

Air quality

The following information details the evidence and reasoning behind the HFEA's current policy position on the level of air quality required under the Tissue Directive.

1. Air quality requirements

The draft second technical annex of the EU Tissues and Cells Directive states that where tissues and cells are exposed to the environment during processing, without a subsequent inactivation process, an air quality of Grade A is required with a background environment at least equivalent to Grade D.

The Directive states that a less stringent environment may be acceptable in certain circumstances, but does not define what level of air quality this should involve. The HFEA is satisfied that the exemptions to Grade A air apply to assisted conception and have worked to define an appropriate level of air quality for the UK assisted conception sector.

Following consideration of a number of relevant articles, views of practitioners and views of the HFEA EU Tissues and Cells Directive Stakeholders Consultation Forum it was decided that Grade C air quality in the critical work area and a Grade D background environment would achieve the quality and safety appropriate to assisted conception processes.

So from April 2007 the HFEA will require centres to carry out procedures involving manipulation of material in a class II laminar flow cabinet (providing air quality of at least Grade C in the critical work area) and a background environment as close to Grade D as possible.

2. How did the HFEA come to this decision?

2.1 Protecting the gametes/embryos

The principal objective of all assisted conception clinics is to provide the best possible care for patients. In this context high quality is linked to the aim of achieving high pregnancy rate. To do this we must protect the embryo and not just the recipient. Risks to the recipient are addressed through comprehensive screening processes, and as far as cross contamination is concerned, natural conception is far more risky to the recipient than assisted conception techniques.

2.2 Protecting the operators

It is a reasonable requirement for handling of gametes/embryos to be performed under appropriate conditions that protect not only the gametes and embryos from

contamination, but also prevent contamination of the operator and general environment by the gametes and embryos.

Therefore, it is considered appropriate for handling to be performed in 'contained' work stations such as Class II cabinets (Grade C air).

2.3 Current risk of infection in ART

The biggest known risk comes from contaminated sperm samples or existing but undetected abnormal vaginal flora that would not be picked up from ambient conditions or control media. ART is not sterile but bypasses the self defence mechanisms present in the female reproductive tract.

There is an increased contamination risk where material is cultured over time, where work is open plan, and where there are multiple manipulations. Design of processes and facilities should therefore be as simple as possible.

There have been some reports of infection of a small number of women post insemination due to organisms present in ejaculated semen, but none where the infection was attributed to contamination from the air circulating within the laboratory. Due to the minimal number of reports risk analysis is impossible, although it is likely that the risk can be considered as very small. The only logical conclusion from this is that the work practices currently employed by IVF clinics would appear to be suitable in terms of microbial safety and adequate to the purpose. Implementing air quality requirements stricter than Grade C/D would result in an extremely small (probably unquantifiable) reduction in patient risk. Also, the quality changes in ART should be to reduce the risk to the embryo, not just the patient.

Sperm

Human semen is not sterile either at the time of collection or after processing, (although modern sperm washing techniques do reduce the microbial load of the prepared sperm suspension substantially) and it comes into contact with air during the lab procedure. The risk of infection by such organisms from lab processed sperm is order of magnitude less than via normal sexual activity on the part of the recipient. Also, during the preparation process most pathogens will be removed. If the sample is for cervical insemination, this area is in contact with the air normally so there is no additional risk. The risk in processing is contamination between samples and from operator to sample.

Surgically retrieved gametes can not be deemed sterile because operating theatres are not considered to be part of the 'controlled process'. No operating theatre has Grade A conditions.

Oocytes

Oocytes would not normally come into contact with air in natural conception suggesting that a clean environment is appropriate in the laboratory. The

procedure of oocyte retrieval does not expose the oocytes to ambient air since they are aspirated under negative pressure directly from the ovarian follicles through aspiration sets into sterile tubes.

Oil used in the process of ICSI may be an effective barrier against microbial contamination of oocytes. However, advice from the MHRA is that oil overlay is not adequate to seal embryos from the air and volatile organic compounds concentrate in oil.

Embryo transfer and donor insemination

The act of passing a catheter into the uterine cavity does not pose any greater risk than a cervical smear or endometrial biopsy – procedures that are not required to be performed under any special air quality standards. A patient's risk of infection from ambient air is far greater during a laparoscopy.

It is extremely rare to see a clinical infection related to the DI or embryo transfer process. There is a low prevalence of infected embryo cultures therefore the risk of infection from embryo transfer is low. Most infected cultures in ART centres are attributable to either carry over micro organisms from heavily infected semen or from contaminated culture oil.

2.4 Quality of embryos

Embryos would not normally come into contact with air in natural conception suggesting that a clean environment is appropriate in the laboratory. However, air quality is not the significant factor in maintaining quality. Additional parameters that matter include:

- temperature (spindle formation collapses if too cool)
- pH
- humidity
- CO₂ levels
- speed of processing
- culture conditions (media is developed on assumptions concerning current processes such as handling times and temperature. If one aspect changes this will have a knock on effect)

The sterilisation processes and equipment required to maintain Grade A conditions would harm embryos by affecting some, or all, of these parameters, and exposing embryos to excess volatile organic compounds from the cleaning products. Also, there has been some question raised about inline air purifiers which vibrate inside the incubator and can potentially cause problems. A major concern of high velocity clean air is increased risk of damage to the embryos. The impact of laboratory environment on the end product can not be fully audited until years after treatment when all the embryos have been used and the treatment outcomes known. However, it remains impossible to tell whether an embryo survives or dies due to laboratory environment, genetic factors, environment in the uterus, or one of many other factors.

2.6 Reports from clinics which already have Grade C/D air quality

Reports from clinics which already have Grade C/D air quality have been positive. One clinic in Sweden has implemented this air quality since 1997. To date none of their microbiology tests have come back positive and their live birth rates are high (enabling them to undertake 70% one embryo transfer).

2.7 Cost and working environment

It is estimated that a Grade A environment would at least double the cost of every step of the embryology process. Working in Grade A environment is not particularly pleasant or healthy for the practitioner, and can therefore only be done for short periods. ART centres would therefore need twice as many embryologists (and there is currently a national shortage of embryologists).

In order to achieve Grade C air in processing areas and Grade D background this will still require a lot of work for most ART laboratories and will be difficult for small IUI centres, or other ART centres located in older buildings, to achieve. It would be likely that if Grade A air quality was implemented.

If Grade A air quality was required it is likely that a large number of smaller services would be forced to close due to the high cost of equipment and tests (e.g. a particle counter could cost around £8000). Clinicians are of the opinion that this money would be better spent on measures which are proven to increase pregnancy outcome (e.g. the best media and incubators).

3. Studies referred to:

The origin, effects and control of air pollution in laboratories used for human embryo culture.

Hall J, Gilligan A, Schimmel T, Cecchi M, Cohen J. Human Reprod. 1998 Dec;13 Suppl 4:146-55

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Cohen J, Gilligan A, Esposito W, Schimmel T, Dale B. Hum Reprod. 1997 Aug;12(8):1742-9

Monitoring vocs in air – the development of ISO standards and a critical appraisal of the methods.

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Control of air quality in an ART lab.

Boone WR, Johnson JE, Locke AJ, Crane MM 4th, Price TM. Fertil Steril. 1999 Jan;71(1):150-4.

Establishing quality control in the new IVF laboratory.

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Culture and quality control of embryos.

Cohen J, Gilligan A, Willadsen S. Hum Reprod. 1998 Jun;13
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Optimisation of conditions for IBF and embryo culture

Loumaye E, de Cooman S, Thomas K. Rev Med Brux. 1985 Nov;6(9):611-4.