Background:

- Peak Incidence in both men and women is between 20 and 35 years of age.
- Crohn’s Incidence is 10.7/100,000.
- Ulcerative Colitis is 12.2/100,000.
- Women with IBD have higher rates of voluntary childlessness and have fewer children than the general population which evolves from misinformation regarding fertility, safety of medications, and heritability of the disease.

Preconception Visit:

Fertility:

- Rates of fertility among those with inactive IBD are similar to the general population, however, specific subgroups can have impaired fertility:
  - **Crohn’s Disease** – decreases fertility both directly, by inducing inflammation in the fallopian tubes and ovaries, and indirectly, through surgical interventions and tubal adhesions.
    - AMH levels in patients were significantly lower than age and BMI matched controls and a higher crohn’s disease activity index was correlated with a lower AMH (which is a measure of disease activity).
  - **Ulcerative Colitis** – Proctocolectomy with ileal pouch-anal anastomosis (IPAA) can severely reduce female fecundity likely due to the location of surgery (near the pelvic floor) and formation of post-op adhesions. In a study of 21 women who underwent IPAA for UC, postop HSG produced normal findings in only 7 patients. Laparoscopic vs open procedures are associated with reduced rates of infertility.
    - After IVF, these patients have similar rates of live births as those without IBD or IPAA.
    - Subtotal colectomy with ileorectal anastomosis does not appear to reduce fertility as the procedure does not invade the pelvis.
- Those with active disease have increased rates of infertility due to inflammation of fallopian tubes and ovaries, dyspareunia resulting from perianal disease, decreased libido, or depression.

**IBD appropriate cancer screening:**

- Colonoscopy with endoscopy (for Crohn’s) with multiple biopsies every 1-2 years after 8 years of diagnosis.
- Sooner if comorbid primary sclerosing cholangitis or a family history of colon cancer.

**Baseline Labs:**

- CBC, Vitamin B12, Folic Acid, Iron, and Vitamin D.
- Women on low residue diets (low fiber), have ileal involvement, and are taking sulfasalazine should be on at least 2 mg of folic acid daily.
Women who are having difficulty conceiving or have previous miscarriages should be screened for Vitamin D deficiency and potentially celiac disease, especially in the presence of gastrointestinal symptoms.

As Vitamin D has been shown to be involved with implantation, one study showed women whose levels \( \leq 20 \text{ ng/mL} \) had decreased clinical pregnancy rates (20\% vs 31\%) and decreased implantation rates (13\% vs 21\%).

One study showed the rate of celiac disease in infertile women to be 2.1\%.

However, in women who had a negative fertility workup, as many as 5.9\% had celiac disease.

**Preconception counseling:**

- Clinical remission, defined as normal bowel movements without bleeding or abdominal pain, should be achieved for at least 6 months prior to attempting conception.
- Active disease is characterized by diarrhea, bleeding, abdominal pain, weight loss, as well as increased CRP/ESR, anemia, and inflammation on colonoscopy.
- Active disease is associated with decreased ability to conceive, greater risk of flare during pregnancy, and increased risk of adverse pregnancy outcomes.
- Appropriate and effective contraceptive use should be discussed to avoid unintended pregnancy or conception during active disease.
- Women with IBD use contraception at a lower rate due to lack of education as well as active disease leading to surgery or immunosuppressive therapy.

A medication plan should be discussed, as women have the greatest risk of flares after discontinuing medications:

- Methotrexate should be discontinued at least 3-6 months prior to attempting contraception (including the FOB).
- Sulfasalazine and Methotrexate can cause reversible oligospermia that resolves with discontinuation of use (men should also use contraception for at least 4 months after stopping methotrexate).
- Preconception counseling and education regarding the low risk of most medications used to treat IBD and the high risk of significant flare during pregnancy are important in improving compliance and relieving anxiety during pregnancy.

Any IBD patient, who has not successfully conceived after 6 months of effort, can be offered a consult with REI.

The risk of passing on IBD to offspring is between 4-8 \% and up to 30\% if both parents suffer from IBD and may present with an earlier onset and more severe disease.

**Pregnancy:**

- The risk of flare, for most, during pregnancy is the same as the non-pregnant IBD patient with exceptions:
  - With ulcerative colitis, among women with active disease at conception: 45\% will have a worsening flare, 24\% will have stable disease, and 25\% will improve.
  - With Crohn’s disease, among women with active disease at conception: 33\% will have a worsening flare, 33\% will have stable disease, and 33\% will improve.
- Women with ulcerative colitis tend to have higher rates of disease activity due to placental secretion of proinflammatory cytokines; they are also often undertreated during pregnancy.
- Relapses are more common during the first trimester.

- Women with IBD are at increased risk of complications, which include miscarriage, stillbirth, preterm birth, and small-for-gestational age neonates. This is secondary to inflammation leading to an overactive immune system coupled with the environmental and physiologic conditions that tip the scale in favor of preterm birth:
  - **Immune system:** A pathogen can lead to activation of both the innate (leukocytes → phagocytosis) and adaptive (B cells and T cells) immune system which ultimately leads to inflammation.
  - **Inflammation:** In normal pregnancy, proinflammatory cytokines dominate in the 1st and 3rd trimester, while anti-inflammatory cytokines dominate in the 2nd trimester. When defects in this process occur, they can result in preterm birth. Inflammation in IBD is secondary to both pathogens and damaged cells. This process becomes prolonged and chronic. Gram negative bacteria activate pro-inflammatory cytokines and COX-2 gene which leads to secrete of prostaglandins (PGE2=cervidil).
  - **Prostaglandins:** levels of prostaglandins rise prior to parturition and levels of PGE2 are elevated in patients with IBD, mounting the adaptive immunity response and perpetuating the inflammatory cascade.
  - **Malnutrition:** Inadequate weight gain during pregnancy can contribute to the risk of SGA in neonates.

- Flares are usually treated with corticosteroids, rectal 5-ASA or bowel surgery. The highest risk for preterm birth and SGA are among those with flaring disease and those treated with thiopurines. SGA is more common if the flare is later in the pregnancy.
- Stillbirth is an uncommon, but possible, complication of Crohn’s disease.
- Neonatal hypoglycemia is a common complication likely secondary to prematurity, SGA, or maternal corticosteroids.

**Antenatal surveillance:**

- Serial growth scans after 20 weeks should be considered, especially with active disease, women have inadequate weight gain, and women managed with steroids.
- Gastroenterologist with/without MFM should be involved during the pregnancy.

**Medications during pregnancy and lactation:**

- Many women do not breastfeed due to misconceived notions about the safety of medications with lactation.
  - **Antibiotics:** Metronidazole should be limited to short courses with avoidance during the first trimester due to potential association with cleft lip/cleft palate, breastfeeding is not recommended, but if needed, women can discard milk 12-24 hours after the dose. Ciprofloxacin is not recommended due to its affect on growing cartilage, however is compatible with breast feeding. Augmentin is the preferred antibiotic, both safe in pregnancy and compatible with breastfeeding.
  - **Corticosteroids:** Prednisone and budesonide are most commonly used. Some reported adverse outcomes with use include orofacial clefts in the 1st trimester (although absolute risk is 0.2-0.4%), LBW infants,
gestational diabetes, preterm birth from PPROM (due to stimulation of fetal cortisol \(\rightarrow\) increased prostaglandins), exacerbated PIH, fetal adrenal insufficiency (usually with long-term administration of high doses) and infant infections within the first 4 months of life. However, studies have been conflicting and a small case series showed no adverse pregnancy outcomes or congenital anomalies with budesonide. Steroids should be used minimally in the first trimester and at the lowest possible dose for as short a duration as possible. Both are compatible with breastfeeding.

- **Aminosalicylates**: Sulfasalazine and mesalamine (5-ASA, nonenteric coated) are considered safe for pregnancy and lactation. They are anti-inflammatory agents which inhibit TNF and leukotrienes. Patients on sulfasalazine should be on 2 mg of folate. Possible infant side effect is diarrhea.

- **Thiopurines**: 6-Mercaptopurine (6-MP) and azathioprine have shown teratogenicity in animals with no replicable pattern of defects in humans. They are purine antagonists which inhibit DNA/RNA synthesis and act as immunosuppressant’s. Can be associated with preterm birth and SGA. Compatible with breastfeeding, however women can be advised to wait 4 hours after taking the medication before breastfeeding.

- **Cyclosporine**: Used for severe steroid refractory ulcerative colitis and should be used at the lowest possible dose. It inhibits calcineurin and subsequently, IL-2 and activation of T cells, acting as an immunosuppressant. It has been associated with preterm birth and SGA. Breastfeeding is contraindicating while taking cyclosporine.

- **Anti-Tumor Necrosis Factor Agents**: Act as immunosuppressant’s. Studies have revealed they are safe enough to use during pregnancy, but there is insufficient information to make any firm conclusions. Can be detected in infants for up to 6 months after delivery. Majority of transfer to placenta occurs in the 3rd trimester. Certolizumab (cinzia) does not cross the placenta and therefore can be safely continued throughout pregnancy. Infliximab (remicade), adalimumab (humira) and golimumab are usually stopped in the 3rd trimester around 30-32 weeks if mom has stable, inactive disease. Can always be resumed for flares. It is resumed 24 hours after vaginal delivery and 48 hours after cesarean delivery if there is no infection or complication. No increased risk of adverse pregnancy complications or birth defects, however infants can be prone to infection up to 12 months of age, and should not receive a live vaccine in the first 6 months of life (i.e. Rotavirus). Compatible with breastfeeding.

- **Antidiarrheal drugs**: Kaopectate and Metamucil are usually recommended.

### Imaging during Pregnancy:

- MRI should be the diagnostic imaging modality of choice and gadolinium should be avoided in the first trimester (can be used if benefits > risks if used at a low dose such as 0.3 mmol/kg/day).

### Surgery during Pregnancy:

- Non-emergent surgeries should be performed during the second trimester, including endoscopy.
- Flexible sigmoidoscopy can be safely completed in any trimester and a full colonoscopy should be performed with anesthesia and fetal monitoring if necessary.
- Women are at risk for severe bleeding, medically refractory disease, perforation, and obstruction which may require emergent surgery.
Delivery:

- Women with IBD have a 1.5-2 fold increase in the rate of cesarean delivery, up to 44%. This is primarily for elective reasons (fear of complications such as perineal trauma, anal sphincter damage, worsening perianal disease, or ileal pouch dysfunction).
- Active perianal disease is the only gastrointestinal contraindication to a vaginal delivery, patients with rectal disease in Crohn’s may prefer cesarean delivery.
- Vaginal delivery does not interfere with pouch function or increase risk of ostomy complications.
- Stress dose steroids may be needed if flares are treated with corticosteroids.

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