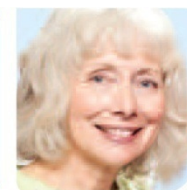


IBD & She

Focusing on Living While Managing IBD



*A program for women, their loved ones, and healthcare professionals
hosted by two women physician experts and researchers in IBD*

Co-sponsored by
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Postgraduate Institute
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Disclosure of Conflicts of Interests

Sunanda V. Kane, MD, MSPH

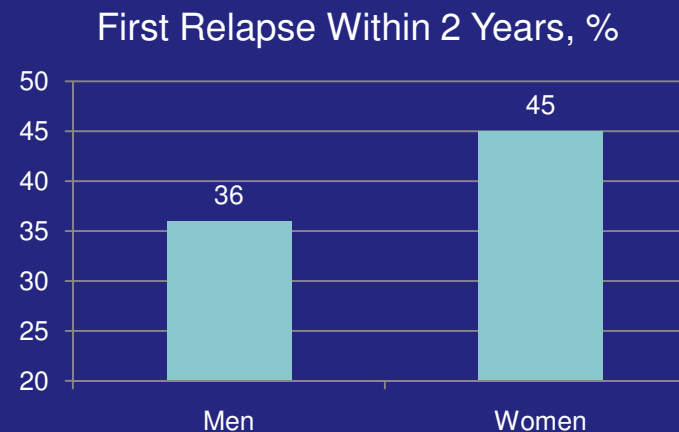
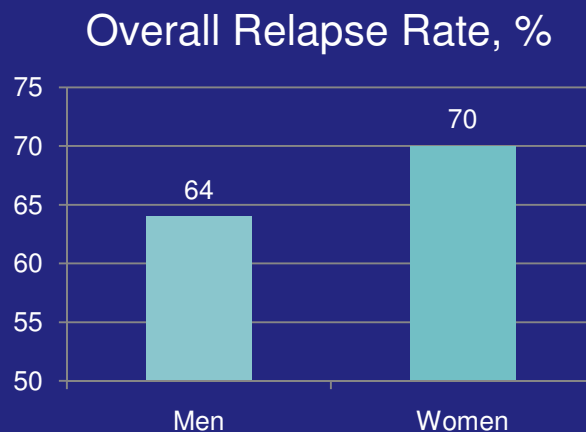
Dr. Sunanda V. Kane has an affiliation with Kyorin Pharmaceuticals (*Speakers Bureau*); Shire, Elan (*Research*).

Today's Goals

- **Identify the gender-specific impact of IBD**
- Understand potential gynecological issues in IBD
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Disease Course by Gender

- 10-year study on the rate of relapse of ulcerative colitis in men and women
 - 771 patients from 8 countries
- Relapse rate for women was 20% higher than in men
- Time to first relapse sooner in women than men



The Effect of Smoking on Crohn's Disease in Women

- There are now two studies that have specifically addressed the gender effect of tobacco
- Women smokers undergoing surgery are 5 times more likely to have a recurrence than non-smokers, and recur more quickly¹
- Women smokers hastened onset of disease and increased the need for immunomodulators²

¹Kane SV. *Gastroenterol.* 2002;124(5):A1169.

²Cosnes J. *J Clin Gastro and Hepatol.* 2004;2:41-48.



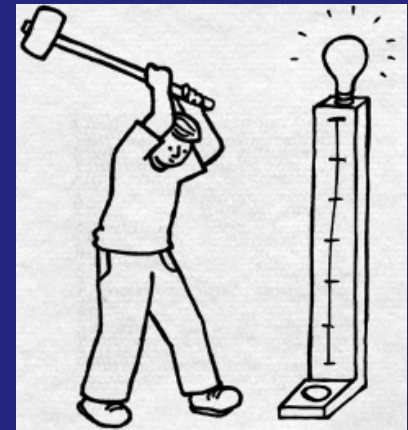
Gender-Related Impact of IBD



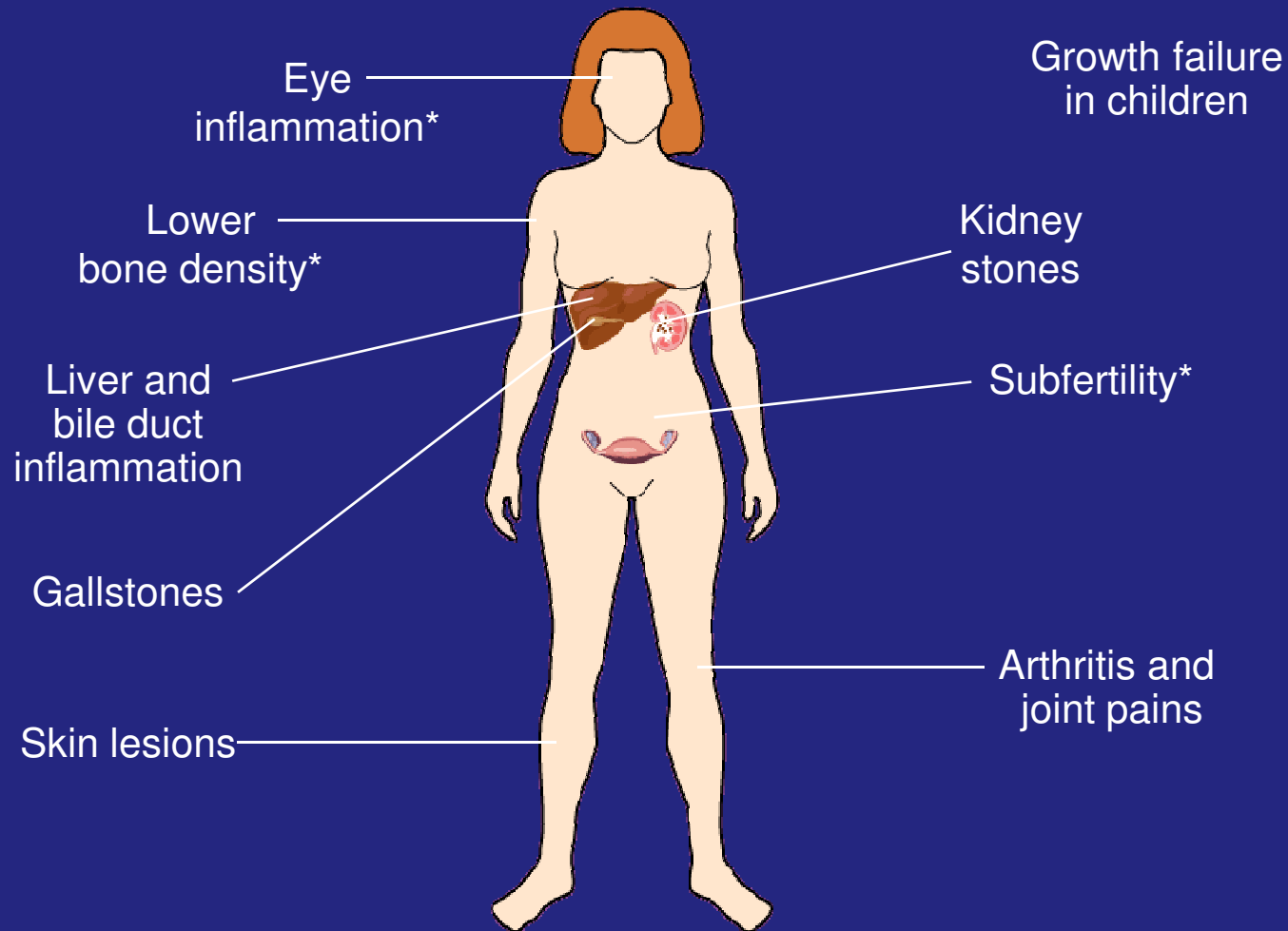
	Women	Men
Reproductive issues	↓ fertility after IPAA or proctocolectomy ↑ risk of relapse of disease active at time of conception	↓ fertility with sulfasalazine
Disease-related concerns	↑ concern re: body stigma, loss of bowel control	—
Sexuality	↓ sexual activity because of dyspareunia, abdominal pain, etc	↓ libido and sexual satisfaction after proctocolectomy

Physical Complications of IBD on Sexuality

- Impact of disease
 - Perianal complications
 - Draining cutaneous fistulae
 - Skin lesions
 - Arthritic deformities
 - Pain
 - Fatigue
- Impact of treatment
 - Surgical scars
 - Stoma
 - Medication side effects



IBD: Systemic Complications



*Higher incidence in women.

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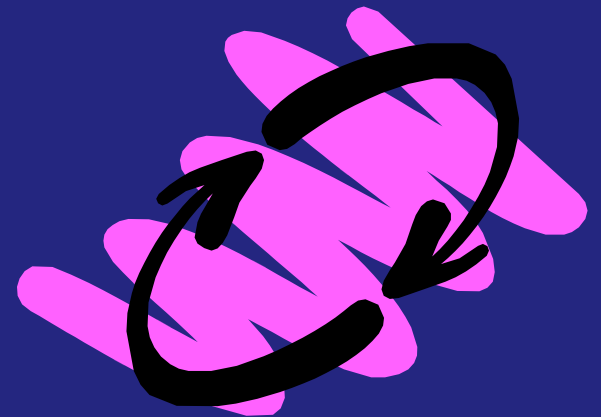
Menses & Pre-Adolescence

- Possible delayed onset of menses in pre-adolescent girls
- Delayed growth rates
- Delayed maturation & secondary sex characteristics

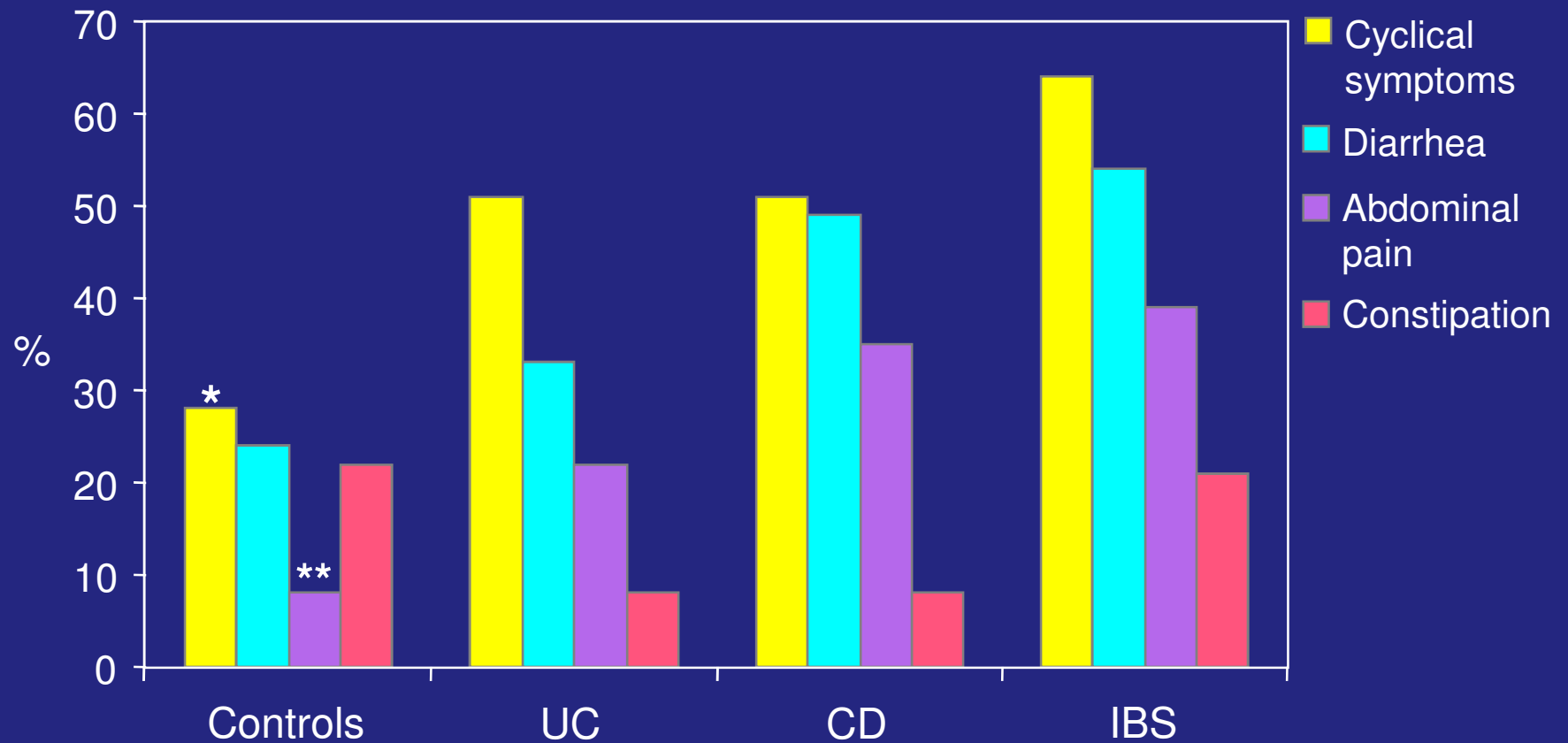


Menstrual Cycle and Bowel-Pattern Fluctuations

- Bowel-pattern fluctuation is common during the menstrual cycle
- IBD symptoms may increase during the menstrual cycle
- Menses suppression with birth control medication may be needed if debilitating symptoms are present



Change in Symptoms During Menses



* $P=0.01$ for all disease groups vs control for cyclical symptoms.

** $P=0.03$ for all disease groups vs control for abdominal pain.

Kane S. *Am J Gastroenterol.* 1998;93:1867-1872.

General Guidelines for Oral Contraceptive (OCP) Use

- OCPs used for contraception should probably have a lower estrogen content
- OCPs should be avoided in women with known history of high coagulation
- OCPs should be avoided in IBD-associated liver disease



What to Expect With Menopause

- Does the course of menopause change when IBD is involved?
- Are the indications more sever/altered from non-IBD related menopause?
- Should female IBD patients be aware of or prevent issues?
 - Vaginal fistulas

Hormone Replacement Therapy (HRT) & Menopause

- 65 patients: 20 UC 45 CD
- Patients on HRT significantly less likely to flare within the first 3 years after menopause



Incidence of Abnormal Pap Smears in IBD

- Abnormal Pap smears associated with both infection and progression to cancer
- Women with IBD were more likely to have an abnormal Pap smear
- Use of azathioprine ↑ risk three-fold

Risk of Abnormal Pap Smears

- Canadian case control study of Pap smears
- 19,692 abnormal results matched to 57,898 controls
- Does not appear to be a difference in ulcerative colitis
- Risk is ↑ 66% in Crohn's disease when on OCP
- Risk is ↑ 40% when on steroids & immunosuppressants

Conclusion: It is the immune suppression and not IBD that increases the risk for abnormal Pap smears

HPV Vaccines

- Gardasil currently approved for 9-26 years
 - Covers HPV 6,11,16,18
 - Data submitted to FDA for 27-45
- Cervarix
 - Covers serotypes 16,18
 - FDA panel approval for ages 10-25
 - Different formulation



Significance of NOD2

- One copy of mutated gene
 - 1.5- to 4-fold risk
- Two copies: 15- to 40-fold risk
 - 10% of CD patients carry two copies
 - 28% of CD patients carry one copy
 - Actual disease presence with one or two gene copies is less than 10%

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Intimacy and Sexuality

- All relationships are complex
 - IBD adds an additional layer
- Sharing information can relieve stress and anxiety related to holding back and dealing with it alone
 - May be more difficult for new relationships rather than established relationships
 - Who to tell, what to tell, how much to tell
 - IBD affects both partners

Sexuality

- IBD has both direct and indirect effects
- Direct effects
 - Fatigue, diarrhea, abdominal pain
 - Amenorrhea, low libido
 - Surgery related complications
- Indirect effects
 - Depression, altered body image
 - Fear of incontinence

Summary

- Women *are* different from men
- Smoking is BAD
- Menstrual cycle can affect disease course
- Oral contraceptives not likely high risk
- IBD does not affect menopause
- Discuss HPV infection with your physician

Disclosure of Conflicts of Interests

Uma Mahadevan-Velayos, MD

Dr. Uma Mahadevan-Velayos has an affiliation with Centocor, Abbott, UCB, Elan, Biogen, Shire, and Takeda (*Consultant*); Abbott (*Research*).

Today's Goals

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Health Care Maintenance

- Vaccinations
 - No live virus vaccines while on biologics or during pregnancy (MMR, varicella)
 - Hepatitis A, B, flu shot
- Cancer screening
 - Colonoscopy
 - Pap smear
 - Skin
- Laboratory tests
 - Vitamin B12, folate, 25-OH vitamin D, iron, liver, hematocrit



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Before Pregnancy

- Disease under good control
 - 33% chance of flare during pregnancy
- Healthcare maintenance up to date
- Identification of a high-risk obstetrician
- Counseling regarding use of IBD medications during pregnancy and breastfeeding



Common Questions

- Inheritance
- Fertility
- Pregnancy outcomes
- Safety of medications
- Management of flares



Solutions

- Communication with a trustworthy and safe partner
- Getting disease under control
- Sharing your symptoms with your doctor
- Seeking counseling to help with coping with disease

Will My Child Get IBD?

- Increased risk of CD and UC in offspring of patients with IBD¹
 - 5% if one parent has CD
 - 1.6% if one parent has UC
 - Familial CD has earlier onset than sporadic cases at an average age of 22 years vs. 27 years respectively³
- If both parents have IBD, a child's risk is as high as 35% for developing IBD²
- Inheritance is multifactorial with a role for as yet undefined environmental triggers so pregnancy should not be discouraged for this reason

1. Orholm M. *Am J Gastroenterol.* 1999;94(11):3236-3238.

2. Bennett RA. *Gastroenterology.* 1991;100(6):1638-1643.

3. Polito JM. *Gastroenterology.* 1996;111(3):580-586.

What Are My Chances of Getting Pregnant?

- With both UC and CD, the risk of fertility prior to surgery appears to be similar to the general population
 - For a man or woman with IBD, the chance of conceiving is the same as anyone else their age
- Fertility after surgery for an ileoanal J pouch for ulcerative colitis can drop by 40%–80%

How Will I Do During Pregnancy?

Retrospective cohort study Kaiser Northern California

N=461 IBD, 493 control

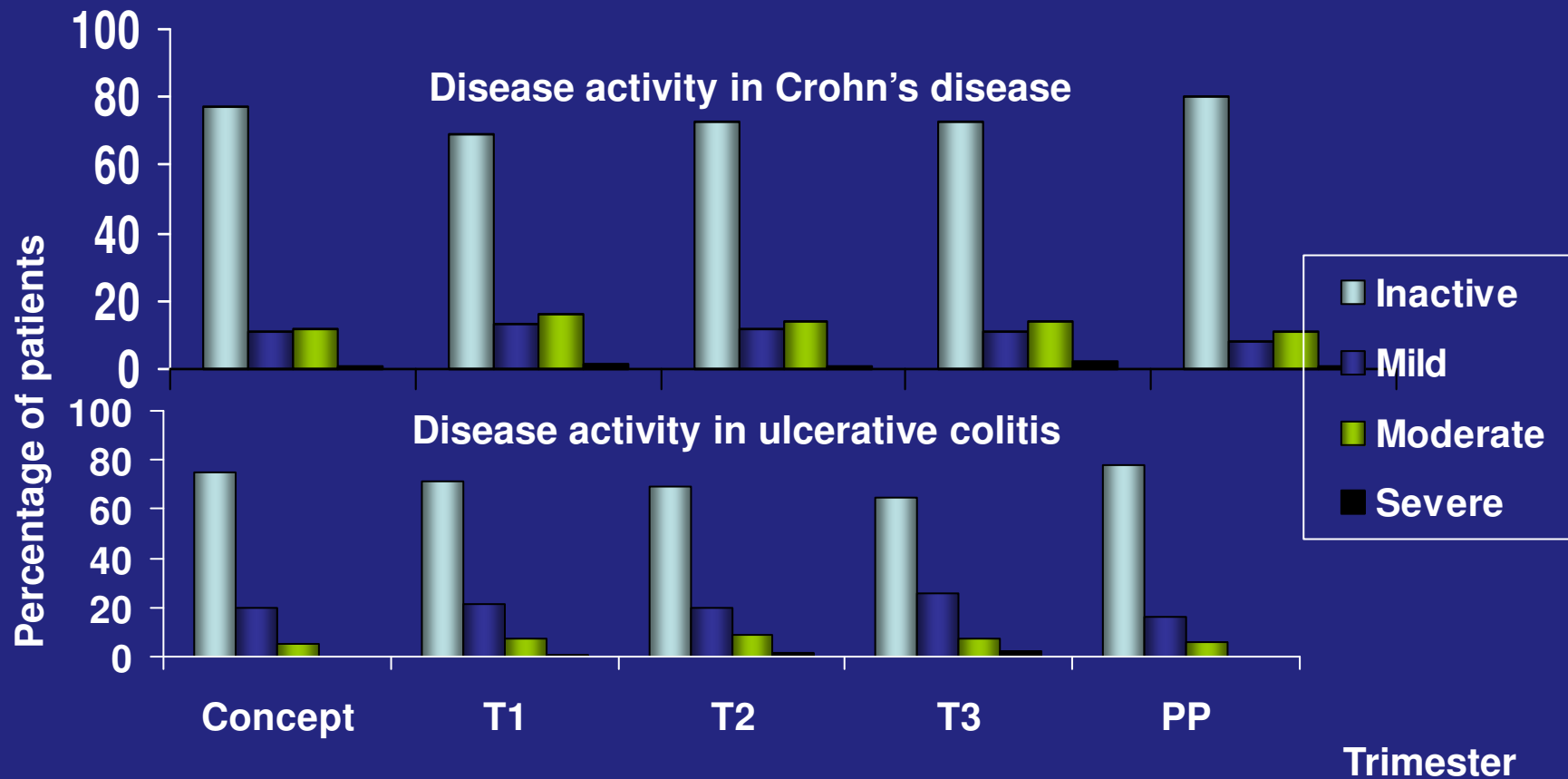
5-ASA (51%), corticosteroids (21%), immunosuppressants (4%)

Adverse Outcomes	OR*	95% CI
Conception (miscarriage)	1.65	1.09–2.48
LBW, stillbirth, preterm birth	1.54	1.00–2.38
Complicated labor + delivery	1.78	1.13–2.81
Newborn outcomes	1.89	0.98–3.69

*Controlled for maternal age, current ETOH, current tobacco, Caucasian ethnicity, number of prenatal visits (except conception)

Disease Activity During Pregnancy in Women With IBD

- Most patients are in remission during pregnancy. Even with remission, risk of adverse outcomes are higher.
- Risk of flare during pregnancy is 33%



Medical Therapy: FDA Pregnancy Category

Category	Description
A	Controlled studies show no risk
B	No evidence of risk in humans
C	<ul style="list-style-type: none">• Animal reproduction studies show adverse effects• No adequate studies in humans• Benefits in pregnant women may be acceptable despite potential risk
D	Positive evidence of risk
X	Contraindicated in pregnancy

Fish Oil

- Essential fatty acids (EFA) and docosahexaenoic acid (DHA)
 - Potential antithrombotic effect
 - Prolong gestation
 - No evidence of prevention of proteinuric pregnancy
- ? benefit in Crohn's disease

Safety of Medications

Drug	FDA	Birth Defects	Lactation	Notes
Mesalamine	B	Low risk	Compatible	Rare diarrhea
Sulfasalazine	B	Low risk	Compatible	Folic Acid 2 mg daily
Corticosteroids	C	Low risk- T1 cleft palate	Compatible	Gestational DM
Budesonide	C	Low Risk	Compatible	Little data
Metronidazole	B	Low risk- T1 cleft palate	Not advised	Short term use
Ciprofloxacin	C	Not advised – bone	Maybe compatible	Avoid use
Augmentin	B	Low risk	Compatible	Good alternative

Safety of Medications

Drug	FDA	Birth Defects	Lactation	Notes
Azathioprine/6M P	D	Low risk	Compatible	Hold BF for 4 hours
Methotrexate	X	High risk	Not advised	Stop 3-6 mos. prior
Infliximab	B	Low risk	Compatible	Hold in T3
Adalimumab	B	Low risk	Compatible	Hold in T3
Certolizumab	B	Low risk	Compatible	continue
Natalizumab	C	Low risk	Likely compatible	

Medications to Avoid

Drug	Pregnancy Category	Notes
Diphenoxylate	C	Teratogenic in animals
Loperamide	B	Increase in CV defects in 1 study
Bisphosphonates	C	<ul style="list-style-type: none">• Animal studies: alendronate crosses placenta• 24 pregnancies, no increased teratogenic risk¹
Methotrexate	X	<ul style="list-style-type: none">• Known abortifacient• Teratogenic (skeletal defects; cleft palate)
Thalidomide	X	<ul style="list-style-type: none">• Birth defects

6MP/Azathioprine (D) and Teratogenicity

- 189 pregnant women on AZA contacted 1 of 7 teratogen information services vs. 230 pregnant women who took non-teratogenic treatments¹
 - Rate major malformations 3.5 % vs. 3.0% ($P=.775$)
- Swedish Medical Birth Register²
 - 476 women used AZA in early pregnancy
 - Most common indication was IBD (>300)
 - Rate of CA 6.2% AZA vs. 4.7% other
 - OR 1.41, 95% CI: 0.98-2.04
 - Increased rate of VSD/ASD
 - OR 3.18, 95% CI: 1.45–6.04

1. Goldstein. *Birth Defects Res A Clin Mol Teratol*. 2007;79:696-701.

2. Cleary. *Birth Defects Research*. 2009;85:647-654.

Breastfeeding on AZA/6MP

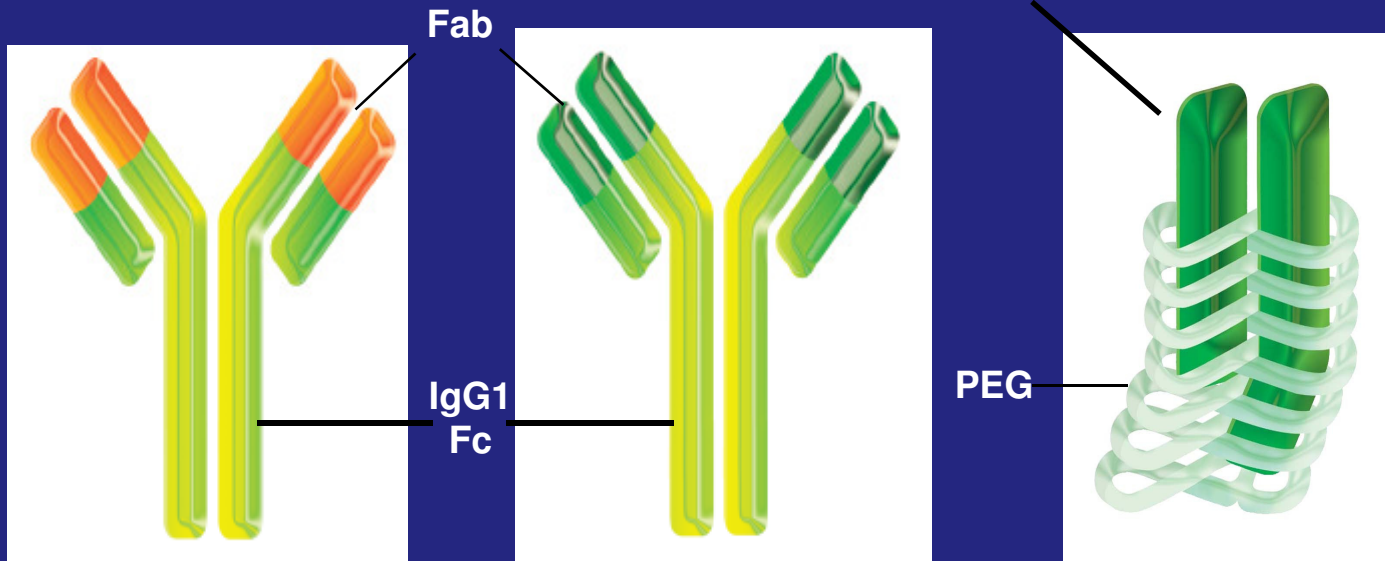
- 8 lactating women received AZA 75-200 QD
 - Milk and plasma at 30, 60 min and every hour × 5
- Variation in bioavailability reflected in wide range in milk and plasma first 3 hours
- Major excretion in breast milk within 4 hours of drug intake
- Worst case scenario: max concentration 0.0075 mg/kg
 - In most cases, will be <10% of maximum concentration

Biologics (B)

Infliximab

Adalimumab

Certolizumab
pegol



Chimeric

Human

PEGylated
humanized
Fab' fragment
2 × 20 kDa
PEG

Monoclonal
antibody

PIANO: Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes

- Patients classified by exposure to four groups of drugs taken b/w conception and delivery:
(413 patients)
 - Unexposed: no immunomodulators/biologics
 - Mesalamine, steroids, antibiotics allowed
 - Group A: AZA/6MP
 - +/- Unexposed medications
 - Group B: INF, ADA, CZP
 - +/- Unexposed medications
 - Group AB: Combination therapy
 - +/- Unexposed medications

PIANO: Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes

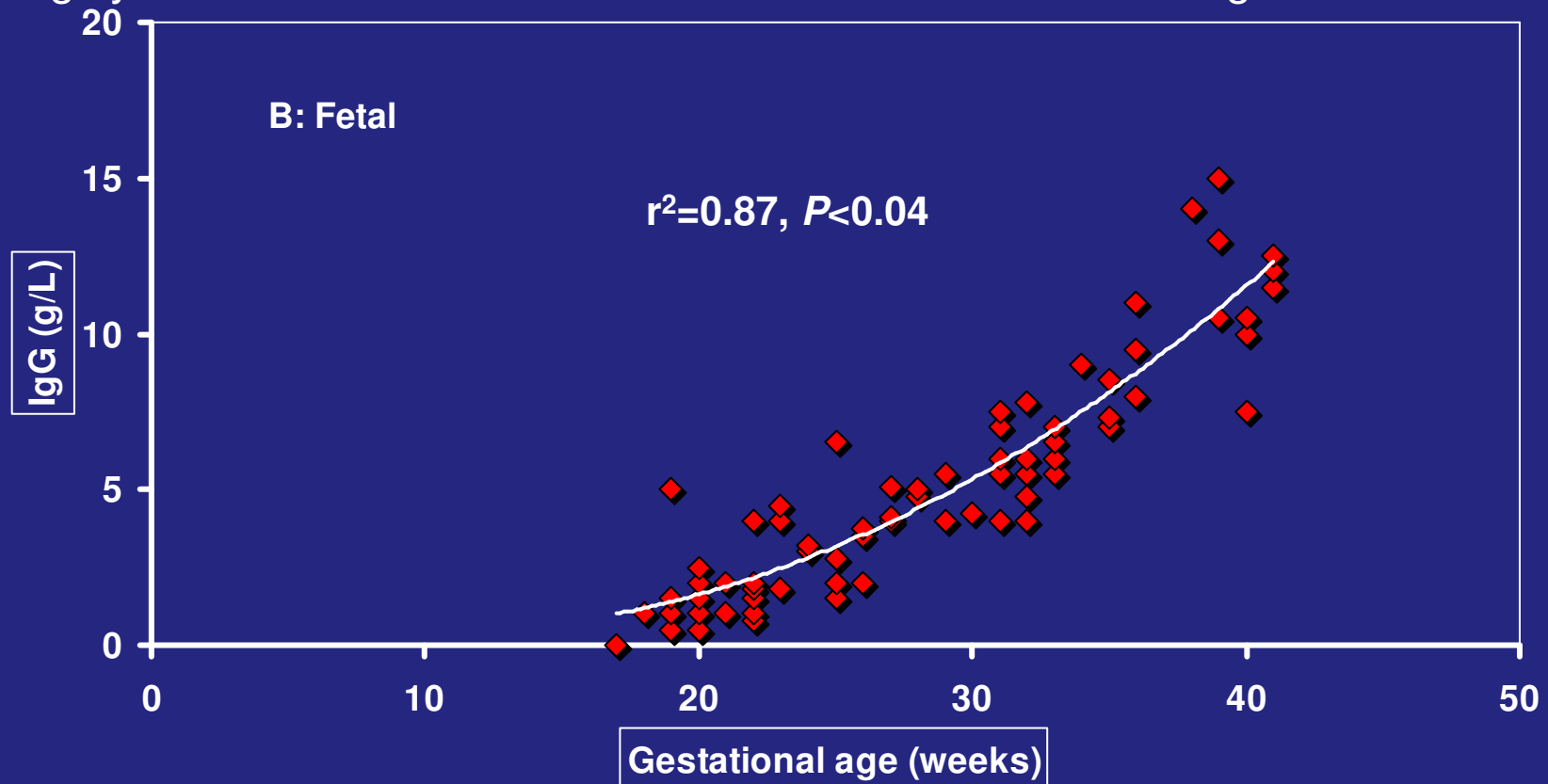
- 413 patients divided into 4 groups:
 - No imm, AZA/6mp, biologic, combination
- Medication use not associated with increased risk of:
 - Any complication
 - Preterm birth, low birth weight
 - Cesarean section
 - Congenital anomalies: 17 anomalies/15 births
- Biologic exp: increased risk of NICU stay
- Combination exp: increased risk of infection at 1 year of age

Join registry: www.ccfa.org/trials

Search: PIANO

Placental Transfer of IgG Ab

- INF and ADA are IgG1 antibodies
- Fc portion of IgG actively transported across placenta by specific neonatal FcR
- Highly efficient transfer in 3rd T leads to elevated levels of drug in newborn



Wiley-Blackwell Publishing Ltd. Malek A, Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol.* 1996;36(5):248-255.

Image Courtesy of Sunanda Kane, MD.

Placental Transfer

- Infliximab crosses placenta at high rate in T3
 - Adalimumab assumed to be same
- Certolizumab with no to minimal transfer
- Current expert recommendation
 - Discontinue infliximab at week 30
 - Discontinue adalimumab at week 30-34
 - Continue certolizumab throughout
 - If mom flares, treat her!
- Breastfeeding compatible
- No *live virus* vaccine to infant if INF/ADA *in utero*
 - Babies have normal response to standard vaccines in first 6 months

Delivery

- Delivery is at the discretion of the obstetrician
- Only considerations for Cesarean section specific to IBD
 - Active perianal disease at the time of delivery
 - Ileoanal J pouch

Management of Flares

- Medication choices are similar
 - Avoid new AZA/6mp in pregnancy
 - Avoid mnzl, steroids in T1
- Imaging
 - MRI preferred to CT, though no gadolinium in T1
- Endoscopy
 - Unsedated flexible sigmoidoscopy
- Surgery
 - Indications similar to non-pregnant patient
 - T2 best time to operate

Synopsis

- Chances of getting pregnant similar to the general population
- Small risk of passing on IBD to offspring
- Increased risk of adverse outcomes during pregnancy (though the majority of moms have healthy babies)
- Most medications compatible with use in pregnancy and breastfeeding
- Recommendations:
 - Control disease prior to conception
 - Continue most medications
 - Multidisciplinary approach: high-risk obstetrician, pediatrician, surgeon if needed

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- **Focus on living while managing IBD**

Focus on Living While Managing IBD

- Make a life plan: education, family, friends, hobbies
- Educate yourself on your disease
- Maintain communication with your GI & your GYN
 - Stay up to date on doctor visits
- Create a support system
 - Family members, friends, IBD community
 - IBD support groups
 - Online
 - In person
 - Accept support from others
 - Offer support when you can

Focus on Living While Managing IBD

- Stress is inevitable and can exacerbate symptoms
 - Minimize stressful situations
 - Find outlets to help yourself deal with & work through stress
- Combating pain
 - Chart your pain and symptoms
 - Communicate with your doctor
 - Work with pain management team
- Combating exhaustion
 - Maintain a balanced diet
 - Manipulate your schedule to get enough sleep for your body
 - Build your support system, ask for help when you need it

Questions & Answers

Program Evaluation

www.RMEI.com/CCFAevaluation

CNE Credit (for nurses only)

Please complete the evaluation form online
at www.cmeuniversity.com.

Click on “Find Post-Test/Evaluation by Course”
on the navigation menu, and search by
project ID 7342. Upon successfully completing
the evaluation, your certificate will be made
available immediately.

Please print your certificate for your records.