# IBD AND PREGNANCY

INSELSPITAL
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Pascal Juillerat

ECCO Guidelines/Consensus Paper

## The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease

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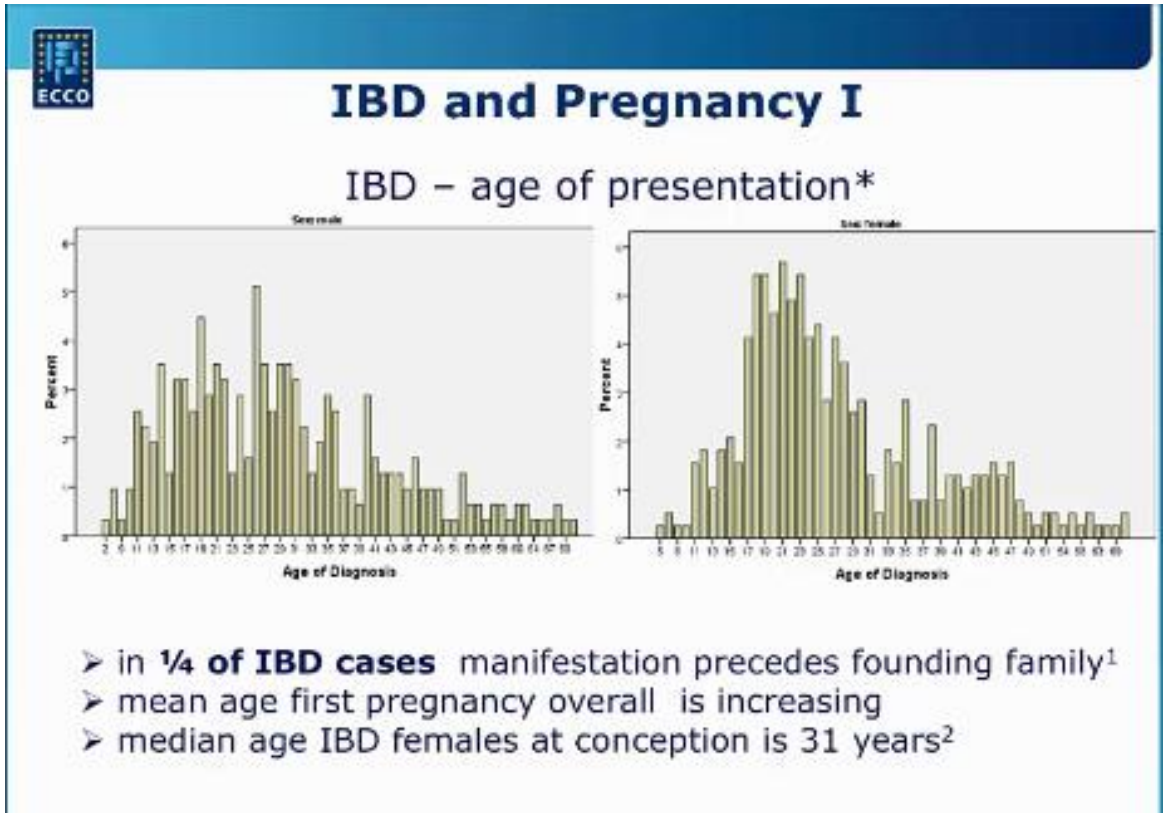
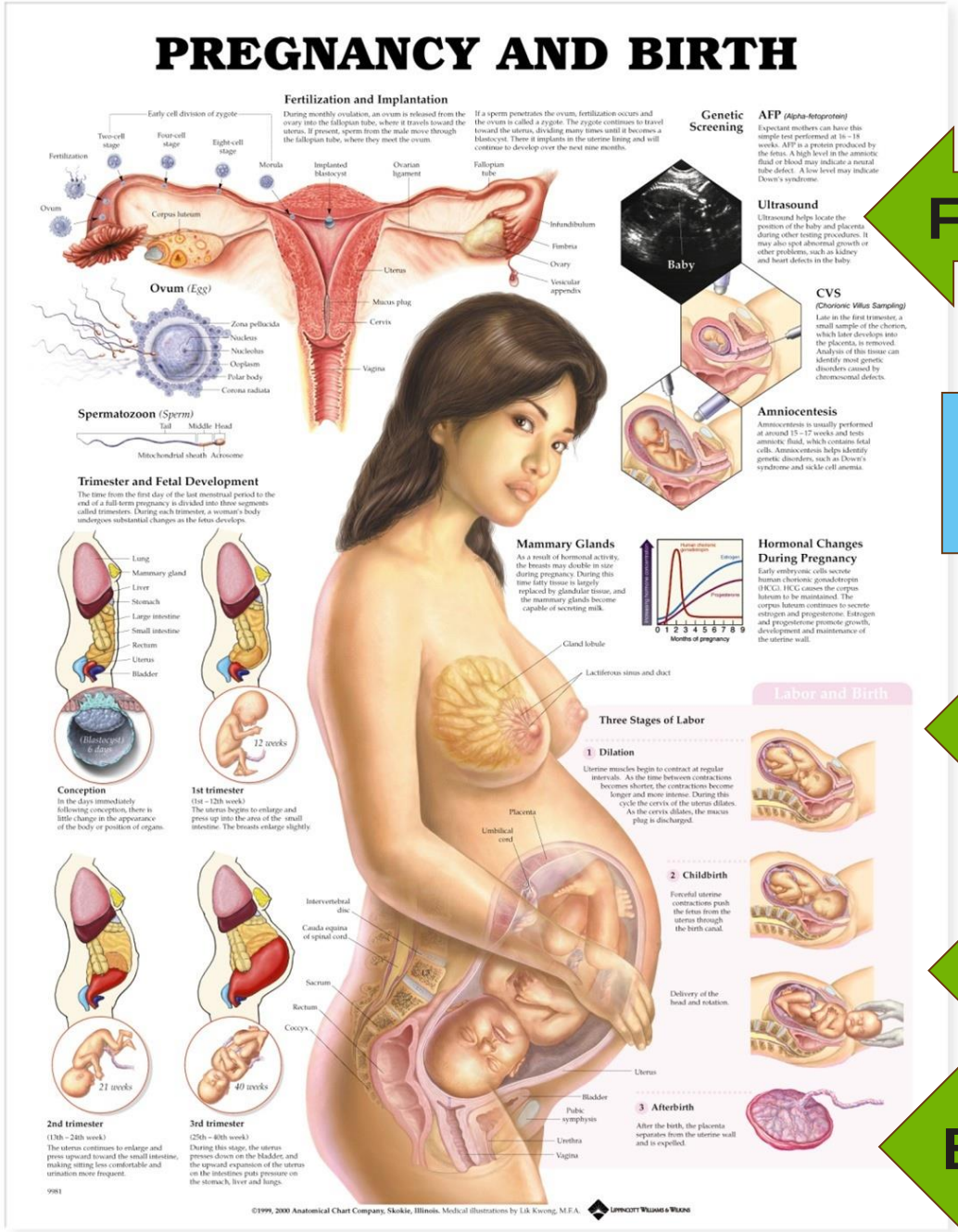
# INTRODUCTION

- General consideration about IBD and pregnancy ?






Fertility

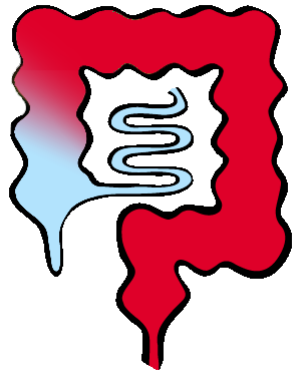
Course of disease

Breastfeeding

DRUGS

Pregnancy

Birth



# 1. FERTILITY / PRE-COUNSELING

Fertility in IBD

Select one:

- a. Is decreased due to voluntary childlessness ✓
- b. Is decreased in all IBD patients
- c. Is in general not decreased in IBD, regardless of the type of the disease or surgical procedures in the past
- d. Is not affected by disease activity

# 1. FERTILITY / PRE-COUNSELING

## - Factor of hypofertilty (at least 2-3) ?

**ECCO Statement 2A**

There is no evidence that ulcerative colitis or inactive Crohn's disease affect fertility [EL3]. However, active Crohn's disease may reduce fertility and hence it is advisable to strive for remission [EL3]. High levels of voluntary childlessness in women with Inflammatory bowel disease indicate the need for better education [EL4]

**ECCO Statement 2B**

There is no evidence that medication affects fertility in females [EL4]. In males sulphasalazine causes reversible oligospermia [EL3]

*+ MTX*

**ECCO Statement 2C**

Pelvic surgery may lead to impotence or ejaculatory problems in men [EL4]

**ECCO Statement 2D**

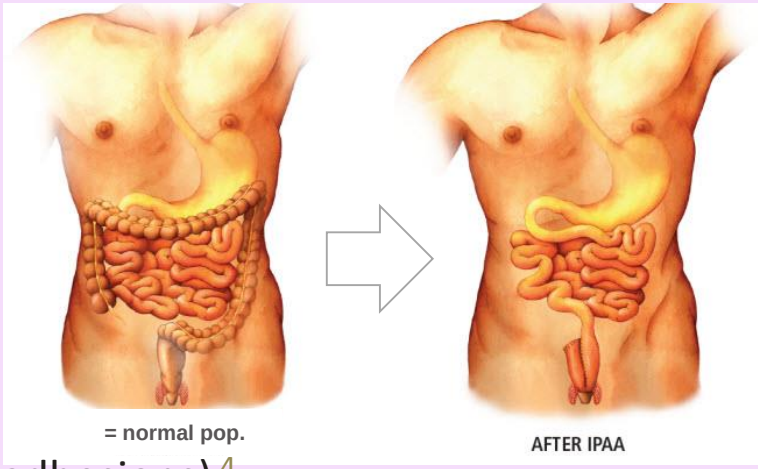
Pelvic and, to a lesser extent, abdominal surgery for IBD increases the risk of subfertility in females [EL1]. A laparoscopic approach to ileal pouch anal anastomosis may lower infertility rates compared with an open surgical approach [EL2]

# FERTILITY IN UC

**Ulcerative colitis:** highest risk is after total colectomy with ileal pouch anal anastomosis (IPAA
– should be avoided! 2-3x ↑ risk of infertility [1,2]

→ subtotal colectomy prefered.

*Fertility … at 5 years [3]:*
*90%* *40%*




[1] Waljee A, *et al.* Gut 2006;55:1575–80 (metanalysis).
[2] Rajaratnam SG, *et al.* Int J Colorectal Dis 2011 (metanalysis).

[3] Lee S, Crowe M, Seow CH, et al. The impact of surgical therapies For inflammatory bowel disease on female fertility. Cochrane Database Syst Rev. 2019;23:7 CD012711.

→ laparoscopic IPAA better than open surgery (less adhesions) [4].

[4] Beyer-Berjot L, Panis Y. A. total laparoscopic approach reduces the infertility rate after ileal pouchanal anastomosis: a 2-center study. Ann Surg 2013;258:275–82.

# DRUGS AND FERTILITY

**Crohn's disease: subfertility** is mainly reported with active disease [1].

1) disease itself and activity [1]

2) currently improved with better medication [2]: ↑ remission

3) a reduced birth rate is observed in patients with IBD = volountary childlessness (14% -18% vs 6%)[3]

**Medications : mostly *Sulfasalazin* – meta-analysis of 4 studies (77 SASP; 49 5-ASA) :**

MTX, MMF, thalidomide (DNA damage)

**Risk of oligospermia, OR 17**

**Methotrexate Reduces DNA Integrity in Sperm From Men With Inflammatory Bowel Disease**

Dana Ley,[1] Jeffrey Jones,[2,3] John Parrish,[4] Sana Salih,[5] Freddy Caldera,[6] Edna Tirado,[7] Benjamin Leader,[7] and Sumona Saha[6]

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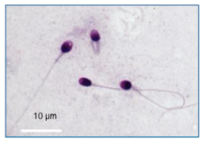
7 men with IBD (cases)

(4 with Crohn's disease, 3 with ulcerative colitis)

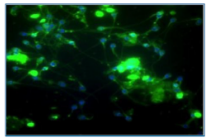
Exposed to methotrexate for at least 3 months

compared to

1,912 age-matched men at fertility centers (controls)




All cases had normal basic semen analyses according to WHO criteria



Cases had significant increases in DNA fragmentation index and oxidative stress adducts compared to controls

Gastroenterology 2018

Review: Male fertility and therapy for IBD
Camparison: 02 Oligospermia rate in patients treated for IBD
Outcome: 01 Patients with oligospermia according SASP or 5-ASA treament

| Study or sub-category | SASP n/N | 5-ASA n/N | OR (fixed) 95% CI | Weight % | OR (fixed) 95% CI | Year |
|---|---|---|---|---|---|---|
| Riley et al | 6/16 | 0/9 | | 22.92 | 11.76 [0.58, 237.99] | 1987 |
| Zelissen et al | 8/16 | 2/11 | | 32.15 | 12.00 [1.58, 91.08] | 1988 |
| Kjaergaard et al | 3/8 | 1/8 | | 36.84 | 4.20 [0.33, 53.12] | 1989 |
| Di Paolo et al | 42/42 | 8/18 | | 8.08 | 105.00 [5.60, 1968.48] | 2001 |
| Total (95% CI) | 77 | 46 | | 100.00 | 16.59 [5.01, 54.89] | |

Total events: 59 (SASP), 11 (5-ASA)
Test for heterogeneity: Chi²=2.80, df = 3 (P=0.42), P = 0%
Test for overall effect: Z = 4.60 (P < 0.00001)

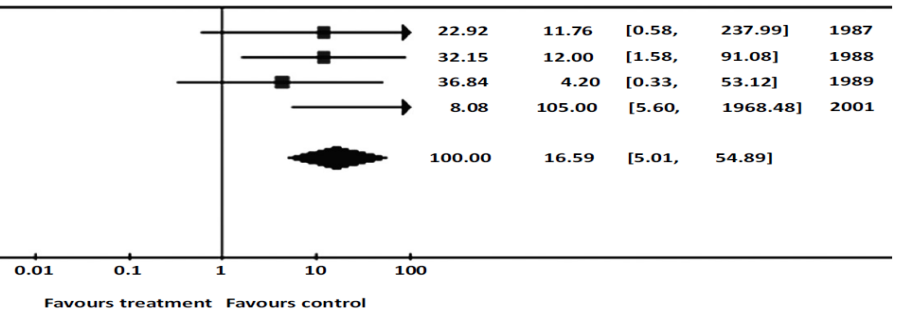



**Fig. (3).** Oligospermia rate in IBD patients treated with SASP or 5-ASA, N= Number of total patients, n= number of patients exhibiting oligospermia, CI= Confidence Interval, OR= Odds Ratio.

# INHERITANCE

Multifactorial

- One parent with CD
  - 5% chance for offspring
- One parent with UC
  - 1.6%
- If both parents have IBD a child' risk of IBD is higher
  - 10-20%

**ECCO Statement 4A**

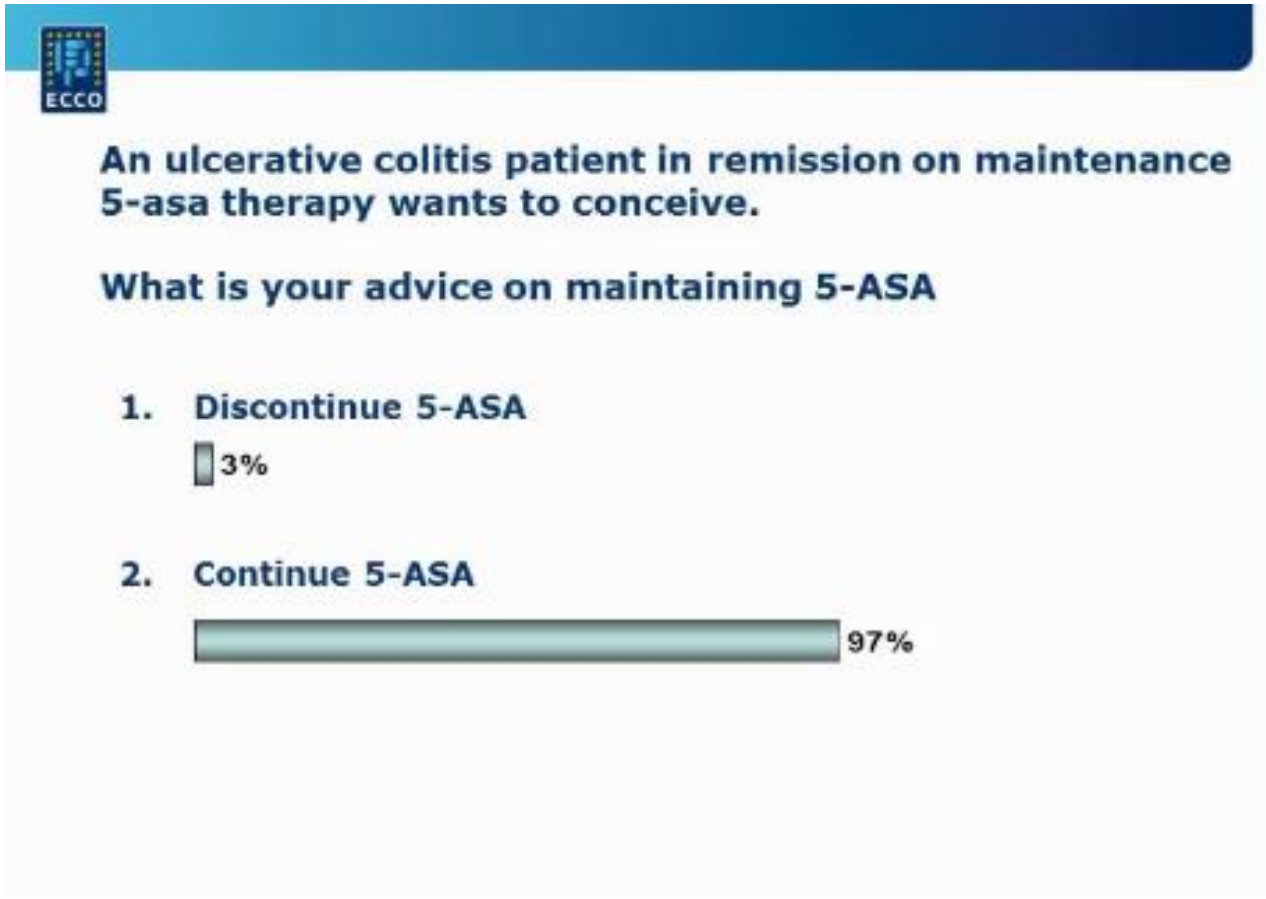
Children of parents with IBD have an increased risk of developing inflammatory bowel disease. The risk is higher for Crohn's disease, and if both parents are affected [EL 3]. In Crohn's disease, transmission is more common from mother to child than from father to child, and female offspring are at higher risk than male offspring [EL 3]

Pregnancy should not be discouraged for this reason!

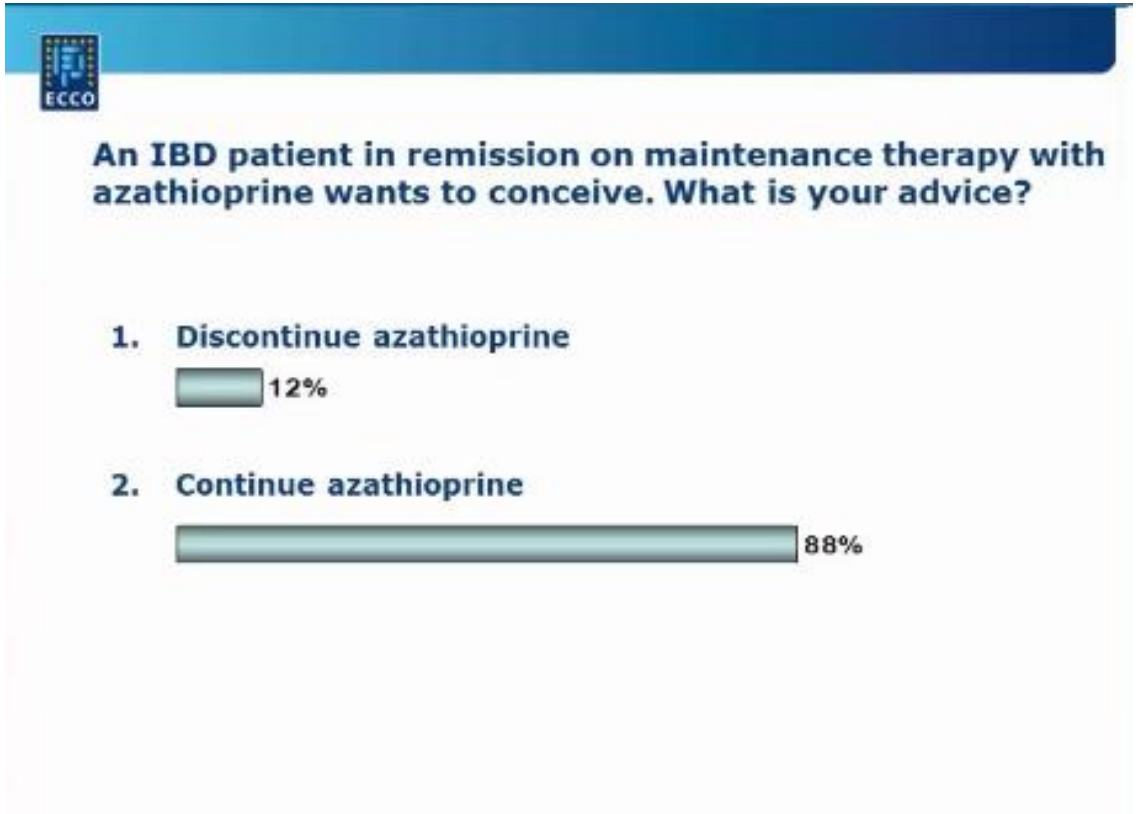
# 1. FERTILITY / PRE-COUNSELING

## How to deal with medications ?

# 1. FERTILITY / PRE-COUNSELING



# 1. FERTILITY / PRE-COUNSELING



# 1. FERTILITY / PRE-COUNSELING

**Appropriate information given to the patient is needed to prevent non compliance/ spontaneous discontinuation of the treatment due to fear of adverse events during this period, because exacerbations of disease are often due to discontinuation of maintenance therapy during pregnancy or breastfeeding [1,2] .**

***→ Associated with frequent postpartum flares [3]***

**New ECCO Statement proposal**

**Exacerbations of disease may result from discontinuation of maintenance therapy during pregnancy or breastfeeding. Appropriate counseling of the patient might be helpful in preventing non adherence to the treatment due to fear of potential harm to the unborn child [EL5].**

Please make your decision!

| | | | |
|---|---|---|---|
| **Total number of votes:** | | 14 | |
| **Distribution of answers:** | agree: | 13 of 14 | 92.86 % |
| | rather agree: | 1 of 14 | 7.14 % |
| | indecisive: | 0 of 14 | 0.00 % |
| | rather disagree: | 0 of 14 | 0.00 % |
| | disagree: | 0 of 14 | 0.00 % |

**93% agreement !**

**Comments:**

for answer 'rather agree'

- Ideally this counselling should occur prior to pregnancy. The counselling should also be done by GI.

# 2 . DURING PREGNANCY

## How fluctuates disease activity ? :

Most pregnancy with IBD will be **uncomplicated**, especially if patient **in remission** / minor disease activity at time conception

**1/3 will relapse** during pregnancy, as often as without pregnancy

**UC relapse more** often during pregnancy / UC have higher risk of post – partum flare

Pregnancy **protective effect on CD** , also postpartum (less surgical interventions, lower relapse rate)

# ECCO – EPICOM STUDY

**Disease activity** – at conception / first trimester – :

145 CD patients:

N= 126 (86.9%) in remission → 105 (86%) maintained remission ; 38 **(14%) relapsed.**

N=19 (13.1%) w/ active disease →14 **(74%) obtained remission**; 5 (26%) remained active.

187 UC patients:

N= 148 (79%) in remission → 109 (74%) maintained remission ; 39 **(26%) relapsed**.

N=39 (21%) w/ active disease →26 **(67%) obtained remission**; 13 (33%) remained active.

**Flares during pregnancy** :

CD - 15%

**UC 30%**

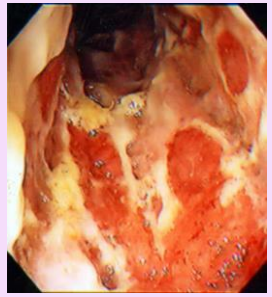
Bortoli A, Pedersen N, Duricova D, D'Inca R, Gionchetti P, Panelli MR, et al. Pregnancy outcome in inflammatory bowel disease: prospective European case–control ECCO-EpiCom study, 2003–2006. Aliment Pharmacol Ther 2011;34:724–34

**ECCO Statement 3A**

If conception occurs at a time of quiescent disease, the risk of relapse is the same as in nonpregnant women [EL3]. Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy [EL3]. Pregnancy may influence the course of inflammatory bowel disease [EL3]

# IBD ACTIVITY AND PREGNANCY OUTCOME

Globally with both IBD, **with active disease** :



-1- ↑ rates of **spontaneous abortion**

-2- ↑ **low** birth **weight**

-3- ↑ **preterm** birth

But **no** increase in *malformations* due to the disease itself.

**ECCO Statement 5A**

Appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy [EL5]. Acute flares during pregnancy carry a high risk of adverse maternal and fetal outcome, and are best treated appropriately and without delay to prevent these complications [EL3]

Pregnancy in healthy women and in female IBD patients in remission and during the disease flare – mean percentage based on European and American trials.

| % | Healthy fetus | Congenital abnormalities | Premature delivery | Abortion |
|---|---|---|---|---|
| **Healthy women** | 83 | 2 | 6 | 9 |
| **CD - remission** | 82 | 1 | 7 | 10 |
| **CD - flare** | 54 | 1 | 25 | 20 |
| **UC - remission** | 84 | 1 | 6 | 9 |
| **UC – flare** | 65 | 2 | 12 | 21 |

Abbreviations:CD-Crohn's disease; UC-ulcerative colitis;Source: "Crohn's disease, ulcerative colitis and pregnancy" A. Dignass

# IBD ACTIVITY AND PREGNANCY OUTCOME

## Other factors affecting pregnancy outcome

**disease activity,**

**older age**

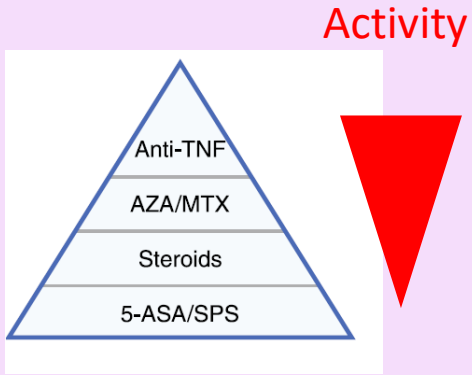
**smoking**

**alcohol**

*lower birth weight in UC*

*Preterm delivery in CD*

**IBD-related medication.**




*5-ASA monotherapy had lower probability of preterm delivery in UC and caesarean section in CD while combination therapy increased the risk of these events.*

Bortoli A, Pedersen N, Duricova D, D'Inca R, Gionchetti P, Panelli MR, et al. Pregnancy outcome in inflammatory bowel disease: prospective European case–control ECCO- EpiCom study, 2003–2006. Aliment Pharmacol Ther 2011;34:724–34

# 2 . DURING PREGNANCY

## How to deal with medications ?

# 2 . DURING PREGNANCY

Female, 30 years:

- UC, flare, 5 weeks pregnant, severe colitis, alternative diagnosis excluded
- Current treatment: Oral steroids for 2 weeks, azathioprine, infliximab every 6 weeks

Now start intravenous CS?

Select one:

- (●) a. Yes, although it is not a safe option ✓ Correct
- ( ) b. No, steroids are worse than disease flare for the pregnancy outcome
- ( ) c. Yes, it is a safe option in pregnancy

Check

# 2 . DURING PREGNANCY

Female, 30 years:

- UC, 8 weeks pregnant
- Response to steroids but flare by tapering
- Infliximab discontinued by patient

## Restart infliximab?

Select one:

a. Yes, although it is not a safe option ✓ Correct

b. Yes, it is a safe option in pregnancy

c. No, anti-TNFs are worse than disease flare for pregnancy outcome

Check

# 2 . DURING PREGNANCY

## 5-aminosalicylates during pregnancy

Select one:

- a. Have insufficient data on the safety profile during pregnancy
- b. Have been shown to be safe in a dose up to 4g/deay
- c. Should be discontinued in the last trimester of the pregnancy
- d. Have been shown to be safe in a dose up to 3g/day ✓

# 2 . DURING PREGNANCY

## Corticosteroids during pregnancy

Select one:

- a. Their use during the first trimester is related to increased risk of congenital malformations
- b. Hydrocortisone, dexamethasone and betamethasone are effective inactivated by placental enzyme 11ß-hydroxysteroid dehydrogenase
- c. Prednison and prednisolone are corticosteroids of choice for maternal indication during pregnancy ✓
- d. Prolonged treatment with dose more than 15mg/day is sage

# 2 . DURING PREGNANCY

## AntiTNF during pregnancy

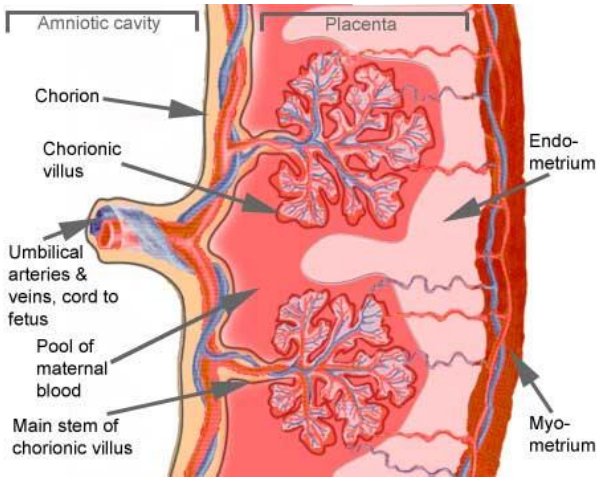
Select one:

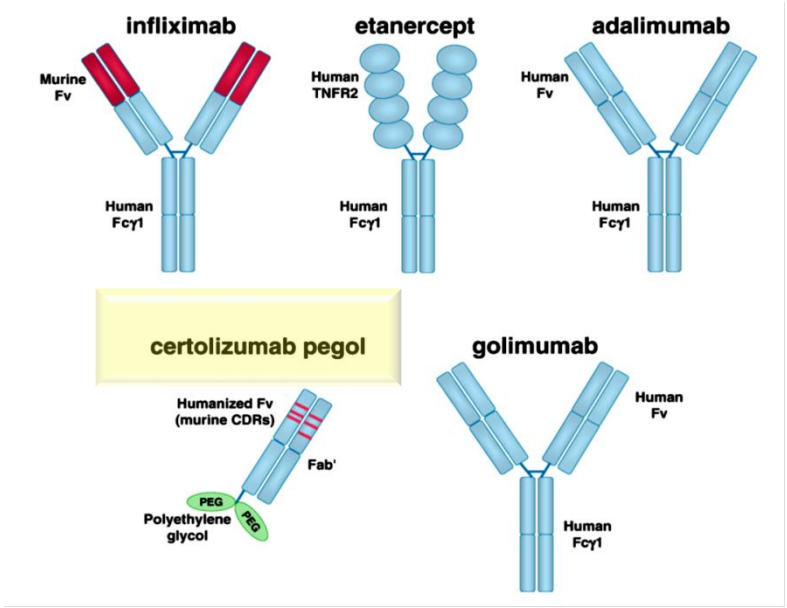
- a. Their use during the pregnancy is related to increased congenital malformations
- b. Stopping the treatment more than 10 weeks prior delivery does not reduce the neonatal levels assessed at birth
- c. Cross the placenta from the second trimester on ✓
- d. In monotherapy, their use leads to an increased risk of infections in the newborn

# 2 . DURING PREGNANCY

- **Special situation with a drug ?**

Certolizumab is a pegylated Fab' fragment of an anti-TNF monoclonal antibody without Fc fragment and would theoretically be **expected not to cross the placenta**, although *human data on this topic are still lacking*.




Recommendations: **not to switch** to certolizumab during pregnancy if Anti-Therapy is working well, but rather **anticipate** pregnancy in some patients and start, first line, certolizumab

# 2 . DURING PREGNANCY

## How to deal with Anti-TNF agents ?





### Long-Term Safety of *In Utero* Exposure to Anti-TNFα Drugs for the Treatment of Inflammatory Bowel Disease: Results from the Multicenter European TEDDY Study

M. Chaparro, MD, PhD[1], A. Verreth, MD[2], T. Lobaton, MD, PhD[3], E. Gravito-Soares, MD[4], M. Julsgaard, MD, PhD[5], E. Savarino, MD, PhD[6], F. Magro, MD, PhD[7], I. Avni Biron, MD[8], P. Lopez-Serrano, MD, PhD[9], M.J. Casanova, MD, PhD[1], M. Gompertz, MD[10], S. Vitor, MD[11], M. Arroyo, MD[12], D. Pugliese, MD[13], Y. Zabana, MD, PhD[14], R. Vicente, MD[15], M. Aguas, MD, PhD[16], A. Bar-Gil Shitrit, MD[17], A. Gutierrez, MD, PhD[18], G.A. Doherty, MB, PhD, FRCP[19], L. Fernandez-Salazar, MD[20], J. Martínez Cadilla, MD[21], J.M. Huguet, MD, PhD[22], A. O'Toole, MD[23], E. Stasi, MD[24], N. Manceñido Marcos, MD, PhD[25], A. Villoria, MD, PhD[26], K. Karmiris, MD, PhD, FEBGH[27], J.F. Rahier, MD, PhD[28], C. Rodriguez, MD[29], M. Diz-Lois Palomares, MD, PhD[30], G. Fiorino, MD, PhD[31], J.M. Benitez, MD[32], M. Principi, MD[33], T. Naftali, MD[34], C. Taxonera, MD, PhD[35], G. Mantzaris, MD, PhD[36], L. Sebkova, MD[37], B. Iade, MD[38], D. Lissner, MD[39], I. Ferrer Bradley, MD[40], A. Lopez-San Roman, MD, PhD[41], I. Marin-Jimenez, MD, PhD[42], O. Merino, MD[43], M. Sierra, MD[44], M. Van Domselaar, MD[45], F. Caprioli, MD, PhD[46], I. Guerra, MD[47], P. Peixe, MD[48], M. Piqueras, MD[49], I. Rodriguez-Lago, MD[50], Y. Ber, MD[51], K. van Hoeve, MD[52], P. Torres, MD[3], M. Gravito-Soares, MD[4], D. Rudbeck-Resdal, MD[5], O. Bartolo, MD[6], A. Peixoto, MD[7], G. Martin, MD[8], A. Armuzzi, MD, PhD[53], A. Garre, MSc[1], M.G. Donday, MSc[1], F.J. Martín de Carpi, MD[13] and J.P. Gisbert, MD, PhD, Professor[1]

OBJECTIVES: **The long-term safety of exposure to anti-tumor necrosis factor (anti-TNFα) drugs during pregnancy has received little attention. We aimed to compare the relative risk of severe infections in children of mothers with inflammatory bowel disease (IBD) who were exposed to anti-TNFα drugs *in utero* with that of children who were not exposed to the drugs.**

METHODS: **Retrospective multicenter cohort study. Exposed cohort: children from mothers with IBD receiving anti-TNFα medication (with or without thiopurines) at any time during pregnancy or during the 3 months before conception. Non-exposed cohort: children from mothers with IBD not treated with anti-TNFα agents or thiopurines at any time during pregnancy or the 3 months before conception.**

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**ECCO Statement 4E**

Since detectable levels of anti-TNF in the offspring are present in the first 6 months at least, live vaccines should be avoided in this period [EL5]. Current vaccination strategies with non-live vaccines do not differ from those for infants unexposed in utero to anti-TNF agents [EL4]

**ECCO Statement 4F**

Timing of the last dose of the anti-TNF drug should consider both maternal disease activity and drug placental transfer. When considered appropriate by the clinician and the patient, to limit the transport of the anti-TNF to fetus, the anti-TNF drug should be discontinued around gestational week 24–26 [EL3]

# 2 . DURING PREGNANCY

**How to deal with medications ?**

**ECCO Statement 4D**

Fetal exposure to most IBD medications is considered of low risk to the child, except for methotrexate and thalidomide [EL2]. Fetal exposure to thiopurines is not associated with an increased risk of infections in the first year [EL3]. The risk of infection with anti-TNF agents alone or in combination with immunomodulators is controversial [EL4]

**What to use in case of relapse ?**

**ECCO Statement 5C**

In cases of relapse, depending on the disease phenotype and activity, 5-ASA or corticosteroids are the preferred therapies [EL5]. Anti-TNF agents can be considered to treat flares in appropriate situations [EL5]

# SUMMARY DRUGS TABLES

| Considered safe | Probably safe | Contraindicated |
|---|---|---|
| 5-Aminosalicylates [B], [C] (Asacol), Sulfasalazine [B] | Infliximab, Adalimumab [B] , Golimumab<br>Certolizumab [B] | Methotrexate [X] |
| Azathioprine [D] , 6MP | Vedolizumab, Ustekinumab (few data) | Thalidomide [X] |
| Corticosteroids [C] | Tacrolimus / Cyclosporin (no data) [C] | Tofacitnib |
| Metronidazole, Cipro [C] | Budesonide [C] | upadacitinib |

CAVE:

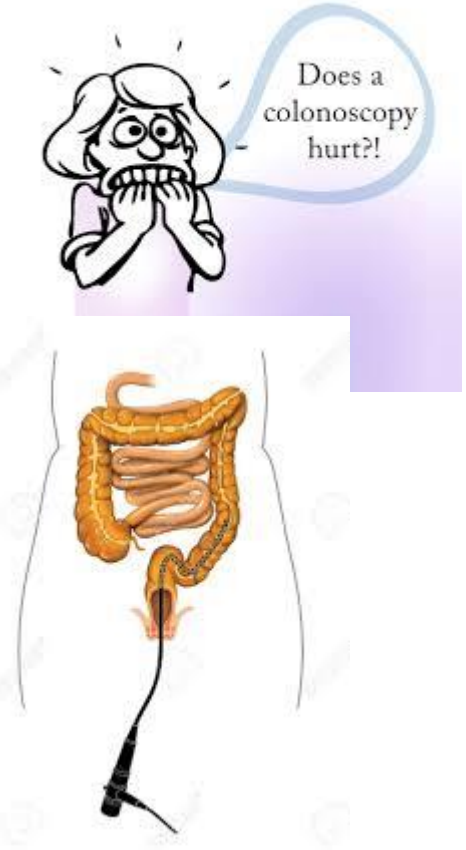
- Metronidazol: not during the second and third months of pregnancy
  → risk of higher rates of cleft lip with or without cleft palate.
- Ciprofloxacin (or quinolones): In the second or third trimester only.
  →Not first semester, associated with arthropathies.
- Methotrexate: discontinue 3-6 months before conception.

# 2 . DURING PREGNANCY

Colonoscopy during pregnancy

Select one:

- a. Is a safe procedure and should be performed in case of suspected flare to confirm the diagnosis ✓
- b. The preparation with polyethylene glycol is not considered to be safe
- c. Is not safe and should always be avoided
- d. The supine position of the patient should be preferred to left side position



# 2 . DURING PREGNANCY

**ECCO Statement 7G**

Gastroscopy [EL3], sigmoidoscopy/colonoscopy, and ERCP [endoscopic retrograde cholangiopancreatography] [EL4] are generally considered to be safe in pregnancy; however, these procedures should only be done when there is a strong indication and should be performed in the second trimester whenever possible [EL5]. Hemostasis measures are safe and should be carried out with precautions [EL5]

**ECCO Statement 7I**

Close attention should be paid to appropriate drug selection, using drugs most tried and tested in pregnancy and using the minimum dose possible to achieve the desired effect [EL4]. Sedative drugs should be administered to provide patient comfort, while avoiding over-sedation [EL 5]

**ECCO Statement 7H**

Procedure time and radiation exposure should be kept to a minimum [EL4]. Endoscopic procedures should be managed in conjunction with specialists in obstetrics and obstetric anesthesia [EL5]. Pregnant patients should be placed in the left pelvic tilt or left lateral position before, during and after the endoscopic procedure, to avoid vena caval compression [EL5]. Presence of fetal heart sounds should be confirmed before sedation is begun and after the endoscopic procedure [EL5]

- Propofol not evaluated during pregnancy: **avoid**
- BZ / diazepam: **avoid** (particulary during 1. trim)

  - Cave risk aspiration during OGD
  - Always use satuation monitoring
    - Minimal dose of sedation

# 3. DELIVERY

Mode of delivery in IBD patients

Select one:

- a. In patients with perianal disease, the risk of 4th degree laceration during vaginal delivery increased and C-section is thus preferred mode of delivery ✓
- b. Patients with ileo-anal pouch should preferentially have vaginal delivery
- c. All IBD patients should delivery by C-section
- d. Should be solely guided by obstretic considerations

# 3. DELIVERY

Female, 30 years:

- Ulcerative colitis
- 31 weeks pregnant
- Flare during pregnancy, disease not well controlled prior prgnancy

What is your advice on mode of delivery?

Select one:

a. Vaginal delivery

b. Caesarean section ✓ There is no right or wrong answer

Check

# 3. DELIVERY

## DELIVERY ?

**ECCO Statement 4B**

Cesarean delivery is more frequent in women with IBD; and there is an increased risk of low birthweight and preterm birth [EL2]. Disease activity at conception or during the pregnancy is associated with preterm birth and low birthweight [EL 3]

**ECCO Statement 4C**

Adverse fetal outcomes such as low APGAR scores, seizures or admission to an intensive care unit and death, are not increased in babies born at term [EL2]. The risk of congenital abnormalities in offspring from women with inflammatory bowel disease does not seem to be increased [EL2]

**ECCO Statement 3B**

The mode of delivery is subject to a multidisciplinary approach and should primarily be governed by obstetric indications [EL5]

**ECCO Statement 3C**

Cesarean section is indicated in active perianal disease or active rectal involvement [EL5]. An ileoanal pouch or an ileorectal anastomosis in women with IBD is a relative indication for a cesarean section but the decision should be made on an individual basis [EL5]

# 4. POSTPARTUM

**ECCO Statement 3D**

There is no increased risk of a flare in the postpartum period for women with CD remaining on their maintenance therapy [EL 2]. In women with UC the risk of a postpartum flare may be increased [EL4]



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# 4. BREASTFEEDING

Breastfeeding in IBD

Select one:

- a. For breastfeeding during antiTNF therapy good quality data on its safety are available
- b. Patients with IBD should not breastfeed as none of the IBD drugs are safe during breastfeeding
- c. Prednison should be used with a pump&dump approach ✓
- d. Thiopurines are not safe during breastfeeding

# 4. BREASTFEEDING

Female, 30 years:

- Infliximab 10mg/kg administered at week 31
- Premature delivery at week 32 of a healthy baby girl
- Vaginal delivery
- No breastfeeding

## Breastfeeding and infliximab?

Select one:

- a. Yes - low risk ✓ There is no right or wrong answer
- b. No - high risk

Check

# BREASTFEEDING - DRUG SUMMARY

| Considered safe | Probably safe[1] | Contraindicated |
|---|---|---|
| Sulfasalazine | Budesonide | Metronidazole |
| Mesalazine | Azathioprine *w/ 4 h delay* | Cyclosporine |
| Prednisone | 6-MP | Methotrexate |
| *w/ 4 h delay* | Infliximab **and other anti-TNFs / Biologics** | |
| | Ciprofloxacin → | |
| | Amoxicillin/clavulanic acid | |

[1] Consider, if available, drug monitoring in infants.

*from: Mottet C., Juillerat P., Michetti P. Pregnancy and Breastfeeding in Patients with Crohn's Disease. Digestion 2007; 76:149-60*

# TAKE HOME MESSAGE

In IBD patients (majority in chilbearing age) → conception and pregnancy issues should be early discussed and planed.

Consider conception with appropriate treatment and quiescent disease. MTX and Thalidomide are teratogenic.

Consider a multidisciplinar approach – Obstetrician

Regular Fup during Pregnancy - CAVE: compliance

C-Section preferred for CD patients with perianal disease

UC with IPAA.

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*Danke für Ihre Aufmerksamkeit und Ihre Teilnahme !*