Published in final edited form as:
Clin Gastroenterol Hepatol. 2013 March ; 11(3): 286–e24. doi:10.1016/j.cgh.2012.11.011.

Placental Transfer of Anti-Tumor Necrosis Factor Agents in Pregnant Patients with Inflammatory Bowel Disease

Uma Mahadevan[*], **Douglas C. Wolf**[∞], **Marla Dubinsky**[”], **Antoine Cortot**[^], **Scott D. Lee**[+], **Corey A. Siegel**[#], **Thomas Ullman**[′], **Sarah Glover**[Φ], **John F. Valentine**[λ], **David T. Rubin**[π], **Jocelyn Miller**[Δ], and **Maria T. Abreu**[♥]

[*] Division of Gastroenterology, Department of Medicine, University of California, San Francisco

[∞]Atlanta Gastroenterology Associates, Atlanta, GA

[”]Dept of Pediatrics Cedars Sinai Medical Center, Los Angeles, CA

[#]Dartmouth-Hitchcock Medical Center, Lebanon, NH

[^]Hepato-Gastroenterolgie Cite Hospitaliere, Lille, France

[+]University of Washington, Seattle, WA

[′]Mt. Sinai School of Medicine, NY, NY

[Φ] University of Illinois, Chicago, IL

[Φ] University of Florida, Gainesville, FL

[λ] University of Utah, Salt Lake City, UT;

[π]University of Chicago, IL

[Δ]Kaiser Permanente, Irvine, CA

[♥]University of Miami, FL

Abstract

Background & Aims—Some women with inflammatory bowel disease (IBD) require therapy with tumor necrosis factor (TNF) antagonists during pregnancy. It is not clear whether these drugs are transferred to the fetus, via the placenta, and then cleared, or whether structurally different TNF antagonists have different rates of transfer.

Methods—We studied 31 pregnant women with IBD receiving infliximab (IFX, n=11), adalimumab (ADA, n=10), or certolizumab (CZP, n=10). Serum concentrations of the drugs were measured at birth in the mother, infant, and in cord blood, and then monthly in the infant until the drugs were undetectable. Drug concentrations in the cord and the infant at birth were compared with those of the mother.

Results—Concentrations of IFX and ADA, but not CZP, were higher in infants at birth and their cords than in their mothers. The levels of CZP in infants and their cords were <2 μg/ml. The

Correspondence: Uma Mahadevan MD Associate Professor of Medicine Center for Colitis and Crohn's Disease, UCSF 2330 Post Street #610, San Francisco, CA 94115 Telephone: 415-502-4444 Facsimile: 415-502-2249 uma.mahadevan@ucsf.edu.

Disclosures: Dr. Mahadevan and several of the authors serve as consultants and/or received research support from UCB, Janssen and Abbott

Author Contributions: All authors participated by contributing patients to the study, collecting samples and assisting in writing and editing the manuscript.

Animal species: Human

median level of IFX in the cord was 160% that of the mother, the median level of ADA in the cord was 153% that of the mother, and the median level of CZP in the cord was 3.9% that of the mother. IFX and ADA could be detected in the infants for as long as 6 months. No congenital anomalies or serious complications were reported.

Conclusions—The TNF antagonists IFX and ADA are transferred across the placenta and can be detected in infants at birth; the drugs were detected in infants up to 6 months after birth. CZP has the lowest level of placental transfer, based on levels measured in cords and infants at birth, of the drugs tested.

Keywords

Ulcerative Colitis; Crohn's Disease; treatment; safety; pregnancy

Introduction

Women of reproductive age diagnosed with inflammatory bowel disease (IBD) face the dual challenge of being healthy enough to conceive and carry a successful pregnancy while protecting the fetus from potential adverse effects of medical therapy needed to maintain remission. As therapeutic options for IBD evolve, more patients are in a position to consider pregnancy; however, the safety profile of these medications during gestation has not been fully established.

Women with IBD have higher risks of pregnancy complications such as spontaneous abortion, preterm birth and complications of labor and delivery compared to the age matched general population, even when their disease is inactive.[1] In addition, active disease is associated with a further increase in preterm birth[2] and likely miscarriage. As stopping effective medications for IBD can lead to a high risk of flare within a year, this is not a preferred option for woman IBD patients contemplating pregnancy.[3] This is the reason why most guidelines recommend continuing therapy through the majority of pregnancy.[4] The actual qualitative and quantitative exposure of the fetus and newborn to drug and the subsequent risk of birth defects, infection and immune suppression are not fully understood in IBD patients.

In the pregnant woman, maternal antibodies are transported across the chorionic villi by the neonatal Fc receptor (FcRn) to provide immunity to the newborn. Immunoglobulin G (IgG) concentrations in fetal blood increase steadily from early in the second trimester until delivery, with most antibodies being transferred during the third trimester. IgG1 is the most efficiently transported immunoglobulin subclass. [5-6]

Infliximab (IFX) (Janssen, Malvern, PA) and adalimumab (ADA) (Abbott, Abbott Park, IL) are both complete anti-tumor necrosis factor (TNF) α antibodies that have shown efficacy for induction and maintenance of remission in patients with Crohn's disease (CD).[7-8] Certolizumab pegol (CZP) (UCB, Brussels, Belgium) is a PEG (polyethylene glycol)-ylated Fab′ fragment of a humanized anti-TNFα monoclonal antibody and has also shown efficacy in Crohn's disease.[9] IFX and ADA should theoretically cross the placenta at high rates in the third trimester as they are both of the IgG1 subclass. CZP does not have an Fc portion and in theory should not be actively transported across the placenta. Any transfer should be by passive diffusion and should result in minimal concentrations in the newborn. In support of this hypothesis, a study of pregnant rats[10] receiving a murinized IgG1 antibody of TNFα and a murinized PEGylated Fab′ fragment, demonstrated much lower concentrations of drug in the infant and in breast milk after exposure to the Fab′ fragment compared to the full IgG1 antibody. The aim of this study was to determine the cord blood and infant serum concentrations of IFX, ADA and CZP on day of birth in infants exposed to one of these 3

anti-TNFα agents *in utero* and compare these levels to those of the mothers. A secondary aim was to determine the duration of post-partum exposure to anti-TNFα in newborns with detectable anti-TNFα levels at birth.

Methods

Pregnant women with Crohn's disease receiving IFX, ADA or CZP were identified in our practice, by referring physicians and through the Crohn's Colitis Foundation of America (CCFA) PIANO (Pregnancy IBD and Neonatal Outcomes) Registry.[11] With respect to recruitment from PIANO, patients on anti-TNF agents during pregnancy were identified through the database and the sites were contacted to see if the patients were interested in contributing samples. If they consented to participate, plasma was collected from the mother, the cord blood and the infant on the day of birth and shipped to the appropriate lab for testing. In a subset of infants, blood was collected after day 1 of birth due to logistical reasons. If concentrations were detectable in the newborn, they were offered retesting monthly until concentrations were undetectable. Blood was collected in lithium heparin, spun and separated into cryotubes, and then stored frozen at −70°Celsius (C) prior to shipping. Breast milk from mothers receiving CZP only was collected in clean plastic tubes and frozen. An enzyme-linked immunosorbent assay (ELISA) was used to measure drug concentrations in plasma and milk. Methods for plasma drug concentrations were similar for all 3 agents.

IFX serum levels were commercially tested by Prometheus Labs (San Diego, CA) with a lower limit of quantification of 1.41 μg/ml as described previously. [12] Briefly, the IFX assay is a microplate ELISA in which IFX bound to immobilized TNF-α is detected with horseradish peroxidase–conjugated antihuman IgG (Fc-specific). The cutoff value, based on the mean (+3 standard deviation) value in serum samples from 40 patients who had never received IFX, is 1.40 μg per milliliter. Concentrations below the cutoff value are reported as negative.

ADA serum levels were measured by Abbott Laboratories (Ludwigshafen, Germany) using a fully validated enzyme linked immunoassay method in double-antigen bridging format. Streptavidine pre-coated microtitre plates were coated with biotinylated recombinant TNF-α. Calibration standards, quality controls, and study samples were pipetted into the individual wells. Captured ADA molecules were detected by the addition of a TNF-α-horseradish peroxidase conjugate followed by tetramethylbenzidine substrate. The resulting colour intensity was proportional to the ADA content of the sample. The assay is fully validated to conform to regulatory guidelines and has been used in all the clinical trials performed with ADA. Intra assay controls are run in each assay and the assay is only valid if they are within the acceptance criteria (± 25%). In addition, the standard curve also has acceptance criteria which have to be passed in each assay (±−20%). The lower limit of quantification was 3.13 ng/mL in 10% serum, the concentration used in this assay.

CZP samples were sent to UCB Celltech, Slough, U.K. The stability of CZP and antibodies to CZP has been demonstrated in whole blood at +4°C, room temperature, and +37°C for 48 hours. CZP stability has also been shown in plasma at −20°C and −70°C for 2 years [UCB data on file]. For CZP, serial dilutions of CZP standard or sample were added to microtiter plates coated with recombinant human TNFα (Strathman Biotech, Hanover, Germany). Captured CZP was revealed with horseradish-peroxidase-conjugated goat anti-human kappa light chain (Cappel, ICN, Costa Mesa, CA, USA) followed by tetramethyl benzidine substrate. This assay was fully validated for use with human plasma, is fully validated to conform to regulatory guidelines and has been used in all the clinical trials performed with CZP. Intra assay controls are run in each assay and the assay is only valid if they are within

the acceptance criteria (± 25%). In addition, the standard curve also has acceptance criteria which have to be passed in each assay (±−20%). [UCB data on file] To assess suitability for measurement in milk, unexposed breast milk samples were spiked with CZP at 30, 8 and 1 μg/ml and demonstrated full recovery of drug, with no background signal in the control unexposed sample. Among CZP exposed patients, nuclear magnetic resonance (NMR) spectroscopy was used to measure the total polyethylene glycol (PEG) concentrations in plasma samples only. The NMR measurement quantifies the total PEG which is made up of the intact CZP and free PEG. Therefore, the level of free PEG can be calculated by subtracting the level of PEGylated Fab' calculated by ELISA from the total PEG determined by NMR. The samples and serial dilutions of CZP in control human plasma were analyzed using a modification of an existing validated method, with the modification necessary due to the different volumes of plasma available for analysis.

One patient had breast milk samples collected on the day of CZP injection, 3 days later and then 6 days after injection. Breast milk samples were not analyzed by the NMR method as it was not validated for quantification in this matrix.

Results

Thirty one women were enrolled in the study – 11 exposed to IFX, 10 to ADA and 10 to CZP. There were 2 sets of twins in the CZP group for a total of 33 infants. Maternal characteristics are noted in Table 1.The median age of the mothers was 32.5 years [range 22-42].

Infliximab

Of the 11 mothers who received IFX (Table 2), only 4 patients were on standard 5 mg/kg every 8 week dosing; 1 was on 10 mg/kg every 6 weeks; 1 on 10 mg/kg every 8 weeks; and 5 on 5 mg/kg every 6 weeks. Five of 11 deliveries were by cesarean section. The median gestational age was 40 weeks [38-41]. The median gestational weight was 3260 g [2834-3968]. There were 6 female infants and 5 male infants. There were no reported birth defects or neonatal intensive care (NICU) stays for any of the infants. One infant had hand-foot-mouth at age 9 months and recurrent respiratory tract infections. A second infant had an upper respiratory infection at 2 weeks. Nine of 11 infants were breastfed and all mothers had been on IFX prior to pregnancy and continued it in the post-partum.

The median time from last IFX dose to delivery was 35 days [2-91]. In every case, the cord or infant level of IFX was higher than the mother's at the time of delivery. Infants had day of birth levels ranging from 2.9- 39.5 μg/ml which took anywhere from 2 to 7 months to become undetectable. The median ratio, as expressed as a percentage, of cord to maternal drug level was 160% [87-400]. Two patients had a flare of disease in the third trimester and the post-partum and one patient had a flare only in the post-partum despite having their last dose of drug within 14 days of delivery.

Adalimumab

Of the 10 mothers on ADA (Table 3), 9 took 40 mg every other week and one took 40 mg weekly. All mothers were on ADA prior to pregnancy and 9/10 continued it in the post-partum. Five of 10 deliveries were by cesarean section. The median gestational age was 39 weeks [38-41]. The median gestational weight was 3388 g [3090-3742]. There were 5 female and 5 male infants. There were no reported birth defects, infections or NICU stays for any of the infants. One infant had brief pulmonary edema at birth which resolved. Six of 10 infants were breastfed.

The last dose was given a median of 5.5 weeks prior to delivery [.14-8]. In every case, infant or cord blood levels were higher than the mother's plasma level of ADA on the day of birth and the median ratio of cord to maternal ADA level was 179% [98-293]. Infant levels at birth ranged from 4.28-17.7 μg/ml. Levels were detectable for at least 11 weeks from birth. Of the 5 patients with a post-partum flare, two also had flares in the third trimester and 3/5 (60%) with flares stopped drug at least 35 days prior to delivery.

Certolizumab

Five mothers received CZP for the first time during pregnancy. Of the 10 mothers receiving CZP (Table 4), the last dose was given a median of 19 days prior to delivery [5-42]. Six of 10 deliveries were by cesarean section. The median gestational age was 37.8 weeks [36-40] with both sets of twins born preterm (at 36 weeks gestation). The median gestational weight was 2800 g [1956-4110] with 5 of the infants defined as low birth weight (<2700 g); 3 of 5 preterm infants (<37 weeks) were from the twin pregnancies. There were 8 female infants and 4 male infants. There were no reported birth defects, infections or NICU stays for any of the infants. Nine of 12 infants were breastfed and the mothers of 8/9 of these infants continued to receive CZP in the post-partum.

PEG was detected in all plasma from mothers, except for mothers 4 and 8 whose levels were below the lower limit of quantification (9μg/mL). No PEG was detected in any of the infant plasma or cord plasma. For the babies 4, 5, 8, 9A, and 10A&B the volume of plasma was below that required for analysis and therefore was made up with control human plasma. This dilution increased the lower limit of quantification and this increase is shown in Table 4.

For patient number 8 and 9, the results for each twin (A, B) are reported separately. In every case, the concentrations in the infant were less than 2 μg/ml, so further testing was not done on the infant. The median ratio of cord to maternal CZP level was 3.9% [1.5-24].

For patient 2, concentrations were checked a second time when the infant was 1 month of age. The mother was receiving CZP 400 mg every 4 weeks and received a dose 1 week prior to delivery and 3 weeks after delivery. The infant was breastfed. At week 4 from delivery, the mother's plasma level of CZP was 22.93 μg/ml and the infant's level was 0.84 μg/ml. PEG levels in the mother were 29.3 μg/ml, and were undetectable in the infant. Breast milk was sampled at 1 and 2 weeks from delivery. Three more breast milk samples were collected after the first-post delivery injection (week 3) at 4 hours post injection, 3 days post injection and 6 days post injection. Concentrations in each of the 5 breast milk samples were undetectable.

Discussion

In this study of 31 pregnant women with Crohn's disease who gave birth to 33 infants, IFX and ADA demonstrated significant placental transfer as measured by cord blood levels at birth. CZP, however, had only minimal placental transfer to the infant, suggesting passive diffusion rather than active transfer. CZP was not detected in breast milk. In the mothers with sufficient PEG to measure, there were only low levels of free PEG when comparing the total PEG levels with the CZP levels. Due to the sensitivity of the assay it is impossible to say how much free PEG could be present in the cord blood and infants but it appears that free PEG does not accumulate in the fetus to any significant degree. There were no reported birth defects or serious adverse outcomes related to medication use in any of the pregnancies.

As IFX and ADA are both complete IgG1 antibodies, which are actively transported across the placenta, transfer would be expected to increase significantly in the third trimester with

minimal active transfer in the first trimester during the crucial period of organogenesis.[5-6] The first such observation of IFX levels in the newborn was a case report [13] that noted higher than detectable IFX concentrations in an infant born to a mother on IFX therapy every 4 weeks. Our observation that day of birth IFX concentrations are higher in the infant than in the mother is consistent with another study of four patients where IFX was stopped at 21, 26 and 30 weeks prior to delivery.[14]

Previously, IFX had not been detected in significant levels in breast milk[15-16]; however, a recent study found that levels (100 ng/ml) could be detected at 1/200th the level in maternal serum 2-3 days after infusion.[17] Another study of 3 patients also detected ADA concentrations in breast milk[18] with a peak at 6 days post-injection. These concentrations were 1/100th of serum concentrations. This suggests that both IFX and ADA are inefficiently transferred to breast milk and their use is compatible with breastfeeding. The one patient on CZP tested in this study did not have detectable levels, though it is feasible that there may be minimal transfer with this agent as well at the nanogram level.

Infliximab is a pregnancy category B agent with cumulative evidence suggesting it is low risk drug during pregnancy. [19,20] A series[21] of 22 patients reports exposure to IFX within 3 months of conception, continued until 20 weeks of gestation and then stopped to minimize placental transfer. In the third trimester, several of the patients flared, there were 4 miscarriages, 1 stillbirth at 36 weeks (umbilical strangulation), 2 preterm births, 3 low birth weight infants and no congenital anomalies.

ADA and CZP are also pregnancy category B drugs. Three case reports[22-24] and the OTIS (Organization for Teratology Information Specialists) registry[25] suggest ADA is low risk in pregnancy. There was no difference in the rate of spontaneous abortion and stillbirth for those with CD compared with the general population and the rates of congenital malformation and preterm delivery are also within the expected range. For CZP, 16 pregnancies are reported in the package insert: 4 healthy infants, 8 therapeutic abortions, 1 spontaneous abortion, 1 preterm birth and 2 unknown.

While the above data support the use of anti-TNF therapy during pregnancy, several concerning findings have also been reported. A study by Carter et al[26] notes congenital anomalies reported to the US Food and Drug Administration (FDA) among infants exposed to anti-TNFα agents. The authors stated that there were 34 specific types of congenital anomalies in total, and 19 (56%) of those had features that were part of the VACTERL spectrum. They concluded that this commonality raised concerns of a possible causative effect of the TNF antagonists; however, as the most common anomaly in their series was a cardiac defect (one of the most common anomalies in the general population) the association is only speculative. Furthermore, by the nature of voluntary reporting to the FDA, the denominator of pregnant mothers' treated with TNF antagonists is not known and therefore it is not clear if the rate of occurrence is higher than expected.

The PIANO registry (Pregnancy in IBD And Neonatal Outcomes)[11] is a prospective registry of over 1000 pregnant women with IBD. An analysis of over 896patients who completed pregnancy (326 unexposed, 204 immunomodulator exposed, 291 biologic exposed and 75 exposed to combination biologic and immunomodulator) did not find an increase in congenital anomalies by drug exposure. However, at 12 months of age, infants exposed to combination therapy with an immunomodulator plus either ADA or IFX had a significant increase in infections [1.35 (95% CI 1.01-1.80] compared to infants exposed to monotherapy. However, the same was not true for CZP combination therapy exposed infants suggesting a role for newborn exposure to anti-TNFα and immune development. These results are preliminary as the entire cohort has not reached 12 months of age and the

majority of the infections were minor (upper respiratory infections and otitis media). As infants may have therapeutic levels of IFX and ADA for several months from birth, response to vaccination is also a concern. There is a case report of a infant exposed *in utero* to IFX who received the Bacillus Calmette–Guérin (BCG) vaccine at 3 months of age.[27] The infant became ill and died at 4.5 months of age of disseminated BCG. This case has emphasized the importance of withholding live vaccines to infants under 6 months of age exposed to IFX or ADA *in utero*. In our experience, infants exposed to IFX *in utero* have appropriate response to standard early vaccinations. [28] However, live vaccinations are contraindicated if concentrations of anti-TNF agents are detectable in the infant (first 6 months of life for IFX and ADA exposure). In the past, live vaccines were first encountered by infants in the United States at one year of age (varicella, measles-mumps-rubella) at which point IFX/ADA concentrations should be undetectable. However, currently, rotavirus live vaccine is given orally at 2 months of age. Despite its mode of administration and being significantly attenuated, the safety of this vaccine in this setting is not known and the mother and pediatrician should be cautioned against its use if either IFX or ADA concentrations may be present. Outside the US, the infant may be exposed to other live vaccines in the first 6 months including BCG, oral polio and smallpox.

There was a wide range in maternal levels at birth for all 3 agents likely reflecting the mother's dose, dosing interval and individual pharmacokinetics as well as the immature reticuloendothelial systems of the newborns which are slow to clear antibody. For example, ADA patient # 1 and #2 received their last dose 7 and 56 days prior to delivery, yet the infants had a similar concentration of drug at birth (6.17 and 6.01 ug/ml respectively). The same is true for IFX patient #4 and #7 who received their last dose at 14 and 55 days from delivery but had similar infant serum drug levels of 23.6 and 28.2 ug/ml respectively. Therefore, attempting to time the last dose of anti-TNF agent prior to delivery will not consistently result in low results for all patients. However, it will certainly result in a lower level for the individual patient and lower subsequent cord blood levels compared to dosing close to delivery.

Based on the results of this study and available safety data, IFX, CZP and ADA can be used through conception and the first and second trimester of pregnancy on schedule. However, the significant placental transfer and subsequent slow post-partum clearance of IFX and ADA raise concerns about its use during the third trimester. At this time, we do not know what a safe or harmful level of drug in the newborn is and what the full consequences of neonatal anti-TNF exposure to newborn development will be. The risks and benefits of therapy should be individualized and pediatricians should be cautioned to monitor for potential infections and other abnormalities. This concern must be balanced against the risk of disease flare which has far more consequences to neonatal development. Significant disease flare will increase the risk of adverse outcome [2], impact nutritional status, and may require the use of potentially harmful diagnostic testing, medication, and even surgery. Additionally preterm birth, a known sequelae of disease flare, is a strong predictor of poor newborn and childhood outcomes.[29] Physicians may want to consider minimizing or avoiding adalimumab and infliximab use within 4-8 weeks of delivery to minimize placental transfer if the mother is in a stable remission. While the half-life of ADA is similar to IFX, given the biweekly dosing of ADA, it may need to be continued later into the course of the pregnancy than infliximab to reduce the risk of flares in the mother. Based on the minimal placental transfer described in this study, CZP can be continued on schedule throughout pregnancy until delivery without concern for significant placental transfer. As detectable CZP levels in the newborn are minimal and there is no detectable transfer in breast milk, rotavirus vaccine can be given to the CZP exposed infant on schedule. However, this is not the case with ADA and IFX exposure as live vaccine should be withheld for at least 6 months unless levels in infant serum can be documented to be negative. In the pregnant

woman and the woman considering pregnancy in the very near future, CZP may be considered as the anti-TNFα agent of choice given its lack of placental transfer; however the ultimate decision needs to be based on the clinical scenario and patient preference. Furthermore if a pregnant patient is doing well on ADA or IFX, there is no indication, and even a potential risk, of switching to CZP as the goal remains to maintain a quiescent disease state which is critical for a successful pregnancy.

Acknowledgments

With special thanks to Yelena Idomsky and Albina Gitis at UCSF. Dr. Y Beral (Maternity of Calais), Dr. S Depret (Maternity J de Flandre ,CHRU , Lille) and L Dubuquoy (Inserm U 995 ,Lille), France.

Grant support: Abbott Labs provided support for the study and performed the assays for adalimumab levels; UCB performed the assays for certolizumab pegol levels; Prometheus labs provided research rates to perform the assays for infliximab levels. Crohn's Colitis Foundation of America Senior Research Award. None of the sponsors had any input into study design.

Abbreviations

ADA	adalimumab
BCG	Bacillus Calmette–Guérin
CD	Crohn's Disease
CZP	certolizumab pegol
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
IBD	Inflammatory Bowel Disease
IFX	infliximab
Ig	Immunoglobulin
LOQ	lower limit of quantification
NICU	(Neonatal Intensive Care Unit)
NMR	Nuclear Magnetic Resonance
OTIS	Organization of Teratology Information Specialists
PEG	Polyethylene glycol
TNF	Tumor necrosis factor

REFERENCES

1. Mahadevan U, Sandborn WJ, Li DK, et al. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology. 2007; 133:1106–12. [PubMed: 17764676]
2. Norgard B, Hundborg HH, Jacobsen BA, et al. Disease Activity in Pregnant Women With Crohn's Disease and Birth Outcomes: A Regional Danish Cohort Study. Am J Gastroenterol. 2007; 102:1947–54. [PubMed: 17573787]
3. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? The American journal of gastroenterology. 2011; 106:199–212. quiz 213. [PubMed: 21045814]
4. Mahadevan U, Cucchiara S, Hyams JS, et al. 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. The American journal of gastroenterology. 2011; 106:214–23. quiz 224. [PubMed: 21157441]

5. Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012; 2012:985646. [PubMed: 22235228]
6. Simister NE. Placental transport of immunoglobulin G. Vaccine. 2003; 21:3365–9. [PubMed: 12850341]
7. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002; 359:1541–9. [PubMed: 12047962]
8. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006; 130:323–33. quiz 591. [PubMed: 16472588]
9. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med. 2007; 357:228–38. [PubMed: 17634458]
10. Nesbitt A, Brown D, Stephens S, et al. Placental Transfer and Accumulation in Milk of the Anti-TNF Antibody TN3 in Rats: Immunoglobulin G1 Versus PEGylated Fab'. Am J Gastroenterol. 2006 Abstract 119.
11. Mahadevan U Martin C, Sandler RS, et al. PIANO: A 1000 Patient Prospective Registry of Pregnancy Outcomes in Women With IBD Exposed to Immunomodulators and Biologic Therapy Gastroenterol. 2012; 142:S–149. (Abstract).
12. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003; 348:601–8. [PubMed: 12584368]
13. Vasiliauskas EA, Church JA, Silverman N, et al. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. Clin Gastroenterol Hepatol. 2006; 4:1255–8. [PubMed: 17045211]
14. Zelinkova Z, de Haar C, de Ridder L, et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Alimentary pharmacology & therapeutics. 2011; 33:1053–8. [PubMed: 21366638]
15. Kane S, Ford J, Cohen R, et al. 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; 43:613–6. [PubMed: 19142167]
16. Peltier M, James D, Ford J, et al. Infliximab levels in breast-milk of a nursing Crohn's patient. American Journal of Gastroenterology. 2001; 96:P258.
17. Ben-Horin S, Yavzori M, Kopylov U, et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. Journal of Crohn's & colitis. 2011; 5:555–8.
18. Ben-Horin S, Yavzori M, Katz L, et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol. 2010; 8:475–6. [PubMed: 20005982]
19. Katz JA, Antoni C, Keenan GF, et al. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol. 2004; 99:2385–92. [PubMed: 15571587]
20. 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. [PubMed: 15771759]
21. Schnitzler F, Fidder H, Ferrante M, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. Inflammatory bowel diseases. 2011; 17:1846–54. [PubMed: 21830263]
22. 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; 51:2045–7. [PubMed: 17009112]
23. Mishkin DS, Van Deinse W, Becker JM, et al. Successful use of adalimumab (Humira) for Crohn's disease in pregnancy. Inflamm Bowel Dis. 2006; 12:827–8. [PubMed: 16917239]
24. Vesga L, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. Gut. 2005; 54:890. [PubMed: 15888806]

25. Chambers CD, Johnson DL, Jones KL. Adalimumab and pregnancy outcome: The OTIS autoimmune diseases in pregnancy project. American Journal of Gastroenterology. 2006; 101:S421–S422.

26. Carter JD, Ladhani A, Ricca LR, et al. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. J Rheumatol. 2009; 36:635–41. [PubMed: 19132789]

27. Cheent K, Nolan J, Shariq S, et al. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's Disease. Journal of Crohn's and Colitis. 2010

28. Mahadevan U, Kane S, Church J, et al. The Effect of Maternal Peripartum Infliximab Use on Neonatal Immune Response. Gastroenterology. 2008; 134:A–69. (abstract).

29. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. Childs Nerv Syst. 2010; 26:1139–49. [PubMed: 20349187]

Table 1

Maternal Characteristics

	IFX	Range	ADA	Range	CZP	Range
N	11		10		10	
Median Maternal Age (yrs)	36	29-40	32.5	25-40	28	22-42
Disease type (CD:UC)	7:4		8:2		10:0	
Median Disease Duration (years)	10	2-24	11	2-24	6.5	1-10
Concomitant Medications						
• None	2		7		5	
• 5 Aminosalicylates	7		3		2	
• Azathioprine/6MP	3		0		2	
• Prednisone	2		1		3	
Patients exposure to anti-TNF agent by Trimester (n)						
Conception/Trimester 1	11		10		7	
Trimester 2	11		10		9	
Trimester 3	11		10		10	
Post-Partum	11		9		9	
Median Number of drug doses in pregnancy	--		18	14-32	8	3-12

IFX - infliximab; ADA - adalimumab; CZP - certolizumab

Table 2

Concentrations of infliximab detected on day of birth

Pt [#]	IFX dose (mg/kg)	IFX interval (wks)	Time dose to birth (days)	IFX (μg/ml) at Birth			Ratio cord/Mother (%)	Month IFX undetectable	Newborn Complications
				Mom:	Cord:	Infant			
1[^]	10	6	14	40 (6 wks)	--	39.5[*] (6 wks)	--	7	None
2	5	6	30	15.1	--	25.3	--	5	Meconium
3[#^]	5	6	2	1.4	2.0	2.9[*] (2 wks)	143%	2	Hand-foot-mouth (9mos); respiratory distress (11 mos)
4[#^]	5	6	14	19.2	26.5	23.6	138%	7	Oral candida (10 wks); GERD (4 mos)
5	5	8	91	3.8	3.3	4.2	87%	2	Jaundice
6	5	8	15	4.8	8.8	8.7	183%	3	None
7	5	8	55	14.5	20.5	28.2	141%	4	URI 2 weeks
8	5	6	46	16.5	26.5	27.5	160%	5	None
9	5	8	35	2.2	8.4	10.6	381%	4	None
10	5	6	77	4.1	13.6	4.7[*] (4 wks)	332%	--	None
11	10	8	74	5.1	20.4	8.4[*] (4 wks)	400%	4	None

[*] In some cases infant levels were not obtained on the day of birth but a few weeks later

[#] Flare of disease in trimester 3

[^] Flare of disease in post-partum

Table 3

Concentrations of Adalimumab detected on day of birth

Pt [#]	ADA dose	ADA interval	Time dose to birth (days)	ADA(μg/ml) at Birth			Ratio Cord/Mother	Follow ADA Levels (time)	Newborn Complications
				Mom:	Cord:	Infant			
1[#^]	40 mg	EOW	7	6.05	9.29	6.17	153%	--	None
2[^]	40 mg	EOW	56	1.84	5.39	6.01	293%	1.94 (6 wks)	Pulmonary edema, brief at birth
3[#^]	40 mg	EOW	7	3.84	4.57	--	119%	--	None
4[#]	40 mg	EOW	42	0	0.16	--	--	--	None
5	40 mg	EOW	35	2.2	4.18	4.28	190%	.934 (8 wks)	None
6	40 mg	EOW	42	3.21	4.74	4.87	148%	1.31 (7 wks)	None
7[^]	40 mg	EOW	42	3.36	8.94	8.09	266%	0.529 (11 wks)	None
8	40 mg	Weekly	1	16.1	19.7	17.7	122%	--	None
9	40 mg	EOW	49	2.24	4.95	4.64	220%	--	None
10	40 mg	EOW	7	8.48	8.29	9.17	98%	--	None

[#] Flare of disease in trimester 3

[^] Flare of disease in post-partum

Table 4

Concentrations of Certolizumab pegol detected on day of birth.

		Day of Birth CZP concentrations (μg/ml)			Ratio Cord/Mother	Day of Birth PEG concentrations (μg/ml)		
		Lower limit of Quantification <0.41				Lower limit of Quantification <9		
Mother #	Last Dose (days)	Mother	Cord	Infant		Mother	Cord	Infant
01	14	18.83	1.65	-	8.8%	33.4	*	*
02	7	59.57	0.94	1.02	1.6%	51.3	*	*
03	28	4.87	1.19	1.22	24%	*	*	*
04	17	20.13	0.57	0.44	2.8%	34.7	*	*
05	21	16.49	<0.41	<0.41	2.5%	27.7	*	No sample
06	24	34.65	1.66	1.58	4.8%	34.4	*	*
07	28	1.87	<0.41	<0.41	22%	*	*	*
08-A	42	6.32	<0.41	0.58	6.4%	11.1	*	*
B			<0.41	<0.41	6.4%		*	*
09-A	6	42.7	1.28	1.34	3.0%	62.1	*	*
B			1.16	1.18	2.7%		*	*
10	5	37.83	0.55	0.6	1.5%	74.9	*	*

○ For babies 4,8, and 10B LLOQ was 18 ug/ml. For babies 9A, 10A , LLOQ was 36 μg/ml

*Below Lower Limit of Quantification(LLOQ) PEG = 9 μg/ml.