Media regurgitation after intrauterine insemination: Is the uterus half empty or half full?

Reproductive medicine is a fast-moving, ever-evolving field of scientific advancements made possible through complex and cutting-edge research that constantly pushes forward our ability to diagnose and treat the several causes of infertility. The next big breakthrough in our field may very well incorporate artificial intelligence, gene editing, noninvasive molecular techniques, or perhaps something that is yet to be discovered. Although it is easy to become immersed in the new and shiny research in our field, we often overlook some of the simple everyday questions that remain unanswered.

Has a patient ever asked you to explain the machine learning methods being employed to automate and improve embryo selection techniques? Probably not, but if they did, there would be several recent publications on the topic that could be referenced. Instead, a patient's questions are usually more tangible. For example, a patient may ask whether live birth after intrauterine insemination (IUI) is more likely if the procedure is performed by a physician compared with that by a nurse. This is a basic question, and the answer is no (1). Another patient may feel a small amount of fluid leak vaginally after an IUI, presumably sperm wash media that regurgitated, and wonder whether this will decrease the chance of pregnancy. This is another basic question, and until recently, the answer was "we don't know."

However, in this issue of *Fertility and Sterility*, Craig et al. (2) evaluated the association between media regurgitation after IUI and live birth outcomes to answer this common question. The investigators reasonably hypothesized that media regurgitation would decrease the total motile sperm count (TMSC) within the endometrial cavity, leading to a lower live birth rate given the well-described association between the TMSC and IUI outcomes (3). Interestingly, this hypothesis was proven to be incorrect. Craig et al. (2) performed a retrospective cohort study of 1,957 IUI cycles in 660 patients with a mean age of 31.9 ± 4.9 years. Among this cohort, media regurgitation was observed after 36.5% (715 of 1,957) of inseminations. Pregnancy outcomes were compared between IUI cycles with and without regurgitation using a cluster-weighted generalized estimating equations method to estimate modified Poisson models with robust standard errors to account for patients contributing multiple cycles to the analysis. When cycles with media regurgitation were compared with cycles without regurgitation, there were no statistically significant differences in live birth (6.3% vs. 6.8%), clinical pregnancy (10.5% vs. 10.0%), or positive pregnancy test (15.0% vs. 15.4%).

From a descriptive standpoint, this study was able to identify that media regurgitation after IUI is a rather common event with an incidence of approximately 1 of 3 inseminations. This number is particularly reliable because of the consistent use of ultrasound to confirm IUI catheter location within the endometrial cavity before insemination at the study center. While the investigators recognize that the use of ultrasound to guide IUI catheter insertion does not improve pregnancy outcomes in large studies, it does allow for the confirmation of catheter location in what is otherwise a blind procedure (4). One potential cause of media regurgitation after IUI is an accidental intracervical insemination if the catheter tip does not pass the internal cervical os or if it curls up within the cervix. The consistent use of ultrasound is, therefore, a strength of this study design by confirming that the sperm was correctly deposited within the endometrial cavity in each case.

The similar live birth rate between groups reported in this study was an unexpected finding given that media regurgitation is assumed to contain sperm and, therefore, the regurgitation group would be expected to have a lower overall TMSC within the endometrial cavity. One potential explanation for this observation could be that the regurgitation cohort had a high enough TMSC such that losing some sperm did not impact the chance of pregnancy, given that there is no improvement in pregnancy above a threshold TMSC of approximately 9–10 million (4). To test this hypothesis, the investigators performed a sensitivity analysis of postpreparation TMSC and stratified patients into 3 groups: TMSC of <5 million, TMSC of 5–10 million, and TMSC of >10 million. On the basis of the known linear decline in the IUI pregnancy rates as the TMSC declines below 9–10 million, it can be expected that patients with the lowest TMSC would be the most likely to have lower live birth rates if there was an association between media regurgitation and live birth. However, the results of the sensitivity analysis were consistent with the primary analysis in that no statistically significant differences in live birth rates were observed between cycles with regurgitation and no regurgitation in each TMSC group, including the TMSC < 5 million group with a live birth rate of 5.2% in patients with regurgitation and 4.9% in patients with no regurgitation. It is always possible that the reduction in power that occurs with stratification may have limited the ability to observe an association in the lowest TMSC group; however, it is reassuring that the absolute difference in the live birth rate between the regurgitation and no regurgitation groups in patients with a TMSC of <5 million was only 0.3%, mitigating the concern of study power in this sensitivity analysis.

Considering the results reported in this study, 2 potential explanations remain to explain the lack of association between media regurgitation and live birth. The first is that while the occurrence of media regurgitation in some patients is immediate and obvious before speculum removal, perhaps a much higher proportion of patients than we recognize experience a slower regurgitation of media through the mucus channel that is created by the insemination catheter after the speculum is removed. It has been reported that lying in the supine position for 10 minutes after IUI is associated with higher pregnancy rates, presumably because of less

media regurgitation and increased retention of sperm within the endometrial cavity (5). Even though all patients in this study remained supine for 5–10 minutes after IUI, as is seen with media regurgitation that is immediately visualized, lying in the supine position does not completely prevent regurgitation, and a slow regurgitation that is not visualized may also occur in a portion of patients. Second, while media regurgitation presumably contains sperm, it would be difficult to assess the amount of motile sperm that is lost at the time of regurgitation. It is possible that less viable sperm is lost at the time of regurgitation than would be estimated on the basis of the volume of media visualized.

Overall, this study is an excellent example of how a well-designed study can help to answer a very basic question. These results are sure to be clinically useful given the high incidence of media regurgitation; patients can be reassured that this is typically not because of a procedural error and occurs in approximately one-third of inseminations. Most importantly, media regurgitation after IUI does not appear to be associated with a decreased chance of live birth, even in men with a low TMSC.

Phillip A. Romanski, M.D.
Pietro Bortoletto, M.D.
Alexis P. Melnick, M.D.

The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical Center, New York, New York

https://doi.org/10.1016/j.fertnstert.2021.10.013

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/34035

REFERENCES

1. Goldman RH, Batsis M, Hacker MR, Souter I, Petrozza JC. Outcomes after intrauterine insemination are independent of provider type. Am J Obstet Gynecol 2014;211:492.e1–9.
2. Craig LB, Arya S, Burks HR, Warta K, Jarshaw C, Hansen KR, et al. Relationship between semen regurgitation and pregnancy rates with intrauterine insemination. Fertil Steril 2021;116:1526–31.
3. Muthigi A, Jahandideh S, Bishop LA, Naeemi FK, Shipley SK, O'Brien JE, et al. Clarifying the relationship between total motile sperm counts and intrauterine insemination pregnancy rates. Fertil Steril 2021;115:1454–60.
4. Hansen KR, Peck JD, Coward RM, Wild RA, Trussell JC, Krawetz SA, et al. Intrauterine insemination performance characteristics and post-processing total motile sperm count in relation to live birth for couples with unexplained infertility in a randomised, multicentre clinical trial. Hum Reprod 2020;35:1296–305.
5. Saleh A, Tan SL, Biljan MM, Tulandi T. A randomized study of the effect of 10 minutes of bed rest after intrauterine insemination. Fertil Steril 2000;74:509–11.