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Fertility and Pregnancy in Inflammatory Bowel Diseases (IBD)
Fact Sheet for Advanced Practice Providers

Millions of people in the United States suffer from IBD, many of whom are diagnosed during their reproductive years. It is our responsibility as clinicians to educate our patients on fertility and pregnancy along with our OB/GYN colleagues. Prepregnancy counseling with a maternal fetal medicine expert is highly recommended.

The facts below can be shared with your female and male patients during your conversation.

Common IBD Medications, Fertility, and Pregnancy for Men and Women:

- **5-ASA's/Aminosalicylic Acids:**
    - Women: Most do not affect fertility and are considered safe during pregnancy.
        - Olsalazine, however, has been shown to cause teratogenic effects on mice and rat studies (Mahadaven, 2006).
        - Sulfasalazine crosses the placenta, but no teratogenicity is noted. It is, however, recommended to increase folic acid intake to 2 mg/kg to decrease the risk of neural tube defects while on sulfasalazine (Damas et al., June 2015).
    - Men: Sulfasalazine can cause reversible decrease in sperm motility and sperm count (Janneke van der Woude, C. Journal of Crohn's and Colitis Foundation, Nov 2010). A small study of men taking sulfasalazine for their IBD showed that 86% had abnormal semen analysis, and 72% had oligospermia (Birnie et al., 1981).
- **Corticosteroids:**
    - Women: While prior studies showed an association with cleft palate, subsequent retrospective data of IBD female patients that received corticosteroids during the first trimester had a similar risk of developing congenital abnormalities as IBD women who were not exposed to steroids (Damas, 2015).
    - Men: Definite conclusions regarding the effects of corticosteroids on male fertility cannot be drawn at present because of insufficient data. One study found a reversible reduction in fertility in rats exposed to corticosteroids despite no changes in sperm count and motility. In a study of 70 men with CD and a group of age-matched controls, no correlation between male infertility and steroid use was found. In a study of IBD patients undergoing azathioprine (AZA) treatment, the additional administration of corticosteroids had no negative influence on seminogram (Shin & Okada, 2016).
- **Thiopurines**:
    - Women: In a meta-analysis of 3045 females with IBD, exposure was associated with preterm birth, but not congenital abnormalities or low birth weight (Akvari et al., 2013).
    - Men: Azathioprine and 6-MP do not reduce semen quality (Mahadaven, 2006).
- **Methotrexate**:

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- Women: Known teratogen must be avoided during pregnancy. Women should be counseled to stop methotrexate at least 3- 6 months prior to conception (Cao & Grimm, 2021).
- Men: A transient effect on sperm quality with low dose methotrexate has been reported, while many case studies do not confirm deleterious effects on pregnancy outcomes. The risk of direct toxic effect on the fetus through MTX exposed seminal plasma is negligible (Grosen et al., 2017). Most literature recommends stopping methotrexate 3 – 4 months prior to conception (Shin & Okada, 2016 and Levy et al., 2016).

- **Anti-TNF:**
  - Women: Safe during pregnancy and breastfeeding (Mahadaven, 2006). Certolizumab does not cross the placenta, as it does not contain the Fc portion of the antibody (Hashash and Kane, 2015) and may be an option for women who are concerned. However, safety has been documented with use of these medications and should not be changed during pregnancy.
  - Men: Exposure to anti-TNF therapy in men before a planned conception does not seem to cause embryo toxicity (Shin & Okada, 2016).
- **Anti-Integrin:**
  - Women: In a literature review of pregnancy outcomes in women on vedolizumab and neonatal outcomes in newborns of females with prior VDZ exposure, 284 pregnancies of women treated with VDZ and 213 pregnancy outcomes were identified. No studies provided evidence of safety concerns with VDZ. Reports of pregnancy and neonatal outcomes were in line with expected numbers in the IBD population (Terjung et al., 2020).
- **Anti IL12/23**:
  - Women: The effect of ustekinumab on human fertility has not been studied. However, no adverse effects on female fertility parameters were identified in a female fertility toxicity study done on mice (Jannsen Research & Development LLC, 2020). Five combined clinical trials of ustekinumab for UC and CD showed that in 39 patients who became pregnant, there was no reported increased risk of negative outcomes (Abraham at el., 2022).
  - Men: Lack of available data
- **P19 subunit inhibitor of IL-23 (Risankizumab):**
  - Women: Lack of available data
  - Men: Lack of available data
- **Pan Janus Kinase (Jak) Inhibitor (Tofacitinib):**
  - Women: Data is limited, however, a study by Mahadevan et al. (2018) indicated pregnancy and newborn outcomes among patients with both maternal and paternal exposure in UC studies appeared to be similar to those reported by other patients on tofacitinib in the general population. However, due to limited data, this medication is contraindicated in pregnancy (Mahadevan et al., 2020).
  - Men: Lack of data available

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- **Jak-1 Inhibitor (Upadacitinib):**
    - Women: Lack of available data
    - Men: Lack of data available
- **Shingosine-1-Phosphate Inhibitor (Ozanimod):**
    - Women: A published abstract reported on pregnancy outcomes for 83 patients with UC, Crohn's disease, or relapsing MS with exposure during the first trimester. Data indicated that the rate of spontaneous abortion and pre-term birth matched that of the general population (Dubinsky et al., 2021). No teratogenicity was noted. However, the current recommendation is to avoid use during pregnancy.
    - Men: Lack of data available

Genetics and IBD:

- Children of parents with IBD are 2 – 13 times more likely to develop IBD compared to the general population (Habal and Huang, 2012).
- Hereditary risk: If one parent has IBD, there is an 8 - 11% risk of the offspring developing IBD. If both parents have the disease, the risk is between 20 – 35% (Habal and Huang, 2012).
- The rate at which patients with Crohn's disease report a family history of CD varies from 2 - 14%, and any type of IBD from 5 - 16% (Halme et al., 2006).
- Patients with ulcerative colitis possess a family history of UC from 7 - 11%, and any type of IBD from 8 - 14% (Halme et al., 2006).

Contraception and IBD:

- Patients with IBD have a -two-fold increased risk for VTE and PE (Martin et al., 2016). Patients should consult with their OB/GYN about the risk/benefit ratio of combined contraceptives, as well as non-hormonal and progestin-only based options.
- Oral medications should be considered and discussed as they may be less efficacious than expected, due to malabsorption in select patients with severe disease (Martin et al., 2016). The majority of absorption of OCPs occurs in the small bowel so patients with CD who have significant small intestinal inflammation or resection may experience malabsorption and reduced efficacy. There are no studies on patients with CD, however, data from patients with jejunoileal bypass supports this notion (Martin et al., 2016).
- Depot medroxyprogesterone acetate (DMPA) is the most popular injectable contraceptive in the United States, however, DMPA was associated with bone density loss in a systematic review. Many IBD patients are at risk of bone health issues. The Centers for Disease Control and Prevention (CDC) suggests that the benefits of DMPA may outweigh the risks in women with IBD (Martin et al., 2016).
- Long-acting reversible contraceptives, such as copper or levonorgestrel IUDs or etonogestrel implants, are highly effective forms of contraception that, with typical use, have efficacy rates similar to those of sterilization procedures. In a 1-year period, less than 1% of women will have an unintended pregnancy with typical use. The CDC recommends these forms of contraception in women with IBD without restriction (Martin et al., 2016).

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Factors affecting Fertility and Pregnancy in IBD:

- Evidence suggests that women with IBD have a near normal ability to conceive, yet choose not to have children 2-3 times more often than their peers (Marri et al., 2007).
- IBD is often diagnosed in women of childbearing age, with about 50% diagnosed under age 30, and 25% having their first pregnancy after diagnosis (Beaulieu and Kane, 2015).
- Fertility rates in women with quiescent IBD and no prior pelvic surgery have similar infertility rates to the general population, ranging between 5 and 14% (Ananthakrishnan, 2017; McConnell & Mahadevan, 2016; Tavernier et al., 2013).
- Women with active IBD have decreased fertility. It was found that women had decreased fertility in a 9-month period after a flare, compared to women who did not flare. Similar patterns were found when examining women with CD and UC separately (Ban et al., 2015).
- Disease activity at time of conception can impact pregnancy. It can be associated with preterm birth, low birth weight, and fetal loss. When disease is active at the time of conception, we follow "the rule of thirds." One third of women will get better, one third will stay the same, and one third will worsen (Beaulieu & Kane, 2011).
- Women should be in clinical and endoscopic remission at least 6 months prior to conception, as patients with quiescent IBD are as fertile as the general population (Van der Woude, 2010).
- Theoretically, surgical interventions that spare deep pelvic dissections, such as ileorectal anastomosis or subtotal colectomy with rectal stump and temporary ileostomy, may reduce the risk of infertility (Scoglio, Ahmed & Fichera, 2014).
- Women who undergo a proctocolectomy with ileostomy or creation of an IPAA experience a reduction in fecundity (Martin, Kane, and Feagins, 2016). According to the literature, there is a 3-fold increased risk for infertility in patients with an IPAA: 15 - 48% in women post-IPAA (Waljee et al., 2006).
- Fecundity rates are more compromised in women who undergo open IPAA compared to laparoscopic IPAA (Hashash and Kane, 2015). A small survey suggests that 70% of patients who underwent laparoscopic IPAA were fertile postoperatively, compared to 39% who underwent an open procedure (Bartels et al., 2012).
- Among women after IPAA, dyspareunia affected 8% early and 11% late postoperative, and fecal leakage during intercourse affected 3% of women (Farouk et al., 2000).
- With pelvic dissection, adhesions may form in female patients, affecting fallopian tube patency. For this reason, if female patients have not completed their family, it is recommended that they avoid dissection until later in life (Hashash and Kane, 2015). Other options include subtotal colectomy with end-ileostomy, with Hartman's pouch or In Vitro Fertilization.
- A study of 49 patients with Crohn's disease and 71 with ulcerative colitis indicated that infertile women with IBD achieve rates of live births after IVF that are comparable to infertile women without IBD (Oza et. al., 2015).
- In vitro fertilization is a common, safe, and successful method to achieve pregnancy even in women with UC who have had prior surgery (Pabby et al., 2015).

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Fertility In Men

- Proctocolectomy with IPAA in men may be associated with sexual dysfunction, erectile dysfunction, and retrograde ejaculation (Mahadevan, 2006). Erectile dysfunction and ejaculatory dysfunction can range from 0-26% (Allocca et al., 2018)
- Erectile dysfunction can occur in rates of up to 40% in men with IBD, compared to 15% in the general population of the same age (Perez de Arce et al., 2021).
- Ten years after an IPAA, retrograde or no ejaculation was reported by 3% of men (Farouk et. al., 2000).
- An 18 – 50% greater infertility rate has been reported in men with Crohn's Disease, compared to both men with ulcerative colitis and the general male population (Allocca et al., 2018).
- Disease activity has been reported to significantly impact libido, sexual activity, and sexual satisfaction. In a cross-sectional study of 280 men with IBD, sexual impairment was observed in 67% of IBD patients with active disease, compared with 21% of patients in remission (Allocca et al., 2018).

Mode of Delivery

- The overall incidence of cesarean delivery among women with Crohn's disease was similar to women without inflammatory bowel disease (Burke et al., 2017). However, patients with both active and inactive perianal Crohn's disease had a higher rate of C-section, with an increase found among subgroups with active and inactive perianal disease (Burke et al., 2017).
- A retrospective study of 369 women with IBD recorded cesarean delivery rates of 52% in CD patients and 48% in UC patients. The strongest predictor of C-section delivery was history of perianal disease and prior C-section. Of those that had a C-section with perianal disease, 42% had active perianal disease during pregnancy (Sharaf and Nguyen, 2018).
- In women with UC, the highest predictor of Cesarean delivery was a history of colectomy (Sharaf and Nguyen, 2018).
- Cesarean delivery increased the post-partum length of stay by 1.1 days on average for both CD and UC patients (Sharaf and Nguyen, 2018).
- The mode of delivery for IBD patients is complex and warrants multi-disciplinary collaboration between OB and GI teams.

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