

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

The Possible Effects of Inflammatory Bowel Disease Medications on Sperm Quality



Anne Grosen, MD, PhD
Resident
Department of Hepatology and Gastroenterology
Aarhus University Hospital
Aarhus, Denmark

G&H How is infertility defined in men, and what are possible causes of reduced fertility, particularly in men with inflammatory bowel disease?

AG The World Health Organization (WHO) defines infertility as the failure to achieve clinical pregnancy after 12 months of regular unprotected sexual intercourse. Infertility affects approximately 15% of couples in the Western world. A male factor is responsible for, or contributes to, approximately 50% of infertility cases. Often, individuals are subfertile rather than infertile (ie, sterile). Reduced fertility in men can result from various conditions, for example, obstruction of the genital tract, varicocele, ejaculatory dysfunction, genital infection, endocrine disturbance, or cryptorchidism. In approximately 30% of cases, it is not possible to determine the cause of infertility, which is known as idiopathic male infertility. In patients with inflammatory bowel disease (IBD), previous surgery, disease activity, different types of medications, and poor nutritional status (eg, leading to zinc deficiency) can adversely affect sperm quality or lead to sexual dysfunction.

G&H How can male fertility be evaluated?

AG Traditionally, male fertility is evaluated by a semen analysis. WHO has provided recommendations on how to perform the examination and also reference values for the basic semen evaluation method that is used worldwide. This analysis assesses the concentration of sperm cells within the sample, the volume of the semen sample,

the morphology of the sperm cells, and their motility. However, this microscopic analysis has several limitations. It is subjective and can be influenced by interobserver variation. In addition, the sperm cell only delivers nuclear material to the egg cell, and that parameter is not assessed by basic WHO semen analysis. Therefore, my colleagues and I, as well as other groups, have focused on alterations in sperm DNA integrity to supplement sperm evaluation as a marker of male fertility. The DNA fragmentation index (DFI), assessed by sperm chromatin structure assay, is negatively associated with the likelihood of pregnancy. A DFI above 20% is associated with reduced fecundability and is traditionally chosen as the cutoff level. It should be stressed that a high DFI does not preclude the possibility of natural conception, nor does a low DFI guarantee fertility.

Spermatogenesis, the process of producing sperm cells, takes approximately 3 months. Studies evaluating drug effects must take this into account to ensure that the sperm cells being evaluated have been exposed to a drug for a minimum of 1 spermatogenic cycle. The ejaculate, semen, consists of only 5% sperm cells; the rest is seminal plasma from seminal vesicles, the prostate, and other sex glands.

Because of the mechanisms of action of drugs, potential effects on male fertility may occur during spermatogenesis through a direct cytotoxic or genetic effect on the sperm cells if the drugs or cytokines can cross the blood-testis barrier that protects these cells during spermatogenesis. Further, transmission of drugs in the ejaculate can affect the sperm cells or have a teratogenic effect on the fetus in an exposed female partner. Finally, a

drug can have a systemic effect on the hypothalamic-pituitary-gonadal axis. This could lead to impaired spermatogenesis or sexual dysfunction in patients (erectile dysfunction, ejaculatory dysfunction, or low libido), which does not change sperm quality but may affect a man's ability to produce children.

G&H Have thiopurines been shown to affect male fertility, including sperm?

AG Because of their mode of action, it is possible that thiopurines could lead to DNA mismatch repair or strand breaks in DNA. This has given rise to longstanding concern and debate on whether thiopurines have an adverse effect on male fertility. A cross-sectional study by Valer and colleagues in 2017 found no difference in basic semen parameters between IBD patients on and off thiopurine therapy. Reassuringly, the next year, Simsek and colleagues reviewed the literature and did not find an association between sperm quality and thiopurines in 83 men exposed to thiopurines who had various conditions, not just IBD.

To investigate possible effects on sperm DNA integrity and drug levels in semen, my colleagues and I compared sperm samples from 40 patients with IBD on thiopurines with 40 healthy volunteers. We also sampled 10 patients on and off thiopurine therapy. We found no difference in sperm DNA fragmentation between the healthy volunteers and the patients on maintenance therapy (DFI of 15% vs 13%, respectively), and did not see a change in DFI in the paired samples. In addition, we found that sperm motility was a little lower in the patients compared with the healthy controls, although there was no significant change in motility in patients off and on therapy. Sex hormones were not affected. Furthermore, we could not detect the free thiopurine metabolites (methylmercaptipurine metabolites and thioguanine nucleotides) within the sperm cells, and thioguanine nucleotides were not incorporated in the sperm cell DNA.

Female exposure of drugs in seminal plasma was assessed by measuring 6-mercaptopurine in seminal plasma. 6-mercaptopurine was detected in the seminal plasma shortly after ingestion. Even if all of the drug in the seminal plasma was absorbed in a vagina, the detected amount would lead to a blood concentration of 0.01% in an exposed female after vaginal absorption compared with the male blood concentration. We also know that seminal plasma does not enter the uterus because it causes uterine cramps. Thus, the only way a fetus could be exposed to paternally emitted drugs during intercourse would be across the placenta after vaginal absorption. Therefore, the detected amount of 6-mercaptopurine in seminal plasma is negligible and does not possess a risk for the fetus in a

pregnant partner. For the same reason, condom use is not necessary.

We can thus conclude from all of the studies regarding semen quality that there is no risk from thiopurines. Male patients can continue thiopurines if they want to father children. This is also supported by research on fetal outcomes after paternal thiopurine therapy. In the largest cohort study to date on thiopurines, Nørgård and colleagues looked at 699 exposed fetuses and did not find increased risk for congenital anomalies, preterm birth, or being small for gestational age. These findings were confirmed in a recent study by Meserve and colleagues of 461 patients on thiopurines in the largest study to date in terms of men exposed to immunosuppressive and/or biologic agents and birth outcomes.

G&H What data are currently available regarding the potential effects of anti-tumor necrosis factor inhibitors on male fertility?

AG Tumor necrosis factor (TNF) alpha plays an important but unclear role during spermatogenesis, so anti-TNF inhibitors could theoretically affect male fertility. In 2005, Mahadevan and colleagues published the first study raising suspicion that infliximab might have a negative impact on sperm motility and morphology. Conversely, in a study by Villiger and colleagues in 2010, men with spondyloarthritis had reduced sperm motility when they had active disease, whereas when they entered remission and were treated with anti-TNF inhibitors, their sperm quality was comparable with that of healthy controls. Other studies have found no effect or a positive effect with anti-TNF inhibitors.

In 2019, my colleagues and I examined 28 patients starting infliximab or adalimumab, as well as 17 patients stopping it, to evaluate potential effects on sperm DNA integrity and to assess drug transmission in semen. As expected, starting anti-TNF inhibitors improved inflammatory markers and sex hormones when patients achieved remission on these therapies; in contrast, no difference in sex hormones was seen in patients who stopped anti-TNF inhibitors. In addition, we saw a minimal but significant positive effect on sperm DNA integrity with initiation of anti-TNF therapy; patients had a DFI of 12.8% before starting anti-TNF inhibitors, and when achieving remission on those therapies, their DFI decreased to 10%. However, a significant change was not seen in patients who stopped anti-TNF inhibitors. Furthermore, we did not see changes in the basic semen parameters of volume or concentration or sperm number, motility (as others have seen), or morphology.

In addition, we measured the drugs in seminal plasma from the samples collected while patients were on

maintenance therapy. We detected infliximab and adalimumab in all of the samples, and the levels in semen were 1% to 2% of the patient's blood level.

As for birth outcomes, Meserve and colleagues also looked at more than 1000 pregnancies after paternal exposure to anti-TNF inhibitors around conception in their aforementioned study, and found no increased risk for congenital anomalies, low birth weight, or preterm birth. That is encouraging, and I think the data are firm enough to conclude that anti-TNF inhibitors do not have a negative effect on sperm quality or birth outcomes.

G&H Has any research been conducted on whether newer agents such as vedolizumab and ustekinumab affect sperm?

AG There is not yet much research on vedolizumab (Entyvio, Takeda). In 2019, my colleagues and I published the only study looking at sperm quality. We published a case report of 15 patients on maintenance vedolizumab and compared them with 40 healthy volunteers. Sperm quality evaluated by WHO parameters and sperm DNA integrity were comparable between vedolizumab-treated patients and healthy volunteers. Furthermore, we looked at 3 patients before and after treatment initiation and found no difference in sperm quality or DFI. As with anti-TNF inhibitors, vedolizumab levels in seminal plasma were 1% of the serum level. Thus, female exposure after vaginal absorption is negligible, and, as with anti-TNF inhibitors, condom use is not necessary.

Our data are in line with studies evaluating pregnancy outcomes following paternal vedolizumab exposure peripartum. The aforementioned study by Meserve and colleagues also included 18 pregnancies from fathers who were exposed to vedolizumab. There was no increased risk for congenital anomalies, preterm birth, or low birth weight. Although the data on vedolizumab are reassuring thus far, more studies are needed, including larger studies with paired semen sampling.

As for ustekinumab (Stelara, Janssen), there are no human data on sperm quality. Consequently, dermatology and rheumatology guidelines advise that ustekinumab be stopped in male patients 15 weeks prior to conception. Updated guidelines for IBD patients are expected from the European Crohn's and Colitis Organisation this year. However, the data regarding female exposure are reassuring, and as a result, ustekinumab is recommended in the United States for female patients with IBD throughout pregnancy, as well as during breastfeeding.

Animal studies on semen quality in monkeys have shown that twice-weekly ustekinumab did not have any effect on fertility. In the study by Meserve and colleagues from last year, pregnancies from 114 males exposed to

ustekinumab did not have an increased risk for congenital anomalies, preterm birth, or low birth weight. Further data are needed on the effects of ustekinumab on semen quality, the amount excreted in seminal plasma, and effect on DNA integrity, but outcome studies are encouraging thus far in this patient group.

G&H Have there been any studies on sperm and Janus kinase inhibitors such as tofacitinib?

AG Tofacitinib (Xeljanz, Pfizer) is a small molecule, so it might act differently from the aforementioned IBD drugs. Janus kinase (JAK) receptors are present in human sperm, and studies indicate that JAKs may be involved in sperm motility. Thus far, no human data are available on the effect on sperm quality.

In 2018, Mahadevan and colleagues reported on outcomes from 84 pregnancies after paternal exposure to tofacitinib. In total, 65% were healthy newborns, 8% spontaneous abortions, 1% neonatal death, and 25% lost to follow-up or listed as pending at the time of publication. There were no fetal deaths or congenital malformations. Based on these data, exposure around conception appears to lead to birth outcomes comparable with the general population.

G&H What data are currently available regarding methotrexate and its potential effects on sperm?

AG Few studies have investigated the effect of methotrexate on sperm DNA integrity, although its mode of action could potentially increase the rate of DNA fragmentation. In 2018, Ley and colleagues looked at 6 patients with IBD on low-dose maintenance methotrexate and found increased DFI despite normal basic sperm parameters. However, the authors did not perform paired comparison of samples on and off methotrexate therapy, and so were unable to conclude whether the observed effects could be ascribed to methotrexate. In 2020, the authors published an abstract with additional data on the same group. They looked at 9 patients on methotrexate and compared them with 7 nonexposed men with IBD. There was no difference between DFI in the 2 groups, although the DFI was significantly higher in IBD patients on methotrexate compared with the control group. Again, paired samples were not included. Conversely, a study by Estop and colleagues in 1992 of 4 patients with rheumatoid arthritis did not observe an increase in chromosome breakage on vs off methotrexate therapy.

Last year, my colleagues and I compared 14 patients on maintenance low-dose methotrexate therapy with a group of 40 healthy volunteers. There was no difference

in DFI (11.5% vs 15.0%; $P=.06$). We were able to collect 5 paired samples on and off methotrexate therapy and did not see any change in DFI (12% on vs 14% off). There were also no differences in the basic parameters of sperm concentration, motility, and morphology between the groups. Serum testosterone was not affected by methotrexate therapy. We detected all of the intracellular metabolites methotrexate polyglutamates 1 to 5 in blood, but reassuringly, only extracellular methotrexate polyglutamate 1 could be detected in semen. We concluded that patients on low-dose methotrexate have comparable sperm quality to healthy volunteers and that low-dose methotrexate does not increase sperm DNA fragmentation. Our data do not support cryopreservation of semen before treatment initiation, and family planning should not be postponed when methotrexate therapy is needed.

Our findings are in line with outcome studies. The aforementioned study by Meserve and colleagues included 171 patients on methotrexate and found no increase in congenital anomalies, low birth weight, or preterm birth. Likewise, a study by Winter and colleagues in 2017 looked at 193 cases and did not find an increased risk for congenital abnormalities, preterm birth, or being small for gestational age. Importantly, the 2020 guideline from the American College of Rheumatology now conditionally recommends that methotrexate be continued in men who are planning to father children.

G&H Do you have any advice for patients and physicians?

AG In general, male patients should be reassured that with the evidence thus far on commonly used IBD drugs, there is no increased risk of adverse effects on sperm quality; however, more research is needed on tofacitinib, ustekinumab, and methotrexate before conclusions can be drawn. Patients should be advised to adhere to their treatment and discuss family planning with their physicians.

As for physicians, this is an issue that matters to patients, so it is important to bring it up and talk to patients. In my experience, most male patients want to talk about this issue but may not know how to bring it up.

G&H What are the next steps in fertility research in addition to further studies on individual IBD drugs?

AG Traditionally, research within fertility and family planning has focused on female patients, pregnancy

outcomes, and lactation in IBD. Research on male reproductive health has been increasing and hopefully will continue to do so. Before new drugs are approved, it would be useful to have an evaluation of the potential impact on both male and female reproductive health. Whenever effects on male reproductive health are evaluated, there should be a combined examination of sperm quality and sexual health in general, as well as pregnancy outcomes.

Disclosures

Dr Grosen has no relevant conflicts of interest to disclose.

Suggested Reading

Estop AM, Cieply K, Van Kirk V, et al. Sperm chromosome studies in patients taking low dose methotrexate. *Am J Hum Genet.* 1992;51:A314.

Grosen A, Bellaguarda E, Nersting J, et al. Low-dose methotrexate therapy does not affect semen parameters and sperm DNA [published online August 31, 2021]. *Inflamm Bowel Dis.* doi:10.1093/ibd/izab205.

Grosen A, Bungum M, Christensen LA, et al. Semen quality and sperm DNA integrity in patients with severe active inflammatory bowel disease and effects of tumour necrosis factor-alpha inhibitors. *J Crohns Colitis.* 2019;13(5):564-571.

Grosen A, Bungum M, Hvas CL, Julsgaard M, Cordelli E, Kelsen J. Vedolizumab does not impair sperm DNA integrity in men with inflammatory bowel disease. *Gastroenterology.* 2019;156(8):2342-2344.

Grosen A, Kelsen J, Hvas CL, Bellaguarda E, Hanauer SB. The influence of methotrexate treatment on male fertility and pregnancy outcome after paternal exposure. *Inflamm Bowel Dis.* 2017;23(4):561-569.

Grosen A, Nersting J, Bungum M, et al. Sperm DNA integrity is unaffected by thiopurine treatment in men with inflammatory bowel disease. *J Crohns Colitis.* 2019;13(1):3-11.

Ley D, Jones J, Parrish J, et al. Methotrexate reduces DNA integrity in sperm from men with inflammatory bowel disease. *Gastroenterology.* 2018;154(8):2064-2067.e3.

Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis.* 2018;24(12):2494-2500.

Meserve J, Luo J, Zhu W, et al. Paternal exposure to immunosuppressive and/or biologic agents and birth outcomes in patients with immune-mediated inflammatory diseases. *Gastroenterology.* 2021;161(1):107-115.e3.

Nørgård BM, Magnussen B, Larsen MD, Friedman S. Reassuring results on birth outcomes in children fathered by men treated with azathioprine/6-mercaptopurine within 3 months before conception: a nationwide cohort study. *Gut.* 2017;66(10):1761-1766.

Simsek M, Lambalk CB, Wilschut JA, Mulder CJJ, de Boer NKH. The associations of thiopurines with male fertility and paternally exposed offspring: a systematic review and meta-analysis. *Hum Reprod Update.* 2018;24(2):192-206.

Valer P, Algaba A, Santos D, et al. Evaluation of the quality of semen and sexual function in men with inflammatory bowel disease. *Inflamm Bowel Dis.* 2017;23(7):1144-1153.

Villiger PM, Caliezi G, Cottin V, Förger F, Senn A, Østensen M. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. *Ann Rheum Dis.* 2010;69(10):1842-1844.

Winter RW, Larsen MD, Magnussen B, Friedman S, Kammerlander H, Nørgård BM. Birth outcomes after preconception paternal exposure to methotrexate: a nationwide cohort study. *Reprod Toxicol.* 2017;74:219-223.