Fertility, Pregnancy, and Lactation

24

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Abstract

Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal tract that affects men and women in their young and reproductive years of life. Anxieties about potentially harmful medication, the effect of pregnancy on disease, the effect of disease on the fetus, and the potential of passing on of disease to offspring result in a relatively high "voluntary" childlessness in young women with IBD. A careful consultation with the parents-to-be on these justified concerns is necessary and involves a proactive approach.

24.1 Introduction

In this chapter different aspects of reproduction and pregnancy in women with IBD will be discussed.

Since IBD affects men and women in their reproductive years of life, questions arise around fertility and the possible effect of IBD itself or medication. Furthermore, the effect of IBD on pregnancy and the use of medication during pregnancy and lactation are discussed in this chapter.

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24.2 Fertility in IBD Females

Learning Targets

- Women with quiescent IBD are as fertile as the general population.

Medication prescribed for the treatment of IBD is not associated with lower fertility rates in IBD females compared to the general population. It is known that if patients are in remission, the females are as fertile as the general population (Hudson et al. 1997); however fertility might be reduced in patients with:

- Active Crohn's disease
- Pelvic or abdominal surgery for IBD [e.g., ileal pouch-anal anastomosis (Cornish et al. 2007; Waljee et al. 2006; Rajaratnam et al. 2011)]

Reasons for this decreased fertility probably include induction of inflammation to the ovaries and fallopian tubes in active Crohn's disease and the occurrence of dyspareunia when there is active perianal disease (van der Woude et al. 2015). Further, surgical interventions for IBD may cause tubal adhesions. Patients who have an ileal pouch-anal anastomosis (IPAA), or pouch surgery, have higher rates of tubal obstruction, hydrosalpinx, and destruction of the fimbria, all of which can lower fertility. In the case of an IPAA, patients who underwent a laparoscopic intervention have a

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lower infertility rate than patients who underwent open surgery (Beyer-Berjot et al. 2013).

24.3 Preconception

Learning Targets

- Counseling of IBD patients with a pregnancy wish should focus on the importance of disease remission before conception.
- Preconception care leads to less disease relapse during pregnancy.
- Lifestyle advice is part of counseling (e.g., stop smoking, use of folic acid).

Timely preconception counseling in patients with an active pregnancy wish has been shown to result in less relapses during pregnancy. This is related to medication adherence during pregnancy (de Lima et al. 2016a).

In addition to emphasizing the importance of medication adherence, it is advised to discuss the following factors during preconception counseling:

- The importance of a sustained remission of, at least, 6 months prior to conception
- Risk-benefit of current meds and possible adjustments
- Lifestyle advice such as cessation of smoking, alcohol use, and supplementation of folic acid
- Information about the heredity of IBD
- The effect of medication on breastmilk
- And the mode of delivery as advised with regard to the disease location

Since disease activity increases the risk of relapse during pregnancy and negatively influences fertility, it is advised to strive for a (sustained) remission of approximately 6 months prior to conception (van der Woude et al. 2015; Nguyen et al. 2016). In the majority of patients, medication is needed to accomplish sustained remission, and appropriate treatment of IBD should be maintained to reduce the risk of disease activity during pregnancy. To increase the adherence and correct usage of IBD medication during pregnancy, personalized consultation is of great importance.

General lifestyle advice is also part of a preconceptional care and should include counseling about supplementation of folic acid, cessation of smoking, and alcohol use.

An additional serious concern for IBD patients is the risk of their offspring developing the disease. Children of parents with IBD have an increased risk of developing IBD. When one parent is affected with IBD, the overall risk for their children is 2–13 higher than the general population (Orholm et al. 1999). When both parents are affected, the risk becomes much higher, around 30% (Bennett et al. 1991).

Further, mode of delivery and breastfeeding should be discussed during counseling. Active perianal disease is an indication for a cesarean section. Overall mode of delivery is subject to a multidisciplinary approach and primarily decided by an obstetrician on individual basis.

24.4 Pregnancy

Learning Targets

- There is a higher risk of adverse pregnancy outcomes in case of disease activity during pregnancy.
- Most IBD medication can be used during pregnancy and outweighs the risks of a flare.

During pregnancy acute disease flares carry a high risk of adverse maternal and fetal outcome. Disease activity at time of conception and during pregnancy is associated with a higher rate of spontaneous abortion, preterm delivery, thromboembolic events, emergency cesarean section, and low birth weight. According to current European guidelines, appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy (van der Woude et al. 2015).

24.4.1 Medication

Below different IBD medications are discussed in further detail.

24.4.1.1 Aminosalicylates

Aminosalicylates are considered low-risk medication during pregnancy (Rahimi et al. 2008). However, sulfasalazine interferes with the resorption of folic acid which is important for women to take before and during the first 12 weeks of pregnancy. Therefore, it is advised to change to other IBD medication before pregnancy or increase the dose of folic acid to 2 mg/day (Norgard et al. 2001). Medication containing dibutyl phthalate coating should be avoided during pregnancy (van der Woude et al. 2015; Hernandez-Diaz et al. 2013). Animal studies showed an increased risk of malformation in the male urogenital tract and a possible association with precocious puberty (Hernandez-Diaz et al. 2013; Jurewicz and Hanke 2011).

24.4.1.2 Corticosteroids

Corticosteroids (CS) are used most often in the case of a disease relapse and can be used during pregnancy. CS cross the placenta, but the placenta is able to convert the medication into a less active metabolite by the enzyme 11-hydroxygenase. Studies show conflicting data regarding risk of malformations when mothers used corticosteroids during pregnancy. In one study the risk for orofacial malformations was increased in the children of mothers receiving corticosteroids in the first trimester (Carmichael et al. 2007; Park-Wyllie et al. 2000), but the risk was small and other studies did not report malformations (Lin et al. 2014; Ban et al. 2014; Hviid and Molgaard-Nielsen 2011). There are also no reports on adverse pregnancy outcomes due to budesonide (Beaulieu et al. 2009). Hydrocortisone, betamethasone, and dexamethasone should be avoided, since they are longer-acting medicine and less efficiently metabolized by the placenta.

There are reports of neonatal adrenal suppression when there is exposure to corticosteroids in utero (Homar et al. 2008). Therefore it is advised to consult a pediatrician who is able to examine the cortisol levels of the newborn.

The risk of maternal complications such as gestational diabetes and hypertension seems to be increased during pregnancy (Martel et al. 2005). Follow-up by a gynecologist/obstetrician is therefore necessary.

Overall the use of corticosteroids during pregnancy is of low risk, but risks and benefits should be considered when prescribing these medications.

24.4.1.3 Immunomodulators

Thiopurines are considered of low risk, and it is advised to continue these medications during pregnancy. Azathioprine and 6-mercaptopurine are converted into the active metabolite 6-TGN and 6-MMP. It was shown that 6-TGN crosses the placenta (de Boer et al. 2006). Recent studies reported no adverse pregnancy outcomes for children exposed to thiopurines in utero (Kanis et al. 2017; Casanova et al. 2013; Coelho et al. 2011; Shim et al. 2011). Limited data for 6-TG as a medicine is known; however it is transferred across the placenta.

Use of methotrexate (MTX) is prohibited. MTX is teratogenic and therefore contraindicated, at least, 6 months prior to conception and during pregnancy (Kozlowski et al. 1990). In the unfortunate case that MTX is not stopped before pregnancy, the drug needs to be stopped immediately, and high-dose folate should be started. Further counseling with an obstetrician to discuss therapeutic abortion should be considered.

24.4.1.4 Anti-TNF Agents

Most commonly prescribed biologicals are infliximab (IFX) and adalimumab (ADA). These two IgG1 antibodies cross the placenta in the second and third trimester of pregnancy (Kane and Acquah 2009). Although exposure to IFX or ADA does not seem to increase the risk of adverse pregnancy outcomes, the long-term effect on children who were exposed in utero remains unknown. Therefore, discontinuation of the treatment during pregnancy might be considered to limit this intrauterine exposure. If the disease is in sustained remission, it is possible to stop these agents around week 20 of pregnancy. Stopping anti-TNF therapy during second and third trimester does not increase the flare rate (de Lima et al. 2016b).

It is advised to measure cord blood levels. Anti-TNF cord blood levels are dependent on the stop

week of the anti-TNF. However, when anti-TNF is continued, the drugs levels of the infant will exceed the levels measured in the mothers (Zelinkova et al. 2011). These high levels of anti-TNF in the fetal blood do not seem to have an influence on the pregnancy outcome (Zelinkova et al. 2013). In the first year of life, there is also a normal growth and development of the children (Mahadevan et al. 2012). The achievement of milestones in children exposed to anti-TNF agents, thiopurines, or combination therapy was similar or better than the cohort who was not exposed to medication (Mahadevan and Sandler 2014). For monotherapy with anti-TNF, no increased infection rate in the infants has been reported. In the case of combination therapy with anti-TNF and thiopurine, there was a higher rate of infection in the infants (Mahadevan et al. 2012). It is recommended to follow up drug levels every 3 months, until drug levels are undetectable. When levels are still detectable, infants should be considered immune suppressed. Therefore administration of live vaccines should be avoided in the first 9 months of life, and it is advised to not bring the children to daycare until drug levels are acceptable.

Thalidomide use has been associated with fetal malformations and neonatal mortality rate of 40% (Smithells and Newman 1992). Therefore thalidomide is contraindicated during pregnancy.

Golimumab data on pregnancy outcomes are limited, but because of the similarity of the safety profile to other anti-TNF, it is considered of low risk.

Certolizumab pegol (CZP) is transferred across the placenta by passive diffusion. Due to this mode of action, the levels of CZP reaching the fetus are probably much lower when compared to ADA and IFZ. No increase in adverse pregnancy outcomes was found when using CZP (Clowse et al. 2015).

24.4.1.5 Anti-integrins

Vedolizumab is an IgG1 antibody and will be actively transferred across the placenta during the second and third trimester. The data on outcome of children exposed to vedolizumab is very limited. One report, limited by sample size and follow-up, showed the outcomes of 24 women exposed to vedolizumab during pregnancy, which identified no new safety concerns (Mahadevan et al. 2017). Vedolizumab is gut specific which leads to the hypothetical concern that there might be an increased risk of gastrointestinal infections, such as rotavirus in the infants.

24.4.1.6 Anti IL-12/IL-23 Agents

Ustekinumab has just recently been added as treatment medication for IBD. It has been available for the treatment of psoriatic arthritis and psoriasis for a couple of years, and the experience of this medication in pregnancy is from case studies around psoriasis and psoriatic arthritis (Rocha et al. 2015; Adrulonis and Ferris 2012; Alsenaid and Prinz 2016; Sheeran and Nicolopoulos 2014). No adverse pregnancy outcomes were noted in these cases. Rheumatologists give the advice that, since there is limited evidence, alternative medicine should be considered during pregnancy (Gotestam Skorpen et al. 2016).

24.5 Lactation

Learning Targets

- Breastfeeding is possible for women with IBD (also when taking IBD medication).
- Women with IBD might have concern about the transfer of medication into breastmilk.
- Data on transfer of medication into breastmilk is sparse, and long-term studies need to be done.

In general breastfeeding is supported because there are many advantages for the mother and child and is not associated with a higher chance of relapse in women with IBD (Barclay et al. 2009). It is known that IBD women breastfed their baby for a shorter period compared to the general population (Bergstrand and Hellers 1983). Reasons for this are concerns about the transfer of medication into the breastmilk and fatigue of the mother. In Table 24.1 the different IBD medication and their risk during lactation are shown. It is important to note that for some drugs there is limited data.

Table 24.1 IBD drugs and their risk during lactation

Drugs		Risk during lactation
Aminosalicylates		
• Mesalazine	Very little excretion into milk	Low risk
• Sulfasalazine		Lows risk
Corticosteroids		Low risk
• Prednisone		
• Prednisolone	Delay breastmilk for 4 h	
• Budesonide	Very little excretion into milk	
Thiopurines		
• Azathioprine (AZA)	Undetectable or low levels	Low risk
• 6-mercaptopurine (6-MP e.g., mercaptopurine)	Undetectable or low levels	Low risk
• 6-thioguanine (6-TG)		Limited data available, probably low risk
Methotrexate		High risk, do not use
Anti-TNF		
• Adalimumab	1/100 of the maternal drug levels detected	Low risk
	1/200 of the maternal drug levels detected	Low risk
• Infliximab		Limited data available, probably low risk
• Thalidomide		Limited data available, probably low risk
• Golimumab	Not detectable	High risk, do not use
• Certolizumab pegol		Low risk
Vedolizumab		Limited data available, probably low risk
Ustekinumab		Limited data available, probably low risk

Aminosalicylates and corticosteroids are excreted into breastmilk but are considered of low risk (Diav-Citrin et al. 1998; Ost et al. 1985; Habal et al. 1993). Small concentrations of thiopurine have been detected in breastfed babies from mothers who were using thiopurines (AZA/6-MP), but there were no adverse outcomes detected in these children (Gardiner et al. 2006; Angelberger et al. 2011). For 6-thioguanine (6-TG), this data is not available, but by mode of action, it is considered of low risk.

Studies on IFX and ADA showed no impact on the infection rate in the infants, although the medicines are excreted into breastmilk in small quantities (Ben-Horin et al. 2011; Ben-Horin et al. 2010).

So far only animal studies have reported on vedolizumab and ustekinumab. These medicines are considered of low risk by their mode of action (Martin et al. 2010; Takeda 2014), but in the absence of sufficient data, it is advised to not breastfeed infants when mothers take vedolizumab or ustekinumab.

24.6 Conclusion

All clinicians, including IBD nurses, have a role in advising patients with IBD having children.

The key messages are:

Fertility

- Women with quiescent IBD are as fertile as the general population.

Preconception

- All women of reproductive age should receive preconception counseling.
- Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy.

Pregnancy

- There is a higher risk of adverse maternal and fetal outcome in case of disease activity during pregnancy.

- Appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy.

Lactation

- Breastfeeding is possible for women with IBD (also when taking IBD medication), but data on transfer of medication into breastmilk is sparse and long-term studies need to be done.

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