Jeroen D. Kok, "Is Subfertility a Medical Condition?" *The Journal of Clinical Ethics* 18, no. 1 (Spring 2007): 49-52.

Is Subfertility a Medical Condition?

Jeroen D. Kok

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We need to consider this question when we address the ethical issues brought to our attention by Ferber. The view on the problem of subfertility varies strongly from one person to another. Where some will judge the inability to achieve pregnancy to be a case of bad luck or even not a problem at all, others will perceive or experience it as a nuisance, a dysfunction of the body, a disability, or maybe even a disease. To the last group, the author's statement that *in vitro* fertilization (IVF) is a physical solution to merely an emotional problem could be offending. Whatever someone's view on subfertility is, it will strongly affect the way and the degree that this individual will appreciate solutions to it, including advantages and disadvantages or risks related to these solutions.

In healthcare systems in the majority of Western Europe, reproductive medicine is not driven by commercial interests or by the desire to make money by creating "babies-on-demand." Therefore, because a physician does not have to weigh the best interests of patients against the need or desire to work more time-efficiently or more cost-efficiently, he or she can carefully select patients and treatments *lege artis*. Thus, the risk of overtreating subfertile couples with unnecessary, early, or overly aggressive IVF treatments should be low. For commercial subfertility institutes, where profitability and unconditional customer satisfaction prevail, this remains to be seen. Against that background and with the rising number of commercial and private fertility clinics worldwide, I share the concern for "overtreatment" implied by Ferber.

The fact remains that patients who are attending subfertility clinics are genuinely suffering from their childlessness.[1] Typically in our clinic, by the time an infertile couple would decide, in concert with their physician, to proceed with IVF, they will have gone through a difficult and lengthy period (often of several years) of extensive testing and less invasive but unsuccessful treatments. Only by then it is, without a question, in their best interest to be offered a safe and efficient, in terms of (cumulative) live birth rate, IVF treatment. To achieve this, at least some degree of ovarian stimulation is required, because having more than one oocyte available creates a level of redundancy to compensate for loss encountered at several critical stages in an IVF treatment, such as fertilization.

In this context, research is being done to predict the individual threshold and sensitivity to these stimulatory hormones, potentially allowing the development of individually tailored stimulation regimes.[2] Until this results in usable and reliable knowledge and techniques, standardized stimulation protocols will be used, meaning we will continue to encounter cases in which ovaries turn out to be more strongly stimulated than desired, especially in the first treatment cycle.[3] Regretfully, this brings along the risk of OHSS, a side-effect that is taken very seriously by those who are professionally involved, as judged by both the amount and content of the literature on the background, aetiology, ethics, consequences, prevention, and treatment of OHSS.[4] Nevertheless, there can never be enough awareness of the fact that severe OHSS is potentially lethal.

In the desire to improve the help given to subfertile patients, research focuses on every step of IVF

treatment, including ovarian stimulation,[5] with the aim of finding the optimal treatment. Optimal, in this context, implies the painful awareness of our limitations and that every treatment has its side-effects, and that the benefits of a treatment should be weighed carefully against its disadvantages. It also implies that the "optimal treatment" is dynamic in nature. That is to say, the "optimal treatment" is questioned, modified, reevaluated, and updated constantly, based on newly gained insight and knowledge. The article by Abramov and colleagues[6] is valuable because it warned of a potentially rising trend in the incidence of OHSS. Additionally, it presented an attractive opinion based on rather raw statistics, and it concluded with an appeal for reconsideration of ovarian stimulation strategies. This has nothing to do with "blowing the whistle," but it is an example of expression of the typically more implicit self-reflection that is characteristic for medical research. The proof of this, for instance, can be seen in the increasing numbers of articles that discuss or even advocate for mild or minimal stimulation regimes[7] following the period in which maximizing the number of oocytes obtained was considered beneficial. It explains why the appeal by Abramov and colleagues did not evoke the reaction Ferber expected, but this does not mean their message was being ignored.

The above-mentioned trend toward milder stimulation and IVF treatments is not only visible in the literature, but also in the daily practice of our clinic. Rough data from the period 1996 to 2002 indicate that the mean number of oocytes obtained in the first treatment cycle dropped from almost 11 to less than eight. The number of cases in this group with more than 20 oocytes obtained after ovarian stimulation decreased from more than 8 percent to less than 2 percent in this period, and I assume this decreasing trend has continued since.[8] Because we increasingly aim for mild ovarian stimulation (and single embryo transfer), in our clinic, cases with more than 20 oocytes after ovarian stimulation are considered a rarity nowadays.

A physician should, on pure medical and ethical grounds, carefully assess the benefits, drawbacks, and risks when determining whether a patient is eligible for IVF. The patient should be well informed about all these considerations. When the risks are acceptable to both the professional and the patient, there are no ethical objections to proceed with a carefully performed IVF treatment, if that is the best possible treatment for the patient's involuntary childlessness.

NOTES

1. L. Schmidt, "Psychosocial Burden of Infertility and Assisted Reproduction," *Lancet* 367, no. 9508 (February 2006): 379-80.

2. B. Imani et al., "Prediction of the Individual Follicle-Stimulating Hormone Threshold for Gonadotropin Induction of Ovulation in Normogonadotropic Anovulatory Infertility: An Approach to Increase Safety and Efficiency," *Fertility and Sterility* 77, no. 1 (January 2002): 83-90.

3. J.D. Kok et al., "A High Number of Oocytes Obtained after Ovarian Hyperstimulation for In Vitro Fertilization or Intracytoplasmic Sperm Injection is not Associated with Decreased Pregnancy Outcome," *Fertility and Sterility* 85, no. 4 (April 2006): 918-24.

4. I. Levin et al., "Increased Erythrocyte Aggregation in Ovarian Hyperstimulation Syndrome: A Possible Contributing Factor in the Pathophysiology of this Disease," *Human Reproduction* 19, no. 5 (May 2004): 1076-80; E. Pau, "Plasma Levels of Soluble Vascular Endothelial Growth Factor Receptor-1 May Determine the Onset of Early and Late Ovarian Hyperstimulation Syndrome," *Human Reproduction* 21, no. 6 (June 2006): 1453-60; B. McElhinney et al., "Ovarian Hyperstimulation Syndrome and Assisted Reproductive Technologies: Why Some and Not Others?" *Human Reproduction* 17, no. 6 (June 2002): 1548-53; D. Neubourg and J. Gerris, "Can We Eliminate Severe Ovarian Hyperstimulation Syndrome?" *Human Reproduction* 20 (August 2005): 2369; E.G. Papanikolaou et al., "Incidence and Prediction of Ovarian Hyperstimulation Syndrome in Women Undergoing Gonadotropin-Releasing Hormone Antagonist In Vitro Fertilization Cycles," *Fertility and Sterility* 85, no. 1 (January 2006): 112-20; P.E. Egbase, M. Al Sharhan, and J.G. Grudzinskas, "Ethical Issues on Studies on the Prevention of Severe Ovarian Hyperstimulation Syndrome," *Human Reproduction* 14 (November 1999): 2924; A. Wiser et al., "Outcome of Pregnancies Complicated by

Severe Ovarian Hyperstimulation Syndrome (OHSS): A Follow-Up Beyond the Second Trimester," *Human Reproduction* 20 (April 2005): 910-4.

5. S.J. Muasher, R.T. Abdallah, and Z.R. Hubayter, "Optimal Stimulation Protocols for In Vitro Fertilization," *Fertility and Sterility* 86, no. 2 (August 2006): 267-73; C. Dorn, "FSH: What is the Highest Dose for Ovarian Stimulation that Makes Sense on an Evidence-Based Level?" *Reproductive Biomedicine Online* 11, no. 5 (November 2005): 555-61; C. de Klerk et al., "The Psychological Impact of Mild Ovarian Stimulation Combined with Single Embryo Transfer Compared with Conventional IVF," *Human Reproduction* 21, no. 3 (March 2006): 721-7; A. Sophonsritsuk et al., "Comparison of Outcomes and Direct Cost between Minimal Stimulation and Conventional Protocols on Ovarian Stimulation in In Vitro Fertilization," *Journal of Obstetrics and Gynaecology Research* 31, no. 5 (October 2005): 459-63; M. Arslan et al., "Controlled Ovarian Hyperstimulation Protocols for In Vitro Fertilization: Two Decades of Experience after the Birth of Elizabeth Carr," *Fertility and Sterility* 84, no. 3 (September 2005): 555-69; "Erratum," *Fertility and Sterility* 84, no. 5 (November 2005): 1557; S.L. Tan et al., "A Randomized, Double-Blind, Multicenter Study Comparing a Starting Dose of 100 IU or 200 IU of Recombinant Follicle Stimulating Hormone (Puregon) in Women Undergoing Controlled Ovarian Hyperstimulation for IVF Treatment," *Journal of Assisted Reproductive and Genetics* 22, no. 2 (February 2005): 81-8.

6. Y. Abramov, U. Elchalal, and J.G. Schenker, "Severe OHSS: An 'Epidemic' of Severe OHSS: A Price We Have to Pay?" *Human Reproduction* 14, no. 9 (September 1999): 2181-3.

7. B.C. Fauser et al., "Minimal Ovarian Stimulation for IVF: Appraisal of Potential Benefits and Drawbacks," *Human Reproduction* 14, no. 11 (November 1999): 2681-6; de Klerk et al., see note 5 above; M.J. Pelinck et al., "Minimal Stimulation IVF with Late Follicular Phase Administration of the GnRH Antagonist Cetrorelix and Concomitant Substitution with Recombinant FSH: A Pilot Study," *Human Reproduction* 20, no. 3 (March 2005): 642-8; S.C. Williams et al., "Minimal Ovarian Hyperstimulation for In Vitro Fertilization Using Sequential Clomiphene Citrate and Gonadotropin with or without the Addition of a Gonadotropin-Releasing Hormone Antagonist," *Fertility and Sterility* 78, no. 5 (November 2002): 1068-72; Sophonsritsuk et al., see note 5 above; M.J. Pelinck et al., "Cumulative Pregnancy Rates after Three Cycles of Minimal Stimulation IVF and Results According to Subfertility Diagnosis: A Multicentre Cohort Study," *Human Reproduction* 21, no. 9 (September 2006): 2375-83; D. de Jong, N.S. Macklon, and B.C. Fauser, "A Pilot Study Involving Minimal Ovarian Stimulation for In Vitro Fertilization: Extending the 'Follicle-Stimulating Hormone Window' Combined with the Gonadotropin-Releasing Hormone Antagonist Cetrorelix," *Fertility and Sterility* 73, no. 5 (May 2000): 1051-4.

8. Unpublished and exploratory data by J.D. Kok from the clinical database of the Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Netherlands, 1996-2002.