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COMMENTARY

Implementation of cleanroom technology in reproductive laboratories: the question is not why but how

Sandro C Esteves *, Fabiola C Bento

ANDROFERT, Andrology and Human Reproduction Clinic, Center for Male Reproduction, Campinas, São Paulo, Brazil
* Corresponding author. *E-mail address:* s.esteves@androfert.com.br (SC Esteves).

Abstract Two articles recently published in *Reproductive BioMedicine Online* described how fertility centres in the USA and Brazil implemented air quality control to newly designed facilities. In both case scenarios, a highly efficient air filtration was achieved by installing a centred system supplying filtered air to the IVF laboratory and other critical areas, combining air particulate and volatile organic compound (VOC) filtration. Evaluating retrospective data of over 3000 cycles from both centres, live birth rates were increased by improvements in air quality and laboratory environment. This commentary discusses some of the key aspects of air contamination in the IVF settings, and highlights the fact that a risk management analysis taking into consideration all variables that play a role in air contamination is paramount for the reduction of the risk of poor IVF outcomes due to improper air quality conditions.

KEYWORDS: air quality, assisted reproductive techniques, cleanroom, laboratory environment, volatile organic compounds

Introduction

It is well known that human gametes and embryos cultured *in vitro* are sensitive to toxic agents. Airborne toxicants may negatively impact embryo development, and consequently, implantation rates (Hall et al., 1998). Recognizing that such effects can be counteracted to some extent by controlling laboratory air quality, regulatory directives, namely the European Union Tissues and Cells Directive (Commission of the European Parliament, 2004) and the Brazilian Tissues and Cells Directive (ANVISA. Brazilian National Agency for Sanitary Surveillance, 2006), dictate specific requirements for air quality control within reproductive laboratories in addition to other measures aimed at increasing quality in all units performing assisted reproduction techniques. While both regulatory directives aim to safeguard public health in line with the precautionary principle (Commission of the European Union Communities, 2000), thus preventing transmission of infectious diseases via transplanted tissues and cells, they require different strategies to mitigate the air-related risks (Esteves and Agarwal, 2013).

Driven by recognizing the importance of laboratory air quality to IVF success or compliance to regulatory requirements, many practitioners have installed filtration systems in their units (Esteves and Bento, 2013; Knaggs et al., 2007; Legro et al., 2010; Van Voorhis et al., 2010). In a recent issue of *Reproductive BioMedicine Online*, Heitmann and colleagues reported how measures to control air contamination were implemented to their newly designed facility (Heitmann et al., 2015). The authors contributed a detailed description of their filtration system and construction methods, which included removal of both particulate matter and volatile organic compounds (VOC). Not surprisingly, air quality conditions were superior in the new site, and were associated

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with significantly higher embryo development, implantation and live birth rates in couples undertaking treatment in their new facility.

Attention to VOC and good laboratory practices

We concur with Heitmann and colleagues that VOC removal should be an integral element of air cleanness in IVF. Removal of VOC is achieved by potassium permanganate-impregnated, pelletized coconut shell-based activated, carbon filters (Chiang et al., 2001; Hall et al., 1998). In an article published earlier in *Reproductive BioMedicine Online*, we also described how we implemented cleanroom technology in our newly constructed IVF unit, combining both air particle and chemical filtration (Esteves and Bento, 2013). Equally important were the methods to reduce contamination, including training laboratory personnel and validating/monitoring the installations during routine workload. Personnel should understand the principles of air quality control, including the function of airflows and airlocks, hygiene, dress code and the use of cleaning agents. Evaluating results over a 9-year period, we demonstrated the feasibility of operating under these optimum environmental conditions, which resulted in an increase in live birth rates. Interestingly, embryo development was markedly better as air quality improved. Lastly, periodic air quality monitoring ensured that air quality requirements established by the Brazilian regulatory agency were met.

In both aforementioned studies, an air filtration system controlling indoor particulate and VOC was implemented using a centralized system supplying filtered air not only to the IVF laboratory but also to adjacent areas where important IVF processes take place; namely, operating room and embryo transfer room. Humidity and temperature were controlled to ensure optimum VOC desorption efficiency. In addition, construction materials and laboratory furniture that emitted low VOC were carefully selected.

Understanding air contamination in the IVF environment

Because bacteria, fungi and spores can attach themselves to particles, an important goal of air filtration in the IVF environment is to decrease the number of particles in air suspension through the use of high efficiency filtration systems. Removal of airborne particulates by forcing movement of air using positive air pressurization through a series of filters of increasing efficiency, which is achieved by decreasing the diameter of the membrane pores, equates to an increase in air quality (National Environmental Balancing Bureau, 1998). Although air particle filtration is a logical concept, VOC are 100 to 1000 times smaller than the effective pore size of high-efficiency particulate air (HEPA) filters, and therefore cannot be trapped by such filters. VOC, which are constantly generated by materials and cleaning agents used in the laboratory, react with the indoor ozone. These chemical reactions produce submicron-sized particles and harmful by-products that have been associated with poorer IVF outcomes. In the IVF setting, VOC can be found in CO_2 gas cylinders, insulation used in air handling systems, refrigerant gases and cleaning agents. Plastic ware, construction materials and furniture are also important sources of VOC.

Best practice statements on how to implement air filtration to IVF laboratories still lacking

Although Heitmann and colleagues' as well as our own experience with IVF laboratory air filtration has been reassuring, best practice statements on how to implement air filtration to IVF laboratories are still lacking. Specialized air filtration equipment such as the above-mentioned ones is costly, as is its maintenance and filter replacement. A less expensive alternative, particularly for existing IVF laboratories, would be to incorporate portable freestanding commercial units (Lawrence et al., 2007). Notwithstanding, risk minimization and quality management, as thoughtfully discussed by Mortimer, should be considered as equally powerful tools to improve effectiveness and safety of IVF (Mortimer, 2005).

In conclusion, accumulating evidence indicates that laboratory air quality plays a significant role in IVF outcome. Implementation of air quality control by the combination of particulate matter and chemical filtration seems sound, but guidelines on the target limits and best practice statements on how to implement air quality control to IVF are still lacking. Built-in systems and portable units are the current alternatives to supplying filtered air to the IVF laboratory and adjacent areas. Irrespective of whether it is a new facility or an existing one, optimum environments can be set up by equipping laboratory and associated premises with properly dimensioned filtration systems. Equally important are the measures to avoid contamination. A risk management analysis taking into consideration all variables that influence laboratory environment, including but not limited to air quality, is critical for improved outcomes.

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