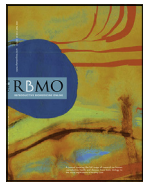
RBMO



LETTER

Adjustment for non-confounders could increase systematic error

We read with interest the article by *Drakopoulos et al. (2019)*. The ongoing pregnancy rate/cycle (OPR) in the conventional stimulation group was 4 times higher than in the modified natural cycle (MNC)-IVF group [crude odds ratio (OR) 4.1, 95%CI 1.6–10.9, $P = 0.002$]. The crude OR was even higher for live birth/cycle (5.4, 95%CI 1.6–18.2, $P = 0.002$). However, after adjustment for 'confounders', the OR for OPR was no longer statistically significant (2.56, 95%CI 0.9–7.6).

We respectfully argue that oocyte number and embryo availability are not confounders. True confounders should not be directly related to the exposure (namely mode of ovarian stimulation) or to an intermediate between the exposure and outcome (*Skelly et al., 2012*). The number of oocytes, and consequently embryo availability, could be affected by a causal link between mode of ovarian stimulation and IVF outcome (*Connell et al., 2019*; *Magnusson et al., 2018*; *Polyzos et al., 2018*; *Smeltzer et al., 2019*).

Although the use of multivariate logistic regression improves the internal validity of study results, over-adjusting for non-confounders increases, rather than decreases, bias resulting in loss of precision of effect size for the exposure (*Brookhart et al., 2010*; *Liu et al., 2017*). This unwarranted statistical impact along with low event rate in advanced-age Bologna poor responders and residual unmeasured confounding in retrospective studies could even reverse effect direction and lead to the opposite conclusion.

We agree with *Drakopoulos et al. (2019)* that MNC-IVF might represent a patient-friendly approach. However, according to their study results, it was associated with poorer outcome compared to conventional stimulation.

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