**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 825**

**Columns: REVIEW**

**Tumor necrosis factor-alpha inhibitor therapy and fetal risk: A systematic literature review**

**Marchioni RM *et al*.** TNF-alpha inhibitor therapy and fetal risk

Renée M Marchioni, Gary R Lichtenstein

**Renée M Marchioni,** Department of Internal Medicine, Pennsylvania Hospital of the University of Pennsylvania Health System, Philadelphia, PA 19107, United States

**Renée M Marchioni,** Division of Gastroenterology and Hepatology, University of Connecticut Health Center, Farmington, CT 06032, United States

**Gary R Lichtenstein**, Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, United States

**Author contributions:** Marchioni RM and Lichtenstein GR designed the concept for this review; Marchioni RM performed the literature search; Marchioni RM and Lichtenstein GR analyzed the data; Marchioni RM composed the paper.

**Correspondence to:** **Renée M Marchioni, DO,** Division of Gastroenterology and Hepatology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06032, United States. marchioni@resident.uchc.edu

**Telephone:** +1-860-6793878 **Fax:** +1-860-6793159

**Received:** October 17, 2012  **Revised:** March 1, 2013

**Accepted:** March 15, 2013

**Published online:**

**Abstract**

Tumor necrosis factor-alpha inhibitors (anti-TNFs) are effective in the treatment of inflammatory bowel disease (IBD) recalcitrant to conventional medical therapy. As the peak incidence of IBD overlaps with the prime reproductive years, it is crucial to establish pharmacologic regimens for women of childbearing age that achieve effective disease control without posing significant fetal harm. A systematic literature review was performed to identify all human studies with birth outcomes data after maternal exposure to infliximab, adalimumab, or certolizumab pegol within 3 mo of conception or during any trimester of pregnancy. Live births, spontaneous abortions or stillbirths, preterm or premature births, low birth weight or small for gestational age infants, and congenital abnormalities were recorded. Fifty selected references identified 472 pregnancy exposures. The subsequent review includes general information regarding anti-TNF therapy in pregnancy followed by a summary of our findings. The benefits of biologic modalities in optimizing disease control during pregnancy must be weighed against the potential toxicity of drug exposure on the developing fetus. Although promising overall, there is insufficient evidence to prove absolute safety for use of anti-TNFs during pregnancy given the limitations of available data and lack of controlled trials.

© 2013 Baishideng. All rights reserved.

**Key words:** Tumor necrosis factor-alpha inhibitors; Pregnancy; Congenital abnormalities; Safety; Infliximab; Adalimumab; Certolizumab

**Core tip:** A systematic literature review was performed to identify all human studies with birth outcomes data after maternal exposure to infliximab, adalimumab, or certolizumab pegol within 3 mo of conception or during any trimester of pregnancy. After systematic literature review investigating tumor necrosis factor-alpha inhibitor therapy and fetal risk, there is insufficient evidence to prove absolute safety for the use of biologics (specifically infliximab, adalimumab, and certolizumab pegol) during pregnancy.

Marchioni RM, Lichtenstein GR. Tumor necrosis factor-alpha inhibitor therapy and fetal risk: A systematic literature review.

*World J Gastroenterol* 2013;

**Available from:** URL: http://www.wjgnet.com/esps/

**DOI:** http://dx.doi.org/10.3748/wjg.v19.i0.0000

**INTRODUCTION**

Inflammatory bowel disease (IBD) encompasses the diagnoses of Crohn’s disease (CD) and ulcerative colitis (UC). These are chronic relapsing gastrointestinal illnesses that involve proinflammatory molecules. The onset of IBD has a bimodal distribution, with a higher peak in the younger population aged 15-30 years; fifty percent of patients afflicted by IBD are diagnosed before the age of 35[1]. Hence, the peak incidence for developing these conditions overlaps with the prime reproductive years[2,3].

Effective control of IBD is essential during pregnancy. Active disease or disease flares have been associated with adverse obstetrical outcomes[4]. About 50% of the pregnancies in North America are unplanned, and less than half of females realize their pregnancy status by week four of gestation[5]. Inadvertent fetal exposure to medications during the crucial stages of organogenesis is thus possible and common. For these reasons, preconception discussions addressing risks and benefits of pharmacologic therapy during pregnancy are clinically warranted for all patients of childbearing potential.

The decision to pursue or maintain certain drug regimens throughout the prenatal and pregnancy periods may pose a significant challenge; the risks of disease activity must be weighed against the potential side effects of medical therapy. Untreated disease may create greater risks to a pregnancy than the drugs themselves[2]. Identifying the safest management strategy is crucial, as medication use during pregnancy impacts maternal disease activity, fetal development, and pregnancy outcomes.

Tumor necrosis factor-alpha (TNF-alpha) is a pleiotropic cytokine that plays a role both in pregnancy and in the pathophysiology of inflammatory conditions including IBD. Mouse models have demonstrated that TNF-alpha is one of several cytokines bearing a potent regulatory effect on early development[6]. It controls cyclooxygenases that affect blastocyst implantation, vascular permeability of the endometrium, and uterine deciduation[7]. TNF-alpha also contributes to the process of labor by stimulating uterine contractions in conjunction with other inflammatory cytokines[8]. The production of TNF-alpha increases throughout pregnancy and reaches a peak at the onset of labor. High levels of TNF-alpha have been implicated in such pregnancy complications as infection and fetal growth retardation and have even been linked to early and unexplained spontaneous abortions[8,9].

There is a characteristic abundance of gut inflammation in IBD originating via various mechanisms at the cellular and subcellular levels. TNF-alpha is a key cytokine in the development and perpetuation of this abnormal immune response[10]. Several studies support the heightened production of TNF-alpha in the intestinal mucosa of patients with CD, and the levels are increased in both inflamed and histologically normal mucosa[11-13]. Increased TNF-alpha has also been linked to such rheumatologic and dermatologic conditions as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis.

TNF-alpha inhibitors (anti-TNFs) are drugs that block the action of TNF-alpha and neutralize its biologic effect. This class has demonstrated efficacy in controlling disease activity associated with various inflammatory conditions. Infliximab (IFX), adalimumab (ADA), and certolizumab pegol (CTZ) are three such synthetic antibodies available in the United States for the treatment of IBD. Of these, infliximab has been the most highly studied.

Recognizing the effects of maternal drug use on fetal development is an important aspect of providing care to pregnant patients and women of childbearing age with IBD. There is limited data, though, pertaining to the safety of biologic agents when used during pregnancy. The United States Food and Drug Administration (FDA) lists anti-TNF agents as category B drugs[14-16]. (Category B specifies that animal studies do not indicate fetal risk and there are no controlled studies in women or that animal studies have demonstrated adverse effects but controlled studies in women have failed to demonstrate risk). A recent consensus statement declared anti-TNF agents to be low risk during certain stages of pregnancy[17]. Some case reports and small case series reporting anti-TNF exposure and pregnancy outcomes have been published. However, large population-based studies are sparse, and there is a lack of prospective data in pregnant women. In addition, there is a relatively short number of post-marketing years since the advent of biologics, thus narrowing the safety information pool even further. The increasing use of antibody-based therapeutics fosters the need for further study in this group of patients.

A systematic literature review was performed to investigate fetal risks associated with maternal exposure to TNF-alpha inhibitors (IFX, ADA, and CTZ) during pregnancy.

**METHODS**

***Search strategy***

The search strategy was developed with the assistance of a medical librarian. Databases searched included MEDLINE, EMBASE, SCOPUS, and BIOSIS Previewsthrough November 2011 and were restricted to studies published in English and performed in humans. Structured searches were conducted using both medical subject heading terms and keyword/exploded terms as follows: (“congenital abnormalities” OR “congenital disorders” OR “pregnancy” OR “safety”) AND (“infliximab” OR “adalimumab” OR “certolizumab”). Titles and abstracts were screened for relevance; reference lists of the applicable publications were hand-searched to identify additional studies.

***Eligibility criteria***

Case reports, case series, or observational studies published in article or abstract form were eligible for inclusion if there was documented female exposure to IFX, ADA, or CTZ within three months of conception or during any trimester of pregnancy and if > one of the following birth outcomes was assessed: live births, spontaneous abortions (SA), stillbirths (SB), preterm or premature births (PTB/PMB), low birth weight (LBW)/small for gestational age (SGA), or congenital abnormalities (CA). Studies were excluded if there was insufficient detail to link specific anti-TNF exposure with birth outcomes. One investigator independently performed the searches described above and reviewed the citations (titles and abstracts) to determine eligibility. Discrepancies were resolved by the second investigator.

***Data extraction***

A standardized form was used to abstract the following data points from each study: anti-TNF drug exposure, indication for anti-TNF agent, pregnancy stage (s) of exposure by trimester, live births, and birth outcomes as aforementioned. Spontaneous abortions were defined as fetal death at < 20 wk, stillbirths as fetal death at > 20 wk or at weight > 350-500 g if gestational age unknown, preterm deliveries as < 37 wk gestation, premature deliveries as < 37 wk gestation and prior to completion of organ development, and low birth weight newborns as < 2500 g. Small for gestational age infants were described by authors as smaller than average size given the number of pregnancy weeks.

**SEARCH RESULTS**

The initial search yielded 11 452 citations. Fifty studies (Table 1)[18-68] met inclusion criteria for full review, including 13 case series, 36 case reports, and 2 prospective studies with control groups. Reports in Table 1 are categorized by biologic agent and study type, and details of maternal anti-TNF exposures and pregnancy outcomes are presented.

The total number of patients exposed to anti-TNFs was 472 (IFX 194/ADA 261/CTZ 17). Table 2[69-73] displays anti-TNF exposures and birth outcomes for the following categories: live births, spontaneous abortions, stillbirths, preterm/premature births, low birth weight/small for gestational age, and congenital abnormalities. Outcomes in Table 2 have been listed by anti-TNF exposure (IFX, ADA, and CTZ) and indication (for all medical conditions and for IBD patients alone), and results are compared to the general US population.

Table 3 summarizes the reported congenital abnormalities associated with live births (4.1%). Among 19 congenital anomalies (IFX 9/ADA 10/CTZ 0), no specific pattern of birth defects was identified[74-76].

**DISCUSSION**

We performed a systematic literature review to assess the risk of adverse birth outcomes after maternal exposure to IFX, ADA, or CTZ and identified 50 references with a total of 472 fetal exposures.

 The subsequent discussion highlights each biologic agent in the context of pregnancy and provides a summary of our data.

**INFLIXIMAB**

Infliximab (Remicade) is a human-murine chimeric monoclonal antibody that neutralizes the activity of TNF-alpha. It is composed of a human immunoglobulin G1 (IgG1) constant region and a murine variable region. Its efficacy in IBD has been documented in randomized controlled trials in the treatment of moderate to severe CD refractory to conventional therapy as well as enterocutaneous fistulae[77,78]. The drug can reduce the need for corticosteroids and, in patients who respond to initial dosing, IFX is effective for the maintenance of response and prolonged remission in CD[79,80].

IFX is classified by the US FDA as pregnancy category B. Murine models show no evidence of teratogenicity or embryotoxicity. However, anti-TNF-alpha antibodies vary among species; data cannot simply be paralleled to human pregnancy outcomes. Infliximab does not cross-react with TNF-alpha in species other than humans and chimpanzees, and it has not been tested in animal reproduction studies[14].

IFX is not thought to cross the placenta in the first trimester due to its human IgG1 constant region[81], but this subclass is known to efficiently cross in the late second and third trimesters[26]. Given this timing, the infant is somewhat shielded from drug exposure during the critical period of organogenesis. IFX levels can be detected in newborns of exposed mothers, and the drug remains in the system for up to six months after delivery[19,50]. This bears important consequences in terms of newborn infection risks and vaccination responses[17]. Discontinuing infliximab in the third trimester is an option to decrease late placental transport to the newborn.

**ADALIMUMAB**

Adalimumab (Humira) is a fully human monoclonal IgG1 antibody against TNF-alpha. It has proven effective for inducing and maintaining remission in CD[82,83], especially in those who have lost response to or have become intolerant of infliximab[84].

ADA is classified as an FDA pregnancy category B drug. In an embryo-fetal perinatal developmental toxicity study, cynomolgus monkeys were administered ADA at extreme dosages of up to 100 mg/kg (This is 266 times human AUC when dispensed as 40 mg subcutaneously with methotrexate weekly or 373 times human AUC when dispensed as 40 mg subcutaneously without methotrexate). No evidence of fetal harm due to ADA was recorded. Adequate and well-controlled studies have not been conducted in pregnant women. Again, animal reproduction and developmental studies are not always indicative of human response, and ADA must be used with caution in pregnancy[15]. There is no long-term data regarding effects of adalimumab on the developing fetus.

Less information exists on the transplacental diffusion of ADA throughout the trimesters compared to infliximab. Determining the time course of drug administration and when to potentially discontinue ADA during pregnancy is not well-defined due to shorter dosing intervals and limited ability to commercially measure ADA levels. Withholding the drug in the third trimester may be considered to reduce late placental transport to the newborn. Mahadevan *et al*[17]suggests discontinuation 8-10 wk prior to estimated date of delivery.

**CERTOLIZUMAB PEGOL**

Certolizumab pegol (Cimzia) is a recombinant humanized anti-TNF-alpha fragment antigen binding (Fab’) fragment. The antibody fragment is bound to a polyethylene glycol molecule that extends the drug’s half-life to approximately two weeks in the plasma, thereby reducing dosing frequency[85]. Studies have demonstrated the efficacy of CTZ for induction and maintenance of remission in CD[86].

CTZ is a pregnancy category B drug. It does not cross-react with mouse or rat TNF-alpha. Reproduction studies in rats have thus been performed using a rodent anti-murine TNF-alpha pegylated Fab' fragment (cTN3 PF) that is similar in function to CTZ. These studies have been conducted using doses up to 100 mg/kg and have revealed no evidence of impaired fertility or fetal adversities due to cTN3 PF. Adequate and well-controlled studies have not been performed in pregnant women. As animal reproduction studies are not always indicative of human response, this drug must be used with caution in pregnancy[16].

The molecular structure of CTZ lacks an Fc portion, so its cross-placental transfer is different from that of IFX and ADA. The Fab' fragment may passively cross the placenta in low levels during the first trimester, an event that is not expected with the IgG1 antibody. Although CTZ therapy would likely not need to be discontinued in the third trimester, it is important to recognize that the transplacental transfer of this drug occurs during a critical period of organogenesis in the first trimester.

In an animal model, pregnant rats received a murinized IgG1 TNF-alpha antibody and a PEGylated Fab' fragment of the antibody. Lower levels of the drug were detected in the infant and in breast milk with the Fab' fragment versus the full antibody[87]. Mahadevan *et al*[66]demonstrated these findings in two human patients receiving certolizumab during pregnancy. The drug was administered to both women two weeks prior to delivery. Although the mothers’ drug levels were higher on the date of delivery, newborn cord blood levels were low.

There are few published reports on the use of CTZ during pregnancy. As with the other anti-TNF agents, it is possible that the Fab' fragment passively crosses the placenta at low levels in the first trimester. The drug must be further studied in humans to fully appreciate the course of drug transfer during gestation and subsequent effects on fetal development and pregnancy outcomes.

**SUMMARY OF DATA**

Our review indicates that rates of SA and CA in anti-TNF-exposed patients are similar to rates in the general US population[69-73] and in women with IBD unexposed to anti-TNF agents[74-76]. The live birth rate in the anti-TNF-exposed group (85.8%) is higher than that of the general US population (64.6%); this holds true for all patients exposed to IFX or ADA regardless of underlying inflammatory disease and perhaps reflects a state of controlled disease activity. The live birth rate for patients exposed to CTZ (47.1%) is lower than that of the general population, although there is a very small collective sample size. The rates of SA and SB for all groups are similar to the general US population[72] with the exception of IFX-exposed patients, in whom the rate of SB is just slightly higher. The PTB/PMB rate in the anti-TNF-exposed group (19.9%) is higher than in the US population (12.3%)[72], perhaps due to an underlying predisposition as in the setting of IBD[76]. LBW/SGA infants are more common in ADA- and CTZ-exposed patients than in the general US population[73], again possibly reflecting the underlying disease itself or the severity of disease activity.

In general, pregnancy does not increase the risk of disease exacerbation in CD or UC[88,89]. Approximately one-third of women with inactive IBD at the time of conception are expected to flare during pregnancy and the puerperium[90]. Alternatively, if pregnancy overlaps with a period of active IBD, the disease may be difficult to control[91]. Active disease at the time of conception has been associated with increased rates of PTB[89] and fetal loss[92], and disease flares during pregnancy have been associated with PTB and LBW[4,93]. Studies are mixed regarding the risk of congenital malformations among IBD progeny, with some data showing an increased risk for both CD and UC patients[94] or for UC patients alone[95,96] and other data showing no increased risk in CD or UC[97,98].Regardless of disease activity, women with IBD have an increased risk for such adverse pregnancy outcomes as PTB, SB, LBW, SGA, and delivery complications such as cesarean sections compared to the general population[97-101]. In our study, no discernible increased risks for SA or CA were identified. Overall, unless there is a clear risk of fetal harm (i.e. an FDA category X drug) that dictates otherwise, maintenance therapy is conventionally continued throughout pregnancy to optimize maternal disease control and prevent relapse or progression[102].

This systematic review has limitations. Pooling data from different studies yields inherent heterogeneity based on study designs, study populations, and recording of birth outcomes data. As evidenced, there are a limited number of reported pregnancy exposures to anti-TNF agents, many published as case reports or case series with small sample sizes; these do not necessarily reflect outcomes that can be extracted to the general population. Our review is affected by the limitations of the individual studies, including the inability to adjust for maternal disease activity and severity, concomitant medication or substance use, comorbidities, or other maternal characteristics. Additionally, there exist potential publication bias against negative outcomes and recall bias involving drug exposure and timing of administration during conception and pregnancy. The decision to exclude studies based on the English language and on the inability to link specific anti-TNF exposure with birth outcomes may have discounted pertinent publications. Although care was taken to account for evident overlap, it is possible that repeated data exists given the nature of our information (for example, a case report that has also been reported within drug registry data).

A growing body of evidence supports that IFX, ADA, and CTZ are low risk in pregnancy[17], and studies beyond those included in our data set are underway to further elucidate fetal risk and optimal timing of biologic administration during pregnancy[103,104]. Thus far, it is believed that IFX and ADA are most compatible for use during conception and at least the first and second trimesters considering mechanisms of placental transport[17,102]; further human data are needed to generate safety guidelines for the use of CTZ. In a recent study of pregnant women receiving biologic therapy, IFX and ADA were shown to be transplacentally transferred to infants at birth, with high levels of drug in cord blood and detectable drug levels up to six months after birth. CTZ was found to be least detectable in both cord blood and infant serum after birth. Of note, no CA or significant fetal complications were reported in this study[104].

Future efforts are promising and include the expansion of drug safety data registries and the development of larger prospective trials to help definitively quantify fetal risk and to facilitate clinical decision-making in treating women with IBD during their childbearing years. One such project is the highly anticipated Pregnancy IBD and Neonatal Outcomes study, a prospective data collection from multiple IBD centers in the United States[105]. This large cohort registry not only accounts for maternal factors including IBD activity, medication use, delivery methods and pregnancy complications but also tracks data over time from the neonatal period through children’s first year of life. Similarly, post-marketing surveillance data may uncover additional consequences of fetal exposure to biologic agents over time.

While evidence in the field is mounting, caution should indefinitely be exercised. Given the limitations of the available data and lack of controlled trials, there is insufficient evidence to prove absolute safety for use of anti-TNFs during pregnancy. Although the benefits of therapy in optimizing disease activity during gestation may lend to more favorable pregnancy outcomes based on a controlled disease state, definitive safety of drug exposure on the developing fetus has not been confirmed.

Medical management decisions during the preconception and pregnancy periods will inevitably vary by case based on respective risk-to-benefit ratios, details of disease activity, response to alternative therapies, and individual preferences. Women and men of childbearing age should be educated about the effects of IBD on pregnancy and the potential implications of treatment on fetal development. In addition, patients should be encouraged to discuss reproductive plans with their physicians in order to achieve remission prior to conceiving. Ideally, the primary preconception goal should be quiescent disease, as this lends to the most favorable pregnancy outcomes.

**CONCLUSION**

After systematic literature review investigating TNF-alpha inhibitor therapy and fetal risk, there is insufficient evidence to prove absolute safety for the use of biologics (specifically infliximab, adalimumab, and certolizumab pegol) during pregnancy.

**REFERENCES**

1 **Munkholm P**. Crohn's disease--occurrence, course and prognosis. An epidemiologic cohort-study. *Dan Med Bull* 1997; **44**: 287-302 [PMID: 9233548]

2 **Andres PG**, Friedman LS. Epidemiology and the natural course of inflammatory bowel disease. *Gastroenterol Clin North Am* 1999; **28**: 255-81, vii [PMID: 10372268 DOI: 10.]

3 **Moscandrew M**, Kane S. Inflammatory bowel diseases and management considerations: fertility and pregnancy. *Curr Gastroenterol Rep* 2009; **11**: 395-399 [PMID: 19765367]

4 **Leimkühler AM**. [Psychosocial after care: studies of the value of psychosocial measures in clinical practice]. *Fortschr Neurol Psychiatr* 1990; **58**: 301-309 [PMID: 2172128]

5 Centers for Disease Control official website. Available from: URL: http: //www.cdc.gov/reproductivehealth. Accessed: March 4 2012.

6 **Tartakovsky B**, Ben-Yair E. Cytokines modulate preimplantation development and pregnancy. *Dev Biol* 1991; **146**: 345-352 [PMID: 1864460 DOI: 10.1016/0012-1606(91)90236-V]

7 **Imseis HM**, Zimmerman PD, Samuels P, Kniss DA. Tumour necrosis factor-alpha induces cyclo-oxygenase-2 gene expression in first trimester trophoblasts: suppression by glucocorticoids and NSAIDs. *Placenta* 1997; **18**: 521-526 [PMID: 9290146 DOI: 10.1016/0143-4004(77)90005-4]

8 **Daher S**, Fonseca F, Ribeiro OG, Musatti CC, Gerbase-DeLima M. Tumor necrosis factor during pregnancy and at the onset of labor and spontaneous abortion. *Eur J Obstet Gynecol Reprod Biol* 1999; **83**: 77-79 [PMID: 10221614 DOI: 10.1016/S0301-2115(98)00252-8]

9 **Yu XW**, Yan CF, Jin H, Li X. Tumor necrosis factor receptor 1 expression and early spontaneous abortion. *Int J Gynaecol Obstet* 2005; **88**: 44-48 [PMID: 15617704 DOI: 10.1016/j.ijgo.2004.08.020]

10 **Magro F**, Portela F. Management of inflammatory bowel disease with infliximab and other anti-tumor necrosis factor alpha therapies. *BioDrugs* 2010; **24** Suppl 1: 3-14 [PMID: 21175228 DOI: 10.2165/1158290-000000000-00000]

11 **Reimund JM**, Wittersheim C, Dumont S, Muller CD, Baumann R, Poindron P, Duclos B. Mucosal inflammatory cytokine production by intestinal biopsies in patients with ulcerative colitis and Crohn's disease. *J Clin Immunol* 1996; **16**: 144-150 [PMID: 8734357 DOI: 10.1007/BF01540912]

12 **Reimund JM**, Wittersheim C, Dumont S, Muller CD, Kenney JS, Baumann R, Poindron P, Duclos B. Increased production of tumour necrosis factor-alpha interleukin-1 beta, and interleukin-6 by morphologically normal intestinal biopsies from patients with Crohn's disease. *Gut* 1996; **39**: 684-689 [PMID: 9026483 DOI: 10.1136/gut.39.5.684]

13 **Riegel D**, Büermann L, Gross KD, Luszik-Bhadra M, Mishra SN. Existence and stability of magnetic 3d moments in noble- and transition-metal hosts. *Phys Rev Lett* 1989; **62**: 316-319 [PMID: 10040201 DOI: 10.1053/gast.2000.18160]

14 Infliximab (Remicade) package insert. Johnson & Johnson. Manufactured by Centocor Ortho Biotech, Inc: 2005. Malvern, PA, USA.Available from: URL: http: // www.remicade.com. Accessed October 12 2011.

15 Adalimumab (Humira) package insert. Abbott Laboratories. Manufactured by Abbott Laboratories: 2007. North Chicago, IL, USA. Available from: URL: http: // www.humira.com. Accessed October 12 2011.

16 Certolizumab pegol (Cimzia) package insert. UCB, Inc. Manufactured by UCB, Inc: 2008. Smyrna, GA, USA. Available from: URL: http: // www.cimzia.com. Accessed October 12 2011.

17 **Mahadevan U**, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, Sandborn WJ, Colombel JF. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol* 2011; **106**: 214-23; quiz 224 [PMID: 21157441 DOI: 10.1038/ajg.2010.464]

18 **Chambers CD**, Johnson DL, Jones KL. Pregnancy outcome in women exposed to anti-TNF medications: the OTIS Rheumatoid Arthritis in Pregnancy Study. *Arthritis Rheum* 2004; **50**: S479

19 **Mahadevan U**, Terdiman JP, Church J. Infliximab levels in infants born to women with inflammatory bowel disease. *Gastroenterol* 2007; **132**: A144

20 **Berthelot JM**, De Bandt M, Goupille P, Solau-Gervais E, Lioté F, Goeb V, Azaïs I, Martin A, Pallot-Prades B, Maugars Y, Mariette X. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. *Joint Bone Spine* 2009; **76**: 28-34 [PMID: 19059799 DOI: 10.1016/j.jbspin.2008.04.016]

21 **Chakravarty EF**, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. *J Rheumatol* 2003; **30**: 241-246 [PMID: 12563675]

22 **Correia LM**, Bonilha DQ, Ramos JD, Ambrogini O, Miszputen SJ. Inflammatory bowel disease and pregnancy: report of two cases treated with infliximab and a review of the literature. *Eur J Gastroenterol Hepatol* 2010; **22**: 1260-1264 [PMID: 20671559 DOI: 10.1097/MEG.0b013e28329543a]

23 **Hyrich KL**, Symmons DP, Watson KD, Silman AJ. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. *Arthritis Rheum* 2006; **54**: 2701-2702 [PMID: 16871549 DOI: 10.1002/art.22028]

24 **Kane S**, Ford J, Cohen R, Wagner C. Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. *J Clin Gastroenterol* 2009; **43**: 613-616 [PMID: 19142167 DOI: 10.10.1097/MCG.0b013e31817f9367]

25 **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**: 2385-2392 [PMID: 15571587 DOI: 10.1111/j.172-0241.2004.30186.x]

26 **Mahadevan U**, Kane S, Sandborn WJ, Cohen RD, Hanson K, Terdiman JP, Binion DG. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. *Aliment Pharmacol Ther* 2005; **21**: 733-738 [PMID: 15771759 DOI: 10.1111/j.1365-2036.2005.02405.x]

27 **Rosner I**, Haddad A, Boulman N, Feld J, Avshovich N, Slobodin G, Rozenbaum M. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology (Oxford)* 2007; **46**: 1508; author reply 1508-1509 [PMID: 17684027 DOI: 10.1093/rheumatology/kem068]

28 **Schnitzler F**, Fickler HH, Ferrante M, Noman M, Van Assche GA, Spitz B, Vermeire S, Rutgeerts P. Intentional treatment with infliximab during pregnancy in women with inflammatory bowel disease*. Gastroenterol* 2007; **132**: A144

29 **Weber-Schoendorfer C**, Fritzsche J, Schaefer. Pregnancy outcomes in women exposed to adalimumab or infliximab: The experience of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. *Reprod Toxicol* 2011; **31**: A267-268 [DOI: 10.1016/j.reprotox.2010.12.052]

30 **Zelinkova Z**, de Haar C, de Ridder L, Pierik MJ, Kuipers EJ, Peppelenbosch MP, van der Woude CJ. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther* 2011; **33**: 1053-1058 [PMID: 21366638 DOI: 10.1111/j.1365-2036.2011.04617.x]

31 **Akinci A**, Ozçakar L. Infliximab use during pregnancy revisited. *Acta Reumatol Port* ; **33**: 374-375 [PMID: 18846021]

32 Angelucci E, Cesarini M, Vernia P. Inadvertent conception during concomitant treatment with infliximab and methotrexate in a patient with Crohn’s disease: Is the game worth the candle? Inflamm Bowel Dis 2010; 16: 1641-1642 [PMID 20186946 DOI: 10.1002/ibd.21226]

33 **Angelucci E**, Cocco A, Viscido A, Caprilli R. Safe use of infliximab for the treatment of fistulizing Crohn's disease during pregnancy within 3 months of conception. *Inflamm Bowel Dis* 2008; **14**: 435-436 [PMID: 18050300 DOI: 10.1002/ibd.20319]

34 **Antoni C**, Dechant C, Hanns-Martin Lorenz PD, Wendler J, Ogilvie A, Lueftl M, Kalden-Nemeth D, Kalden JR, Manger B. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. *Arthritis Rheum* 2002; **47**: 506-512 [PMID: 12382299 DOI: 10.1002/art.10671]

35 **Arai K**, Takeuchi Y, Oishi C, Imawari M. The impact of disease activity of Crohn’s disease during pregnancy on fetal growth. *Clin J Gastroenterol* 2010; **3**: 179-181 [DOI: 10.1007/s12328-010-0158-9]

36 **Aratari A**, Margagnoni G, Koch M, Papi C. Intentional infliximab use during pregnancy for severe steroid-refractory ulcerative colitis. *J Crohns Colitis* 2011; **5**: 262 [PMID: 21575893 DOI: 10.1016/j.crohns.2011.02.004]

37 **Burt MJ**, Frizelle FA, Barbezat GO. Pregnancy and exposure to infliximab (anti-tumor necrosis factor-alpha monoclonal antibody). *J Gastroenterol Hepatol* 2003; **18**: 465-466 [PMID: 12653902 DOI: 10.1046/j.1440-1746.2003.02983.x]

38 **Chaparro M**, Gisbert JP. Successful use of infliximab for perianal Crohn's disease in pregnancy. *Inflamm Bowel Dis* 2011; **17**: 868-869 [PMID: 20564533 DOI: 10.1002/ibd.21368]

39 **Cheent K**, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010; **4**: 603-605 [PMID: 21122568 DOI: 10.1016/j.crohns.2010.05.001]

40 **Epping G**, van der Valk PD, Hendrix R. Legionella pneumophila pneumonia in a pregnant woman treated with anti-TNF-α antibodies for Crohn's disease: a case report. *J Crohns Colitis* 2010; **4**: 687-689 [PMID: 21122583 DOI: 10.1016/j.crohns.2010.08.006]

41 **Hou JK**, Mahadevan U. A 24-year-old pregnant woman with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2009; **7**: 944-947 [PMID: 19410016 DOI: 10.1016/j.cgh.2009.04.022]

42 **James RL**, Pearson LL. Successful treatment of pregnancy-triggered Crohn’s disease complicated by severe recurrent life-threatening gastrointestinal bleeding. *Am J Gastroenterol* 2001; **96**: S295 [DOI: 10.1016/S0002-9270(01)03714-5]

43 **Kinder AJ,** Edwardes J, Samanta A, Nichol F. Pregnancy in a rheumatoid arthritis patient on infliximab and methotrexate. *Rheumatology (Oxford)* 2004; **43**: 1195-1196 [PMID: 1537958 DOI: 10.1093/rheumatology/keh264]

44 **Østensen M**, Raio L. A woman with rheumatoid arthritis whose condition did not improve during pregnancy. *Nat Clin Pract Rheumatol* 2005; **1**: 111-14; quiz 1 p. following 114 [PMID: 16932640 DOI: 10.1038/ncprheum0044]

45 **Puig L**, Barco D, Alomar A. Treatment of psoriasis with anti-TNF drugs during pregnancy: case report and review of the literature. *Dermatology* 2010; **220**: 71-76 [PMID: 19940453 DOI: 10.1159/000262284]

46 **Srinivasan R**. Infliximab treatment and pregnancy outcome in active Crohn's disease. *Am J Gastroenterol* 2001; **96**: 2274-2275 [PMID: 11467677 DOI: 10.1016/S0002-9270(01)02550-3]

47 **Steenholdt C**, Al-Khalaf M, Ainsworth MA, Brynskov J. Therapeutic infliximab drug level in a child born to a woman with ulcerative colitis treated until gestation week 31. *J Crohns Colitis* 2012; **6**: 358-361 [PMID: 22405174 DOI: 10.1016/j.crohns.2011.10.002]

48 **Stengel JZ**, Arnold HL. Is infliximab safe to use while breastfeeding? *World J Gastroenterol* 2008; **14**: 3085-3087 [PMID: 18494064 DOI: 10.3748/wjg.14.3085]

49 **Tursi A**. Effect of intentional infliximab use throughout pregnancy in inducing and maintaining remission in Crohn's disease. *Dig Liver Dis* 2006; **38**: 439-440 [PMID: 16563889 DOI: 10.1016/j.dld.2006.01.017]

50 **Vasiliauskas EA**, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: Evidence for transplacental transfer of maternally administered infliximab to the newborn. *Clin Gastroenterol Hepatol* 2006; **4**: 1255-1258 [PMID: 17045211 DOI: 10.1016/j.cgh.2006.07.018]

51 **Wibaux C**, Andrei I, Paccou J, Philippe P, Biver E, Duquesnoy B, Flipo RM. Pregnancy during TNFalpha antagonist therapy: beware the rifampin-oral contraceptive interaction. Report of two cases. *Joint Bone Spine* 2010; **77**: 268-270 [PMID: 20447852 DOI: 10.1016/j.jbspin.2010.02.001]

52 **Xirouchakis E**, Karantanos P, Tsartsali L, Karkatzos E. Pregnancy and Crohn’s disease: Infliximab induction therapy, accidental conception, pregnancy outcome and postpartum complications. *Annals Gastroenterol* 2006; **19**: 138-140

53 **Johnson DJ**, Jones KL, Chambers CD, Salas E. Pregnancy outcomes in women exposed to Adalimumab: The OTIS Autoimmune Diseases in Pregnancy Project. *Gastroenterol* 2009; **136 S1**: A27 [DOI: 10.1016/S0016-5085(09)60125-6]

54 **Johnson DL**, Jones KL, Jimenez J, Mirrasoul N, Salas E,Chambers CD. Pregnancy outcomes in women exposed to adalimumab: the OTIS autoimmune diseases in pregnancy project.Available from: URL: http: //www.otispregnancy.org/readResource.php?r=108643. Accessed October 10 2011.

55 **Abdul Wahab NA**, Harkin R. Humira in pregnancy for Crohn’s disease: A case report. *Ir J Med Sci* 2011; **180**: S132 [DOI: 10.1007/s11845-011-0697-1]

56 **Ben-Horin S**, Yavzori M, Katz L, Picard O, Fudim E, Chowers Y, Lang A. Adalimumab level in breast milk of a nursing mother. *Clin Gastroenterol Hepatol* 2010; **8**: 475-476 [PMID: 20005982 DOI: 10.1016/j.cgh.2009.11.023]

57 **Bosworth BP**, Inra J, Eswaran S, Scherl EJ. Failed use of adalimumab in maintaining remission in Crohn’s disease during pregnancy. *Am J Gastroenterol* 2007; **102**: S322 [DOI: 10.1111/j.1572-0241.2007.01491\_7.x]

58 **Coburn LA**, Wise PE, Schwartz DA. The successful use of adalimumab to treat active Crohn's disease of an ileoanal pouch during pregnancy. *Dig Dis Sci* 2006; **51**: 2045-2047 [PMID: 17009112 DOI: 10.1007/s10620-006-9452-2]

59 **Dessinioti C**, Stefanaki I, Stratigos AJ, Kostaki M, Katsambas A, Antoniou C. Pregnancy during adalimumab use for psoriasis. *J Eur Acad Dermatol Venereol* 2011; **25**: 738-739 [PMID: 20569288 DOI: 10.1111/j.1468-3083.2010.03756.x]

60 **Jürgens M**, Brand S, Filik L, Hübener C, Hasbargen U, Beigel F, Tillack C, Göke B, Ochsenkühn T, Seiderer J. Safety of adalimumab in Crohn's disease during pregnancy: case report and review of the literature. *Inflamm Bowel Dis* 2010; **16**: 1634-1636 [PMID: 20027647 DOI: 10.1002/ibd.21198]

61 **Kraemer B**, Abele H, Hahn M, Rajab T, Kraemer E, Wallweiner D, Becker S. A successful pregnancy in a patient with Takayasu's arteritis. *Hypertens Pregnancy* 2008; **27**: 247-252 [PMID: 18696353 DOI: 10.1080/10641950801955741]

62 **Mishkin DS**, Van Deinse W, Becker JM, Farraye FA. Successful use of adalimumab (Humira) for Crohn's disease in pregnancy. *Inflamm Bowel Dis* 2006; **12**: 827-828 [PMID: 16917239 DOI: 10.1097/00054725-200608000-00020]

63 **Roux CH**, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology (Oxford)* 2007; **46**: 695-698 [PMID: 17158212 DOI: 10.1093/rheumatology/kel400]

64 **Vesga L**, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. *Gut* 2005; **54**: 890 [PMID: 15888806 DOI: 10.1136/gut.2005.065417]

65 **Kane SV**, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am J Gastroenterol* 2009; **104**: 228-233 [PMID: 19098873 DOI: 10.1038/ajg.2008.71]

66 **Mahadevan U**, Abreu MT. Certolizumab use in pregnancy: low levels detected in cord blood. *Am J Gastroenterol* 2009; **136 S5**: A-960 [DOI: 10.1016/S0016-5085(09)60658-2]

67 **Oussalah A**, Bigard MA, Peyrin-Biroulet L. Certolizumab use in pregnancy. *Gut* 2009; **58**: 608 [PMID: 19299393 DOI: 10.1136/gut.2008.166884]

68 **Steinberg SA**, Ullman TA. Certolizumab treatment of linear IgA dermatosis in a pregnant Crohn’s colitis patient: A case study and review of the literature. *Gastroenterol* 2010; **138**: S698 [DOI: 10.1016/S0016-5085(10)63209-X]

69 **Ventura SJ**, Abma JC, Mosher WD, Henshaw SK. Estimated pregnancy rates for the United States, 1990-2005: an update. *Natl Vital Stat Rep* 2009; **58**: 1-14 [PMID: 20121003]

70 **Ventura SJ**, Mosher WD, Curtin SC, Abma JC, Henshaw S. Highlights of trends in pregnancies and pregnancy rates by outcome: estimates for the United States, 1976-96. *Natl Vital Stat Rep* 1999; **47**: 1-9 [PMID: 10635682]

71 **Martin JA**, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJ. Births: final data for 2008. *Natl Vital Stat Rep* 2010; **59**: 1, 3-71 [PMID: 22145497]

72 March of Dimes: Premature Birth; Miscarriage. Available from: URL: http: //www.marchofdimes.com. Accessed October 1 2011.

73 Centers for Disease Control: Birth Defects; Low Birth Weight. Available from: URL: http: //www.ephtracking.cdc.gov. Accessed October 1 2011.

74 **Hudson M**, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997; **58**: 229-237 [PMID: 9252260 DOI: 10.1016/S0020-7292(97)00088-X]

75 **Dominitz JA**, Young JC, Boyko EJ. Outcomes of infants born to mothers with inflammatory bowel disease: a population-based cohort study. *Am J Gastroenterol* 2002; **97**: 641-648 [PMID: 11926208 DOI: 10.1016/S0002-9270(01)04105-3]

76 **Cornish J**, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007; **56**: 830-837 [PMID: 17185356 DOI: 10.1136/gut.2006.108324]

77 **Targan SR**, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035 [PMID: 9321530 DOI: 10.1056/NEJM199710093371502]

78 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340**: 1398-1405 [PMID: 10228190 DOI: 10.1056/NEJM199905063401804]

79 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]

80 **Rutgeerts P**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Hanauer SB. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; **126**: 402-413 [PMID: 14762776 DOI: 10.1053/j.gastro.2003.11.014]

81 **Simister NE**. Placental transport of immunoglobulin G. *Vaccine* 2003; **21**: 3365-3369 [PMID: 12850341 DOI: 10.1016/S0264-410X(03)00334-7]

82 **Hanauer SB**, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130**: 323-33; quiz 591 [PMID: 16472588 DOI: 10.1053/j.gastro.2005.11.030]

83 **Sandborn WJ**, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56**: 1232-1239 [PMID: 17299059 DOI: 10.1136/gut.2006.106781]

84 **Sandborn WJ**, Hanauer S, Loftus EV, Tremaine WJ, Kane S, Cohen R, Hanson K, Johnson T, Schmitt D, Jeche R. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. *Am J Gastroenterol* 2004; **99**: 1984-1989 [PMID: 15447761 DOI: 10.1111/j.1572-0241.2004.40462.x]

85 **Rivkin A**. Certolizumab pegol for the management of Crohn’s disease in adults. *Clin Ther* 2009; **31**: 1158-1176 [PMID: 196953385 DOI: 10.1016/j.clinthera.2009.06.015]

86 **Schreiber S**, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, Bernstein CN, Staun M, Thomsen OØ, Innes A. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005; **129**: 807-818 [PMID: 16143120 DOI: 10.1053/j.gastro.2005.06.064]

87 Nesbitt A, Foulkes R. Placental transfer and accumulation in milk of the anti-TNF antibody TN3 in rats: immunoglobulin G1 versus PEGylated Fab. Am J Gastroenterology 2006; 101: S119.

88 **Nielsen OH**, Andreasson B, Bondesen S, Jacobsen O, Jarnum S. Pregnancy in Crohn's disease. *Scand J Gastroenterol* 1984; **19**: 724-732 [PMID: 6515312]

89 **Nielsen OH**, Andreasson B, Bondesen S, Jarnum S. Pregnancy in ulcerative colitis. *Scand J Gastroenterol* 1983; **18**: 735-742 [PMID: 6669937 DOI: 10.3109/00365528309182088]

90 **Alstead EM**. Inflammatory bowel disease in pregnancy. *Postgrad Med J* 2002; **78**: 23-26 [PMID: 11796867 DOI: 10.1136/pmj.78.915.23]

91 **Korelitz BI**. Inflammatory bowel disease and pregnancy. *Gastroenterol Clin North Am* 1998; **27**: 213-224 [PMID: 9546091 DOI: 10.1016/S0889-8553(05)70354-X]

92 **Morales M**, Berney T, Jenny A, Morel P, Extermann P. Crohn's disease as a risk factor for the outcome of pregnancy. *Hepatogastroenterology* 2000; **47**: 1595-1598 [PMID: 11149010]

93 **Bush MC**, Patel S, Lapinski RH, Stone JL. Perinatal outcomes in inflammatory bowel disease. *J Matern Fetal Neonatal Med* 2004; **15**: 237-241 [PMID: 15280131 DOI: 10.1080/14767050410001668662]

94 **Bortoli A**, Saibeni S, Tatarella M, Prada A, Beretta L, Rivolta R, Politi P, Ravelli P, Imperiali G, Colombo E, Pera A, Daperno M, Carnovali M, de Franchis R, Vecchi M. Pregnancy before and after the diagnosis of inflammatory bowel diseases: retrospective case-control study. *J Gastroenterol Hepatol* 2007; **22**: 542-549 [PMID: 17376049]

95 **Larzilliere I**, Beau P. [Chronic inflammatory bowel disease and pregnancy. Case control study]. *Gastroenterol Clin Biol* 1998; **22**: 1056-1060 [PMID: 10051981]

96 **Nørgård B**, Puho E, Pedersen L, Czeizel AE, Sørensen HT. Risk of congenital abnormalities in children born to women with ulcerative colitis: a population-based, case-control study. *Am J Gastroenterol* 2003; **98**: 2006-2010 [PMID: 14499779 DOI: 10.1111/j.1572-0241.2003.07578.x]

97 **Mahadevan U**, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007; **133**: 1106-1112 [PMID: 17764676 DOI: 10.1053/j.gastro.2007.07.019]

98 **Stephansson O**, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, Falconer H, Ekbom A, Sørensen HT, Nørgaard M. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. *Inflamm Bowel Dis* 2011; **17**: 795-801 [PMID: 20564537 DOI: 10.1002/ibd.21369]

99 **Nørgård B**, Hundborg HH, Jacobsen BA, Nielsen GL, Fonager K. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. *Am J Gastroenterol* 2007; **102**: 1947-1954 [PMID: 17573787 DOI: 10.1111/j.1572.0241.2007.01355.x]

100 **Kornfeld D**, Cnattingius S, Ekbom A. Pregnancy outcomes in women with inflammatory bowel disease--a population-based cohort study. *Am J Obstet Gynecol* 1997; **177**: 942-946 [PMID: 9369849]

101 **Fonager K**, Sørensen HT, Olsen J, Dahlerup JF, Rasmussen SN. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. *Am J Gastroenterol* 1998; **93**: 2426-2430 [PMID: 9860403 DOI: 10.1111/j.1572-0241.1998.00698.x]

102 **Mahadevan U**, Kane S. American gastroenterological association institute medical position statement on the use of gastrointestinal medications in pregnancy. *Gastroenterology* 2006; **131**: 278-282 [PMID: 16831610 DOI: 10.1053/j.gastro.2006.04.048]

103 **Seirafi M**, Treton X, De VroeyB, Cosnes J, Roblin X, Allez M, Marteau P, De Vos M, Flamant M, Laharie D, Savoye G, Peyrin-Biroulet L, Brixi-Benmansour H, Mathieu N, Bouhnik Y, GETAID. Anti-TNF therapy and pregnancy in inflammatory bowel disease: A prospective cohort study from the GETAID. *Gastroenterol* 2011; **140**: S175 [DOI: 10.1016/S0016-5085(11)60708-7]

104 **Mahadevan U**, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, Ullman T, Glover S, Valentine JF, Rubin DT, Miller J, Abreu MT. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 286-292 [PMID: 23200982 DOI: 10.1016/j.cgh.2012.11.011]

105 **Mahadevan U,** Martin CF, Sandler RS, Kane SV, Dubinsky M, Lewis JD, Sandborn WJ, Sands BE. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. *Gastroenterology* 2012; **14**: S149

**P-Reviewers** Mayer RB, Ehrenpreis ED **S-Editor** Gou SX  **L-Editor E-Editor**

**Table 1 Summary of reports of maternal exposure to anti-****tumor necrosis factor agents during pregnancy**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study type** | **Disease** | **Anti-TNF-alpha agent** | **Exposure to other drugs** | **Exposures in pregnancies with documented outcome** | **Maternal exposure: Pregnancy****stage** | **Live births****(*n*)** | **SA/****SB****(*n*)** | **PTB/****PMB****(*n*)** | **LBW/****SGA****(*n*)** | **CA****(*n*)** | **Pregnancy outcomes:****Details/complications** |
| Chambers *et al*[18]  | Prospective  | RA  | IFX  | NS  | 4  | T1  | 3  | 1 SA  | 2  |   |   |   |
| Mahadevan *et al*[19]  | Prospective  | CD: (4) UC: (1)  | IFX  | NS  | 5  | T2/T3 other exposure details NS  | 5  |   |   |   |   |   |
| Berthelot *et al*[20] | Case series  | Rheumatologic Disease  | IFX    | {No}   | 3     | C/T1: 1 C/T1/T2: 2  | 3    |   |   |   |    | {No}- specified no exposure to disease-modifying antirheumatic drugs, methotrexate, or non-steroidal anti-inflammatory drugs  |
| Chakravarty *et al*[21] | Case series  | RA  | IFX  | Some pts  | 1  | Pregnancy, not otherwise specified  | 1  |   |   |   |    |   |
| Correia *et al*[22]  | Case series  | CD  | IFX  | Yes: 1 No: 1  | 2  | C/T1/T2/T3   | 2  |   | 1  | 1 SGA  |   | -1 preterm/premature birth due to placental detachment (31 wk, 1.6 kg with acute respiratory failure requiring mechanical ventilation × 24 h and intensive care × 40 d; healthy at 8 mo follow-up)  |
| Hyrich *et al*[23]  | Case series  | Rheumatologic Disease  | IFX  | Some pts  | 3  | C/T1  | 2  | 1 SA  |   |   |   |   |
| Kane *et al*[24]  | Case series  | CD  | IFX  | Some pts  | 3   | T1/T2/T3: 2 T2/T3: 1  | 3  |   | 1  |   |   |   |
| Katz *et al*[25]  | Case series  | CD: (82) UC: (1) RA: (8) JRA: (2) Unknown:(3)     | IFX  | Some pts  | 100   | C: 53 T1: 30 > 3 mo prior to C: 7 Unknown: 6   | 68  | 10 SA  1 SB  | 1  | 1 LBW  | 3\*  | CA (3): -1 full-term with tetralogy of fallot -1 intestinal malrotation\* -1 developmental delay and hypothyroidism -1 complicated neonatal course: (Respiratory distress/ jaundice/seizure. Mother was also exposed to several antibiotics for pulmonary and urinary infections, azathioprine, hydrocortisone, and total parental nutrition early in pregnancy.)  Miscarriages (14): -10 SA -1 SB (mother exposed to leflunomide) -3 Unknown type  |
| Mahadevan *et al*[26] | Case series  | CD  | IFX  | Some pts  | 10  | T1: 1 T3: 1 C/T1/T2/T3: 8  | 10  |   | 3  | 1 LBW  |   | -1 neonatal jaundice (resolved) -1 complicated neonatal course: term delivery at 39 wk with respiratory distress/desaturation/gastric ulcer day 5; healthy at 6 mo follow-up  |
| Rosner *et al*[27]  | Case series  | Rheumatologic Disease  | IFX  | Yes  | 3  | C/T1/T2/T3  | 3  |   | 1  |   |   | -1 premature rupture of membranes  |
| Schnitzler *et al*[28]  | Case series  | CD/UC/IC  | IFX  | NS  | 10    | C/T1/T2   | 9  | 1 SB  | 2  |    |   |   |
| Weber-Schoenderfer *et al*[29]  | Case series  | NS  | IFX  | NS  | 25  | T1  | 22  | 2 SA  | 4  |   | 2  | CA (2): -1 ventricular septal defect -1 growing hemangioma requiring therapy  |
| Zelinkova *et al*[30]   | Case series  | CD: (3) UC: (1)  | IFX  | Some pts  | 4  | C/T1/T2: 3 C/T1/T2/T3: 1  | 4  |   | 1   |   | 1  | CA (1): -L hand polydactyly (Infant also had respiratory depression after anesthetics that resolved spontaneously. Mother was taking methotrexate two months prior to conception without folic acid supplement.)  |
| Akinci *et al*[31]   | Case report  | Rheumatologic Disease  | IFX  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Angelucci *et al*[32]  | Case report  | CD  | IFX  | Yes  | 1  | C/T1  | 1  |   | 1  | 1 LBW  |   |   |
| Angelucci *et al*[33] | Case report  | CD  | IFX  | Yes  | 1  | T1  | 1  |   |   |   |   |   |
| Antoni *et al*[34]  | Case report  | Psoriatic Arthritis  | IFX  | NS  | 1  | C/T1  | 1  |   |   |   |   |   |
| Arai *et al*[35]  | Case report  | CD  | IFX  | Yes  | 1  | C/T1/T2  | 1  |   |   |   |   |   |
| Aratari *et al*[36]  | Case report  | CD  | IFX  | Yes  | 1  | T2  | 1  |   |   | 1 SGA  |   |   |
| Burt *et al*[37]  | Case report  | CD  | IFX  | Yes  | 1  | C/T1  | 1  |   | 1  |   |   |   |
| Chaparro *et al*[38]  | Case report  | CD  | IFX  | NS  | 1  | C/T1/T2/T3  | 1  |   | 1  |   |   |   |
| Cheent *et al*[39]  | Case report  | CD  | IFX  | NS  | 1  | C/T1/T2/T3  | 1  |   | 1  |   |   | -Infant developed disseminated BCG after vaccination at 3 mo and died at 4.5 mo |
| Epping *et al*[40]  | Case report  | CD  | IFX  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Hou *et al*[41]  | Case report  | CD  | IFX  | NS  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| James *et al*[42]  | Case report  | CD  | IFX  | Yes  | 1  | T2  | 1  |   |   |   |   |   |
| Kinder *et al*[43]  | Case report  | RA  | IFX  | Yes  | 1  | C/T1  | 0  | 1 SA  |   |   |   |   |
| Østensen *et al*[44]  | Case report  | RA  | IFX  | Yes  | 1  | C/T1  | 1  |   |   |   |   | -Oligohydramnios detected on 18 wk ultrasound that resolved with discontinuation of Nimesulide |
| Puig *et al*[45]  | Case report  | Psoriasis  | IFX  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Srinivasan *et al*[46]   | Case report  | CD  | IFX  | Yes  | 1 †  | C/T1  | 1  |   | 1  |   |   | -Preterm premature birth (24 wk) complicated by intracerebral and intrapulmonary hemorrhages and neonate died at 3 d †Case reported by Srinivasan *et al*[46] was also documented by Katz *et al*[25]Mother was also exposed to metronidazole, azathioprine, and mesalamine for fistulizing CD |
| Steenholdt *et al*[47]  | Case report  | UC  | IFX  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Stengel *et al*[48] | Case report  | CD  | IFX  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Tursi *et al*[49]  | Case report  | CD  | IFX  | NS  | 1  | C/T1/T2/T3  | 1  |   | 1  |   |   |   |
| Vasiliauskas *et al*[50]  | Case report  | CD  | IFX  | NS  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Wilbaux *et al*[51]  | Case report  | AS  | IFX  | NS  | 1  | C/T1  | 1  |   |   |   |   |   |
| Xirouchakis *et al*[52]  | Case report  | CD  | IFX  | Yes  | 1  | C/T1  | 1  |   | 1  |   |   | -Preterm (29 wk) birth with neonatal hospitalization × 30 days post-delivery. Baby in “good condition” at follow-up |
| Johnson *et al*[53,54]  | Prospective  | CD and RA  | ADA  | NS  | 94   | T1 other exposure details NS   | 80  | 13 SA  | 12  |   | 7 (among live births)   | CA (7) ( live births): -1 undescended testicle -1 microcephaly -1 congenital hip dysplasia with inguinal hernia -1 congenital hypothyroidism -1 ventricular septal defect -1 bicuspid aortic valve and agenesis of corpus callosum  (twin sibling had patent ductus arteriosus) -1 congenital hydronephrosis  CA (9) (all pregnancies): In addition to above 7 defects were: -1 spina bifida and hydrocephalus  (resulted in elective termination) -1 ectopia cordis and caudal regression  (twin pregnancy resulting in a spontaneous abortion)  |
| Berthelot *et al*[20]  | Case series  | Rheumatologic Disease  | ADA  | {No}   | 2  | C/T1: 1 C/T1/T2/T3: 1  | 2  |   |   |   |    | {No}: specified no exposure to disease-modifying antirheumatic drugs, methotrexate, or non-steroidal anti-inflammatory drugs  |
| Hyrich *et al*[23]  | Case series  | Rheumatologic Disease  | ADA  | Some pts  | 3  | C/T1   | 2   | 1 SA  |   |   |   |     |
| Johnson *et al*[53,54] | Case series  | CD and RA  | ADA  | NS  | 122  | T1 other exposure details NS  | 122  |   |   |   | 5  | CA (5): -2 chromosomal abnormalities -1 atrial septal defect and peripheral pulmonic stenosis -1 ventricular septal defect -1 congenital hip dysplasia  |
| Weber-Schoenderfer *et al*[29]  | Case series  | NS  | ADA  | NS  | 28  | T1  | 24  | 2 SA  | 4  |   |   | -1 infant with autosomal dominant disease (not otherwise specified); paternal inheritance  |
| Abdul Wahab *et al*[55]  | Case report  | CD  | ADA  | Yes  | 1  | C/T1/T2/T3  | 2 (twins)  |   |   | 1 SGA  |   | -Twin-to-twin transfusion syndrome (1 small due to discordance)  |
| Ben-Horin *et al*[56]  | Case report  | CD  | ADA  | NS  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Bosworth *et al*[57] | Case report  | CD  | ADA  | Yes  | 1  | C/T1/T2/T3  | 1  |   | 1  |   |   |   |
| Coburn *et al*[58]  | Case report  | CD  | ADA  | Yes  | 1  | T2/T3  | 1  |   |   |   |   |   |
| Dessinioti *et al*[59] | Case report  | Psoriasis  | ADA  | NS  | 1  | C/T1  | 1  |   |   | 1 LBW  |   | -Infant reported as “normal” at 12 mo follow-up  |
| Jurgens *et al*[60] | Case report  | CD  | ADA  | NS  | 1  | C/T1  | 1  |   |   |   |   |   |
| Kraemer *et al*[61]  | Case report  | Takayasau’s Arteritis  | ADA  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Mishkin *et al*[62]  | Case report  | CD  | ADA  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Roux *et al*[63]  | Case report  | RA  | ADA  | NS  | 1  | C/T1  | 1  |   | 1  |   |   |   |
| Vesga *et al*[64]  | Case report  | CD  | ADA  | Yes  | 1  | C/T1/T2/T3  | 1  |   |   |   |   |   |
| Wibaux *et al*[51]  | Case report  | AS  | ADA  | Yes  | 1   | C/T1/T2  | 1   |   |   |   | 1  | CA (1): -primary craniosynostosis requiring surgery  |
| Kane *et al*[65]  | Case series  | CD  | CTZ  | NS  | 14  | NS  | 5   | 1 SA  |   | 1 SGA  |   |   |
| Mahadevan *et al*[66]  | Case report  | CD  | CTZ  | Yes  | 1  | T2/T3  | 1  |   |   |   |   |   |
| Ousallah *et al*[67]  | Case report  | CD  | CTZ  | NS  | 1  | C/T1/T3  | 1  |   |   |   |   |   |
| Steinberg *et al*[68]  | Case report  | CD  | CTZ  | Yes  | 1  | T2  | 1  |   |   |   |   |   |

CD: Crohn’s disease; UC: Ulcerative colitis; IC: Indeterminate colitis; RA: Rheumatoid arthritis; JRA: Juvenile rheumatoid arthritis; AS: Ankylosing spondylitis; IFX: Infliximab; ADA: Adalimumab; CTZ: Certolizumab pegol; NS: Not specified; Pts: Patients; C: Within < 3 mo prior to conception; T1: First trimester (LMP to 13 wk); T2: Second trimester (14 to 27 wk); T3: Third trimester (28 to 40 wk); SA: Spontaneous abortion; SB: Stillbirth; Preterm birth (< 37 wk gestation); PMB: Premature birth (< 37 wk gestation and prior to organ development); LBW: Low birth weight (< 2500 g); SGA: Small for gestational age (smaller than average size given the number of weeks of pregnancy).

**Table 2 Summary of anti-tumor necrosis factor exposures and birth outcomes *n* (%)**

|  |  |
| --- | --- |
| **Exposures** | **Birth Outcomes, *n* (with relative percents)** |
| **Anti-TNF Exposure** | **Fetal****exposures** | **Live births** | **SA** | **SB** | **PTB/ PMB** | **LBW/****SGA** | **CA** |
| IFX/ADA/CTZ total | 472 | 405 (85.8) | 32 (8.2) | 2 (0.6) | 41 (19.9) | 8 (6.1) | 19 (4.1) |
| IFX1 | 194 | 155 (79.9) | 15 (10.6) | 2 (1.1) | 21 (26.9) | 5 (4.4) | 6 (4.0) |
| IFX in IBD2 | 151 | 117 (77.5) | 11 (8.9) | 2 (1.4) | 16 (36.4) | 5 (4.8) | 4 (3.5) |
| ADA1 | 261 | 242 (92.7) | 16 (6.9) | 0 (0) | 20 (15.9) | 2 (28.6) | 13 (5.4) |
| ADA in IBD2 | 224 | 210 (93.8) | 13 (5.8) | 0 (0) | 15 (17.0) | 2 (28.6) | 12 (5.7) |
| CTZ1 | 17 | 8 (47.1) | 1 (5.9) | 0 (0) | 0 (0) | 1 (12.5) | 0 (0) |
| CTZ in IBD2 | 17 | 8 (47.1) | 1 (5.9) | 0 (0) | 0 (0) | 1 (12.5) | 0 (0) |
| Outcome percents in general US population[69-73] |  | 64.6% | 16.5% | 0.6% | 12.3% | 8.2% | 3%-5% |

1Exposure in all reported medical conditions; 2Exposure in inflammatory bowel disease (IBD) patients. IFX: Infliximab; ADA: Adalimumab; CTZ: Certolizumab pegol; SA: Spontaneous abortion (fetal death at < 20 wk); SB: Stillbirth (Fetal death at > 20 wk or > 350 g if gestational age unknown); PTB: Preterm birth (< 37 wk gestation); PMB: Premature birth (< 37 wk gestation and prior to completion of organ development); LBW: Low birth weight (< 2500 g); SGA: Small for gestational age (smaller than average size given number of pregnancy weeks).

**Table 3 Summary of congenital abnormalities reported**

|  |  |  |
| --- | --- | --- |
| **Congenital abnormalities (*n* = 19)** | **Affected****(*n*)** | **Anti-****TNF exposure** |
| Ventricular septal defect | 3 | IFX (1), ADA (2) |
| Chromosomal abnormalities | 2 | IFX |
| Congenital hip dysplasia | 2 | IFX (1), ADA (1) |
| Intestinal malrotation | 1 | IFX |
| Congenital hypothyroidism | 1 | IFX |
| Hemangiomas | 1 | IFX |
| L hand polydactyly | 1 | IFX |
| Tetralogy of Fallot | 1 | IFX |
| Patent ductus arteriosus | 1 | ADA |
| Atrial septal defect and peripheral pulmonic stenosis | 1 | ADA |
| Bicuspid aortic valve and agenesis of corpus callosum | 1 | ADA |
| Primary craniosynostosis | 1 | ADA |
| Microcephaly | 1 | ADA |
| Congenital hydronephrosis | 1 | ADA |
| Undescended testes | 1 | ADA |

IFX: Infliximab; ADA: Adalimumab; TNF: Tumor necrosis factor.