanercept	MTX, PRED, alendronate	NS
22*	Cystic kidney Single functional kidney	Etanercept	PRED, leflunomide, carisoprodol, cyclobenzaprine, propoxyphene, levofloxacin, IBU, demerol, HCTZ	
23*	Tetralogy of Fallot	Infliximab	MTX	HP
24	Congenital strabismus	Infliximab	None	HP
25	Hydrocele	Infliximab	None	HP
26*	Congenital arterial malformation	Infliximab	None	C
27	Hydrocele	Infliximab	None	HP
28	Congenital megacolon	Infliximab	None	C
29*	Intestinal malformation	Infliximab	None	HP
30*	Trisomy 21 Ventricular septal defect	Infliximab	Mesalamine	HP
31	Optic neuropathy Blindness	Infliximab	MTX, HCTZ/triamterene, famotidine, hydroxychloroquine, IBU, PRED, levothyroxine	HP
32*	Cardiac disorder Congenital hearing disorder	Infliximab	AZA, metronidazole, wellbutrin	HP
33	Teratoma	Infliximab	PRED, AZA	HP
34	Teratoma	Infliximab	None	HP
35*	Hypospadias	Infliximab	None	HP
36*	Laryngeal obstruction Teratoma	Infliximab	AZA, PRED	HP
37	Not specified	Infliximab	None	HP
38*	Hypospadias	Infliximab	MTX	HP
39*	Pulmonary malformation	Infliximab	None	NS
40*	Skeletal dysplasia Spinal disorder	Infliximab	AZA, mesalamine	
41*	Cardiac disorder Congenital cataracts	Infliximab	AZA	NS

* Children born with one or more of the defects that are part of VACTERL association. ** Child diagnosed with VACTERL association. AZA: azathioprine, HCTZ: hydrochlorothiazide, IBU: ibuprofen, NAP: naproxen, PRED: prednisone, MTX: methotrexate. Report source: C: consumer, HP: health professional, NS: not specified.

Table 2. Fifty-four congenital abnormalities were reported in 40 children. The congenital anomalies from the proband case with VACTERL (child 19 in Table 1) have not been included in this table.

Congenital Anomaly	No. of Reports	Incidence in Live births	Poisson probability; cumulative Poisson probability	p
Congenital heart disease*†	4	4–5/1000[38]	0.0961; 0.1847	0.81
Pulmonary†	3	1.9/10,000[39]	0.0026; 0.9976	< 0.0001††
Malformation†				
Cystic kidney†	3	1/4000[40]	0.0048; 0.9995	< 0.0001††
Teratoma	3	1/4000[41]	0.0048; 0.9995	< 0.0001††
Ventricular septal defect†	2	12.1/10,000[39]	0.2614; 0.7703	0.47
Atrial septal defect†	2	2.5/10,000[39]	0.0419; 0.9947	0.0005††
Tracheal stenosis†	2	1/50,000[42]	0.0004; 0.9999	< 0.00001††
Hypospadias	2	18.4/10,000[43]	0.2124; 0.7639	0.26
Trisomy 21	2	1/600[44]	0.264; 0.5881	0.79
Hydrocele	2	9.9/1000[45]	0.0001; 0.0001	0.01
Cystic hygroma	1	5.1/10,000[46]	0.3496; 0.8393	0.49
Duane's syndrome	1	1–5% with strabismus[47]	0.0048; 0.9998	0.0007††
Talipes†	1	0.5–7/1000[48]	0.0629; 0.0779	0.18
Ventricular hypokinesia†	1	5–8/100,000[49]	0.0814; 0.9962	0.0001††
Cleft palate	1	5.2/10,000[39]	0.3457; 0.8485	0.51
Trisomy 18†	1	1/5000[50]	0.2088; 0.9685	0.07
Limb malformation†	1	1/10,000[51]	0.1198; 0.9918	0.004
Anencephaly	1	3.6/10,000[39]	0.3017; 0.9113	0.29
Single functional kidney†	1	1/1000[52]	0.3476; 0.6005	0.98
Tetralopgy of Fallot†	1	1/10,000[39]	0.1198; 0.9918	0.004
Strabismus†	1	2.5/1000[53]	0.1103; 0.1424	0.32
Arterial malformation†	1	1.1/10,000[39]	0.1298; 0.9897	0.004
Megacolon	1	1/5000[54]	0.2088; 0.9685	0.07
Intestinal malformation†	1	4.5/1000[43]	0.0127; 0.0147	0.10
Optic neuropathy	1	1/16,000[55]	0.0789; 0.9965	0.0002††
Skeletal dysplasia†	1	3.5/10,000[39]	0.2973; 0.9155	0.27
Spinal disorder†	1	3/1000[56]	0.0667; 0.0828	0.25
Congenital cataracts	1	3,10,000[57]	0.2731; 0.9351	0.08
Congenital hearing	1	1/2000[58]	0.3457; 0.8485	0.48
Disorder				
Blindness	1	3/10000[59]	0.2731; 0.9351	0.20
Laryngeal obstruction†	1	1/10000[60]	0.1198; 0.9914	0.004
"Collagen disorder"	1	?		
"Aneurysm"	1	?		
"Furuncle"	1	?		
Not specified	5			
Total	54			

* The heading "congenital heart disease" does not include the other separate heart defects listed on this table (ventricular septal defect, atrial septal defect, ventricular hypokinesia, tetralogy of Fallot). † Anomalies associated with VACTERL. †† Statistically significant ($p < 0.001$).

In 24/41 cases (59%) the mother was taking no other concomitant medications (Table 1). For those mothers taking concomitant medications, the most common medications used included prednisone (8), azathioprine (5), methotrexate (5), ibuprofen (4), and hydrochlorothiazide (3). Of these, only methotrexate is clearly teratogenic. There was no trend in observed anomalies in the 5 women who were taking concomitant methotrexate.

Regarding perinatal demise, there were 3 cases of spontaneous abortions (Table 1; Subjects 4, 11, and 14) and 2 induced abortions (Table 1; Subjects 17 and 21). All were in etanercept-treated mothers.

Of note, 2 of these 41 children were twins (Table 1; Subjects 10 and 11). Both had the same congenital anomalies (congenital heart disease and pulmonary malformation), suggesting a common teratogenic exposure. As stated, 1 of these was spontaneously aborted. The mother was taking etanercept without concomitant medications.

DISCUSSION

There have been a significant number of congenital anomalies in children born to mothers taking TNF-α antagonists reported to the FDA. A seemingly high number of these birth defects (~60%) include anomalies that are part of the

well documented non-random association known as VACTERL association. Further, these data could be considered a conservative estimate, since the specific congenital anomaly is not specified in 5 cases. As stated, we recently had another case of a child with tracheal stenosis, bronchomalacia, patent ductus arteriosis, and a skeletal disorder (probable VACTERL association) born to a mother taking adalimumab throughout her entire first trimester. This second case was not included in the FDA database or any of the statistical analysis. This database also includes a high percentage of children (32%) born with more than 1 congenital anomaly (7 of whom had 2 anomalies that are part of VACTERL). As a comparison, approximately 14% of children born with congenital anomalies have multiple congenital anomalies[11].

Since congenital anomalies are present in 3%–5% of all live births[12] and VACTERL occurs in 1.6/10,000 live births[5], you would expect to see ~1.6 cases of VACTERL association in every 300–500 children born with congenital anomalies. We have now seen 2/42 (4.8%) cases of VACTERL [compared to historical controls of 0.005% (1.6/300); $p < 0.001$; 0.9984 cumulative Poisson probability and 23/40 (58%) others with similar defects.

Cytokines play a critical role in both normal and abnormal human fetal development. In particular, TNF-α has been identified in the ovary, uterus, placenta, and embryo[13]. Previously, it was felt that the only role of TNF-α in human gestation was that of triggering immunological pregnancy loss and as a mediator of embryopathic stresses[13]. However, it is now known that TNF-α has a dual, almost paradoxical, role in embryological development. It also protects embryos from developmental toxicants[13-16]. This multifunctional cytokine is a powerful activator of both apoptotic and anti-apoptotic signaling cascades involved in embryological development[13,15]. While the precise role of TNF-α in human fetal development is not fully elucidated, it is clear that this cytokine will not only boost cell death to kill the embryo if harmful assaults produce structural anomalies, but it also stimulates protective mechanisms preventing birth defects as the fetus continues to develop[13-16]. Interestingly, TNF-α single nucleotide polymorphisms have been linked to human conotruncal heart defects[17] (tetralogy of Fallot, VSD, etc.) and limb deficiencies[18]. Therefore, drugs that decrease embryologic TNF-α levels can interfere with these signaling cascades, its protective effects, and potentially increase the risk for anomalies.

Maternal IgG readily crosses the placenta[19]. Most IgG antibodies, in general, cross the placenta and IgG1 antibodies are preferentially transferred[20]. The Fc region of IgG is required for its transport across the placenta[19]. Therefore it would be logical that an Fc receptor-construct fusion protein (etanercept) and monoclonal IgG1 antibodies (infliximab and adalimumab) would as well. Indeed it has been demonstrated that these drugs cross the placenta to the fetus[21,22]. The timing of when they are first able to cross is not completely understood.

Although animal reproduction studies were performed prior to each of these drugs being approved, animal studies are not always predictive of human response. Etanercept was studied at 60–100 times the standard human dose; however, the area under the curve systemic exposure levels were estimated to be 4 times the normal human dose[23]. Further, these tests were performed on only 8 rats and 6 rabbits[24]. Since infliximab does not cross-react with TNF-α in species other than humans and chimpanzees, animal reproduction studies have not been conducted with this drug[25]. In spite of these obvious limitations, the 3 TNF-α antagonists are rated category B by the FDA, meaning they are presumed to be safe based on animal studies.

Other drugs that inhibit TNF-α have been linked to congenital anomalies. The 2 most notable are thalidomide and valproic acid. Importantly, the anomalies that these drugs cause are the same as many of those that encompass VACTERL association. Of note, early animal reproduction studies revealed no signs of teratogenicity with thalidomide[26]. It is now well known that pre-axial limb defects are most characteristic of thalidomide embryopathy[6]. However, other anomalies caused by thalidomide include spinal defects, cardiac malformations (usually conotruncal defects), anal atresia, and renal anomalies[27]. Thalidomide has also been associated with birth defects not traditionally associated with VACTERL, but birth defects do appear in our data, namely strabismus, Duane's syndrome (a congenital disorder of eye movement), and congenital hearing loss[6]. It is also important to note that congenital anomalies do not occur in all cases exposed to thalidomide. There is approximately a 20% risk of thalidomide embryopathy if a fetus is exposed during the critical period[28]. If the mother stops the drug before that crucial period, the risk is less. Valproic acid has a definite association with neural tube defects[8,9] and has been suggested to cause limb malformations[29], cardiac anomalies[29], tracheomalacia[30], and hypospadias[31]. This same drug also has anti-TNF-α properties[10]. Valproic acid doubles the risk of neural tube defects to the fetus, but the likelihood is still rare (2% vs 1%)[29].

There are existing data regarding TNF antagonists and pregnancy. OTIS is a collaborative research group prospectively following women exposed to TNF-α antagonists during pregnancy. To date, they have published data on 44 women exposed to etanercept or adalimumab during their first trimester and there have been 6 congenital anomalies in 5 children[2,3]. In the adalimumab registry, specifically, 21.6% of the women experienced spontaneous abortions versus 6.4% in the disease control group[3]. Another study tracked 22 pregnancy outcomes in women after exposure to TNF-α antagonists, without any reported congenital anomalies, but only 2 patients were exposed to the drug until pregnancy confirmation[32]. A database review of 96 women

exposed to infliximab during pregnancy has been published[33]. Fifty-eight of 96 women (60%) received infliximab during their first trimester and none of the women received the drug throughout the duration of their pregnancy. Five infants were born with complications including tetralogy of Fallot and intestinal malrotation. A British register has collected data on 23 women exposed to anti-TNF-α therapy at the time of conception[34]. All but 2 of these patients discontinued their therapy during the first trimester. There was a high spontaneous miscarriage rate of 6/23 (26%), 3 elective terminations, and 14 live births, the latter without any "major fetal abnormalities." Another retrospective series of 10 women with Crohn's disease exposed to infliximab throughout pregnancy yielded 3 premature births with complications but no congenital malformations[35]. Finally, another group reported the findings of 3 women who unexpectedly became pregnant while receiving anti-TNF therapy. One patient elected for therapeutic termination; of the remaining 2, 1 had a child born with adrenal congenital hyperplasia[36]. As stated, the majority of pregnant mothers exposed to thalidomide, and the vast majority of those exposed to valproic acid, have normal healthy children in spite of the fact that these are known teratogenic drugs. Therefore case series or small registries of pregnant mothers who took TNF-α antagonists that show a limited number of birth defects, or even none at all, need to be interpreted in the proper context.

Our study has several limitations. The most obvious is that the number of pregnant women who have been treated with TNF-α antagonists is unknown. Further, there is no active control group to determine an odds ratio, so historical controls were utilized. As with any voluntary postmarketing adverse event reporting database, there is reporter bias. Adverse events are likely to be reported, whereas pregnant women exposed to TNF-α antagonists without adverse events will not report this. Also, the database itself is quite limited in its content. VACTERL is thought to occur in the children of diabetic mothers at increased frequency[37]; there is no maternal medical history given in this database, but the medications are listed and only one mother (Subject 9, Table 1) was taking any type of glucose-lowering therapy. Also, it is difficult to know if this same study method were applied to the FDA database for other medications known to have no association with VACTERL, what proportion of children would have anomalies that are part of VACTERL. Finally, several of the birth defects in this database can occur without any association with VACTERL (e.g., VSD, ASD), but are considered part of this spectrum for the analysis here. In spite of these limitations, these data do raise concerns.

Taken together, these data tell us that a significant number of congenital anomalies in children of pregnant mothers taking a TNF-α antagonist have been reported to the FDA. The majority of these anomalies are consistent with those seen in VACTERL association. Historical controls suggest that these anomalies are occurring more frequently than expected. Other drugs that are known to inhibit TNF-α are known teratogens and cause similar anomalies. It is most prudent to err on the side of caution when dealing with pregnancy and potentially teratogenic drugs. These data suggest a possible causative effect of the TNF-α antagonists. Although questions remain, we suggest that clinicians should not prescribe TNF antagonists to women during pregnancy.

REFERENCES

1. Chambers CD, Tutuncu ZN, Johnson D, Jones KL. Human pregnancy safety for agents used to treat rheumatoid arthritis: adequacy of available information and strategies for developing post-marketing data. Arthritis Res Ther 2006;8:215.
2. Chambers CD, Johnson DL, Jones KL. The OTIS Collaborative Research Group. Pregnancy outcome in women exposed to etanercept: The OTIS Autoimmune Diseases in Pregnancy Project [abstract]. Washington, DC: American Academy of Dermatology, Feb 3-5, 2007.
3. Chambers CD, Johnson DL, Jones KL. The OTIS Collaborative Research Group. Pregnancy outcome in women exposed to adalimumab: The OTIS Autoimmune Diseases in Pregnancy Project [abstract]. Barcelona: EULAR, June 14, 2007; THU0162.
4. Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor inhibition and VATER association: a causal relationship? J Rheumatol 2006;33:1014-7.
5. Barnes JC, Smith WL. The VATER association. Radiology 1978;126:445-9.
6. Miller MT, Stromland K. Teratogen update: thalidomide: a review, with a focus on ocular findings and new potential uses. Teratology 1999;60:306-21.
7. Matthews SJ, McCoy C. Thalidomide: a review of approved and investigational uses. Clin Ther 2003;25:342-95.
8. Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. Lancet 1982;2:937.
9. Lammer EJ, Sever LE, Oakley GP Jr. Teratogen update: valproic acid. Teratology 1987:35:465-73.
10. Ichiyama T, Okada K, Lipton JM, Matsubara T, Hayashi T, Furukawa S. Sodium valproate inhibits production of TNF-alpha and IL-6 and activation of NF-kappa-B. Brain Res 2000;857:246-51.
11. Ofori B, Oraichi D, Blais L, Rey E, Bérard A. Risk of congenital anomalies in pregnant users of non-steroidal anti-inflammatory drugs: A nested case-control study. Birth Defects Res B Dev Reprod Toxicol 2006;77:268-79.
12. Centers for Disease Control and Prevention (CDC). Birth defects: frequently asked questions. Internet. Available from: http://www.cdc.gov/ncbddd/bd/facts.htm. Accessed Oct 31 2008.
13. Toder V, Fein A, Carp H, Torchinsky A. TNF-alpha in pregnancy loss and embryo maldevelopment: a mediator of detrimental stimuli or a protector of the fetoplacental unit? J Assist Reprod Genet 2003;20:73-81.
14. Torchinsky A, Shepshelovich J, Orenstein H, et al. TNF-alpha protects embryos exposed to developmental toxicants. Am J Reprod Immunol 2003;49:159-68.
15. Toder V, Carp H, Fein A, Torchinsky A. The role of pro- and anti-apoptotic molecular interactions in embryonic maldevelopment. Am J Reprod Immunol 2002;48:235-44.
16. Torchinsky A, Fein A, Toder V. Teratogen-induced apoptotic cell death: does the apoptotic machinery act as a protector of embryos exposed to teratogens? Birth Defects Res C Embryo Today 2005;75:353-61.

17. Shaw GM, Iovannisci DM, Yang W, et al. Risks of human conotruncal heart defects associated with 32 single nucleotide polymorphisms of selected cardiovascular disease-related genes. Am J Med Genet A 2005;138:21-6.
18. Carmichael SL, Shaw GM, Iovannisci DM, et al. Risks of human limb deficiency anomalies associated with 29 SNP's of genes involved in homocystein metabolism, coagulation, cell-cell interactions, inflammatory response, and blood pressure regulation. Am J Med Genet A 2006;140:2433-40.
19. Simister NE, Story CM, Chen HL, Hunt JS. An IgG-transporting Fc receptor expressed in the syncytiotrophoblast of human placenta. Eur J Immunol 1996;26:1527-31.
20. Glezen WP, Alpers M. Maternal immunization. Clin Infect Dis 1999;28:219-24.
21. Vasiliauskas EA, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: evidence for transplacental transfer of the maternally administered infliximab to the newborn. Clin Gastroenterol Hepatol 2006;4:1255-8.
22. Giroir BP, Peppel K, Silva M, Beutier B. The biosynthesis of tumor necrosis factor during pregnancy: studies with a CAT reporter transgene and TNF inhibitors. Eur Cytokine Netw 1992;3:533-8.
23. Etanercept (Enbrel) package insert. Amgen Wyeth. Manufactured by Immunex Corp., Thousand Oaks, CA, USA, 6/05/2003. Internet. Available from: www.enbrel.com. Accessed Oct 31 2008.
24. Nonclinical Pharmacology and Toxicology Review of BLA 98-0286. Data on file at the FDA. Internet. Available at: http://www.fda.gov/cder/biologics/review/etanimm110298r5.pdf. Accessed Oct 31 2008.
25. Infliximab (Remicade) package insert. Johnson & Johnson. Manufactured by Centocor, Inc., Malvern, PA, USA. Internet. Available from: www.remicade.com. Accessed Oct 31 2008.
26. Brent RL, Holmes LB. Clinical and basic science lessons from the thalidomide tragedy: what have we learned about the causes of limb defects? Teratology 1988;38:241-51.
27. Lenz W. A short history of thalidomide embryopathy. Teratology 1988;38:203-15.
28. Newman CG. Teratogen update: clinical aspects of thalidomide embryopathy — a continuing preoccupation. Teratology 1985:32:133-44.
29. Koren G, Nava-Ocampa AA, Moretti ME, Sussman R, Nulman I. Major malformations with valproic acid. Can Fam Physician 2006;52:441-7.
30. Ardinger HH, Atkin JF, Blackston RD, et al. Verification of the fetal valproate syndrome phenotype. Am J Med Genet 1988;29:171-85.
31. Kallen B. Valproic acid is known to cause hypospadias in man but does not reduce anogenital distance or causes hypospadias in rats. Basic Clin Pharmacol Toxicol 2004;94:51-4.
32. Strangfeld A, Listing J, Rau R, et al. Pregnancy outcome after exposure to biologics: results from the German biologics register RABBIT [abstract]. Arthritis Rheum 2007;56 Suppl:S311.
33. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol 2004;99:2385-92.
34. Hyrich KL, Symmons DP, Watson KD, Silman AJ; British Society for Rheumatology Biologics Register. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. Arthritis Rheum 2006;54:2701-2.
35. Mahadevan U, Kane S, Sandborn WJ, et al. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. Aliment Pharmacol Ther 2005;21:733-8.
36. Roux CH, Brocq O, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology paitents exposed to anti-tumor necrosis factor (TNF)-alpha therapy. Rheumatology Oxford 2007;46:695-8.
37. Castori M, Rinaldi R, Capocaccia P, Roggini M, Grammatico P. VACTERL association and maternal diabetes: a possible causal relationship? Birth Defects Res A Clin Mol Teratol 2008;82:169-72.
38. Hoffman JIE. Natural history of congenital heart disease. Problems in its assessment with special reference to ventricular septal defects. Circulation 1968;37:97–125.
39. Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health, CDC. Internet. Available from: http://www.cdc.gov/ncbddd/bd/monitoring.htm
40. Bisceglia M, Galliani CA, Senger C, Stallone C, Sessna A. Renal cystic diseases: a review. Adv Anat Pathol 2006;13:26-56.
41. Shetty SC, Gupta S, Cherian M, Chary G, Shariff S. Mature teratoma of the nasal vestibule: a case report. Ear Nose Throat J 2000;79:620-3.
42. Das BB, Nagaraj A, Rao HA, Rajagowda KB. Tracheal agenesis: Report of three cases and review of literature. Am J Perinatol 2002;19:395-39.
43. Michigan Birth Defects Registry, Michigan Department of Community Health. Internet. Available from: www.mdch.state.mi.us/pha/osr/index.asp?Id=7. Accessed Oct 31 2008.
44. Antonarakis SE, Peterson MB, McInnis MG, et al. The meiotic stage of nondisjunction in trisomy 21: determination by using DNA polymorphisms. Am J Hum Genet 1992;5:1411-6.
45. Choi H, Kim KM, Koh SK, et al. A survey of externally recognizable genitourinary anomalies in Korean newborns. J Korean Med Sci 1989;4:13-21.
46. Forrester MB, Merz RD. Descriptive epidemiology of cystic hygroma: Hawaii, 1986 to 1999. South Med J 2004;97:631-6.
47. DeRespinis PA, Caputo AR, Wagner RS, Guo S. Duane's retraction syndrome. Survey Ophthalmol 1993;38:258-88.
48. Engesaeter LB. Increasing incidence of clubfoot: changes in the genes or the environment? Acta Orthop 2006;77:837-8.
49. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. N Engl J Med 1994;331:1564.
50. Brewer CM. Survival in trisomy 13 and trisomy 18 cases ascertained from population based registers. J Med Genet 2002;39:54.
51. Statistics Canada. Vital statistics, Vol. 1. Births and deaths: Table 1. Vital statistics summary, 1984 and 1985 (Catalogue 84-204). Ottawa: Minister of Supply and Services; 1985.
52. Kiprov DD, Calvin RB, McLuskey RT. Focal and segmental glomerulosclerosis and proteinuria associated with unilateral renal agenesis. Lab Invest 1982;46:275-81.
53. Nordlow W. Squint: the frequency of onset at different ages and the incidence of some associated defects in a Swedish population. Acta Ophthalmol 1964;42:1015-37.
54. Salomon R, Attie T, Pelet A, et al. Germline mutations of the RET ligand GDNF are not sufficient to cause Hirschsprung disease. Nat Genet 1996;14:345-7.
55. Xu L, Wang Y, Jonas JB. Incidence of nonarteritic anterior ischemic optic neuropathy in adult Chinese: the Beijing Eye Study. Eur J Opthalmol 2007;17:459-60.
56. Kacinski M, Swierczynska A, Jaworek M, Zajac A. Non traumatic spinal syndromes in children. Przegl Lek 2005;62:1281-6.
57. Rahi JS, Dezateux C. National cross sectional study of detection of congenital and infantile cataract in the United Kingdom: role of childhood screening and surveillance. BMJ 1999;318:362-5.
58. Kemper AR, Downs SM. A cost-effectiveness of newborn hearing screening strategies. Arch Pediatr Adolesc Med 2000;154:484-8.
59. Robinson GC, Jan JE, Kinnis C. Congenital ocular blindness in children, 1945 to 1984. Am J Dis Child 1987;141:1321-4.
60. Rahbar R, Rouillon I, Roger G, et al. The presentation and management of laryngeal cleft: a 10-year experience. Arch Otolaryngol Head Neck Surg 2006;132:1335-41.