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MINI-REVIEW

The oviduct: a neglected organ due for re-assessment in IVF

Yves Ménézo [a,*], Pierre Guérin [b], Kay Elder [c]

[a] *Laboratoire CLEMENT, 17 Avenue d'Eylau, 75016 Paris, France*; [b] *Ecole Natonale vétérinaire, Vetagro-sup, 1 Avenue Bourgelat, 69280 Marcy l'Etoile, France*; [c] *Bourn Hall Clinic, Cambridge, CB3 2TN, UK*

* Corresponding author. *E-mail address:* yves.menezo@gmail.com (Y Ménézo).

Professor Yves Ménézo is a biochemist who obtained his PhD in applied biology from the University of Lyon. He received his Doctor of Science in 1979. He was Director of Research at the National Institute of Agronomical Research in France and Associate Professor at the Louisiana State University between 1987 and 1993, and then Head of the Assisted Reproduction and Genetics unitat the Merieux Foundation. He has developed several patents on culture media and hormone treatments. He has authored more than 250 publications and book chapters and has received several awards such as laureate of the French Academy of Medicine and gold medal of the Institute Dexeus.

Abstract The oviduct has long been considered a 'pipeline', a tube allowing transit of spermatozoa and embryos; this perspective has been reinforced by the success of human IVF. Evidence accumulated over several decades, however, indicates that embryos can modulate the metabolism of tubal cells in their environment. Human IVF culture media is based on formulations that pass mouse embryo assays as quality control: the requirements of mouse embryos differ from those of human embryos, and therefore conditions for human IVF are far removed from the natural environment of the oviduct. The preimplantation environment, both *in vitro* and *in vivo*, is known to affect the health of offspring through mechanisms that influence imprinting. Recent studies also show that male accessory glands act in synergy with the oviduct in providing an optimal environment, and this represents a further perspective on the oviduct's contribution to harmonious embryo development and subsequent long-term health. The metabolism of the human embryo is far from being understood, and a 'return' to in-vivo conditions for preimplantation development is worthy of consideration. Although results obtained in rodents must be interpreted with caution, lessons learned from animal embryo culture must not be neglected.

KEYWORDS: oviduct, preimplantation embryo

Introduction

The oviduct has long been considered as merely a 'pipeline', a tube that allows transit first of spermatozoa, and then the embryo; this perspective has been reinforced with the advent of human IVF. Abundant, research, however, dating from as early as the 1970s suggests that, in addition to mere transit, the oviduct actively participates in other functions, such as storage of sperm cells, smoothly managing their binding and subsequent release (Pollard et al., 1991). It also actively manages transport of embryos (Villalón et al., 1982), with the capacity to distinguish between an unfertilized oocyte

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and an early stage embryo. In some species (e.g. the mare Betteridge et al., 1979), unfertilized oocytes are held at the utero–tubal junction, with the early cleaving embryo apparently holding a key that allows entry into the uterus.

Observations over several decades have revealed that tubal epithelium (Freese et al., 1973) and secretions (Georgiou et al., 2005; Hess et al., 2013) both undergo metabolic and biochemical changes when the embryo lies within their vicinity. Encephalins and other peptides mediate interactions between the oviduct, the ovary and the fertilized embryo (Cupo et al., 1987; Kent, 1975) via biochemical exchanges of information. The nature of these exchanges is difficult to ascertain, as the protein content of an early stage embryo is around 50 ng. The absolute amounts are minute and highly specific, so that the biochemical exchanges are difficult to quantify. This situation has led to aberrant assumptions and statements (see HLA-G, Ménézo et al., 2006).

An important feature to be remembered is that the process of imprinting occurs early after conception; lessons learned from animal embryo culture must not be neglected, although results obtained in rodents must be interpreted with caution, as the mouse is not an appropriate model for other species. It has now been established that the environment during the preimplantation period affects the health of offspring, both *in vivo* and *in vitro*.

Recent studies have described a role for the male accessory gland in synergy with the oviduct's role in providing an optimal environment for the preimplantation embryo: seminal plasma is not merely a medium for sperm survival (Bromfield et al., 2014; Robertson, 2007). This represents another aspect of the oviduct's contribution to long-term harmonious embryonic development and the subsequent health of the offspring.

Anatomy and regulation of oviduct secretions

The embryonic origin of the female genital tract lies in the mesonephros. After about 10 weeks, the nephric duct and *mesonephric* tubules degenerate, and the *oviducts* and *uterus evolve from the paramesonephric duct*, a transport epithelium containing approximately equal numbers of ciliated and secretory cells, varying according to the anatomical region; the ampulla evolves from the fully secretory region. With the exception of primates, the oviduct in all other mammals is translucent, with a thin wall, in contrast to the muscular oviduct of primates.

In humans, the morphology of the uterus and the oviduct is similar macroscopically, which may explain why tubal ectopic pregnancy is possible, a situation that is never observed in other mammals. Ovarian and uterine blood supplies provide vascularization, and veno–ovarian anastomoses allow a complex 'trialogue' between the oviduct, ovary and uterus. Oviductal secretions are highly dependent on a hormonal (steroid) environment. Peak secretion, targeted towards the ovaries under the influence of oestrogen, is observed around the time of ovulation. The subsequent influence of progesterone targets secretion towards the uterus. The tubal environment is apparently under endocrine regulation during embryonic transport and development, and this is reflected in or mimicked by gene expression in epithelial cells (Bauersachs et al., 2004).

Biochemical composition of oviduct secretions

The main differences between serum and tubal secretions are presented in **Table 1**. The chemical composition of tubal fluids consists of a finely regulated mixture of serum transudate with specific epithelial secretions. Osmolarity and viscosity are similar to serum, around 290 mOsm/kg and 1.8 mPa/s, respectively. An important feature worthy of note pertains to the mouse embryo assay as used in human toxicity tests: a physiological osmolarity of over 280 mOsm causes mouse embryo developmental arrest (Wang et al., 2011). Human tubal fluid has a pH of around 7.2–7.5, regulated by bicarbonate produced by high levels of carbonic anhydrase in the tubal epithelium. The oxygen tension is 60 mmHg, less than one-half that of atmospheric O_2, with a reducing RedOx potential of –0.1 mV. The environment has high levels of antioxidants, such as hypotaurine, which is actively synthesized by the tubal epithelium (Guérin and Ménézo, 1995; Guérin et al., 2001); this topic will be expanded later. It is commonly felt that human preimplantation embryo development benefits from culture under conditions of reduced oxygen tension, such as 5% O_2, 5% CO_2, 90% O_2; this is probably partially true. Together with inappropriate osmolarity, however, most human IVF culture media have poor, if any, protection against reactive oxygen spieces (ROS).

Electrolytes

Two important unique features are high level of potassium, 2–5 times more concentrated than serum, such that a significant discrepancy occurs in Na/K ratio between serum (Na/K = 30) and tubal fluid (Na/K = 10–13); and a higher level of bicarbonate in the oviduct than in serum, owing to high carbonic anhydrase activity. Compared with levels observed in serum, levels of Ca^{++}, Mg^{++}, Na^{+}, Cl^{-}, $PO4^{-}$ are approximately similar. Once again, these unique features are not taken into account in human IVF embryo culture, and their effect on preimplantation embryo development has not been investigated. Zinc, the second most abundant transition metal after iron, is of interest. It prevents toxicity caused by iron and copper, and is involved in numerous important metabolic reactions that are required during mammalian developmental processes. It acts as a co-factor for at least 200 enzymes, including carbonic anhydrase and zinc superoxide dismutase, both present in the oviduct. Zinc prevents oxidative stress by capturing superoxide and hydroxyl radicals through its involvement in metallothioneins and metal-response element-binding transcription factors (Andrews et al., 1991; Ménézo et al., 2013). It plays a major role in regulation of the one-carbon cycle, and therefore also in methylation and imprinting (Ménézo et al., 2013).

Sugar and its metabolites

The concentration of glucose in tubal fluid is one-fifth to one-third lower than in serum, but it does contain fructose. The lactate concentration is much higher, reaching several times the serum value, compared with pyruvate, which is present at low levels in tubal fluid. A high activity of lactic