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## One millimeter in the time of COVID



Call me a 1 mm skeptic. After all, allowing a follicle diameter to grow one millimeter larger seems like a trivial difference in clomiphene intrauterine insemination (IUI) cycles. Nevertheless, the retrospective study of 1,676 clomiphene IUI treatment cycles by Dr. Hancock and colleagues (1) found that a 1 mm difference in follicle size at the time of human chorionic gonadotropin (hCG) trigger raises the odds of clinical pregnancy significantly, with an observed clinical pregnancy rate ranging from approximately 8% for mean follicle diameter of 19 to 20 mm, to 11% for 20 to 21 mm follicles, and 16% for follicles 21 to 22 mm (see Figure 1 in Reference 1). The dramatic increase in the clinical pregnancy rate is impressive and somewhat unexpected. But what is the cost of this approach to our patients, especially in the time of COVID-19?

First, is it biologically plausible that such a small difference in follicle size makes it a large difference in the clinical pregnancy rate? One can make the argument for either “yes” or “no.” Naysayers justifiably point out that size should have little impact on outcomes. After all, oocyte maturation is induced by a luteinizing hormone (LH) surge or hCG administration during ovarian stimulation for in vitro fertilization, and mature oocytes are often retrieved from follicles triggered at a mean diameter of only 10–12 mm. Those who are arguing that size likely matters could argue that the maturing follicle contains increasing concentrations and exposure to many growth factors, enzymes, prostaglandins, and other factors needed for the maturation of the cumulus-oocyte complex and that these are essential for the physical event of oocyte release during ovulation. Additionally, prolonged exposure to estradiol stimulates endometrial growth, as the authors mention in the discussion. Furthermore, the physiologic effect of follicular fluid could have a role in altering oocyte release or pickup of the oocyte cumulus complex by the fimbria.

The conclusions in the Hancock study (1) are strengthened by the very large number of treatment cycles, but as a retrospective study, the results cannot be considered conclusive, and the applicability of the results to other fertility centers may be limited. After all, I suspect that few centers routinely perform more than one ultrasound to monitor follicle growth in a clomiphene IUI cycle, which may be needed to ensure that hCG is administered when the lead follicle mean

diameter reaches 22 mm. Even if follicle growth of 2–3 mm daily is projected, it is unclear if the benefit of performing two or more ultrasound examinations during a treatment cycle justifies the added cost for additional testing and the stress of additional visits to the fertility center for a treatment with a 1 in 6 chance for success, at best.

To complicate the cost/benefit assessment is the care we deliver during the COVID-19 pandemic. As I write this, the United States is nearing 400,000 COVID-19-related deaths. Medical practices, including fertility centers, have minimized non-essential office encounters and procedures to reduce the potential for unintentional COVID-19 exposure. Ultrasound monitoring for clomiphene IUI cycles certainly falls into the category of non-essential, especially since the alternative of using urine LH timed IUI outcomes are comparable to monitored cycles (2). As the pandemic rages, LH timed IUI procedures would appear to provide the greatest degree of safety and the highest level of success. Until it is safe to resume medical care as we have known it, I do not recommend immediately adopting the methods described in this report.

That is not to say that this study is without merit. Even for a skeptic, this is an important study and will change the way I treat my patients with unexplained infertility undergoing monitored clomiphene IUI cycles. As with life in the time of COVID-19, we just need to wait for the right time to incorporate the lessons we have learned—one millimeter can be worth the wait.

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## REFERENCES

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