van Rooij IAJ, Broekmans FJM, te Velde ER, Fauser BCJM, Bancsi LFJMM, de Jong FH, Themmen APN. Serum anti-Müllerian hormone levels: a novel measure of ovarian reserve. *Hum Reprod* 2002;**17**(12):3065–3071.

D. Cahill[1] and E. El Hakim[2,3]
[1]*University of Bristol, Level D, St Michael's Hospital, Bristol BS2 8EG*
[2]*St Michael's Hospital, Bristol*

[3]*Correspondence address. E-mail: samawal77@hotmail.com*

doi:10.1093/humrep/den440
Advanced Access publication on December 10, 2008

Reply: Managing IVF in women with consistently or variably elevated early follicular phase FSH

Sir,

We thank Drs El Hakim and Cahil for their interest and reaction to our paper (de Koning *et al.* 2008).

It is true that the highest measured FSH level is the one that makes clinicians aware of the possible low ovarian reserve. It is known that a normal or moderately elevated FSH can still be found in women with low ovarian reserve due to variable FSH levels and possibly variable cohort size. In our paper, we categorize the women with elevated FSH levels as 'High, High' (H,H group) when they showed an elevated FSH level both in a screening cycle and in the study and as 'High, Low' (H,L group) when they showed high FSH levels in a screening cycle but normal (<10 IU/l) in the study cycle.

The answer to the question whether the women moved between the groups is as follows: of the 11 women in the original H,H group, five had a normal FSH level in the third cycle and of the 11 women in the original H,L group, six had an elevated FSH level in the third cycle. This indeed shows the strong inter individual variation of FSH in these women. And interestingly, this is associated with concomitantly large variation in inhibin B levels in the preceding luteal phase, and in our view, this could be a useful value to evaluate in the cycle immediately before the stimulation for IVF.

The anti-Müllerian hormone (AMH) levels were indeed not different in the patient groups with either normal or elevated Day 3 FSH values and this is in line with observations that AMH does not vary much between the cycles (Fanchin *et al.*, 2005) and is not under a stringent extra ovarian control (La Marca *et al.*, 2006).

Our study was not designed to correlate FSH levels or AMH levels or AFC to clinical pregnancy rates but to describe the endocrinology in the spontaneous cycle of women with elevated FSH levels in the early follicular phase. In a prospective study, these parameters can be studied in this respect.

References

de Koning CH, McDonnell J, Themmen APN, de Jong FH, Homburg R, Lambalk CB. The endocrine and follicular growth dynamics throughout the menstrual cycle in women with consistently or variably elevated early follicular phase FSH compared with controls. *Hum Reprod* 2008;**23**:1416–1423.

Fanchin R, Taieb J, Lozano DHM, Ducot B, Frydman R, Bouyer J. High reproducibility of serum anti-Müllerian hormone measurements suggests a multi-staged follicular secretion and strengthens its role in the assessment of ovarian follicular status. *Hum Reprod* 2005; **20**:923–927.

La Marca A, Stabile G, Artenisio AC, Volpe A. Serum anti-Müllerian hormone throughout the menstrual cycle. *Hum Reprod* 2006; **21**:3103–3107.

C.H. de Koning[1] and C.B. Lambalk
Division of Reproductive Medicine VU University Medical Center, Amsterdam

[1]*Correspondence address. E-mail: rbcdk@xs4all.nl*

doi:10.1093/humrep/den444
Advanced Access publication on January 30, 2009

Why do couples drop-out from IVF treatment?

Sir,

We read with interest Verberg *et al.*'s (2008) recent article 'Why do couples drop-out from IVF treatment? A Prospective Cohort Study' in which the authors suggest that so-called mild treatment protocols might improve IVF outcomes by decreasing the number of patients who discontinue treatment before a pregnancy is achieved. Although we congraulate the authors on attacking this challenging subject and bringing the issue of patient drop-out to the forefront, we have several concerns with the methodology and ultimately of the conclusions in this article.

Despite the claim that there was an equal distribution of reasons underlying patient drop-out, 14% (5/35) of patients in the mild treatment arm and 36% (11/36) of conventionally treated patients had 'unknown' reasons for discontinuing treatment. The large number of patients with essentially 'no data' undermines the ability to draw conclusions with certainty about the psychological effect of the treatment protocol. In addition, since an almost equal fraction of respondents in each group indicated that 'physical or psychological burden of treatment' was the primary reason for discontinuing treatment, it can hardly be concluded that mild-stimulation techniques are the primary factor influencing a patient's persistence. As previously measured by the authors, depression/anxiety scores were not significantly different between groups after treatment, (Heijnen *et al.*, 2007) though a difference might have been expected if the psychological impact of treatment protocol influenced patient resolve.

We have gone on record in the past in asserting that the time has come to define 'patient-friendly' treatment as that which results in a healthy newborn achieved in a safe, cost-effective and timely manner (Flisser *et al.*, 2007). It is clearly erroneous to conclude that patients fare better psychologically when sub-optimal treatment protocols are chosen. In fact, we would claim that the opposite is true. Because of the high likelihood of drop-out, patients must be treated in the most efficient and cost-effective manner possible, and emphasis must therefore be placed on early success.

References

Flisser E, Scott RT, Copperman AB. Patient-friendly IVF: how should it be defined? *Fertil Steril* 2007;**88**:547–549.

Heijnen EMEW, Eijkemans MJC, DeKlerk C, Polinder S, Beckers NGM, Kickert ER, Broekmans FJ, Passchier J, te Velde ER, Macklon NS *et al.* A mild treatment strategy for in-vitro fertilization: a randomized non-inferiority trial. *Lancet* 2007;**367**:743–749.

Verberg MFG, Eijkemans MJC, Heijnen EMEW, Broekmans FJ, de Klerk C, Fauser BJCM, Macklon NS. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum Reprod* 2008; **23**:2050–2055.

Eric Flisser[1] and Alan B. Copperman
Reproductive Medicine Associates of NY, New York, NY, USA

[1]*Correspondence address. E-mail: eflisser@rmaofny.com*

doi:10.1093/humrep/den442
Advanced Access publication on December 10, 2008

Reply: Why do couples drop out from IVF treatment?

Sir,

We are grateful to the authors for the interest shown in our article, and their recognition of the importance of IVF drop out as a cause of reduced cumulative pregnancy rates from IVF treatment. We recognize that in the commercially competitive context in which they work, where patients usually have to finance IVF treatment themselves, there is considerable pressure to achieve 'early success'. However, the use of maximal stimulation regimens to achieve this ignores the impact of treatment burden on patients and offspring. We have therefore argued that IVF success should not be defined in per cycle outcome but over a period of time, or series of cycles (Heijnen *et al.*, 2004). This approach is supported by our recent RCT which demonstrated that a mild approach reduces complications, neonatal morbidity, number of treatment days, and injections and costs while achieving similar cumulative live birth rates over 12 months to conventional approaches. Even when early success is the aim, in many cases this will not be achieved. At this point, drop out rates become a major determinant of cumulative pregnancy rates. Our present study (Verberg *et al.*, 2008) shows that drop out rates are reduced when a mild strategy of treatment is provided.

With regard to the stated reason of drop out of individual cases, the correspondents are correct to note that a proportion of patients did not provide a reason for their drop out and that we can only speculate about their reasons for not responding to our questionnaire. Arguably, the failure of more patients from the conventional treatment group to respond to the questionnaire may reflect a reluctance to respond due to the relatively high impact of the conventional treatment both on a physical and psychological level. However, the fact that in both arms of the study patients indicated that the physical or psychological burden of treatment was the primary reason for drop out emphasizes the importance of reducing the burden of treatment per cycle, if drop out rates are to be reduced.

The correspondents again correctly cite our previous work which indicated that depression/anxiety scores after two completed treatment cycles were not significantly different between the mild and conventional strategy (Heijnen *et al.*, 2007). However, we subsequently showed that failure of IVF treatment after a mild treatment strategy results in fewer short-term symptoms of depression when compared with failure after a standard treatment strategy (de Klerk *et al.*, 2006, 2007), again pointing to an important difference in perceived burden of treatment.

We agree with the correspondents that we should focus on improving the 'patient friendliness' of IVF treatment. In our view, this should include consideration of the resultant child as well as the woman. In a series of studies, we have demonstrated that mild strategy reduces complication, multiple pregnancies, costs, duration of treatment, number of injections needed and now also drop out rates compared with more conventional approaches, while achieving similar cumulative live birth rates over a 12-month period (Heijnen *et al.*, 2007; Polinder *et al.*, 2008 and the papers by de Klerk *et al.*, 2007 and Verberg *et al.*, 2008). The correspondents have asserted that patient-friendly IVF requires early success. We would argue that this philosophy has been a major contributor to the epidemic of multiple pregnancies and high costs and burden of treatment associated with conventional IVF treatment. In the interests of both prospective parents, the child and society, it is now time to move on from the 'big bang' approach to IVF.

References

de Klerk C, Heijnen EM, Macklon NS, Duivenvoorden HJ, Fauser BC, Passchier J, Hunfeld JA. The psychological impact of mild ovarian stimulation combined with single embryo transfer compared with conventional IVF. *Hum Reprod* 2006;**21**:721–727.

de Klerk C, Macklon NS, Heijnen EM, Eijkemans MJ, Fauser BC, Passchier J, Hunfeld JA. The psychological impact of IVF failure after two or more cycles of IVF with a mild versus standard treatment strategy. *Hum Reprod* 2007;**22**:2554–2558.

Heijnen EM, Macklon NS, Fauser BC. The next step to improving outcomes of IVF: consider the whole treatment. *Hum Reprod* 2004; **19**:1936–1938.

Heijnen EMEW, Eijkemans MJC, DeKlerk C, Polinder S, Beckers NGM, Kickert ER, Broekmans FJ, Passchier J, te Velde ER, Macklon NS *et al.* A mild treatment strategy for in-vitro fertilization: a randomized non-inferiority trial. *Lancet* 2007;**367**:743–749.

Polinder S, Heijnen EM, Macklon NS, Habbema JD, Fauser BJ, Eijkemans MJ. Cost-effectiveness of a mild compared with a standard strategy for IVF: a randomized comparison using cumulative term live birth as the primary endpoint. *Hum Reprod* 2008;**23**:316–323.

Verberg MFG, Eijkemans MJC, Heijnen EMEW, Broekmans FJ, de Klerk C, Fauser BJCM, Macklon NS. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum Reprod* 2008; **23**:2050–2055.

M.F.G. Verberg[1], B.C. Fauser and N.S. Macklon
Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Heidelberglaan 100 3584 CS, Utrecht, The Netherlands

[1]*Correspondence address. E-mail: m.f.g.verberg@umcutrecht.nl*

doi:10.1093/humrep/den445
Advanced Access publication on January 22, 2009