Reply: RCT of real versus placebo acupuncture in IVF

Sir,

We refer to the letter by Renckens addressed at our recent publication (So et al., 2009) on the use of acupuncture in IVF treatment, stating that Human Reproduction should not publish papers on absurd forms of treatment such as acupuncture. Although there are no particular comments directed to us, we would like to respond to the opinion stated in the letter and express our views on Traditional Chinese Medicine (TCM) and acupuncture.

(i) The WHO booklet on Standard Acupuncture Nomenclature aims to develop a uniform nomenclature in acupuncture so as to achieve global agreement on a standard acupuncture nomenclature. This has greatly facilitated research and exchange of information in this area. However, it should be clarified that the purpose of this booklet is not to correlate the acupoints with the well-known anatomical landmarks in Western Medicine.

(ii) Different medical systems may have different developments and philosophies. The theory of Yin-Yang used in TCM is certainly different from that of Western Medicine. Although anatomical correlates of acupoints are still not demonstrated, we should not reject the existence of the acupoints and the effects of TCM in clinical trials.

(iii) IVF is not listed as an indication in the WHO report ‘Acupuncture: review and analysis of reports on controlled clinical trials’ because the first randomized study on acupuncture in IVF (Paulus et al., 2002) was published in 2002. Other relevant randomized studies were published in 2006 and several meta-analyses on acupuncture in IVF were published in 2008. There are many meta-analyses on acupuncture in the Cochrane library.

(iv) In our paper, we put down the rationale of choosing the acupoints, which is based on the TCM theory. This intends to give the readers more information about Chinese Medicine. In order for the reader to appreciate the effects of acupuncture, we determined outcome measures that are very well defined, scientifically valid and commonly used in studies in Western Medicine.

(v) We strongly believe that well-conducted RCT, especially double blind, is still the golden method to examine the effectiveness of a therapy, whether the therapy is believed by some to be absurd or not. We will be delighted to learn any other means which are better to study absurd claims. It is also unfair to say that a therapy is absurd just because it is not consistent with our own beliefs. Science has advanced because scientists have continued to challenge and change some of the established concepts by properly conducted experiments. In the assessment of the efficacy of a therapy, a properly conducted RCT is the best experimental approach to prove or refute the efficacy of a form of therapy.

(vi) As the design of studies including those on TCM is evolving and improving, it seems unfair to point out the methodological weakness based on evidence published before 1989. There were also many examples of clinical trials conducted in Western countries with methodological weaknesses. Again, we should always keep the most updated evidence in Science. It is well known that studies with negative results are more difficult to be published than those with positive results. This may be related to the publication policy of journals, rather than where the papers come from. We agree that journals nowadays should not publish papers with serious methodological problems but we strongly disagree that journals do not publish properly conducted RCT on therapies which may appear ‘absurd’ to some readers. Scientific development will be suffocated if journals adopt this approach.

We are of the opinion that well-conducted research in TCM should be continued in order to confirm or refute the effectiveness of TCM in clinical practice. The results of these studies, whether positive or not, should be published in peer-reviewed journals. Last but not least, we thank the reader for the comment which is a reminder that we must continue to conduct studies in the highest scientific standard.

References


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Possible impact of LH-containing gonadotrophins on diploidy rates in preimplantation embryos

Sir,

We have read with great interest the retrospective, controlled cohort study performed by Weghofer et al. about the possible impact of LH-containing gonadotrophins on diploidy rates of preimplantation embryos in patient undergoing long agonist stimulation with either recombinant FSH (rFSH) or hMG. However, we would like to comment on some of the methodological aspects of this study (Weghofer et al., 2008).

No significant differences between rFSH and hMG groups are reported by the authors regarding the mean number of oocytes retrieved (23.7 ± 11.7 versus 20.3 ± 8.4, respectively), the mean number of fertilized oocytes (13.8 ± 5.8 versus 11.9 ± 5.6, respectively) and on the quality of obtained embryos evaluated according to mean number of blastomeres on Day 3 (6.0 ± 1.2 versus 6.2 ± 1.0, respectively), and the mean fragmentation rate (15.8 ± 14.0 versus 16.4 ± 8.4, respectively). Moreover, similar numbers of chromosomally normal Day 3 embryos are reported in both groups (3.1 ± 2.1 versus 3.3 ± 2.5, respectively). The only significant difference between the two
groups is found by analyzing the rate of diploid embryos per analyzed embryo (calculated on a per patient basis) (45.3% in the rFSH group versus 69.8% in the hMG group; P < 0.01).

The major problem of the study is that the mean number of analyzed embryos was significantly higher in the rFSH group than in the hMG group (8.1 ± 5.0 versus 5.3 ± 4.4, respectively). In other terms, 58.6% [(8.1 × 52)/(13.8 × 52) × 100] of the fertilized oocytes were biopsied in the first group and only 44.6% [(5.3 × 52)/(11.9 × 52) × 100] in the second (P < 0.001, by Chi-squared test). No apparent justification is present in the study to explain this difference. One possibility could be that more severe embryo selection criteria for genetical analysis were used in the hMG group when compared with rFSH group. More accurate morphological assessment per se may have increased the proportion of chromosomally normal embryos (Ziebe et al., 2003). A second possibility may be that a higher proportion of embryo developmental arrest was observed in the hMG group. It is stated by the authors that ‘Embryos which did not undergo developmental arrest were available for biopsy’. If this would be the case, as high as ~55% developmental arrest on Day 3 in the hMG group should be better explained by the authors. Moreover, these data would be in contradiction with previous works that reported better embryo quality after stimulation with hMG (Andersen et al., 2006; Ziebe et al., 2007).

A second aspect concerns the fact that a single cell-blastomere biopsy was performed to evaluate the effect of the two ovarian stimulation regimens on embryo aneuploidy rate. Although the biopsy of only one cell does not seem to affect, in general, the efficiency of the FISH PGD procedure (Goossens et al., 2008), the possibility to relate the impact of LH-containing gonadotrophins not only to meiotic completion, but also to mitotic segregation errors would have been interesting. In a recent prospective, randomized controlled trial, Baart et al. (2007) reported that the stimulation protocol is able to affect the rate of embryonic ploidy. The effects of the stimulation regimens were mainly ascribed to the incidence of mosaic embryos. In view of these findings, the analysis of two cells per embryo would have help to better understand the mechanism by which LH supplementation may counteract to better preserve oocyte competence during folliculogenesis.

Because of the methodological pitfalls identified above, the effect of LH-containing gonadotrophins on diploidy cannot be, in our opinion, fully evaluated from the study performed by Weghofer et al. Further studies, designed in a prospective randomized way, analyzing the same proportion of embryos of the same morphological quality are in our opinion required to conclude on this issue.

References


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Reply: Possible impact of LH-containing gonadotrophins on diploidy rates in preimplantation embryos

Sir,

We appreciate Drs Ubaldi’s and Rienzi’s interest in our study (Weghofer et al., 2008). As we pointed out in the Discussion of our paper, retrospective studies, even if case controlled, carry obvious risks of selection biases. We carefully searched for such biases, as noted in the description of statistical methodologies, and were unable to detect any. This, however, of course, still does not preclude such biases, but prevents us from being able to offer an explanation for such potential biases, as suggested by Ubaldi and Rienzi in their letter.

We, therefore, also cannot refute some of their suggested explanations, though fail to see how biases may result in application of more ‘severe’ embryo selection criteria for genetic analysis in hMG than rFSH cycles. In our program, embryo selection is the responsibility of embryologists, who may be aware of stimulation protocols utilized, but do not have guidelines to act upon such knowledge. Selection is based on embryo performance, maternal age and previous IVF cycle history. A selection bias according to the stimulation protocol used is, therefore, unlikely.

Their suggestion that hMG cycle embryos demonstrate higher rates of arrest cannot be as easily refuted and may deserve follow-up. Though our data demonstrate a trend towards slightly lower oocyte and embryo numbers in hMG cycles, differences failed to reach statistical significance. One could, moreover, speculate that such an occurrence—if present to a clinically relevant extent—should result in overall lower pregnancy rates in hMG cycles, which quite obviously is contradicted by most of the relevant literature.

Finally, the two colleagues also address in their comments the highly controversial issue of 1- versus 2-cell embryo biopsy. An adequate response to this point would exceed the framework of this