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Editorial

Defining the appropriate laboratory environment for fostering healthy embryogenesis in humans: a place for consensus

When considering the multitude of elements that influence success in human assisted reproductive technology (ART), there is something upon which we all can agree: it is complicated. Specifically, if we consider in total the influential items for the laboratory, the clinical environment, ovarian stimulation and ovulation triggering, the retrieval room, embryo transfer technology and patient-specific characteristics, it is easy to tabulate over 200 factors that can alter outcome (Pool et al., 2012). It gets no easier if the analysis is restricted to the laboratory or even to a consideration within the laboratory of the role of environmental factors such as air quality. It is this complexity – the impossibility of isolating a single factor for experimental evaluation while holding all others constant – that eliminates the randomized controlled trial as the appropriate tool for defining air quality in the IVF laboratory (Cohen and Alikani, 2013). This very much relates to the significance of the 'context' of a given intervention rather than the intervention *per se* – a well-known topic of intense discussion regarding the limitation of evidence-based medicine research strategy (Fauser, 2016).

The difficulty in obtaining direct evidence, along with the unethical aspect of experimentally exposing human gametes and embryos to potential environmental toxins, were two of the premises for a meeting of 13 experts representing academia, private practice and commercial enterprises convened to identify and discuss laboratory environmental influences. The results of their deliberations are presented in this issue of *RBM Online* in the article 'Cairo consensus on the IVF laboratory environment and air quality: report of an expert meeting' (Mortimer et al., 2018) in which the authors list 50 consensus points for the provision of safe air quality, covering laboratory design, construction, operation and engineering controls.

Concerns about the adverse effects of poor air quality upon human embryogenesis have been voiced routinely in the literature since the 1990s, some of which are amalgamated in two timely reviews (Morbeck, 2015; Thomas, 2012). In addition to providing a historical context, Thomas (2012) describes quantitative analytical tests for airborne contaminates including US Environmental Protection Agency (EPA) method EPA TO15, capable of identifying 97 of the 187 hazardous airborne pollutants listed by the EPA, and EPA TO11 which focuses on identifying ketones and aldehydes, including formaldehyde. He further suggests design controls for the laboratory to control airborne contamination and to improve other operational practices relating to aspects such as staging areas, laboratory access and cleaning agents. More recently, Morbeck (2015) examined eight studies concerning the effects of air filtration, both particulate and chemical, upon clinical outcome in IVF. Endpoints ranged from the evaluation of clinical pregnancy rate alone (Jindal et al., 2008; Knaggs et al., 2007) to the inclusion of fertilization, cleavage and blastocyst rates plus clinical pregnancy, implantation and live birth rates (Munch et al., 2015). As Morbeck indicates, while each study noted an improvement in either laboratory and/or clinical outcomes following filtration, nearly all studies housed comparisons that were unmatched and retrospective, thus leaving the possibility that the results were related to another uncontrolled variable and therefore circumstantial. The report by Munch *et al.* is of particular interest as it includes laboratory and clinical data from a period when carbon filtration of laboratory air was present, an interim period when it was inadvertently absent, and then again when carbon filtration was restored. A consideration of all cycles showed that the restoration of carbon filtration resulted in a return to the fertilization, cleavage and blastocyst rates achieved in the original carbon-filtered period from a depressed rate seen during the period when there was a lack of filtration. While this was also true when only ICSI cycles were considered, it did not hold for conventional insemination cycles. In those, neither fertilization nor blastocyst conversion rates were affected by the absence of carbon filtration. Despite the effects seen upon laboratory parameters, there was no significant effect of a lack of carbon filtration upon clinical pregnancy rate, implantation rate and live birth rate when all three periods were compared. In a different setting, Esteves and Bento (2013) reported live birth rates increased while miscarriage rates decreased, both significantly, when IVF patients were treated in a

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new facility constructed in compliance with cleanroom standards for particulates and volatile organic compounds (VOC) as dictated by the Brazilian Cells and Germinative Tissue Directive. As in earlier studies, the retrospective comparison of these 2060 patients was made with a group of 255 patients treated earlier by the same practice in a conventional facility. To reduce the number of variables influencing outcome, Heitmann et al. (2015) compared cycles performed in a new facility, where strategic engineering designs were employed, with those carried out in an old facility housed in operating room space where air was being supplied by the operating room air handler without consistent positive pressure being attained in the laboratory. Environmental improvements were extensive in the new facility and included a dedicated air filtration system employing humidity control, paper filtration, UV light exposure and filtration through a mixed bed of activated charcoal and potassium permanganate prior to HEPA (high efficiency particulate air) final filtration. Construction allowed for a sealed environment, low to no VOC-emitting materials, positive pressure and limited access by authorized personnel. Further, laboratory equipment utilized was the same in both facilities, as were the physicians, embryologists, nurses and protocols. The rate of both embryo implantation and live birth improved significantly in the new facility. Despite the retrospective nature of the comparison, it is likely that this is as close to a valid comparison of environmental influences in the IVF laboratory as can be made.

To an experimentalist, a consensus of opinions carries dubious weight given that it is not a component of the scientific method. Perhaps Bertrand Russell expressed it best in this partial quotation from his 1929 treatise, *Marriage and Morals*, when he quipped 'The fact that an opinion has been widely held is no evidence whatever that it is not utterly absurd. . .'. But in the Cairo consensus we have specific suggestions from a panel of scientists deeply experienced in laboratory design, construction, operation and air quality measures with the safety of human gametes and embryos as the sole endpoint. Anyone considering new laboratory construction, re-vamping of an older facility or seeking appropriate ways to ensure a high-quality environment can now find a practical compendium of what to consider and what to do within a single document. Technology is not free and we owe it to patients to maximize accessibility to treatment as best we can. Adding costs to the construction and operation of our facilities, when unwarranted, thwarts that goal. A responsible part of providing a safe environment is the inclusion of economic considerations in our planning and addressing whatever the environmental testing suggests is required; however, whatever remedy is needed is undoubtedly covered by the Cairo consensus.

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Thomas B. Pool
Bart C.J.M. Fauser
E-mail address: office@rbmonline.com