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Letter to the Editor

Reply: Artificial cycle frozen embryo transfer and obstetric adverse outcomes: association or causation?

Sir,

We appreciate the letter from Andrea Busnelli, Nicoletta Di Simone and Paolo Emanuele Levi-Setti (Busnelli *et al.*, 2023). As nowadays more frozen-thawed than fresh embryo-transfer cycles are performed, discussions on its effectiveness and safety are much needed.

Busnelli and co-authors applied six Bradford and Hill criteria that were written in 1965 as considerations to guide causal inference. It is good to see that this way of qualifying the associations overlaps quite well with the GRADE evidence levels for the different outcomes presented in our review.

We are aware of the potential impact of natural cycle frozen embryo transfer (NC-FET) on laboratory and clinical practice when refraining from artificial cycle frozen embryo transfer (AC-FET) in ovulatory women. We previously studied facilitators and barriers for the introduction of NC-FET in hospitals and patients in the Netherlands (Zaat *et al.*, 2022) and indeed found lack of laboratory capacity and flexibility to be the main barrier for healthcare providers. For more information on how to perform NC-FET we kindly refer to the results of our randomized controlled trial (RCT) in which we compared home-based with hospital-controlled monitoring in 1464 women. Our findings showed that home-based monitoring with urinary LH tests twice daily resulted in comparable pregnancy chances as hospital-controlled monitoring of ovulation to time FET (Zaat *et al.*, 2023). The fast recruitment and participation of 22 centers underline the feasibility in clinical practice. We propose to use the costs saved by home-based monitoring to overcome some extra costs of thaw and transfer in the weekends. Future cost analyses, however, first need to show the true impact of home-based monitoring in weekends.

Introducing NC-FET in selected women only, as suggested by Busnelli *et al.*, to overcome logistic reasons in weekends, should not be pursued in our opinion. First, as there is now overwhelming evidence that NC-FET is the saver option for mother and child, a consistent finding both in randomized trials, adjusted and unadjusted observational studies and also found in the analyses of Busnelli and colleagues. Second, not having to take medication up to 12 weeks of gestation is a further major advantage compared to AC-FET and will likely be more cost-effective. Third, stratification on basis of prognostic parameters is tricky; prognostic models have the tendency to overestimate their true prognostic capacity. And finally, we are, as reproductive medicine specialists, also responsible for the high impact our field has on our planetary health (medication use, transportation to the hospital for monitoring FET cycles). The introduction of NC-FET, especially when home monitoring is used, not only contributes to improved safety for mothers and newborns but also to a more sustainable society, for the future generations we help to conceive.

Conflict of interest

The authors have no commercial interest. We report that we performed an RCT comparing home with hospital-based monitoring in NC-FET that was financially supported by a grant from the Dutch Organisation for Health Research and Development (ZonMw 843002807; www.zonmw.nl).

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