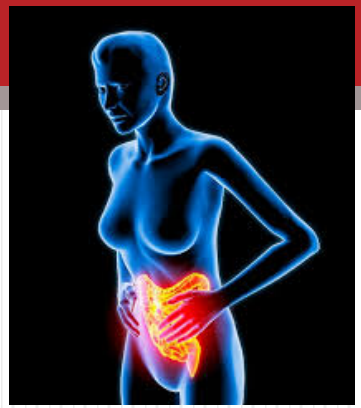
IBD in Pregnancy



Dr. Cynthia Seow
University of Calgary
Saturday Nov 7, 2015
CANIBD meeting

Plenary Presentation Objectives

- Discuss the effect of IBD on fertility, pregnancy and fetal outcomes
- Discuss IBD medications and pregnancy
- Discuss the effect of pregnancy and the postpartum period on IBD

Outline

- Case history interspersed with data slides
- Interactive!!! *Shout if you read that properly!*
- Question and answer throughout presentation
- Summary & Take Home Messages
- Final questions (10 mins)

Financial disclosures

- Dr. Cynthia Seow

	Speaker	Advisory Board	Research
Janssen	√	√	√
Abbvie	√	√	
Shire		√	
Actavis		√	
Takeda		√	

Case History

- 29 year old woman with Crohn's disease is considering pregnancy

- Let's explore how we would best manage her

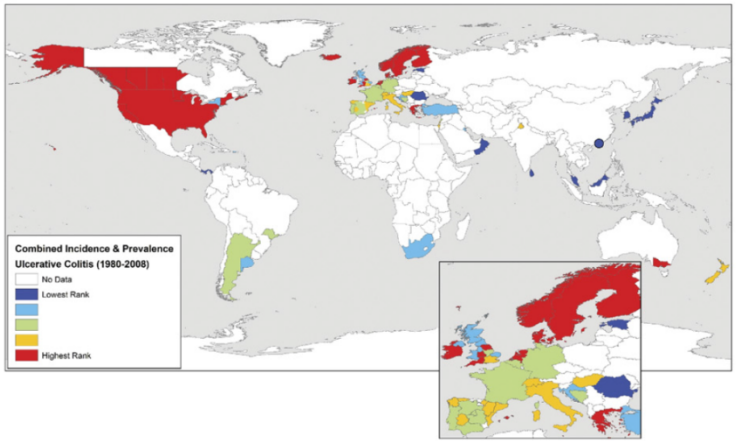
  - pre conception

  - during pregnancy

  - post partum?

Why is IBD in pregnancy an important topic?

- 0.5% of the Canadian population suffers from IBD
- Peak incidence of CD and UC: ages 20-40 years
- Women equally likely to be affected as men



Molodecky NA, et al. *Gastroenterology*. 2012(142);1;46–54.
Rocchi A, et al. *Can J Gastroenterol.* 2012(26);(11):811–17.
Bernstein CN, et al. *Am J Gastroenterol.* 2006(101);7:1559–68.

Case Presentation – Preconception

- 29-year-old woman with ileocolonic and perianal Crohn's disease.
- Medications:
  Azathioprine (150 mg PO daily)
  Infliximab (5 mg/kg every 8 weeks).
- 5 loose bowel movements per day.
- Her abdomen is soft, slightly tender in the right lower quadrant and has no active perianal disease.

- **She is concerned about whether and when she can get pregnant.**

Discussion

- **Q1.** How would you counsel the patient regarding the effect of disease activity on fertility and pregnancy?

Preconception counselling and disease optimization

- Fear of medication adverse effects highly prevalent.

- Poor awareness of the harmful effects of IBD flares.

- Contributor to
  - non compliance, medication cessation
  - voluntary childlessness (14-18% IBD vs 6% non IBD)

Marri SR, et al. *Inflamm Bowel Dis.* 2007;13:591–9.
Selinger CP, et al. *J Crohns Colitis*. 2013;7:e206–13.
de Lima A, et al. *Gastroenterol*. 2014;146:S-444.

Effect of IBD on Fertility

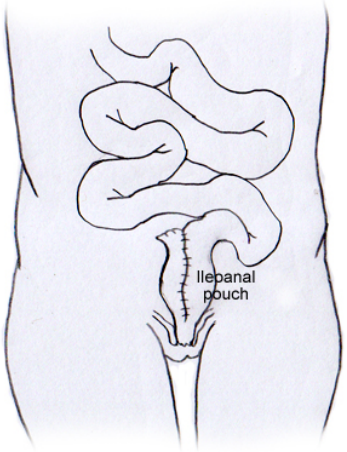
- In the absence of surgery, physiologic fertility rates are the same as the general population.

  [Systematic review 11 studies]

- Infertility rates pre vs. post IPAA (20% vs 63%)
  RR 3.91 (95% CI 2.06-7.44)

  [Metanalysis of 6 studies]

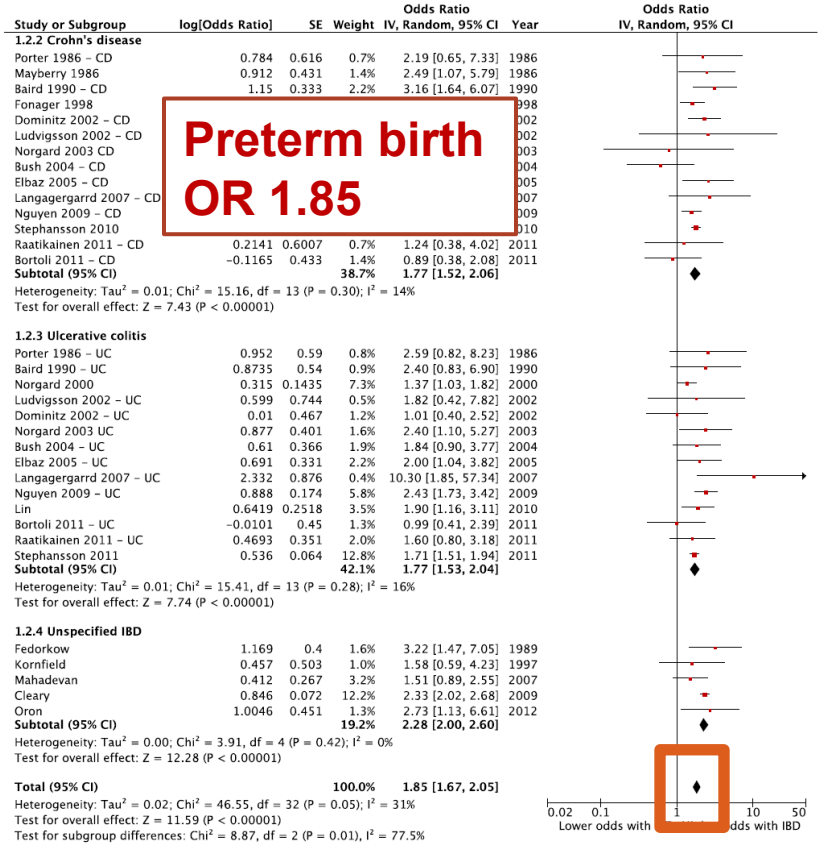
- Consider temporary ileostomy.

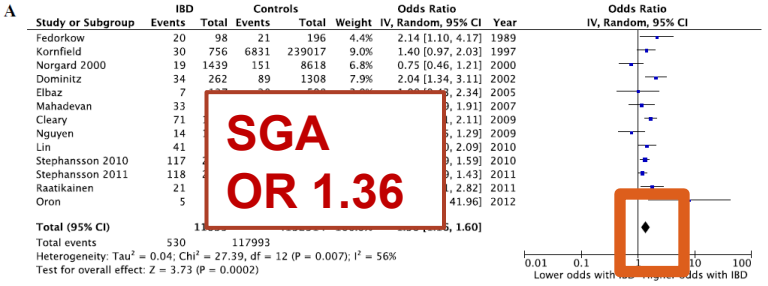


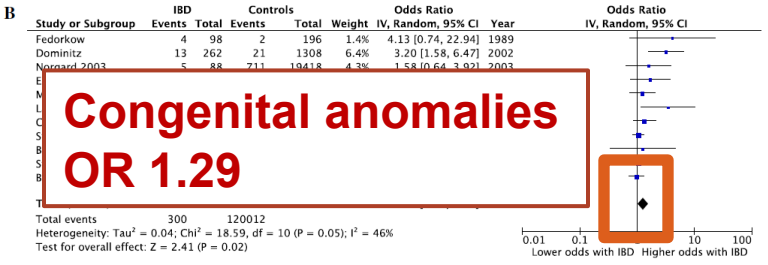
Tavernier N, et al. *Aliment Pharmacol Ther*. 2013;38:847–53.
Rajaratnam SG, et al. *Int J Colorectal Dis*. 2011;26:1365–74.

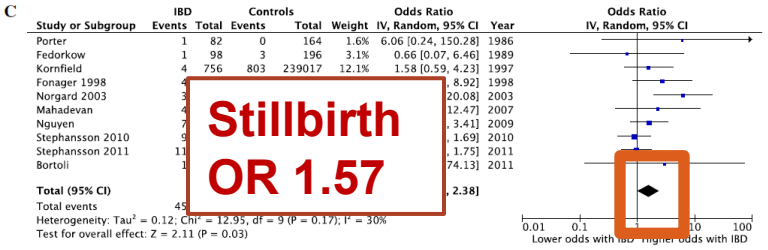
Effect of IBD on Pregnancy

23 studies, (n=15,007 IBD: 4,614,271 controls)





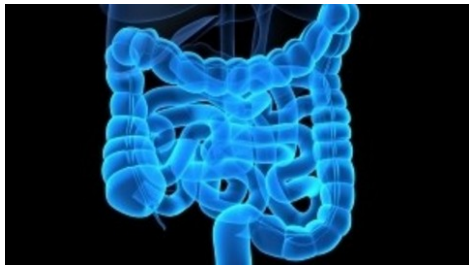




O'Toole A, et al. *Dig Dis Sci*. 2015;60:2750–61

IBD activity during pregnancy

- **Disease course depends on disease activity at conception**
  - Remission at conception
    - ~70% remission
    - ~30% active disease



  - Active disease at conception
    - ~70% persistent activity
    - ~30% improve

Bröms G, et al. *Inflamm Bowel Dis*. 2014;20:1091–8.
Reddy D, et al. *Am J Gastroenterol*. 2008;103:1203–9.
Abhyankar A, et al. *Aliment Pharmacol Ther*. 2013;38:460–6.

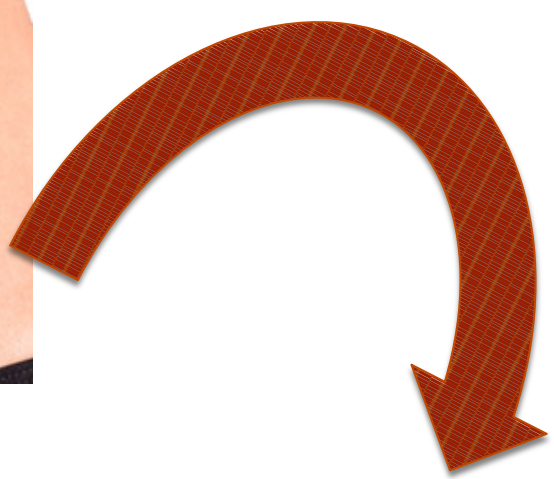
IBD activity during pregnancy

- **Active IBD is associated with increased risk of**

• Premature birth (<37 weeks)	(up to 3-fold increase)
• Low birth weight infants (<2500g)	(up to 3-fold increase)
• Miscarriage (active UC)	aOR 4.10 (95% CI: 1.2–13.9)
• Stillbirth (active CD)	aOR 4.46 (95% CI: 1.7–11.9)

Broms G, et al. *Inflamm Bowel Dis.* 2014;20:1091–8.
Reddy D, et al. *Am J Gastroenterol.* 2008;103:1203–9.
Abhyankar A, et al. *Aliment Pharmacol Ther.* 2013;38:460–6.
Bortoli A, et al. *Aliment Pharmacol Ther*. 2011;34 (7):724–34

So how do you achieve this???

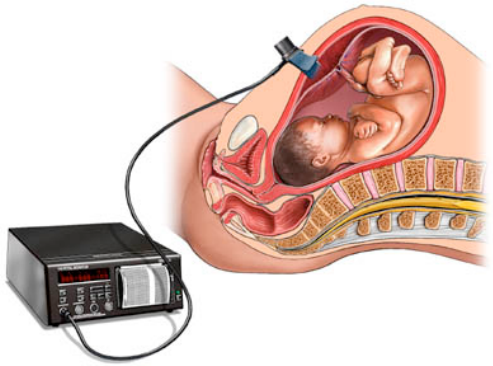


Discussion

- **Q2.** What tests should be arranged to assess disease activity?
- **Q3.** Would you order different tests if she was pregnant?

Disease activity assessment

- Full objective assessment best done **pre conception**
- Biomarkers - validity during pregnancy
- Radiology (sonography or MRI)
- Endoscopy
  - Timing
  - Medications
  - Fetal heart rate monitoring



Shergill AK, et al. *Gastrointest Endosc*. 2012;76:18–24.
de Lima A, et al. *BMC Gastroenterol*. 2015;15:15.
de Lima A, et al. *J Crohns Colitis*. 2015;9:519–24.

Case Presentation – Preconception

- Harvey Bradshaw Index (HBI): 7
- Hemoglobin (Hb): 105 g/L
- White blood cell (WBC) count: 4.6 x 10^9/L
- Platelet count: 235 x 10^9/L
- Ferritin: 10 pmol/L
- C-reactive protein (CRP): 25 mg/mL
- Fecal calprotectin (FCP): 1000 µg/g
- ***Magnetic resonance enterography:*** 10 cm thickened distal ileum
- ***Colonoscopy***: Distal ileal ulcers, mild right-sided colonic disease

Discussion

- **Q4.** Is she in remission and would you change her management?

Case Presentation – Pregnant

- The patient was dose-escalated to 5 mg/kg infliximab every 6 weeks.
- She declined corticosteroids but accepted iron infusions.
- She achieved clinical remission at the 8-week mark.
- She returns to your office 6 months later, indicating she is ~8 weeks pregnant.

- **She would like to stop her azathioprine and infliximab now that she is feeling better.**

Case Presentation – Pregnant

- HBI: 4
- Hb: 110 g/L
- WBC: 4.6 x 10^9/L
- Platelet count: 235 x 10^9/L
- Ferritin: 75 pmol/L
- CRP: 5.7 mg/mL
- FCP: 175 µg/g

Discussion

- **Q5.** Is she now in remission? How will you monitor her disease activity during pregnancy?

- **Q6.** How would you counsel her about ongoing use of azathioprine and infliximab?

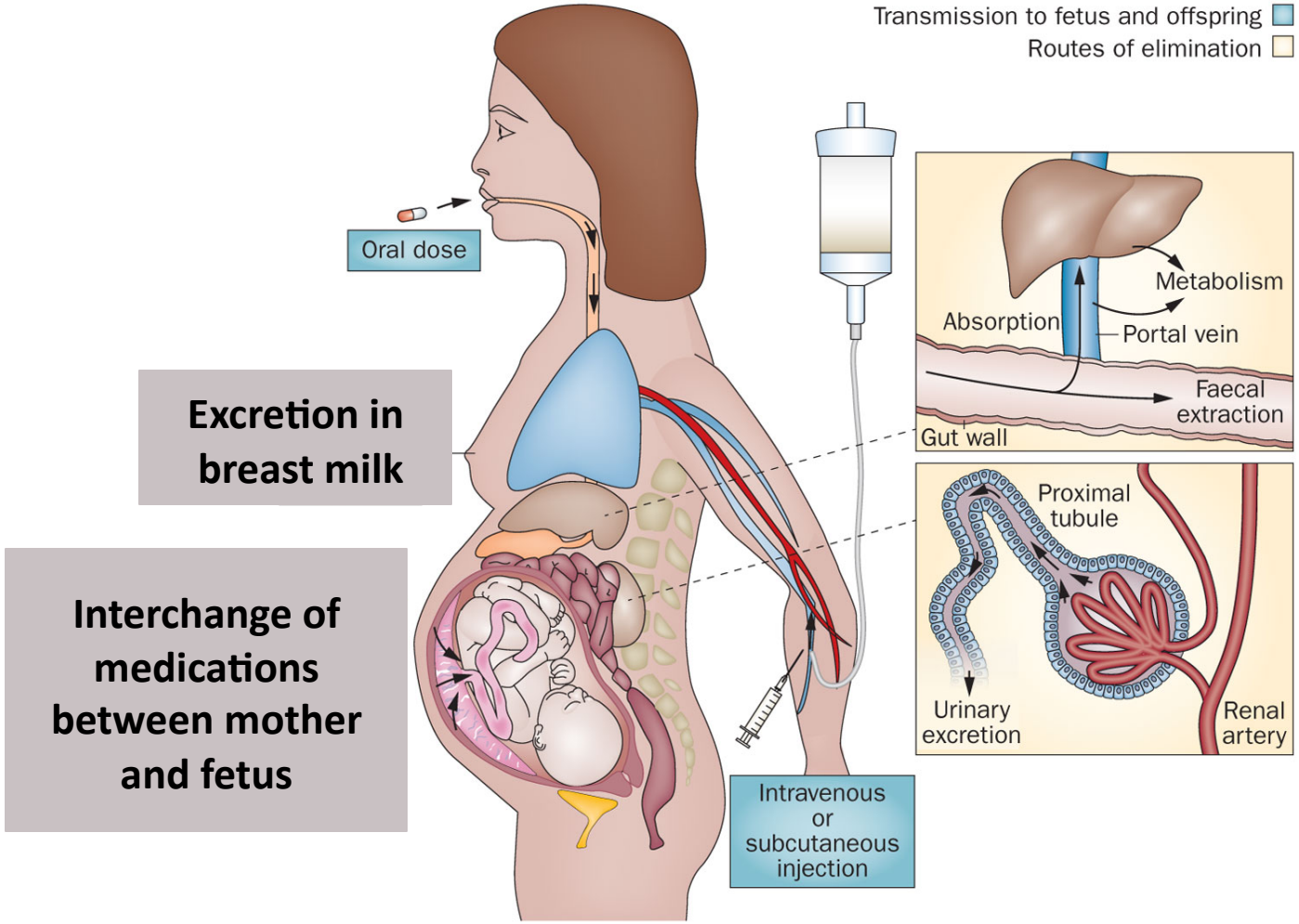
- **Q7**. What adjustments, if any, should be made to the dose and timing of her medications?

Disease optimization throughout pregnancy

- Consultation with an obstetrician, preferably one affiliated with a high risk obstetrics program.

- Ongoing management by GI: **Women overestimate the harmful effects of medication and underestimate the harmful effects of IBD flares during pregnancy**

Women on 5-ASA, thiopurines, or anti-TNF therapy should **continue therapy** throughout pregnancy.



Neilsen. *Nat Rev Gastroenterol Hepatol.* 2013.

Thiopurines

- No increased risk of congenital anomalies
- ?Risk of preterm birth: conflicting evidence (medication vs disease activity)
- Altered maternal thiopurine metabolism during pregnancy
- ?Neonatal anemia

Akbari M, et al. *Inflamm Bowel Dis*. 2013;19:15–22.
Hutson JR, et al. *J Obstet Gynaecol*. 2013;33:1–8.
De Meij TG, et al. *Aliment Pharmacol Ther*. 2013;38:38–43.
Angelberger S, et al. *J Crohns Colitis*. 2011;5:95–100.
Jharap B, et al. *Gut*. 2014;63:451–7.

Anti-TNF therapy

- In general, anti-TNF therapy is associated with a ~2 fold increase in remission rates vs. placebo

Mahadevan U, et al. *Clin Gastroenterol Hepatol.* 2013;11:286–92; quiz e24.
Zelinkova Z, et al. *Clin Gastroenterol Hepatol.* 2013;11:318–21.
Zelinkova Z, et al. *Aliment Pharmacol Ther.* 2011;33:1053–8.
Bortlik M, et al. *Scand J Gastroenterol.* 2013;48:951–8.
Steenholdt C, et al. *J Crohns Colitis.* 2012;6:358–61.

Anti-TNF therapy

- The risk of continuing therapy:
  Neonatal and cord blood levels
  (up to 4-fold higher than maternal peripheral blood)

- Consequences?
  - Increased infections with combination therapy not anti-TNF monotherapy
  - ?Neonatal neutropenia (n=4)
  - Avoid live vaccines in neonates

Narula N, et al. *Inflamm Bowel Dis*. 2014;20:1862–9.
Nielsen OH, et al. *BMC Med*. 2013;11:174.
Marchioni RM, et al. *World J Gastroenterol*. 2013;19:2591–602.
Bortlik M, et al. *Inflamm Bowel Dis*. 2014;20:49–501.
Guiddir T, et al. *Pediatrics*. 2014;134:e1189–93.

Anti-TNF therapy

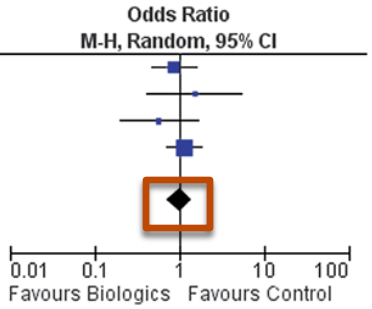
- Anti-TNF therapy is not associated with an increased risk of unfavourable pregnancy outcomes.

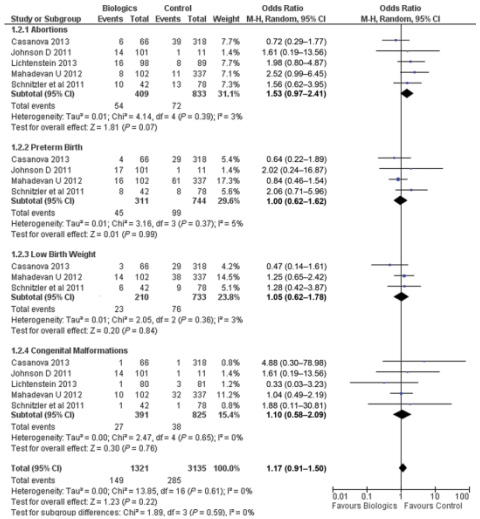
OR 1.00 (0.72-1.41)

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Casanova 2013	17	66	91	318	31.1%	0.87 (0.47–1.58)
Johnson D 2011	47	101	4	11	6.8%	1.52 (0.42–5.53)
Lichtenstein 2013	6	80	10	81	10.0%	0.58 (0.20–1.67)
Mahadevan U 2012	36	102	108	337	52.1%	1.16 (0.73–1.84)
Total (95% CI)		**349**		**747**	**100.0%**	**1.00 (0.72–1.41)**
Total events	106		213			

Heterogeneity: Tau² = 0.00; Chi² = 2.04, df = 3 (*P* = 0.56); I² = 0%

Test for overall effect: Z = 0.02 (*P* = 0.98)





All adverse events: abortion, preterm birth, LBW, congenital malformations

Narula N, et al. *Inflamm Bowel Dis*. 2014;20:1862–9.

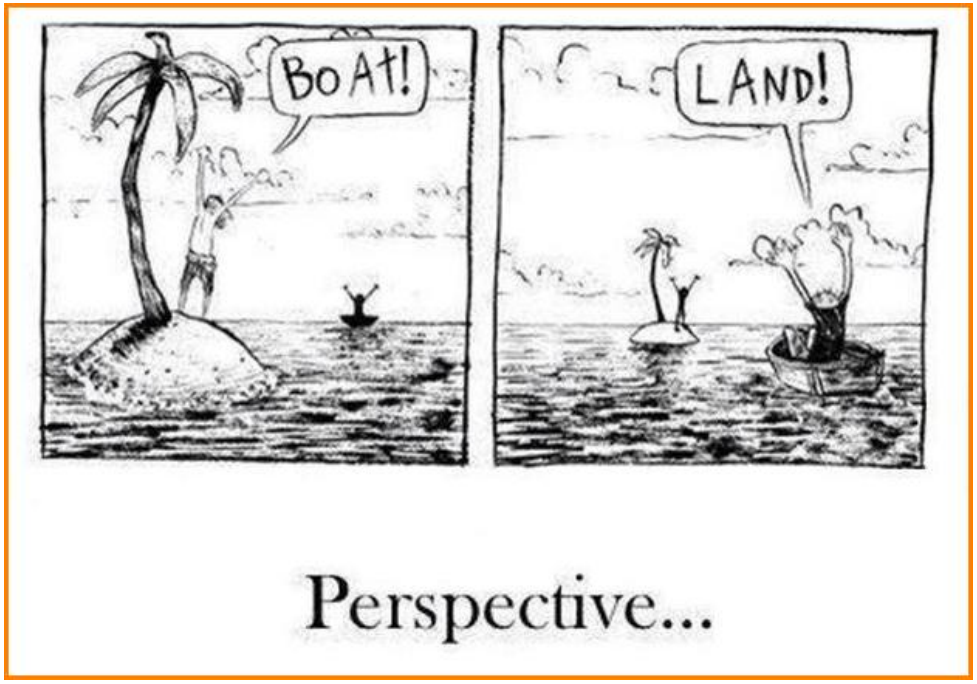
Anti-TNF therapy

- The risks of stopping therapy:
- Case selection
- ?No increased risk of relapse with 2nd trimester cessation
- Intrapartum relapse 8-14%
- Post partum relapse 32%

- Higher rate of unfavourable pregnancy outcomes
- Issues with drug hiatus, relapse, antibody formation.

de Lima A, et al. *Gut*. 2015 May 12. pii: gutjnl-2015-309321. doi: 10.1136/gutjnl-2015-309321. [Epub ahead of print]
Zelinkova Z, et al. *Clin Gastroenterol Hepatol*. 2013;11:318–21.
Seirafi M, et al. *Aliment Pharmacol Ther*. 2014;40:363–73.
Casanova MJ, et al. *Am J Gastroenterol*. 2013;108:433–40.

So what do we do with anti-TNF therapy?



- <u>Modify</u> the dosing schedule, minimise drug hiatus
- Resume post partum 'baby out, drug in'!

- 'The Toronto Consensus Statements for the Management of IBD in Pregnancy'. Nguyen GC*, Seow CH*, Maxwell C, Huang V, Leung Y, Jones J, Leontiadis GI, Tse F, Mahadevan U, and van der Woude CJ, on behalf of the IBD in Pregnancy Consensus Group. *Submitted for publication October 2015.*

Additional considerations

- Dose modification not cessation of anti-TNF therapy
- Don’t start de novo thiopurine therapy intra partum
- Steroids vs anti-TNF
  - Past history of response
  - Trimester
  - Comorbidities: gestational diabetes, hypertension, pre-eclampsia
- Other: 5-ASA (DBP vs DBP-free)

Case Presentation – Pregnant

- You continue azathioprine and infliximab at the current dosing.
- She is referred to the high-risk obstetrics program at your hospital, where she is monitored with perinatal ultrasounds and assessments for fetal growth.
- She is dependent on the infliximab dosing regimen (q 6 weeks) and is scheduled to receive her last intrapartum infliximab at 34 weeks.

Discussion

Q8. What should the patient be told about delivery method (vaginal delivery versus C-section)?

Mode of Delivery

Mode of Delivery

- Decisions regarding cesarean delivery should be based on obstetrical considerations and not IBD diagnosis alone.
- Exceptions are active perianal Crohn's disease, IPAA.
- Anticoagulant thromboprophylaxis for C section

Ilnyckyji A, et al. *Am J Gastroenterol*. 1999;94:3274–8.
Cheng AG, et al. *Inflamm Bowel Dis*. 2014;20:1391–8.
Smink M, et al. *BMC Gastroenterol*. 2011;11:6.
Brandt LJ, et al. *Am J Gastroenterol*. 1995;90:1918–22.

Case Presentation – Pregnant

- She is planned for a vaginal delivery given the absence of active perianal disease.
- However, due to slow progression of labour, she requires a cesarean delivery.
- The C-section goes well, and she has no complications.
- The baby weighs 7 lb 3 oz and is healthy!

Discussion

- **Q9**. What adjustments, if any, should be made regarding her medications after delivery? Should the baby have any special tests?

Post Partum Care

- Continue/resume medications post partum
- Consider neonatal Hb
- Avoid live vaccines within the 1st six months, if exposed to anti-TNF therapy in utero.

Discussion

- **Q10.** She would like to breast feed. How would you counsel her about the use of medications during lactation?

Lactation and IBD

- With the exception of methotrexate, the use of IBD medications should not influence the decision to breastfeed, and vice versa.

- Breastfeeding may be protective against relapse
  - May have a protective effect against the development of early onset IBD in the offspring

Julsgaard M, et al. *Scand J Gastroenterol*. 2014;49:958–66.
Moffatt DC, et al. *Am J Gastroenterol*. 2009;104:2517–23.
Kane S, et al. *Am J Gastroenterol*. 2005;100:102–5.
Barclay AR, et al. *J Pediatr*. 2009;155:421–6.

Conclusions: IBD and pregnancy

- Optimizing mom's health is in the best interest of mom and baby
- Ongoing disease reassessment is necessary
- Continue medications throughout pregnancy

The fun has only just begun….

Questions?

Key References

- Nguyen GC*, Seow CH*, Maxwell C, Huang V, Leung Y, Jones J, Leontiadis GI, Tse F, Mahadevan U, and van der Woude CJ, on behalf of the IBD in Pregnancy Consensus Group. The Toronto Consensus Statements for the Management of IBD in Pregnancy. Submitted for publication October 2015.

- 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. *Am J Gastroenterol*. 2011;106:214–23;quiz 224.

- van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis*. 2015;9:107–24.