COMMENTARY

To pill or not to pill in GnRH-antagonist cycles: the answer is in the data already!

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Abstract The planning of IVF treatment by scheduling menstruation and hence initiation of ovarian stimulation using sex-steroid pre-treatment is commonly used. Pooling data from six randomized-controlled trials encompassing 1343 patients, with and without combined oral contraceptive pill pre-treatment, suggests that the ongoing pregnancy rate per randomized woman is significantly lower in patients with oral contraceptive pill pre-treatment (relative risk [RR]: 0.80, 95% confidence interval [CI]: 0.66–0.97; rate difference [RD]: −5%, 95% CI: −10% to −1%; fixed effects model). This finding remains remarkably robust in multiple sensitivity analyses: exclusion of a study on poor responders, exclusion of the three smallest studies or exclusion of studies with a pill-free interval of less than 5 days, results in RR of 0.78 (95% CI: 0.64–0.94), 0.80 (95% CI: 0.65–0.98) and 0.79, (95% CI: 0.64–0.99), respectively. Furthermore, the finding of a significant reduction in ongoing pregnancy rate is not inconsistent with other evidence from the literature. The potential benefit of using oral contraceptive pill pre-treatment for cycle planning should therefore be balanced against its detrimental effect. Further randomized studies should test whether an effect similar to the one observed after combined oral contraceptive pill usage exists after other sex steroid pre-treatment regimens.

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We read with great interest the manuscript by Garcia-Velasco and Fatemi (2015), recently published in Reproductive Biomedicine Online, on the topic of oral contraceptive pill pre-treatment in ovarian stimulation utilizing gonadotrophin-releasing hormone (GnRH)-antagonists. As a conclusion from a systematic literature review, and after pooling data from six randomized-controlled trials encompassing 1343 patients, we previously reported that the ongoing pregnancy rate per randomized woman is significantly lower in patients with oral contraceptive pill pre-treatment (relative risk [RR]: 0.80, 95% confidence interval [CI]: 0.66–0.97; rate difference [RD]: −5%, 95% CI: −10% to −1%; fixed effects model) (Griesinger et al., 2010).

Garcia-Velasco and Fatemi address several aspects of this systematic review and scrutinize the internal validity as well as the extent to which the conclusions of this study are externally valid (‘clear consensus is lacking on whether pre-treatment with combined oral contraceptives in ovarian stimulation has a negative effect on pregnancy rates and live birth’).

The following addresses the concerns of Garcia-Velasco and Fatemi with the aim to provide a better understanding of
important aspects of the aforementioned systematic review (Griesinger et al., 2010).

The first point of criticism addresses the pooling of studies conducted in normo-responder patients with studies conducted in poor-responder patients. Indeed, the meta-analysis included one single study, performed in 54 poor responders, (Kim et al., 2009) which has contributed to the pooled estimate of a rate difference of −5% in ongoing pregnancy rates with oral contraceptive pre-treatment. However, in order to account for the potential heterogeneity in outcomes by population type, a sensitivity analysis was included in the systematic review, which might have slipped the attention of Garcia-Velasco and Fatemi. The exclusion from the study of poor responder patients indeed increased the effect size to −6% rate difference in ongoing pregnancy rate (RD: −6%, 95%, CI: −11% to −1%; RR: 0.78, 95%, CI: 0.64 to 0.94) – not in favour of oral contraceptive pre-treatment (Griesinger et al., 2010).

Garcia-Velasco and Fatemi next question the pooling of studies of different sample sizes in a meta-analysis. More specifically they express concern that randomized studies with small sample sizes may carry ‘limitations and bias… when looking at pregnancy rates’. Although it is agreed that studies with small sample sizes suffer from imprecise effect size estimates, this is not necessarily a source of bias. Furthermore, a basic principle of meta-analysis dictates that during the process of pooling aggregate data, individual studies are weighted such that larger studies contribute more than smaller studies to the estimated combined effect. The three smaller studies (Cédrin-Durnerin et al., 2007; Huirne et al., 2006; Kim et al., 2009) included in the systematic review contributed only 11% weight to the conclusion, e.g. ongoing pregnancy rate reduction with oral contraceptive pre-treatment (Figure 1 in Griesinger et al., 2010). The exclusion of these three small studies from the meta-analysis does not alter the conclusion (RR: 0.80, 95% CI: 0.65–0.98). Furthermore, different meta-analytical methods of synthesizing aggregate data in a meta-analysis are available and one important difference between these commonly used methods alludes to the way that weight is attributed to individual study. From a sensitivity analysis of the systematic review in question, regarding ongoing pregnancy rate, it becomes clear that the effect direction, the effect size and the precision with which the effect size is estimated (e.g. 95% CI) are not altered by the use of either a fixed-effects model (Griesinger et al., 2010) or random-effects model (Figure 1) for data synthesis.

Next, the potential impact of the clinical heterogeneity between the pooled studies is addressed by Garcia-Velasco and Fatemi. However, the studies included in the systematic review are remarkably homogenous: 96% of patients are normo-responders; all patients randomized to the study arm of the studies received a combined oral contraceptive; in all oral contraceptives the dose of ethinyl oestradiol was 30 μg; and all studies used one of only two gestagens (either desogestrel or levonorgestrel). Furthermore, all patients were treated in a multiple dose GnRH-antagonist protocol and all patients received recombinant FSH for ovarian stimulation. As ‘most relevant’ in terms of clinical heterogeneity, Garcia-Velasco and Fatemi identify the pooling of studies in which the pill-free interval (the period between the cessation of the oral contraceptive and the initiation of ovarian stimulation) was either 2–3 days or 5 days. Although it is acknowledged that this heterogeneity represents a potential limitation to the external validity of the overall finding, we stress that pooling of the three studies on normo-responder patients (Cédrin-Durnerin et al., 2007; Kolibianakis et al., 2006; Tavmergen et al., 2011) exclusively using (at least) a 5-day pill-free interval also suggests that the probability of ongoing pregnancy is significantly decreased after oral contraceptive pre-treatment (RR: 0.79, 95% CI: 0.64–0.99, \( P = 0.04 \)) (Figure 2).

Eventually, Garcia-Velasco and Fatemi address what they perceive as an inconsistency in the literature: While the systematic review in question comparing oral contraceptive pre-treatment with no oral contraceptive pre-treatment in GnRH-antagonist ovarian stimulation for IVF reports a significant reduction in ongoing pregnancy likelihood after oral contraceptive pre-treatment, no such effect was found in a study comparing long GnRH-agonist stimulation with no oral contraceptive pre-treatment with GnRH-antagonist stimulation with oral contraceptive pre-treatment (Garcia Velasco et al., 2011). However, not only is this approach comparing apples with pears, but indeed the study finding of Garcia-Velasco et al. (2011) is remarkably similar to the conclusion of our systematic review in both the direction of the effect as well as its magnitude. The ongoing pregnancy rate in their study is reduced by −6% (95% CI: −18.8% to 6.7%) in patients after oral contraceptive pre-treatment in a GnRH-agonist protocol. In order however, to show that a difference of such magnitude is not attributed to chance but rather represents a true effect, a much larger sample size would be necessary. Thus

![Figure 1](image-url)  
**Figure 1**  
Pooled risk ratio and 95% CI for ongoing pregnancy rate per randomized woman in the six randomized control trials derived from a random effects model. \( \text{OCP} = \text{oral contraceptive pill}; \text{M-H} = \text{Mantel-Haenszel.} \)
the finding of 'no difference' in the study by Garcia-Velasco et al. (2011) may well represent a type II error in statistical hypothesis testing and this study result must therefore not be interpreted as inconsistent with the existing literature.

In conclusion, the available data from randomized studies suggest to this day that oral contraceptive pre-treatment in GnRH-antagonist cycles for IVF is associated with a significantly reduced chance of ongoing pregnancy. This finding remains remarkably robust in multiple different scenarios that address the concerns of Garcia-Velasco and Fatemi (2015) enhancing our confidence that it constitutes an accurate estimate of the underlying effect. In light of this evidence, randomized studies should be performed to prove or disprove whether a similar effect exists after other oral contraceptive or stimulation protocols usage, and in other patient populations.

References


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