Overlooking intention-to-treat results

Sir,

We read with great interest the recently published randomized controlled trial (RCT) comparing clomifene citrate (CC) versus low-dose FSH for ovulation induction (OI) in women with polycystic ovary syndrome (Homburg et al., 2012). The study was well designed and conducted; however, we do not agree with the manner the results were reported and with authors’ conclusions.

As stated by authors ‘the aim of this RCT was to test the hypothesis that the (cumulative) pregnancy rate and live birth rates (LBRs) in OI are higher with low-dose FSH than with CC as a first-line treatment’. Indeed, when evaluating the effectiveness of an intervention in subfertility the primary main outcome of an RCT should be live birth per allocated woman, respecting the intention-to-treat (ITT) principle (ASRM, 2008).

In this trial comparing CC versus low-dose FSH, the ITT analysis was almost omitted, being limited to a few words in the middle of the article: ‘there was a similar proportion of women achieving a clinical pregnancy [80/159; 50.3 versus 59/143 or 41.3%, 95% confidence interval (CI): 22.1–20.3, P = 0.1] or a live birth (72/159 or 45.3 versus 53/143 or 37%, 95% CI: 2.8–19.3, P = 0.12)’. This information can be easily overlooked by a regular reader, since there is no mention to this analysis in the abstract, discussion or conclusion.

The risk ratio (RR) between the two treatments respecting ITT was not significant: the LBR was higher in women allocated to use low-dose FSH comparing with CC, but the estimated effect was relatively imprecise. Considering an RR > 1.2 or < 0.8 as the minimal clinically relevant difference (Martins et al., 2011), the 95% CI included both no effect and appreciable benefit favoring low-dose FSH (RR = 1.22, 95% CI = 0.93–1.61). Similar results were observed for clinical pregnancy: this rate was also higher in women allocated to use low-dose FSH, but the estimated was relatively imprecise with the 95% CI including both no effect and appreciable benefit (RR = 1.22, 95% CI = 0.95–1.56). The imprecise estimates occurred because authors used a very large effect (RR > 1.5) as minimal clinically relevant when calculating the sample size. If authors want to demonstrate an RR > 1.2 with an 80% power with α = 0.05, they should evaluate ~300 subjects per group. This sample size would also provide approximately 200–400 events (live births or clinical pregnancies), which is suggested as the minimum number of events to be observed before stopping a trial because of an early apparent benefit (Mueller et al., 2007).

In summary, the conclusions of this study should be based on this analysis, otherwise the size of the effect of the intervention might be overestimated (ASRM, 2008). Therefore, authors should conclude that while it is unlikely that low-dose FSH will reduce live birth or clinical pregnancy chance when compared with CC, it is still premature to conclude the superiority of this method of OI. This trial should be continued or combined with the results of other trials in a meta-analysis before any further conclusion.

References

ASRM. Interpretation of clinical trial results. Fertil Steril 2008; 90:S114–S120.


Wellington P, Martins1, 2, 3, *, Jaqueline B.P. Figueiredo1, 2, Andréa D.D. Vieira1 and Carolina O. Nastri1, 2

1Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), Av. dos Bandeirantes, 3900, Monte Alegre, 8 andar, Ribeirão Preto CEP: 14049-900, Brazil

2Escola de Ultra-sonografia e Reciclagem Médica de Ribeirão Preto (EURP), Ribeirão Preto, Brazil

3Instituto Nacional de Ciência e Tecnologia (INCT) de Hormônios e Saúde da Mulher, Ribeirão Preto, Brazil

*Correspondence address. Tel: +16-3602-2818; Fax: +16-3633-9946; E-mail: wpmartins@gmail.com
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Reply: Intention-to-treat and per-protocol analyses

Sir,

We thank Martins et al. for their interest in our paper (Homburg et al., 2012) and their letter regarding the relative value of the intention-to-treat (ITT) and per-protocol (PP) analyses.

From a purely statistical point of view, we have no argument with their very reasonable statistical comments. We would, however, like to make the following observations.

We respected the statistical value of the ITT analysis by presenting it first in the results section. It would, however, be inappropriate not to recognize that focusing on ITT rather than PP analysis also has its
limitations, especially when conducting a short straightforward trial amongst every day 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.

Reference

*Correspondence address. E-mail: r.homburg@vumc.nl
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Physiological sex steroid replacement in premature ovarian failure

Sirs,

We read with great interest the paper by O’Donnell et al. (2012), and support the use of a physiological sex steroid replacement (SSR) regimen among women with premature ovarian failure, which would offer therapeutic advantage in terms of improving uterine parameters compared with standard non-physiological SSR.

It is clear from the study that compliance with this regimen is a major issue as out of 34 randomized women only 17 could complete the full course of treatment. Irritant reaction and other side effects are the causes mentioned by authors. The dosage of estrogen needs to be changed from 100 to 150 μg from the second week and the frequency of progesterone pessary needs to be increased to 12 hourly in the second half of the cycle. These could be possible reasons for reduced compliance. We suggest that the use of oral medications in physiological SSR, as is used in standard SSR, would improve compliance.

References

Niraj N. Mahajan1,* and Kshitija Mahajan2
1 Department of Obstetrics and Gynaecology, B.Y.L. Nair Hospital and T. N. Medical College, Mumbai, Maharashtra 400008, India
2 Ruxmani Lying-In Hospital, Mumbai, Maharashtra 400008, India
*Correspondence address. 31, Dhaqnvantri Nagar, Sevagram, Wardha, Maharashtra 442102, India. Tel: +91-9821899581; E-mail: nirajdr@hotmail.com
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Reply: 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 uterus) 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, out 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.