approach for the management of fistulizing disease. Further, antibiotics are used for the treatment of pouchitis. The safety of metronidazole (265), amoxicillin (266) (± clavulanic acid), and ciprofloxacin (267) (recent data has not demonstrated an increased risk of major malformations despite early canine and rodent data suggesting a potential risk of arthropathies) have been well-demonstrated in systematic reviews, meta-analyses, and large observational studies, although these have not necessarily been specific for women with IBD. There are no published human data on rifaximin in pregnancy. Finally, a test for Group B *streptococcus* is done around week 36 of gestation, and intravenous penicillin-based antibiotics are given during labor if this testing is positive. This is an important treatment to prevent infant infection and should be given to the patient with IBD if appropriate based on testing.

Calcineurin inhibitors

There are several meta-analyses on the use of cyclosporine in pregnancy, but data are mainly derived from transplant populations rather than IBD. No increase in congenital malformations were reported; however, other adverse outcomes, including spontaneous abortion, prematurity, pre-eclampsia, and LBW have been reported (268,269). These studies could not differentiate the effect of disease activity from calcineurin inhibitor effect vs other medication effect (for example, in the transplant setting, multiple immunosuppressants may be utilized), nor could they account for existing (non-IBD) comorbidities. It should be noted that the use of calcineurin inhibitors in a transplant setting is for a chronic not acute indication, dosages are different, and the patient profile is quite distinct from a patient with IBD. All reported data are indirect and not necessarily extrapolatable to the IBD population, as the studies also had different outcome measures. Further, the need for careful monitoring and the adverse effect profile may limit acceptability and use of cyclosporine. There are even more limited data for tacrolimus use in pregnancy, again derived from transplant populations.

Calcineurin inhibitor data specific to IBD relates to its use as salvage therapy to avoid colectomy. The largest IBD pregnancy series of calcineurin inhibitor use (N = 8), was reported by the GETAID group. There was 1 *in utero* death; however, the investigators attributed this to protein S deficiency (270). Other case reports of IBD in pregnancy exist, but there is only a single case report of tacrolimus use in a pregnant woman with IBD (271–275). Although cyclosporine may be an option for salvage therapy for severe IBD in pregnancy not responding to steroids, the overall safety data may favor the use of anti-TNFs, given both its effectiveness and safety.

Sphingosine-1-phosphate receptor modulators

Ozanimod and etrasimod are S1P receptor modulators. Teratogenicity has been observed in animal studies. S1P receptors are involved in early developmental processes including angiogenesis, cardiogenesis, limb development, and neurogenesis. Ozanimod was linked to fetal death and severe malformations in rabbits at a dosage equivalent to human exposure (0.92 mg/d). Animal data in rats and rabbits for etrasimod have raised concerns, including embryo lethality and fetal malformations at doses 5 to 6 times higher than those used in human exposure. There is also concern for fetal malformations, skeletal anomalies, and neurobehavioral changes. Recent pharmacovigilance data on ozanimod included 78 pregnancies with 42 live births (10% preterm births) with the remaining comprised of spontaneous abortions and elective terminations (although none were attributed to known congenital anomalies). There were 14 pregnancies in women with UC and 6 pregnancies in women with CD, with no preterm deliveries or congenital anomalies among the reported total of 9 live births. Ozanimod was discontinued in all pregnancies with no exposures beyond the first trimester (276). Etrasimod reports 9 maternal exposures in their clinical program, resulting in 2 healthy newborns, 4 medical terminations, 1 congenital malformation (patent foramen ovale), and 1 spontaneous abortion (277).

Given the lack of data, the oral small molecule class of S1P receptor modulators are currently relatively contraindicated during pregnancy. Shared decision-making is imperative. If there is no effective alternative therapy to maintain maternal health, general principles are that stringent disease control of IBD results in the most favorable maternal and fetal outcomes.

Janus kinase inhibitors

JAKis are small molecules that passively traverse the placenta throughout pregnancy. Concerns about teratogenicity arise from animal studies. Preclinical investigations in rabbits demonstrated that tofacitinib exhibited feticidal and teratogenic effects at a dosage 6.3 times higher than the maximum human dose of 10 mg twice daily (278). Similarly, exposure to a dose equivalent to a human dose of 200 mg of filgotinib resulted in fetal death and severe malformations in rats and rabbits (279). In pregnant rats and rabbits, upadacitinib administration led to musculoskeletal and cardiovascular malformations at doses comparable to those used in humans (280). Human data are limited by small numbers and the fact that most information comes from first trimester exposure before women stopped the drug at detection of pregnancy. Monfared et al report 2 serious congenital malformations in 55 live births exposed to tofacitinib, 1 serious malformation in 21 live births exposed to filgotinib, and no malformations in 30 live births exposed to upadacitinib (281). For tofacitinib, 74 maternal exposures have been reported, with no pattern of spontaneous abortion or congenital anomalies (282). In a total of 128 pregnancies among women exposed to upadacitinib (mean, 5 weeks 3 days), similar results were found (283). Consequently, JAKis are relatively contraindicated during pregnancy. Manufacturers recommend discontinuation of these medications at least 4 weeks prior to planned conception for tofacitinib and upadacitinib, and at least 1 week prior for filgotinib.

A detailed discussion should take place with females of childbearing age regarding the use of oral small molecules. In general, one would discourage use of oral small molecules in the preconception, pregnancy, and lactation phases, unless there is no effective alternative therapy to maintain maternal health. However, this is distinct from simply having childbearing potential. Women with no plans for conception in the immediate future should not be denied small molecules if most appropriate for their disease. For women for whom there is no other option to maintain remission, JAKis can be continued after a detailed benefit (keeping disease under control for better maternal and fetal outcomes, avoiding profound illness in mother including colectomy) to risk (potential risk of birth defects) discussion is had.

USE OF IBD MEDICATIONS DURING LACTATION

Recommendations

21. We recommend breastfeeding as it is not associated with an increased risk of disease exacerbation in women with IBD (Strong recommendation, very low level of evidence).