

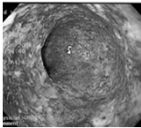
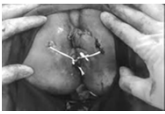
**Biologics in IBD during
Pregnancy**

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Objectives

- To understand why gastroenterologists prefer to continue therapy in pregnant patients
- To review the most current safety data on anti-tumour necrosis factor drugs (infliximab/Remicade, adalimumab/Humira) in pregnancy
- To review transplacental passage of anti-TNF drugs
 - Should we stop early?

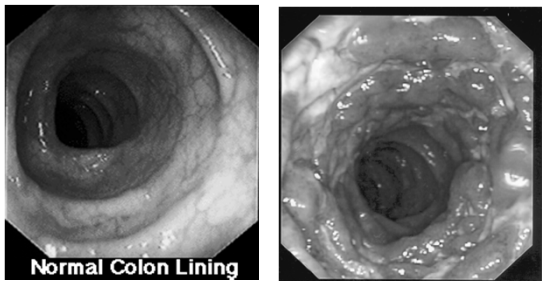
DEFINITION

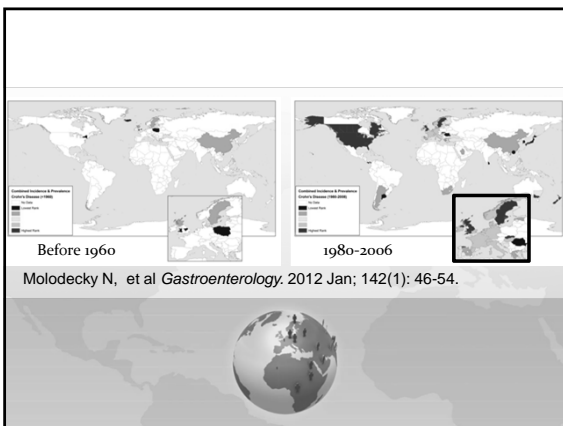


Chronic idiopathic inflammatory disease of the gastrointestinal tract

Crohn's Disease
Ulcerative Colitis

The Problem: IBD is a chronic and potentially debilitating disease of the young that results in significant burden to the patient and the health care system.





IBD affects many Canadians and is costly to our health care system and society.

- 0.5% of the population is afflicted with IBD
 - Over 200,000 Canadians suffer from IBD
- Quality of life for those with IBD is impacted due to ongoing symptoms, social stigma, reduced ability to work and treatment side effects
- **Direct costs** to the health care system are estimated at over **\$750 million** per year
 - Factors include: hospitalizations, medications and physician visits
- **Indirect costs** to the patients and society in Canada are estimated at over **\$1.8 billion** per year.
 - Factors include: long-term work loss, out of pocket expenses for patients and short term work absences.
- There is no known cure for IBD

The Burden of IBD in Canada (CCFC Report): www.ccfc.ca

Background

- Patients with IBD typically are diagnosed prior or during reproductive years
- Goals of treatment and medical options changed dramatically past decade
- Safety of therapy during pregnancy ongoing area of research

Goals of therapy

- Induction of clinical remission
- Maintenance of steroid free clinical remission
- Endoscopic healing
- Normalization of biomarkers: CRP and fecal calprotectin

Why not just stop therapy?

- Disease can flare very quickly after medical cessation, within the timeframe of a normal pregnancy
 - Relapse rate after stopping infliximab + azathioprine/methotrexate in STABLE patients 44% in first year (patients stayed on the azathioprine or methotrexate)
- Risk of antibody formation to our anti-TNF therapy during “drug holidays”
 - Increases risk of reactions or non response
- Active IBD during preconception and pregnancy associated with poorer outcomes

Louis, E et al. Gastroenterol. 2012;142:63-70.
Cassinotti, A et al. Am J Gastroenterol. 2009;104(11):2760-7.
Tretton, X. et al. Clin Gastroenterol Hepatol. 2009;7(1):80-5.

Preconception clinic

- Women with IBD without a history of surgery have similar rates of conception to non IBD women
- Methotrexate contraindicated
- Being in remission on low risk medication is the best option for a health pregnancy
- Continue therapy
 - Includes patients undergoing fertility treatment

Increase in preterm birth

	Relative Risk	95% CI
LBW	1.1	0.3-4.0
LBW at term	0.9	0.1-8.5
Preterm birth	3.4	1.1-10.6
Congenital Anomalies	0.4	0.0-3.9

Danish population
 Active disease n=71 compared to nonactive disease n=86

Norgard B, et al. Am J Gastroenterol.2007;102:1947-1954.

Hospitalization for active disease



Reddy, D. et al. Am J of Gastroenterol 2008;103:1203-1209.

Major Congenital Anomalies

	Odds ratio	95% CI
5-aminosalicylates	0.82	0.42-1.61
Corticosteroids	0.48	0.15-1.50
Azathioprine	1.27	0.48-3.39

1703 children of mothers with IBD – 2.7%
 384,811 children of mothers without IBD – 2.8%
 UK mother-child linked dataset from 1990-2010,
 children born to women 15-45 years old

Ban L, et al. Gastroenterol.2014;146(1):76-84.

Thiopurines and IBD

- Azathioprine (imuran) or 6-mercaptopurine (purinethol)
- FDA category D
- Majority of gastroenterologists recommend continuing therapy preconception and during pregnancy

	Thiopurines N=187	Anti-TNF N=66	Unexposed N=318
-GPO	21%	34.8%	31.8%
-obstetrical	20.9%	30.3%	27.7%
-neonatal	13.9%	21.2%	23.3%

Retrospective multicenter (Spain)

GPO=Global pregnancy outcome
 Outcomes not related to disease activity
 In MV analysis thiopurine only predictor of a lower risk of unfavourable GPO OR=0.6
 95% CI=1.03-2.7,p=0.038

	Thiopurines N=86	Non thiopurine N=84	No treatment N=45
Preterm	21.8%	16.0%	14.8%
Low birth weight	15.8%	13.8%	7.4%
Congenital abnormalities	2	4	0

Nested study within CESAME (France), retrospective/prospective multicenter

Casanova, MJ et al. Am J Gastroenterol. 2013;108:433-440, Coelho, J. Gut. 2011;60:198-203.

Thiopurine metabolism

- Pregnancy has an effect on maternal thiopurine metabolism
 - Decreased 6-TGN (“active ingredient”)
 - Increased 6-MMP (no hepatotoxicity)
- Azathioprine metabolites
 - 6-TGN(detected in umbilical cord blood)
 - 6-MMP (not detected in umbilical cord blood)
- Newborn 6-TGN levels **correlated strongly** with mom ($r=0.74, p<0.0001$)

Change in metabolites

Time	6-TGN	6-MMP	6-MMP/6-TGN ratio
T0 and T1	-9 (8%)	+850 (66%)	+12(107%)
T0 and T2	-30 (26%)	+1040(81%)	+17(156%)
T0 and T3	-17 (15%)	+1358(105%)	+16(149%)
T0 and delivery	-23 (20%)	+1100(85%)	+9(86%)
T0 and postpartum	-13 (11%)	-200(16%)	+3(27%)

Mechanism unknown
 Hypothesis that TPMT activity
 Despite rise in 6-MMP/6-TGN no relapse Cherap, B et al. Gut. 2013;0:1-7.

Anemia in newborns

- Hemoglobin available in 16/31 (52%) newborns
 - 10 (63%) anemia
 - Median 9.25 mmol/L (IQR 8.25-9.60)
- No control group

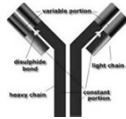
	Median 6-TGN in infants
Anemia	100 pmol/8 x 10 ⁸ RBC
Normal hemoglobin	35 pmol/8x10 ⁸ RBC

Thiopurines – do we change practice?

- All clinical data supports the use of thiopurines during pregnancy
- Not enough data to assume anemia in newborns caused by thiopurines
 - clinical relevance?
- Depending on access “may” consider monitoring metabolites during pregnancy
 - However what would you do with the results?

Anti-tumour necrosis factor (anti-TNF)

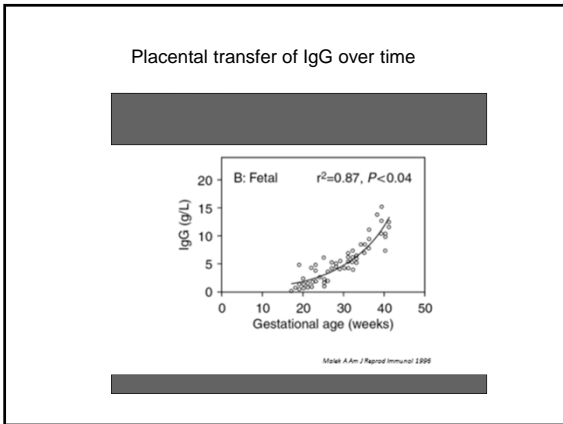
- Pregnancy category B drugs
- Infliximab/Remicade™ – chimeric anti-TNF monoclonal IgG1 antibody, given as infusion every 6-8 weeks
- Adalimumab/Humira™- fully humanized anti-TNF monoclonal IgG1 antibody, given as SC every 1-2 weeks



Biologics

- Infliximab/Remicade
- Adalimumab/Humira
 - Does not cross placenta in 1st trimester
 - Starts to increase 13 weeks
 - At 22 weeks GA increases until delivery
 - No association with congenital abnormalities

Johnson DL. OTIS. Gastroenterol 2009;(abstract); Katz JA. Am J Gastroenterol 2004;99(12):2385-92; Lichtenstein GR. TREAT. Am J Gastroenterol 2012;107(9):1408-22; Schnitzler F. Inflamm Bowel Dis 2011;17(9):1646-54; Mahadevan U. PIANO. Gastroenterol 2012;(abstract)



- Placental transfer**
- Very small amounts in first trimester
 - Increases from 22 weeks gestation age to delivery
 - IFX n=11, ADA n=10
 - Median of 35 days median neonatal IFX 160% of mother
 - Median of 38.5 days median neonatal IFX 179% of mother
- Mahadevan, U et al. Clinical Gastro and Hep 2013;11:286-292

Infliximab levels

Last dose infliximab	Median ratio cord/mother (%)	Month IFX undetectable
35 days (2-91 days)	160% (87-400%)	2-7

N=11
 No birth defects
 2 respiratory infections
 1 hand food mouth disease

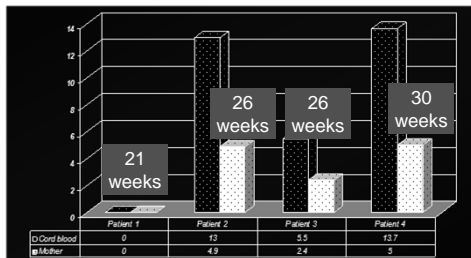
Adalimumab

Last dose adalimumab	Median ratio cord /mother	Time adalimumab undetectable
5.5 weeks (0.14-8weeks)	179% (98-293%)	11 weeks

N=10

1 infant brief pulmonary edema

Levels of IFX depending on last dose



Zelinkova Z, Alimentary Pharmaco Ther 2011;33:1053-1058

Infliximab

Total cord blood samples (n=17)	Mean Cord Blood (mcg/mL)	SEM (mcg/mL)	P-value
<30 weeks IFX (n=12) (average 23)	2.8	1.1	0.02
>30 weeks IFX (n=5) (30-34 weeks)	10	2.3	

Zelinkova, Z et al. Clinical Gastro and Hep 2013;11:318-321.

Adalimumab

Total cord blood samples (n=11)	Mean Cord Blood (mcg/mL)	SEM (mcg/mL)
22 week (21-27)	1.7	0.4

PIANO study

- Prospective study of pregnancy and neonatal outcomes in women with IBD
- April 1 2013 = 1232 women enrolled
- Unexposed = 329
- Azathioprine/Imuran = 242
- Anti-TNF = 357
- Combination azathioprine/anti-TNF= 109

	Azathioprine	Anti-TNF group	Combination
Any complication	1.2 (0.8-1.8)	1.2 (0.8-1.7)	1.7 (1.0-2.8)
Spontaneous abortion	0.5 (0.2-1.5)	1.3 (.6-2.9)	1.4 (0.5-4.1)
Preterm	1.0 (0.6-1.8)	0.8 (0.5-1.3)	2.4 (1.3-4.3)
LBW	0.7 (0.4-1.6)	1.2 (0.6-2.1)	1.5(0.7-3.3)
IUGR	0.8(0.2-2.8)	1.0 (0.3-2.8)	0.5 (0.1-3.9)
Caesarean section	1.0 (0.7-1.4)	1.4 (1-1.9)	1.3 (0.8-2.0)
NICU	1.1(0.6-1.8)	1.2(0.7-1.9)	1.3 (0.7-2.5)
Congenital anomalies	0.8(0.4-1.7)	0.9(0.4-1.7)	0.9(0.3-2.5)

Compared to unexposed group (5-aminosalicylate or nothing). Odds ratio (95 % confidence intervals)

Mahadevan, U. DDW 2013 Postgraduate Course, Orlando, Florida

Are these children as smart?

	Azathioprine	Anti-TNF group	Combination	Unexposed
Number of babies	215	364	137	323

Compared to unexposed group (5-aminosalicylate or nothing) children exposed in-utero always did the same on developmental tests
 Problem solving, gross motor, fine motor, social skills

Mahadevan, U. DDW 2014 1(94)

Do we stop anti-TNF drugs?

- Not if disease is active
- Not if you already know that when you miss a dose you flare right away
- Would have to stop at 22 weeks to minimize completely drug passage
- Small study compared stopping <25 weeks to >25 weeks of pregnancy
 - 2/32 versus 1/22 flared
 - However very small numbers

De Lima, DDW 2014. 350(134)

We don't stop, we alter dosing

- If patient has active disease NO change in dosing, in fact we will increase dosing preconception and consider in early pregnancy to avoid further deterioration
- Stable patients on maintenance
 - Consider last dose in early third trimester between 28-34 weeks of pregnancy (normal pregnancy 40 weeks)

U of Calgary Pregnancy Clinic

- Retrospective data median GA is 38 weeks
- Last dose of IFX 30-32 weeks
- Last dose of ADA 34 week

What about after delivery

- We ask out patients to restart their anti-TNF therapy immediately after delivery
 - Assuming there is no infectious complication
 - Infliximab/Remicade they can get in hospital as an infusion
 - No live virus vaccine for child within first six months of life
 - Ideally we would test the levels

Do we stop imuran?


- If patient is only on imuran we do not stop
- If patient is on imuran and an anti-TNF, case by case
- We don't start imuran for the first time in pregnant patients

Do we start steroids?

- Yes if we have to
- We work closely with high risk obstetrics and maternal fetal medicine clinic
- Need communication from the obstetrician if you are worried about fetal growth or gestational diabetes

Anti-TNF and Lactation

Negligible breast milk anti-TNF levels in a mother treated during pregnancy and lactation



Why?

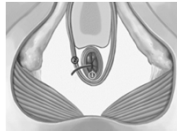
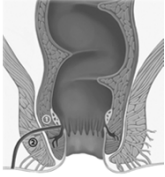
- Large protein size - difficult to pass into breast milk
- Not well absorbed from the gut
- Broken down by digestive enzymes in the baby's GIT

Hrych KL. Rheumatology. 2013 Dec 17; Diav-Citrin O. Reprod Toxicol 2014 Jan 43:78-84; Gisbert JP. Am J Gastroenterol. 2013 Sep;108(9):1436-38; Mahadevan. Am J Gastroenterol 2011;106:214-223; Vasiliadou EA et al. Clin Gastroenterol Hepatol 2006;4:1255; Stengel JP, Arnold HL. World J Gastroenterol 2006;14(19):3035; Kane S et al. J Clin Gastroenterol 2009 Aug 43(7):613; Mottet C, Jullerat P, Pittet V, et al. Digestion. 2007; 78: 149.

Take home messages

- The nurse clinician role is key
 - You help us identify the patients thinking of pregnancy
 - "nervous" patient
- We never stop biologics during pregnancy
 - Adjust the last dose to minimize placental transfer
- Can restart after delivery within a few days
- Breastfeeding is also safe

Mode of delivery in perianal disease



Studies limited
Often don't distinguish between active versus history of perianal disease

What the gastroenterologists fear

- Vaginal delivery leading to perineal injury
 - Non healing wounds
 - Fistulization
 - Worsening continence
- Consensus statement
 - Quiescent or mild disease undergo standard vaginal delivery
 - Active disease undergo caesarean delivery

Caprilli, R et al. Gut 2006;55:36-58

Not a lot of data

- Nationwide Inpatient Sample – using ICD-9 coding
 - Perianal disease increased risk of 4th degree laceration (not specific to CD)
- Questionnaire study
 - Confirmation of perianal disease by chart review
 - 54 vaginal births
 - 15 perianal disease, 4/15 active perianal disease
 - All 4 complained of "subjective worsening" of perianal disease after birth
 - All 11 inactive perianal patients did not complain of perianal symptoms after birth

Hatch, Q. et al. Dis Colon Rectum 014:57:174-178
Ilnyckj, A. et al. Am J Gastroenterol 1999;94:3274-3278

	Previous perianal disease N=15	No previous perianal disease N=39
Episiotomy	10 (67%)	27 (69%)
1 st degree laceration	1 (7%)*	1 (3%)*
2 nd degree laceration	1 (7%)*	5 (13%, 4/5 had epi)
3 rd degree laceration	0	5 (13%, 5/5 had epi)

* No episiotomies

- ### Take home points
- Rare for gastroenterologist to recommend stopping therapy
 - Adjustment in dosing interval for anti-TNF drug
 - Goal is to prevent disease flare
 - Ideally meet patients prior to pregnancy

- ### U of C pregnancy clinic
- Please contact us to discuss patients
 - yvette.leung@albertahealthservices.ca
 - Weekly clinics
 - Trainees
 - Clinical preceptorships

What we really need to know

- Do drug levels in pregnancy change as compared to non pregnant state in anti-TNF drugs?
- If we adjust that last dose in pregnancy depending on trough levels in earlier pregnancy can we change cord levels in newborn?
- Do we need to monitor for anemia in newborns born to mothers with IBD?



Questions?
