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EDITORIAL

Accessible and affordable IVF: is Bob Edwards' dream about to become reality?

In this issue of *Reproductive Biomedicine Online* we publish an important paper plus a commentary on low cost IVF (van Blerkom et al., 2014; Ombelet, 2014). These articles, the broad content of which received considerable press attention after presentation at the London meeting of ESHRE in July 2103, make important claims on our attention. First, the paper by Van Blerkom et al. reports the meticulous development and testing of a simplified laboratory method for human IVF, together with the outcome of a pilot clinical trial using it. The system supports apparently normal fertilization and preimplantation embryogenesis to the hatched blastocyst stage. It could be set up in small centres or developing countries, without the need for specialized equipment such as microprocessor-controlled tissue culture incubators, large-area air filtration systems, available medical-grade gases (N_2, O_2, CO_2), costly culture ware, and ready access to replacement components or the technical expertise to effect repairs. In this system, development occurs entirely undisturbed in a completely closed system, which appears to be controlled for both pH and temperature and which permits limited but timed performance assessments for embryo selection *in situ*. The study also reports a comparison of the outcome of IVF of mouse eggs and their onward culture in the closed system with that achieved in an open (conventional) system, as well as the outcome achieved using human thawed pronucleate or 2-cell eggs in the closed system.

For mice, fertilization rates were: ~81% (130/161) open versus ~84% (128/153) closed system; and rates of development to the expanded blastocyst stage were 87% (74/130) open versus 91% (139/153) closed system, neither being significantly different. However, hatching was higher in the closed system (62%, 86/139) than in the open system (28%, 21/74) ($P < 0.01$). For the human eggs, 61 frozen-thawed tripronucleate embryos (that had resulted from dispermic penetration), 27 normally fertilized bipronucleate embryos and 30 nascent 2-cell embryos were incubated in the closed system. In excess of 80% of these 118 eggs underwent cleavage, but only 32% of the latter two groups (18/57) progressed to the expanded blastocyst stage, of which 55% (10/18) initiated hatching. This blastocyst rate is promising considering the source of these embryos.

Subsequently, the women in 40 couples who consented to take part in the trial were stimulated with a combination of recombinant FSH (Puregon; MSD) or purified urinary FSH (Menopur; Ferring) and GnRH antagonist (Orgalutran; MSD). Of these, 35 were considered suitable for continuation. Aspirated cumulus-oocyte complexes from each woman (totalling 493) were allocated to IVF using either the routine open system or the simplified closed system, resulting in 232 and 199 metaphase II oocytes, respectively. Rates of fertilization and cleavage to day 3 for the open system were (147/232) 63% and (130/147) 88% respectively, and for the closed system were (138/199) 69% and (119/138) 86% respectively. The selection of a single embryo for transfer (SET) to each patient on day 3 was made by an independent embryologist, blind to the culture system used (achieved by the use of photographic images). For 23/35 patients, the embryo selected originated from the simplified closed system. In this group, of the 23 embryos transferred from the closed system, 8 implanted, of which 1 miscarried at eight weeks gestation and 7 healthy babies were born. For the open conventional system, the equivalent numbers were 12 transfers with two clinical pregnancies resulting.

These results are encouragingly impressive. This new methodology addresses a fundamental obstacle to current treatment for many, namely accessibility. It should also reduce costs thereby also making it more widely affordable, although the actual reduction in cost will need to be assessed in different economies, as other essential components of assisted reproduction remain unchanged. The need for affordable and accessible systems in much of the developing world is set out compellingly in the accompanying commentary by Ombelet (2014). We applaud the effort and intent driving this work, which will, if successfully applicable more widely, also facilitate access to IVF for those many couples in the developed world, who currently cannot afford the treatment. The much simplified culture system described here, that produces results very similar to those obtained at highly resourced centres, but without

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the attendant and costly infrastructure typically required by contemporary IVF programmes, represents a potential major break through.

The authors themselves set out some questions that need answering, saying:

> ''Additional studies will be needed to determine the following: (i) whether the outcomes of the simplified culture system can be improved by extending culture to the expanded blastocyst stage; (ii) how the simplified culture system can be implemented in high-resource settings where, for many prospective patients, conventional IVF is currently cost-prohibitive; (iii) how best to proceed in developing countries to make IVF accessible assessable, affordable and acceptable as a treatment for common forms of infertility; and (iv) whether similar pregnancy rates can be achieved using natural cycle IVF or mild/low-cost ovarian stimulation protocols, such as clomiphene citrate alone or in combination with purified urinary FSH.''
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> (van Blerkom et al., 2014)

We agree with these suggestions, but ask some further questions of the authors and thereby inject a note of caution into the discussion. First, this approach must be replicated in different laboratories and under field conditions before we can be truly confident of its robustness. The careful and meticulous commitment and expansive background knowledge and understanding that went into developing this technology will not necessarily be present in other situations. Second, its long-term safety needs to be assessed. Third, it must be widely stressed to all prospective patients that only a subset of them can benefit from its use, if expectations are not to be falsely raised. Fourth, the real cost of the method should be independently assessed by a health economist for hidden infrastructure and personnel costs, and, even if only minor cost reduction is found, this technology could be considered as first line treatment for best-prognosis couples in fully staffed and equipped ART facilities. Finally, the authors will need to prepare experienced embryologists internationally to embrace and adapt to this development rather than feel that some of their skills may become largely redundant, because the results imply that there is only a limited need for embryologists, embryo selection or quality control in simple IVF.

Bob Edwards, who always hoped for just such a breakthrough, would have been delighted to see this landmark publication. We wish this new technology a sound and productive future in the real hope that it is truly the major breakthrough that we can all applaud unreservedly together.

References

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