limitations, especially when conducting a short straightforward trial amongst everyday pragmatic practice such as ours. The difference between ITT and PP analyses is the number of subjects who were randomized but did not actually enter or complete the study. We clearly noted in our paper that only 1 of the 47 reasons for drop out following randomization was for a treatment-related reason (overstimulation in the FSH group; Fig 1). The large majority of the others did not enter the study following randomization or did not complete the study for purely personal reasons completely unrelated to the study itself. Thus, the PP analysis considered those who actually underwent one of the study treatments rather than including those who did not and so the PP analysis is closer to a comparison of the true efficacies of the treatments than ITT.

We are, therefore, confident that our conclusion based on the PP analysis that low-dose FSH is a more successful first-line treatment than clomifene citrate for anovulatory PCOS is the correct one and that an even larger study, if ever performed, will confirm our findings.

References

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Physiological sex steroid replacement in premature ovarian failure

Sirs,

We welcome the support expressed by Drs Mahajan and Mahajan regarding the administration of physiological hormone replacement regimen in women with premature ovarian failure. However, we would like to clarify some of the other points they have made.

It is true that in the trial (O’Donnell et al., 2012) we reported there was a substantial attrition in participants over the course of the trial, but 5 of the 34 randomized in the overall trial had undergone hysterectomy and so were not part of our assessment of uterine effects. What was striking in our trial was that the 12 withdrawals (out of 29 randomized and with intact uteri) occurred predominantly in the initial stages of the trial (10 in the first treatment block—9 of these within the first 6 months—compared with 2 in the second treatment block). As discussed in the paper, it seems likely that withdrawals in this trial were mainly due to the burden of the trial (which addressed other physiological systems in addition to uterine—cardiovascular and bone—and involved numerous follow-up and assessment appointments). This view is supported by the fact that there were 6 withdrawals out of 13 women receiving physiological regimen in the first treatment block, but only 1 out of the 12 receiving physiological regimen in the second treatment block. Furthermore, of all 7 withdrawals on physiological regimen, in only 3 cases was patch irritation mentioned.

If transdermal delivery is a problem for a woman needing this regimen, then oral administration could be considered, as suggested by Drs Mahajan. However, there is as yet no evidence that the effect would be comparable with what we have reported and this alternative route of administration may also result in poorly tolerated side effects. The additional benefits of transdermal delivery [for bone (Crofton et al., 2010) and cardiovascular (Langrish et al., 2009) end-points] also need to be borne in mind.

Reference

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