Ethical recruitment of patients for PGS trial

Sirs,

Ankum et al. (2008), members of a Data Safety and Monitoring Committee (DMC), defended their decision to allow investigators to continue to recruit patients for a study comparing conventional IVF against IVF plus preimplantation genetic screening (PGS) (Mastenbroek et al., 2007) in the face of masked interim data showing superiority of treatment A over treatment B \( (P = 0.02) \). They argued that if the study had been stopped for negative effect of PGS despite not reaching the preset threshold \( (P = 0.0052) \), the trial would have been dismissed by protagonists of PGS as having insufficient statistical power.

We note that the thresholds set by the DMC for stopping the study suggest that it gave equal weight to benefit and harm. This explains its decision to leave the interim data masked. Moreover, there is a strong impression that the study (Mastenbroek et al., 2007) took its point of departure to be the hypothesis that PGS affords benefit. We have some ethical reservations regarding both the decision to set symmetrical criteria for early termination of the study as well as the appropriateness of the DMC’s justification for its decision in the case at issue.

It has been recommended that all randomized trials should be prepared for results with trends in either direction irrespective of how unlikely a negative trend may seem at the outset, and that a lower level of evidence should generally be required for early termination of trials due to negative trends, in particular when prior evidence of benefit is weak (DeMets et al., 1999).

We note that both the DMC (Ankum et al., 2008) and the investigators (Mastenbroek et al., 2007) stress that there was no prior evidence of benefit of PGS, at least as far as the primary and secondary outcomes of the study were concerned. Against this background, we wonder why the DMC set symmetrical thresholds for early termination of the study.

The Declaration of Helsinki states that—‘in medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society’ (World Medical Association, 2004). It is our feeling that in setting symmetrical thresholds the DMC gave the interests of ‘science and society’ similar, if not greater, weight than to those of the study subjects.

Equally, in justifying its decision it gave insufficient consideration to the obligation set by the Declaration of Helsinki. Considerations such as ‘convincing protagonists of PGS’, or even ‘the benefit to future patients’, should not be allowed to overshadow the interests of patients participating in clinical trials.

Finally, the information provided in both articles suggests that the institutional review boards and the Central Committee on Research Involving Human Subjects in the Netherlands may not have been aware of a planned interim analysis, let alone its details. Indeed, the DMC was established at the launch of the study (Ankum et al., 2008), and the interim analysis was planned two months thereafter (Mastenbroek et al., 2007). It is unclear how these institutions could have exercised their duty to protect the interests of the research subjects in the absence of such pertinent information.

References


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Reply: Ethical recruitment of patients for PGS trial

Sir,

In their response to our paper, Zosmer, Epstein and Al-Shawaf have expressed ethical reservations regarding both our decision to set symmetrical criteria for early termination of the preimplantation genetic screening (PGS) trial, as well as the

Sirs,

Letters to the Editor
appropriateness of our justification for doing so (Mastenbroek et al., 2007; Ankum et al., 2008).

Whenever promising new treatments have already been adopted by the field and have been implemented into daily care without randomized trials justifying this course of action, a situation may arise where the question as to which treatment should be regarded as being ‘experimental’ and which one as ‘standard care’ has reversed or has even become irrelevant. Not the old type of management is the one to beat, but the new one which has already been adopted as being the new standard. This situation occurred at the onset of PGS trial, when it had already been suggested that performing IVF without PGS was unethical (Gianaroli et al., 1997, 2005; Munné et al., 1999, 2003, 2006; Kahraman et al., 2000). For this reason, we made a strong plea in our discussion paper underlining the prerequisite of having randomized data before new treatments are being adopted in general practice.

As Data Monitoring and Safety Committee (DMSC) members, we decided to adopt symmetrical criteria for early termination at the interim analysis. This equally valued direct and indirect benefits and burdens for trial participants and those for future patients and society. We acknowledge the authors’ ethical reservations in these matters, and would indeed have set different criteria for early termination if the present study had not been performed as a post hoc randomized controlled trial. We strongly believe that, given these circumstances together with the O’Brien–Fleming criteria which were not met at interim analysis, continuation of the PGS trial was indeed justified (O’Brien and Fleming, 1979). Consequently, this allowed us to speculate on various subjects, e.g. ‘convincing protagonists of PGS’ and ‘the benefit of future patients,’ without crossing the ethical borders set by the declaration of Helsinki, neither in our responsibilities as DMSC-members nor in writing our discussion paper for Human Reproduction.

We would like to stress that the situation in the PGS trial differed fundamentally from those circumstances, where a new treatment is truly experimental and has not yet been adopted in general practice. If the chance of an experimental treatment being superior crumbles as the study progresses in such a trial, it would indeed be unethical to continue, especially when vital outcomes are at stake. But even then the decision to unmask treatment allocation at interim analysis and to truncate the trial prematurely would still bear the risk of regrets later on, since interim findings may have resulted from sheer coincidence after all (Montori et al., 2005).

After publication in the New England Journal of Medicine, the final results of the PGS trial have inspired the current discussions on the status of PGS as part of IVF programs (Munné et al., 2007). This has led to a situation where new international trials on the same subject are being seriously considered in order to try and refute its findings. Only the large size of the PGS trial, the fact that differences were statistically significant and have been published in a high ranking medical journal, seem to have convinced protagonists of PGS that new trials would probably be unethical, thereby benefiting many future patients. For certain, stopping the PGS trial prematurely would have led to many more patients being exposed to PGS.

We thank the authors for their contribution to this discussion and for bringing these matters to our attention, which has given us the opportunity for this response.

References


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