

Oviduct: roles in fertilization and early embryo development

Shuai Li and Wipawee Winuthayanon

School of Molecular Biosciences, College of Veterinary Medicine, Washington State University, Pullman, Washington, USA

Correspondence should be addressed to W Winuthayanon

Email
winuthayanonw@vetmed.wsu.edu

Abstract

Animal oviducts and human Fallopian tubes are a part of the female reproductive tract that hosts fertilization and pre-implantation development of the embryo. With an increasing understanding of roles of the oviduct at the cellular and molecular levels, current research signifies the importance of the oviduct on naturally conceived fertilization and pre-implantation embryo development. This review highlights the physiological conditions within the oviduct during fertilization, environmental regulation, oviductal fluid composition and its role in protecting embryos and supplying nutrients. Finally, the review compares different aspects of naturally occurring fertilization and assisted reproductive technology (ART)-achieved fertilization and embryo development, giving insight into potential areas for improvement in this technology.

Key Words

- ▶ embryo protection
- ▶ embryo transport
- ▶ estrogen and progesterone
- ▶ fallopian tube
- ▶ oviductal fluid

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Introduction

Fertilization is a complex process that enables the reproduction and continuation of the species. In mammals, successful fertilization requires that sperm should survive the extremely harsh environment of the female reproductive tract and reach the site of the newly released egg(s) in the oviduct (or Fallopian tube in humans). The oviduct, a part of the female reproductive tract, is a tube-like structure that connects the ovary to the uterus. The oviduct is composed of the following three main regions ordered from the ovary toward the uterus: the infundibulum (fimbria in humans), in which most cells are ciliated epithelial cells; the ampulla, which contains large numbers of ciliated epithelial cells and is the site of fertilization; and the isthmus, which contains a large number of secretory epithelial cells. With these three distinct structures, the oviduct serves as a passage that transports gametes and the embryo as well as provides important structural, environmental and nutritional

support for early embryonic development. Unlike the ovary and uterus, which have been extensively studied and relatively well understood, the oviduct is less well understood for its contribution in reproduction. Yet, dysregulation or disruption of oviductal function can result in infertility or life-threatening conditions such as ectopic pregnancy.

This review focuses on the oviductal function in establishing successful pregnancy, with new insights based on recent discoveries. This article first explains the oviductal function before fertilization during sperm and egg transport. Then, it describes oviductal function in fertilization, embryo development, embryo transport and abnormalities of the oviduct that could disrupt these processes. Because assisted reproductive technologies (ARTs), such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), can bypass the human Fallopian tubes entirely, this review also outlines the possible adverse outcomes of IVF/ICSI to emphasize

the importance of the oviduct during fertilization and embryo development.

The path to fertilization

At intercourse, sperm entering the vagina have to survive a hostile vaginal microenvironment, including strong acidic conditions (Oberst & Plass 1936), before entering the cervix. The cervical mucus flow flushes out pathogens and removes non-motile sperm (Tung *et al.* 2015), as recently reviewed in Suarez (2016). The flow naturally selects for healthier sperm to advance to the uterus, where phagocytosis continues to remove weaker sperm. Then, the sperm undergo hyperactivation, a process that is required to complete their physiological change to become competent for fertilizing the egg (reviewed in Tosti & Menezo 2016). Only hyperactivated sperm generate a strong counter-beating flagellum to overcome the viscoelastic mucus created by oviductal epithelial cells (Suarez *et al.* 1991, 1992). Details for sperm transport through the female reproductive tract are discussed in the following sections.

Oviduct guides sperm to the fertilization site

There are three potential mechanisms that guide the sperm through the oviduct, including rheotaxis, thermotaxis and chemotaxis.

Rheotaxis

Once sperm enter the oviduct, they will have direct contact with the oviductal fluid, which is generated by the transudate fluid from the systematic circulation and the secretory epithelial cells of the oviduct (Leese 1988). The fluid current is generated by ciliated epithelial cells and tubal contraction, which provides significant support to transport eggs and embryos. For sperm, the contact with epithelia and fluid to cause fertilization requires morphological changes to overcome this upcoming obstacle. One of the tubal current functions is to conduct a rheotaxis mechanism to guide the sperm to the site of fertilization (Fig. 1) (Miki & Clapham 2013). Rheotaxis is a mechanism whereby capacitated sperm can move against the direction of the current.

Soon after the sperm enter the isthmus region of the oviduct, the sperm heads attach to the oviductal epithelial cells. The studies using scanning electron micrographs of

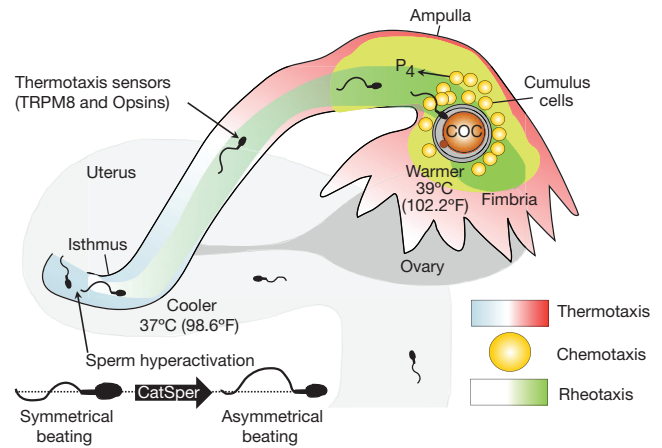


Figure 1

Oviduct-guided fertilization. The oviduct regulates fertilization through sperm guidance and sperm hyperactivation. The sperm guidance is achieved through rheotaxis, thermotaxis and chemotaxis. Rheotaxis is created by tubal fluid, which generates a current flow from the ampulla toward the isthmus of the oviduct. Sperm swim against this current based on the physical rotation of the flagella upon CatSper (Cation channel of Sperm) activation. Thermotaxis is mediated through a Ca^{2+} -sensing transient receptor potential channel (TRPM8) and G protein-coupled receptor (opsins). This thermal sensibility of human sperm can detect a difference of $0.006^{\circ}C$ (Bahat *et al.* 2012). Temperatures depicted ($37^{\circ}C$ vs $39^{\circ}C$) are from the finding in rabbits (Bahat *et al.* 2003). Chemotaxis is driven through progesterone (P_4) released from the cumulus cells and through small cytokines found in the follicular fluid. Together, these processes provide guidance for sperm to swim toward the eggs and be competent for fertilization. COC, cumulus-oocyte complex.

bovine sperm illustrate the physical interaction between the sperm head and cilia on the apical surface of oviductal epithelial cells (Pollard *et al.* 1991). Interaction between oviductal epithelial cells and sperm has also been observed in rabbit (Smith & Nothnick 1997), horse (Dobriniski *et al.* 1997) and human (Morales *et al.* 1996). In mice, the sperm attach to and detach from the oviductal epithelial cells several times before reaching the ampulla (Chang & Suarez 2012). Additionally, recent findings indicate that there are dynamic differences between the physical interactions between the sperm and the oviductal epithelial of the ampullary and isthmus regions (Ardon *et al.* 2016). Ultimately, the attachment of the sperm and the epithelial cells create a deposition or a reservoir of sperm within the oviduct.

Sperm-oviductal epithelial interaction causes the modification of sperm surface proteins and subsequently induces the hyperactivation of the sperm by activating the CatSper (Cation channels of Sperm) on the flagella (Ren *et al.* 2001, Quill *et al.* 2003, Chung *et al.* 2011, Miki & Clapham 2013). Upon CatSper activation, a large Ca^{2+} ion influx in the sperm flagella is triggered, subsequently

altering the beating pattern from symmetrical to aggressive asymmetrical propulsion (Fig. 1). Asymmetrical beating of the flagella produces greater amplitude of force and subsequently aids its speed toward the end of the journey. Studies have demonstrated that CatSper activation and the physical rotation of the sperm flagella are the mechanisms behind rheotaxis (Miki & Clapham 2013). The sperm from male mice lacking CatSper cannot be hyperactivated, and the males are sterile (Ren *et al.* 2001). Therefore, the activation of the CatSper channel and the downstream physiological changes are required for sperm to become fertile.

Thermotaxis

In addition to the CatSper channel, a Ca²⁺-sensing transient receptor potential channel (TRPM8) (De Blas *et al.* 2009) and a G protein-coupled receptor well known for its role in photon sensing in the retina (opsins) (Perez-Cerezales *et al.* 2015) are also present on the sperm. Combined with other recent studies on human sperm, it is possible that sperm have the ability to detect shallow temperature differences of less than one-hundredth of a degree (in Celsius) (Bahat *et al.* 2012). Thermosensing ability allows sperm to be directionally guided according to the oviduct temperature gradient, as previously observed in rabbit, mouse, pig, cow and human (Hunter *et al.* 2000, Bahat *et al.* 2003, 2005, Hunter 2012). Despite the studies conducted concerning the thermosensing channels and the temperature difference in the oviduct, some evidence suggests that the temperature gradient in the oviduct serves to influence gene expression and protein modification of the egg and embryo (Grinstead *et al.* 1985, Ye *et al.* 2007); however, thermotaxis may play a minor role in sperm guidance compared with rheotaxis.

Chemotaxis

Chemotaxis of sperm has been studied in different species and is most well known in sea urchins via resact, a peptide released from the egg (Ward *et al.* 1985). In *Xenopus*, egg jelly also produces allurin as chemotaxis for sperm attraction (Olson & Chandler 1999, Olson *et al.* 2001). In humans, freshly released cumulus-oocyte complexes (COCs) can secrete progesterone (P₄) as a chemoattractant for sperm (Teves *et al.* 2006, Oren-Benaroya *et al.* 2008). Chemokine receptors – CCR1, CCR5 and CCR6 – have been identified on human sperm (Isobe *et al.* 2002, Caballero-Campo *et al.* 2014). CCL20 ligands found in

the follicular fluid can bind to CCR6 and alter sperm directional movement (Caballero-Campo *et al.* 2014). The merging of follicular fluid and the oviductal fluid after ovulation may provide sufficient chemoattractants to ensure the arrival of sperm at the ampulla.

Atrial natriuretic peptide (ANP) and its precursor A (NPPA) are found in pig, mouse, rat and rabbit oviducts (Kim *et al.* 1997, Zhang *et al.* 2006, Bian *et al.* 2012). ANP receptor (NPR1), however, is expressed on the sperm. Upon ANP and NPR1 binding, ANP activates the cyclic GMP-dependent protein kinase pathway (PKG) and induces acrosome reactions in pig, cow and human sperm (Zamir *et al.* 1995, Rotem *et al.* 1998, Zhang *et al.* 2006). This reaction might provide additional evidence regarding the role of ANP as a human sperm chemoattractant (Zamir *et al.* 1993, Anderson *et al.* 1995).

Anandamide (AEA), a phospholipid signaling molecule, acts through cannabinoid receptors 1 and 2 (encoded by *Cnr1* and *Cnr2* genes) and was previously identified to regulate neurological signaling and memory (Subbanna *et al.* 2013, Basavarajappa *et al.* 2014). AEA has been found in oviductal fluid, whereas CNR1 is present on the sperm (Aquila *et al.* 2010, Gervasi *et al.* 2013). AEA regulates sperm metabolism through insulin secretion (Aquila *et al.* 2009), implying the possibility that AEA from the oviduct externally facilitates the metabolism of sperm. Recently published studies suggested that AEA in the oviduct activates CNR2 and transient receptor potential vanilloid 1 (TRPV1) to induce Ca²⁺ influx into the sperm, which become hyperactivated and are released from oviductal epithelia (Gervasi *et al.* 2011, 2016, Osycka-Salut *et al.* 2012, Amoako *et al.* 2013).

Overall, the oviduct guides sperm toward the fertilization site through various comprehensive mechanisms. Most importantly, the oviduct facilitates the hyperactivation of sperm to become fertile.

Egg entering the oviduct

Unlike sperm, eggs are released from the ovary during ovulation and enter the infundibulum (or fimbria). The cumulus cells surrounding the egg form the cumulus-oocyte complex or COC. Once inside the oviduct, the cumulus cells serve as a nutrient support for the egg. The cumulus cells use glucose for their own energy production (Sutton *et al.* 2003) and also produce energy sources (pyruvate and cysteine) that are needed for the cellular functions of the eggs (Tanghe *et al.* 2002, Sutton-McDowall *et al.* 2010). Cumulus cells also bridge

the communication between the environment and the egg through gap junctions (Simon *et al.* 1997, Li *et al.* 2007, Huang & Wells 2010).

The initial attachment of the egg to the oviduct epithelia is accomplished through COC–oviduct epithelia interaction. The filaments of the extracellular matrix from cumulus cells adhere to the glycocalyx at the entrance of the ciliary crowns at the epithelial cells of the infundibulum (Lam *et al.* 2000). Then, the COC is drawn into the oviduct and is ready for fertilization.

Other aspects of oviduct-guided fertilization

Sperm orient themselves by reacting to the oviduct environment to continue along the path of fertilization. The oviduct also reacts to the presence of the sperm and optimizes the microenvironment within the oviductal lumen by regulating fluid viscosity, oviductal muscular contraction and by promoting sperm–egg recognition.

Oviductal fluid

Sperm is bathed in oviductal fluid to advance toward the site of fertilization. The oviductal fluid is generated from secretory cells of the oviduct and is regulated by estrogen (E_2) and other hormones (discussed in detail in a later section). The oviductal protein concentration is the lowest at ovulation and highest around menstruation (Lippes *et al.* 1981). Changes in protein concentration and its content can alter fluid viscosity, hence influencing the flow rate of the fluid. Oviductal epithelial cells sense the change of fluid viscosity by transient receptor potential vanilloid 4 (TRPV4) channel (Andrade *et al.* 2005, Teilmann *et al.* 2005, Lorenzo *et al.* 2008). TRPV4 detects phospholipase in the oviductal fluid and regulates ciliary beat frequency (CBF) to enhance the fluid movement when it is too viscous, as observed in the respiratory tract. The oviduct can also sense the presence of sperm and adjust the protein content by increasing heat shock protein 70 (HSP70) and antioxidants in the oviductal fluid, possibly to help reduce sperm stress (Georgiou *et al.* 2005).

Smooth muscle contraction

The smooth muscle contraction in the oviduct is regulated by prostaglandins (PGs) through prostanoid receptors, which are modulated by E_2 (Spilman & Harper 1975, Ball *et al.* 2013, Huang *et al.* 2015). In humans, the

oviductal PGs are mainly PGE and PGF produced by epithelial cells (Lindblom *et al.* 1983). PGE₂ and PGF_{2 α} increase muscle contraction, whereas PGE₁ decreases muscle contraction (Wanggren *et al.* 2008). Evidence indicates that the contraction is possibly regulated by both E_2 and P₄, as estrogen and progesterone receptors (ESR and PGR) are expressed in the interstitial Cajal-like cells in the muscle cell layer of the oviduct (Cretoiu *et al.* 2009). The function of the muscle contraction is generally recognized to be for sperm transport purposes (Overstreet & Cooper 1978a). Suarez and coworkers suggested that the muscle contraction mainly helps the sperm to pass through the cervix, rather than acting as a rapid transport for sperm to reach the fertilization site (Suarez & Pacey 2006). This idea is strongly supported by experiments in rabbits, in which the sperm that reached the end of the oviduct within a few minutes were damaged (Overstreet & Cooper 1978a,b).

Fertilization

Recent studies demonstrated that heat shock proteins are involved with sperm–egg recognition. Heat shock protein member A2 (HSPA2) is present in the human spermatozoa and binds with arylsulfatase A (ARSA) and sperm adhesion molecule 1 (SPAM1) (Redgrove *et al.* 2012, 2013, Bromfield *et al.* 2016). Both ARSA and SPAM1 are detected in the rabbit and mouse oviduct (Vitaioli *et al.* 1996, Griffiths *et al.* 2008). HSPA2 can also bind with angiotensin-converting enzyme (ACE) and protein disulfide isomerase A6 (PDIA6) to form a complex, and then engage in sperm–zona recognition. Interestingly, oxidative stress of sperm can significantly reduce the binding ability of the ARSA/SPAM1/HSPA2 complex to the zona pellucida (Bromfield *et al.* 2015).

Soon after the egg and sperm convene at the ampulla, fertilization occurs. With the penetration of the sperm into the egg, ovastacin is released from the egg's cortical granules and cleaves the zona pellucida 2 protein (ZP2) (Burkart *et al.* 2012), leading to zona hardening and preventing polyspermy. In a recent study, ZP2 peptide-treated beads, deployed in the mouse female reproductive tract, act as a decoy to attract sperm and form binding, resulting in female infertility (Avella *et al.* 2016). These ZP2 peptide beads efficiently provide a contraceptive mechanism without any pathological defect in the female reproductive tract. Another newly discovered sperm–egg interaction is that of Izumo1 and Juno. Izumo1 is present on the sperm and interacts with the Juno receptor on the egg, causing a rapid shedding of Juno to prevent

polyspermy (Bianchi *et al.* 2014). Juno is a species-specific protein and may contribute to the prevention of cross species sperm–egg recognition (Han *et al.* 2016).

After sperm–egg recognition, the gametes fuse and the pronuclei form. This event leads to embryogenesis, and the next chapter of development begins. Embryogenesis is a very early stage of the development in which the embryo undergoes a few cellular divisions before entering the uterus. It usually takes 3–4 days for human and mouse embryos to develop into the 8-cell (human) or 16-cell (mouse) stage in the oviduct. Those early cell divisions do not increase cell size but rather equally allocate the cytoplasm from the original zygote (Pelton *et al.* 1998). The embryo is transported from the site of fertilization toward the end of the oviduct during the early cleavage stage. At the end of the oviduct, embryos prepare to enter the uterus at the morula and blastocyst stages. The simultaneous embryo development and transport in the oviduct is an inseparable mechanism under normal physiological conditions.

Oviductal influence on embryo development

The pre-implantation embryo is housed inside the oviduct, exposed to and surrounded by oviductal secretory fluid and in contact with the oviductal epithelial cells. The microenvironment within the oviduct provides a stable temperature, optimal pH and dynamic fluid secretions to support embryo development.

Before fertilization, the oviductal fluid serves in the following three major functions: gamete protection, sperm guidance and egg guidance (Ballester *et al.* 2014, Kumaresan *et al.* 2014). After fertilization, the oviduct assists the development of pre-implantation embryos by producing the factors required for embryo cleavage (discussed in following sections). This phenomenon was first described in the sheep model where the oviductal epithelial cells were cultured with the embryos (Gandolfi & Moor 1987). Gandolfi and coworkers found that the blastocyst cleavage rate was at 80% when the embryos were cultured with oviductal epithelial cells, in comparison to a 33% cleavage rate when cultured with fibroblast cells. This finding indicates that the presence of oviductal epithelial cells, and not just any type of somatic cell, is crucial for blastocyst development. The improvement of embryo development after culturing with oviductal epithelial cells or explanted oviduct has also been demonstrated in several species, including mouse (Sakkas & Trounson 1990), pig (White *et al.* 1989),

cattle (Eyestone & First 1989) and human (Yeung *et al.* 1992). These findings indicate that the oviduct epithelia and the oviductal fluid provide the pre-implantation embryos an ideal physiological and biochemical environment to sustain development.

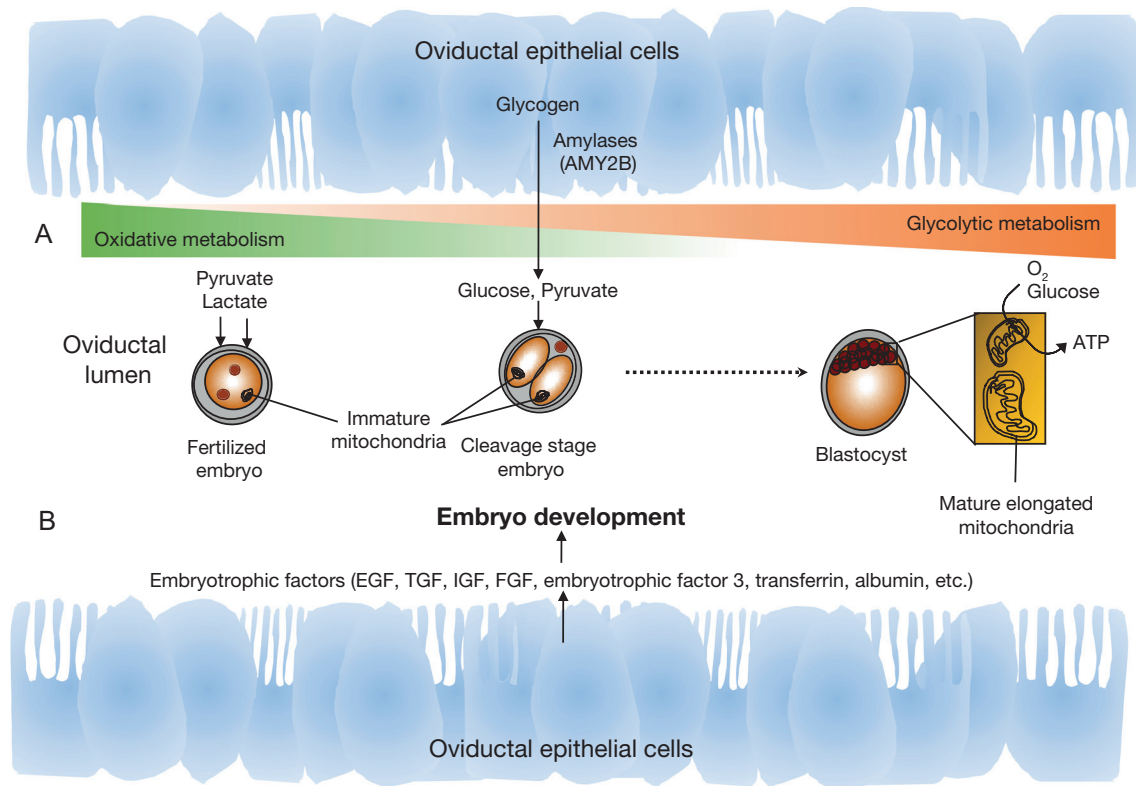
To determine the possible factors secreted from the oviductal epithelial cells that support and promote embryo development, we have outlined the fluid constituents during the early stage of pregnancy. Oviductal fluid is generated by two compositions: (1) the transudation of the systemic circulation and (2) the active biosynthesis from the secretory epithelial cells of the oviduct (Leese 1988). The fluid is composed of albumin, transferrin, glycoproteins, galactose, immunoglobulin, glucose, pyruvate, amino acid, lactate, cytokines, many growth factors and a monitored gas composition (Beier 1974, Leese 1988). The functions of these factors in the oviduct are discussed in the following sections.

Oviductal fluid: influence on embryo nutrient and growth

Nutrients

Early embryos usually stay in the oviduct for 3–4 days (Croxatto 2002). During this time, the fertilized embryos transition from oxidative metabolism to glycolic metabolism (Folmes & Terzic 2014). This transition is accompanied by (1) different nutrient compositions as the embryo travels through the oviduct, (2) maturation of the mitochondria to enable the embryo to establish its own metabolism and (3) a change in oxygen tension parallel to this shift in metabolism (Gardner *et al.* 1996, Absalon-Medina *et al.* 2014).

After the cumulus cells fall off in post-fertilization, the pre-implantation embryos use oxidative metabolism to acquire energy, mostly from pyruvate and lactate as the main sources of energy (Gardner & Leese 1990, Dumollard *et al.* 2007a,b, Absalon-Medina *et al.* 2014). Pyruvate, lactate, lipids and amino acids are present in the oviductal fluid, and the levels of these nutrients fluctuate through the estrous cycle in mice, rabbits, pigs and humans (Nieder & Corder 1982, 1983, Nichol *et al.* 1992, Leese *et al.* 1993, Tay *et al.* 1997). The carboxylic acids are processed through immature mitochondria (characterized by the short and less formed cristae, shown in Fig. 2A) (Motta *et al.* 2000, Trimarchi *et al.* 2000, Dumollard *et al.* 2007a). Several studies in pigs and cattle showed that fatty acids (in a form of acyl-coA) are used as an energy source for the embryo (Sturmeijer *et al.* 2009,

**Figure 2**

The influence of the oviduct on embryo development. (A) The main energy supply for the embryos is pyruvate and lactate. During the very early stage of embryo development, pyruvate and lactate are provided by the oviductal fluid as energy sources for oxidative metabolism. The oviduct can also supply the glycogen as an energy source for the embryos during the cleavage stage. Amylase (AMY2B) is produced within the oviductal epithelial cells and converts glycogen to sugar. At this stage, the mitochondria of the embryos are immature and do not function. During morula and blastocyst stages, the mitochondria are fully mature and can use oxygen and glucose to produce their own energy via glycolysis as they leave the oviduct. (B) At the same time, oviductal epithelial cells provide embryotrophic factors, such as growth factors, to promote cleavage and embryo development. EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; TGF, transforming growth factor.

Sutton-McDowall *et al.* 2012). Acyl-CoA diffuses through the mitochondrial membrane in the presence of carnitine (as a cofactor) through carnitine palmitoyl transferase 1B (CPT1B) and is used for β -oxidation, resulting in the production of acetyl-CoA (Sutton-McDowall *et al.* 2012).

As embryos continue developing, glycolytic metabolism slowly takes over as the mitochondria become mature. However, in human, the metabolic switch is not complete until the blastocyst stage (Sathananthan & Trounson 2000). This glycolytic metabolism requires supplies of glucose and simple sugars. Glycogen granules are present in the ampulla and isthmic secretory cells of the oviduct in monkey and human (Odor *et al.* 1983, Schultka & Cech 1989). In pigs, the glycogen level increases after ovulation (Lindenbaum *et al.* 1983, Gregoraszczyk *et al.* 2000). This evidence suggests that oviduct secretion prepares embryo metabolism transit during the pre-implantation

stage. Additionally, enzyme amylase (AMY2B) plays a major role in converting glycogen into sugar. Several studies indicated that there is an upregulation of AMY2B in the human Fallopian tube (Mc *et al.* 1958, Hochberg 1974, Hayashi *et al.* 1986, Groot *et al.* 1990, Marquez *et al.* 2005). Therefore, it is likely that the compact polysaccharide can be converted into a simple sugar by AMY2B in the oviduct, and these simple sugar molecules can be used in cellular metabolism by both the oviduct and the cleaving embryo.

When human embryos develop into blastomeres, mitochondria are equally divided into each of the cells and are elongated and matured (Fig. 2A). The mature mitochondria can now use oxygen and glucose in glycolysis to provide ATP for further embryo development (Sathananthan & Trounson 2000). In mice, this is evident with the timing of embryo oxygen consumption, which peaks at the blastocyst stage (Leese 2012).

In addition to energy substrates, CO₂ also serves as a carbon source for RNA synthesis (Quinn & Wales 1974, Pike *et al.* 1975). In mouse and rabbit, CO₂ fixation has been demonstrated in early developing embryos (Quinn & Wales 1974, Pike *et al.* 1975). The level of CO₂ is inversely proportional the HCO₃⁻ concentration, which is modulated by the carbonic anhydrase (CA) enzyme expressed in the oviductal epithelial cells (Lutwak-Mann 1955, Ge & Spicer 1988) as well as a Cl⁻/HCO₃⁻ exchanger (solute carrier family 26) expressed in pre-implantation embryos (Lu *et al.* 2016). The HCO₃⁻ level in the oviduct is relatively high compared with other tissues (Vishwakarma 1962, Maas *et al.* 1977), and it has been previously shown that HCO₃⁻ is indispensable for the cleavage of pre-implantation embryos (Kane 1975). These studies indicate that a balance of CO₂ and HCO₃⁻ concentration needs to be fine-tuned not only for optimal pH conditions but also for RNA synthesis and the normal cleavage of the pre-implantation embryo development.

Growth factors

Embryotrophic factor-3 from human oviductal cells plays a significant role in enhancing pre-implantation embryo development by promoting proliferation and inhibiting apoptosis (Xu *et al.* 2004). Epidermal growth factor (EGF) (Adachi *et al.* 1995), transforming growth factor (TGF) (Chegini *et al.* 1994), insulin-like growth factor (IGF) (Carlsson *et al.* 1993, Pfeifer & Chegini 1994, Daliri *et al.* 1999) and fibroblast growth factor (FGF) are all detected in human Fallopian tissues (Fig. 2B). Mouse embryos cultured with EGF, TGF and IGF have an increased number of blastocyst development from 2-cell embryos (Paria & Dey 1990). The co-cultured 2-cell stage embryo and the Fallopian tube epithelial cells significantly increase the cleavage rate and enhance blastocyst development (Takeuchi *et al.* 1992). However, in similar co-culture conditions, inhibition of EGF and TGF will attenuate the development of embryo from the cleavage stage to blastocyst. IGF receptor is also detected in 8-cell stage buffalo embryos (Daliri *et al.* 1999). This suggests that embryotrophic factors, including growth factors in the tubal fluid, can have a direct positive impact on cleavage stage embryo development.

In addition to the growth factors listed previously, hormone-like lipids such as prostaglandins also promote embryo development. In mice, the oviduct produces 10 times more prostaglandin I₂ (PGI₂) at day 2 than day 4 after coitus (Huang *et al.* 2004). The spiked production of PGI₂ is timed with the early cleavage stages of the embryo,

and then the production drops around the time embryos hatch in the uterus. This finding suggests that PGI₂ potentially plays a role in early embryo development. Additionally, several studies demonstrated that addition of transferrin, albumin and selenium can improve bovine and goat embryonic development (Hammami *et al.* 2013, Wydooghe *et al.* 2014, Xie *et al.* 2015, Guimaraes *et al.* 2016). These findings suggest that the presence of growth factors in the tubal fluid may play an important role in promoting and enhancing embryogenesis.

Oviductal fluid: protection against embryo stress

Tubal fluid protects gametes from environmental stress to ensure embryo quality and pregnancy outcome. After the shedding of the cumulus cells, the embryo depends on tubal fluid and internal antioxidant activities to gain protection against reactive oxygen species (ROS)-induced stress (Fig. 3). Two major systems are involved in this process: non-enzymatic and enzymatic antioxidants (reviewed in Guerin *et al.* 2001).

Reduced glutathione (GSH), taurine, hypotaurine and cysteamine (CSH) are the main non-enzymatic antioxidants in the oocytes and embryos (Guerin *et al.* 2001). GSH reduces ROS level in the oocytes and increases the hatching rate of mouse blastocysts when added into the culture medium (Gardiner & Reed 1994). Moreover, considerable amounts of GSH are detected in the mouse oviduct and uterine flushing (Gardiner *et al.* 1998). CSH is

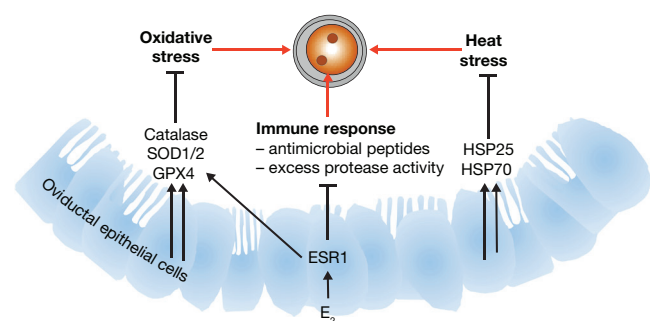


Figure 3

Oviduct-mediated embryo protection against stress and immune responses. Oviductal epithelial cells produce heat shock protein family (HSP25 and HSP70) to handle heat stress. Oviductal fluid also contains catalase, superoxide dismutases (SOD1/2) and glutathione peroxidase (GPX4) to reduce stress of the embryos from reactive oxygen species. In addition to stress, the oviduct also protects the embryos against their own immune system, partly through the E₂/ESR1 signaling, by inhibiting the production of antimicrobial peptides and excess protease activity. ESR1, estrogen receptor α .

present in the secretions of the female reproductive tract (Guyader-Joly *et al.* 1998) and is proposed to act through the hydroxyl radical (OH•) scavenging pathway (Guerin *et al.* 2001). The OH• scavenging pathway may also convert CSH into hypotaurine, a sulfinic acid neutralizing OH• activity, and generate taurine as a byproduct (Guerin & Menezo 1995). Both hypotaurine and taurine are present at high levels in the embryo environment and are produced by the oviduct epithelial cells of cow, sheep, goat and rabbit (Guerin *et al.* 1995, Guerin & Menezo 1995). In addition, albumin and transferrin are highly abundant in the oviductal fluid. Transferrin acts as a metal chelator to prevent the formation of OH• from Fe²⁺ ions (Nasr-Esfahani & Johnson 1992, Guerin *et al.* 2001), whereas albumin is shown to prevent lipid peroxidation in the sperm (Alvarez & Storey 1983), suggesting that both transferrin and albumin may provide indirect protection for the embryos against oxidative stress.

In the enzymatic pathway, catalase, superoxide dismutases (SODs) and glutathione peroxidases (GPXs) are the major enzymes involved in embryo protection (Guerin *et al.* 2001). Catalase is one of the enzymes that converts ROS into H₂O and O₂ (Harvey *et al.* 1995). Similarly, SOD1 and SOD2 bind to ROS byproducts and turn the byproducts into O₂ and hydrogen peroxide (El Mouatassim *et al.* 2000, Jang *et al.* 2010). Catalases, SOD1 and SOD2 are found in the oviduct of mice, cows and humans. Glutathione also plays a similar role in embryonic development and protection (Salmen *et al.* 2005, Hansen & Harris 2015). GPX4 is well known for its function in suppressing cell death and reduction in hydrogen peroxide (Imai *et al.* 1996, Agbor *et al.* 2014). Increase in E₂ induces the GPX4 production in bovine oviduct (Lapointe *et al.* 2005). This evidence indicates that E₂ and the oxidative stress preventing enzymes act in concert to protect the embryos against ROS exposure.

In addition to oxidative stress, embryos also encounter physical stress from the environment. The 1- to 2-cell stage mouse embryo expresses HSP70, which is regulated by heat shock factors (HSFs) (Christians *et al.* 1995, 1997). HSP70 family proteins play an important role in protecting the cell from heat stress by ensuring correct protein folding. Interestingly, the oviduct expresses HSF25 and 70 (Fig. 3), which can potentially provide heat stress protection at the molecular level to ensure correct protein folding in the newly fertilized embryo (Mariani *et al.* 2000, 2003). Mice lacking *Hsf*s had significant increases in cell death when the embryos experienced heat stress for 2 h (Le Masson & Christians 2011). A study in water buffalo indicated

that when the embryos are exposed to heat stress for a prolonged period of time (24 h), the heat also decreases embryo cell numbers (Ashraf *et al.* 2014). These studies suggest that there is a tolerable limit of heat stress that the embryo can handle.

Estrogen-mediated embryo protection against immune system

E₂ and its nuclear receptors (estrogen receptors) play a major role in the reproductive system, from regulating the hormonal cycle, ovulation and sexual behavior to cancer development (Couse & Korach 1999). Numbers of studies demonstrated that E₂ is required for immunoprotection in the female reproductive tract, including the vagina and uterus (Wira *et al.* 2005, Haddad & Wira 2014). However, the actions of E₂ in regulating the immune functions in the oviduct are unclear. Recently, a study indicated another important property that E₂ possesses—embryo protection. E₂ acts through estrogen receptor α (encoded by *Esr1* gene) in the oviductal epithelial cells, which protects embryos from the attack of the maternal immune system. Loss of ESR1 in the oviductal epithelial cells in female mice results in excess protease activity and increased expression of antimicrobial peptides such as defensins. These changes, due to a lack of ESR1 in the oviduct, dampen the plasma membrane integrity of the embryos and ultimately cause embryonic death before the 2-cell stage (Winuthayanon *et al.* 2015). The study demonstrated that the epithelial ESR1 is required to suppress innate immune systems (Fig. 3) by changing gene expression related to inflammation responses in the oviduct during day 1 and 2 of pregnancy. This result suggests that without E₂ signals through ESR1 on the oviductal epithelial cells, newly fertilized embryos will not be able to overcome the mother's immune system. These findings reveal another infertility scenario that previously has not been demonstrated, in which the disruption of E₂ signaling or ESR1 action in the Fallopian tube can cause infertility.

Gas in the oviduct

Little is known about the gas composition in the oviduct or the oviductal fluid. Compared with the 20% oxygen level in the atmosphere, the concentration of oxygen in the oviduct of monkeys, hamsters and rabbits is between 2% and 8% (Mastroianni & Jones 1965,

Yedwab *et al.* 1976, Fischer & Bavister 1993). The relatively low oxygen concentration in mammalian oviducts could result in minimal ROS levels and protect embryos from stress, as high concentrations of oxygen can lead to an increase in ROS and oxidative stress (Catt & Henman 2000).

Dysregulation of H₂S gas in the Fallopian tubes has been linked to impaired embryo transport in humans. H₂S is abundant in the Fallopian tube epithelial cells and synthesized intrinsically through the cell cytoplasm. This signaling pathway is upregulated during pregnancy and is mainly responsible for spontaneous oviduct muscle contraction, which provides a positive factor to the embryo movement toward the uterus (Ning *et al.* 2014). Nitric oxide has been identified in the Fallopian tube; it mediates tubal muscle contraction, with possible roles in the regulation of sperm motility (Ekerhovd *et al.* 1997, Kobayashi *et al.* 2016). Dimethylarginine dimethylaminohydrolase 2 (DDAH2), an enzyme regulating nitric oxide synthesis, is also expressed in the oviduct in the presence of egg and embryo (Georgiou *et al.* 2005). Therefore, H₂S and nitric oxide could contribute to the regulation of tubal contraction during fertilization and embryo transport.

Embryo transport

It is necessary to mention embryo transport, as embryo development and transport occur simultaneously. Embryo transport from the oviduct to the uterus takes approximately 1–10 days, depending on the species (reviewed in Croxatto 2002). In mammals, unfertilized eggs and embryos are transported to the uterus at different rates. In horses, only embryos are transported to the uterus, whereas the unfertilized eggs are retained in the oviduct (Betteridge & Mitchell 1974, Flood *et al.* 1979, Freeman *et al.* 1992). Several studies indicated that horse embryos produced prostaglandin E₂ (PGE₂), which mediates an acceleration of the transit to the uterus (Weber *et al.* 1991a,b). In rats and hamsters, fertilized eggs reach the uterus at higher rates compared with the unfertilized eggs (Villalon *et al.* 1982, Ortiz *et al.* 1986). These findings illustrate that embryo transport is an interactive process between the embryos and the oviduct. Here, the three major elements regulating embryo transport are listed: the beating of ciliated epithelia, tubal fluid flow and tubal muscle contraction (Fig. 4).

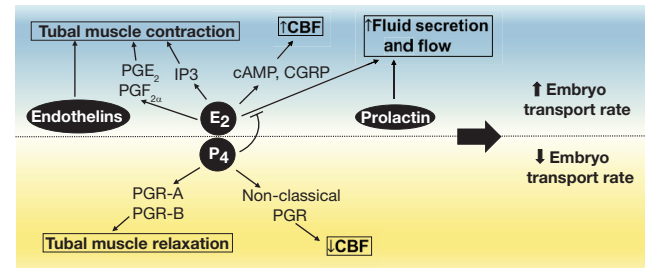


Figure 4

Roles of the oviduct during embryo transport. Embryo transport is composed of tubal muscle contraction and the motility of ciliated epithelial cells. Estrogen (E₂) generally increases the tubal muscle contraction, tubal fluid secretion, and ciliary beat frequency (CBF), which accelerate the embryo transport rate. Opposite to E₂, progesterone (P₄) causes muscle relaxation and decreases CBF to reduce the embryo transport rate. In addition, P₄ also inhibits E₂-induced tubal fluid production. Prostaglandins (PGs) can be produced in the oviductal epithelial cells or induced by E₂ treatment. PGE₂ and PGF_{2α} stimulate muscle contraction in both human and bovine oviducts. Endothelin 1 and 2 are expressed and contribute to the oviduct contraction. IP₃, inositol triphosphate; PGE₂, prostaglandin E₂; PGF_{2α}, prostaglandin F₂; PGR, progesterone receptor.

Ciliary beating

Ciliated epithelial cells have a multiciliated structure on the apical plasma membrane. The beating of the cilia generates the movement of the fluid in the oviduct, which promotes the movement of the embryo.

P₄ and E₂ are the key players in regulating ciliary beat frequency (CBF). P₄ reduces CBF through classical progesterone receptors (PGRs) expressed on the ciliated epithelial cells in a dosage-dependent manner in humans and mice (Mahmood *et al.* 1998, Bylander *et al.* 2010, 2013). A non-classical PGR is expressed in the lower part of the cilia stalk in mouse oviducts (Teilmann *et al.* 2006). Recent studies in mice indicated that low dosage of P₄ and short activation time (within 30 min) are sufficient to reduce oviductal CBF (Bylander *et al.* 2010, 2013). Therefore, extra-nuclear signaling of CBF through non-genomic actions of P₄ without involving a long-delayed genomic regulation may be the cause of direct CBF regulation.

E₂ is required to accelerate the transport of the eggs (Orihuela *et al.* 2001). E₂ acts via a non-genomic pathway through protein phosphorylation of PKC and PKA in rats and cows (Orihuela & Croxatto 2001, Orihuela *et al.* 2003, Wen *et al.* 2012). Moreover, in the oviductal secretory cells, E₂ induces the production of cAMP, which promotes adrenomedullin activation (Liao *et al.* 2013). In rats, adrenomedullin increases CBF by acting through the calcitonin-gene-related peptide (CGRP) receptor in the oviductal epithelial cells (Liao *et al.* 2011).

The findings from muscarinic receptor-knockout (*Chrm1^{-/-}*, *Chrm3^{-/-}*, *Chrm4^{-/-}* and *Chrm5^{-/-}*) mice suggest that the cholinergic neuromuscular system is not required for the ciliary beat function, as the particle transport rate in the oviduct remains unchanged compared with their control littermates (Noreikat *et al.* 2012).

Tubal muscle contraction

The embryos move back and forth along the oviduct due to the contraction of myosalpinx, with the net progress toward the uterus (Talo 1991). However, studies in rabbits and rats showed that inhibition of muscle contractility does not affect the transport of the embryos (Halbert *et al.* 1976, 1989). It suggests that at least in these species, ciliary beating alone is capable of transporting the embryos from the oviduct to the uterus. In humans, oxytocin, P₄, PGs and nitric oxide participate in the tubal muscle relaxation and contraction (Ekerhovd *et al.* 1997, Jankovic *et al.* 2001, Wanggren *et al.* 2008). P₄, through PGR-A and PGR-B relaxes muscle contraction in mice (Conneely *et al.* 2003). Administration of P₄ in the *ex vivo* culture of human Fallopian tube reduces both amplitude and frequency of tubal muscle contraction (Wanggren *et al.* 2006); however, treatment with PGR receptor antagonist, mifepristone, has a minimal effect on the contraction. Nevertheless, the exact signaling pathway, beyond the ligand–receptor interaction, through which P₄ is involved in directing muscle relaxation remains unclear.

E₂ can induce the production of inositol triphosphate (IP3) to increase smooth muscle contraction and accelerate egg transport in the rat oviduct (Orihuela *et al.* 2006). Additionally, E₂, P₄ and endothelin-1 stimulate the release of PGs (PGE₂ and PGF_{2 α}) in bovine oviduct (Wijayagunawardane *et al.* 2001). Both PGE₂ and PGF_{2 α} are shown to stimulate muscle contraction in human and bovine oviducts (Wijayagunawardane *et al.* 2001, Wanggren *et al.* 2008). Endothelin-2 alone can also induce muscle contraction in the rat oviduct through endothelin receptor type A (Al-Alem *et al.* 2007). These findings indicate that ovarian hormones have both direct effects on stimulating the tubal muscle contraction and indirect effects via the induction of PGs.

Cannabinoid receptor 1 and 2 (*Cnr1* and *Cnr2*), which are G protein-coupled receptors, play crucial roles in pregnancy. *Cnr1^{-/-}* and *Cnr1^{-/-}/Cnr2^{-/-}* double-knockout mice have significantly higher number of embryos retained in the oviduct (35–46% retained embryos in the oviduct) compared with

WT control (0% in oviduct) (Wang *et al.* 2004). This suggests that CNR1 and CNR2 are important for normal embryo transport.

Tubal fluid flow

Studies assessing the movement of microspheres showed that the orientation of fluid is toward the uterus in rabbits, sheep, cows and guinea pigs, whereas the flow is oriented toward the ovary in the pigs (Gaddum-Rosse & Blandau 1973, 1976). These results showed that the tubal fluid flow is oriented differently depending on the species. In sheep and rabbits, the oviductal fluid secreted from secretory epithelial cells is increased by female steroid hormones, especially E₂ (Hamner & Fox 1968, McDonald & Bellve 1969). The fluid production is attenuated when P₄ is co-administered with E₂, suggesting that P₄ opposes E₂-induced fluid secretion (Fig. 4). In rabbits, ovariectomy causes decreased secreted fluid in the oviduct, and this fluid level can be restored by E₂ treatment (Bishop 1956), suggesting that E₂ is the major regulator for secretory fluid production within the oviducts. A recent study in mice demonstrated that inhibition of prolactin, a hormone secreted from the anterior pituitary after mating, using bromocriptine severely reduced the oviductal fluid volume and flow (Miki & Clapham 2013). The increased oviductal fluid secretion is mostly due to the increased water availability, which is related to the function of the transmembrane water transport proteins, aquaporins (AQPs). In rats, expression of *Aqp5*, *Aqp8* and *Aqp9* is regulated by both E₂ and P₄ (Branes *et al.* 2005). These findings indicate that E₂, P₄ and prolactin play a major role in fluid production in the oviduct. In summary, an overall action of E₂ is to increase the embryo transport rate by stimulating muscle contraction, inducing fluid production and flow, and increasing the CBF, whereas P₄ has an opposite effect of E₂ by reducing the embryo transport rate.

Recently identified pathways affecting embryo transport

The incidence of ectopic pregnancy is one in every 50 normal pregnancies, and 95% of ectopic pregnancies are associated with defective Fallopian tubes (Tenore 2000). Recent studies demonstrate that some novel pathways contribute to the pathological conditions of Fallopian tubes, with potential ramifications in human infertility.

Pathways crucial for normal oviduct development

In the majority of mammals, including rodents and rabbits, a healthy oviduct is a rather coiled tube with no obstructions within to ensure an open passage for eggs, sperm and embryos (Stewart & Behringer 2012). In humans and non-human primates, however, the coiled structure is not present in the Fallopian tubes. Due to difficulties in obtaining human tissues, scientists have been using genetically engineered mice as a model organism to study the roles of proteins of interest during oviduct development. The recent findings demonstrated that the morphological changes leading to a less coiled or uncoiled oviduct and formation of cysts within the oviduct can result in infertility. Wingless-type integration family member 4 (WNT4) signaling is critical for the development of the female reproductive tract, as female mice lacking *Wnt4* expression showed a non-coiled oviduct that lacked folding (Prunskaitė-Hyyryläinen *et al.* 2016). Moreover, overexpression of Notch in the reproductive tract produced similar phenotypes whereby the oviduct failed to coil (Ferguson *et al.* 2016).

Dicer, an endonuclease responsible for microRNA (miRNA) function, is also crucial for the development of the female reproductive tract. Loss of *Dicer* in the mouse reproductive tract disrupts oviduct organization by reducing both the length and coiling (Nagaraja *et al.* 2008, Gonzalez & Behringer 2009). Additionally, mice lacking *Dicer* also developed oviductal cysts and severe inflammation in the oviduct at the uterotubal junction. These phenotypes lead to degeneration of the eggs and embryo transport failure. WNT7a is another critical signaling pathway involved in early female reproductive tract development, as a loss of *Wnt7a* results in female sterility due to an abnormal development of uterus and oviduct (Parr & McMahan 1998). These findings indicate that signaling molecules involved in WNT, Notch and miRNA regulation play critical roles in oviductal development and coiling.

Pathways crucial for ciliogenesis and ciliary function

In addition to organ morphology, disruption of ciliogenesis and ciliated cell differentiation at a cellular level can lead to embryo transport defects. Ciliated epithelial cells in oviducts create tubal currents and are responsible for the transportation of the embryo (Lyons *et al.* 2006). A comprehensive review regarding cellular and molecular mechanisms governing ciliogenesis is provided in Choksi *et al.* (2014).

Several recent studies discovered that epithelial cells in the female reproductive tract contain a subpopulation of stem-cell-like LGR5 (leucine-rich repeat-containing G-protein-coupled receptor 5)-positive cells (Ng *et al.* 2014). The LGR5-positive cell population has been identified in other tissues, such as the kidney (Barker *et al.* 2012), intestine (Barker *et al.* 2007) and stomach (Barker *et al.* 2010). LGR5-positive cells reside much like regular epithelial cells in the tissue, but the characteristics of these cells remain undifferentiated. The LGR5-positive population can be activated to divide and differentiate into designated cell types and is responsible for tissue renewal and regeneration. In the Fallopian tubes, these stem-like adult epithelial cells are concentrated at the fimbria (Paik *et al.* 2012, Snegovskikh *et al.* 2014).

Notch and WNT signals not only modulate the oviduct development but also mediate the differentiation of adult epithelial stem cells into other cells in Fallopian tubes (Kessler *et al.* 2015). Inhibition of Notch signaling by a γ -secretase inhibitor, dibenzazepine, in the oviduct and the stem-like epithelia leads to a genetic signature of cell differentiation into ciliated epithelium. Inhibition of Notch signaling reduces the number of stem cells in human Fallopian tube 3D organoids, while increasing ciliated cell number. LGR5 also regulates the WNT/ β -catenin signaling pathway and can be used as a marker for adult oviduct epithelial stem cells (Capel 2014, Ng *et al.* 2014, Vieira *et al.* 2015). Studies in mice showed that the deletion of *Lgr5* in female mice resulted in significantly fewer live births (Sun *et al.* 2014). These findings suggested that the number of ciliated epithelial cells in the Fallopian tubes is also controlled by the local stem-cell population via the WNT and Notch signaling pathways.

miRNAs also participate in oviductal ciliogenesis. Lacking *miRNA-34* and *miRNA-499* genes resulted in a loss of cilia in the trachea and oviduct epithelial cells (Wu *et al.* 2014). Additionally, serine/threonine protein kinase (STK36), a regulator of the hedgehog pathway, modulates a central pair construction of the cilia (the two center microtubules in the 9+2 microtubule axonemal structure). A lack of *Stk36* causes an impairment of the cilia orientation and results in a failure to form the directional movement of the cilia in the oviduct (Nozawa *et al.* 2013). Moreover, a global deletion of *Kif19a*, a kinesin family member involved in cilia length regulation, causes female infertility due to elongated cilia in the oviduct (Niwa *et al.* 2012). Elongated cilia in the *Kif19a*^{-/-} oviduct lead to excess mucus and cell debris in the oviductal lumen and blockage of the egg passage.

In addition, female mice lacking *Celsr1* (*Celsr1^{-/-}*), a planar cell polarity gene, showed defective ciliary polarity, which resulted in a random orientation of cilia directionality. The impaired cilia were unable to transport beads in a uniform direction, which disrupted the transportation function of the oviduct (Shi *et al.* 2014). In conclusion, the presence, proper length, proper structure and directionality of the cilia are crucial for the oviduct transport function to support the gametes and embryos.

In vitro fertilization and embryo development

With recent technological advancement such as IVF and ICSI, infertility clinics can now provide solutions to allow infertile couples to conceive their own children. Procedures can bypass the Fallopian tube entirely and transfer the fertilized embryos directly into the uterus. The presence of these technologies questions the role of the oviduct and its necessity for human reproduction. ARTs are common procedure worldwide, including IVF and ICSI. However, not every couple has access to ARTs due to economical limitation. Moreover, there are several concerns regarding the use of ARTs, such as epigenetic change in the embryos due to culture conditions and controlled ovarian hyperstimulation (COH), complicated pregnancy due to multiple gestation and a lack of natural selection (especially with ICSI). Therefore, the medical research community should take precaution and study possible complications with such technologies when bringing hope to many couples experiencing infertility.

For many couples with fertility issues, IVF may be their only hope to have offspring inheriting their genes. It is a technique whereby the clinicians fertilize the eggs with sperm outside the female reproductive tract and incubate the fertilized embryos in a laboratory until they are ready for implantation in the uterus. IVF has been practiced for decades throughout the world and has resulted in over 3.5–5 million newborns across the globe. The international committee for monitoring ART reported that with one million documented cases, the pregnancy rate of IVF/ICSI is 20–30% (Mansour *et al.* 2014) compared with 45–85% after 3–12 month conceived naturally (Luke *et al.* 2012).

A recent study from more than 178,000 women who went through IVF treatment suggested that an overall successful live birth rate through IVF pregnancy is 43% (McLernon *et al.* 2016). When a woman is over 38 years old, live birth success through IVF drops

significantly to 21% (Stern *et al.* 2009). Compared with natural conception, IVF/ICSI-conceived embryos have a significantly higher risk of perinatal mortality, low birth weight and preterm birth (Pandey *et al.* 2012, Pinborg *et al.* 2013, Marino *et al.* 2014). When comparing IVF/ICSI with naturally conceived children, there is a 3–4 times higher chance for imprinting disorders, including Beckwith–Wiedemann syndrome, Prader–Willi syndrome, Angelman syndrome, Silver–Russell syndrome, transient neonatal diabetes mellitus, McCune–Albright syndrome, familial nonchromaffin paraganglioma, maternal hypomethylation syndrome and retinoblastoma in IVF/ICSI children (Owen & Segars 2009, Lazaraviciute *et al.* 2014).

A study comparing 7- to 8-year-old children who were conceived through IVF/ICSI and natural intercourse found that there is no difference in their cognitive ability, but there is an underlying gender difference (Punamaki *et al.* 2016). Naturally conceived boys showed more cognitive developmental problems than girls, whereas no differences were observed between boys and girls conceived through IVF. This study, however, is solely dependent on parental reports and may have a bias between IVF and naturally conceived parents. In terms of imprinting disorder, there is increased evidence of Beckwith–Wiedemann Syndrome in the IVF/ICSI-conceived children (4%) compared with naturally conceived children (0.7–1.2%) in a small cohort of 149 children in the UK (Maher *et al.* 2003). There is reduced methylation in KvDMR, an intronic CpG island in the *KCNQ1* (or *KvLQT1*) gene whose methylation status is associated with Beckwith–Wiedemann Syndrome (Smilnich *et al.* 1999), in the embryonic tissues conceived by the IVF method (Gomes *et al.* 2007).

With ever-improving biotechnology, more studies are required to understand the implications of the health and wellbeing of IVF individuals. As IVF-conceived individuals are still in their reproductive ages, long-term evaluation on transgenerational epigenetic outcomes will be needed.

Epigenetics and environmental factors

Embryos go through epigenetic changes and result in imprinting, which has a long-lasting effect in later development. Cell fate is not determined in the embryo before the morula stage. The early embryos repress epigenetic modification by removing DNA methylation and repressing histone modifications from the 2-cell stage until the blastocyst stage in mice (Reik *et al.* 2001,

Ma *et al.* 2012) and until the 8-cell stage in cows (Dean *et al.* 2001). However, the demethylation timing of DNA methylation in the embryo is on a gene-by-gene basis (Messerschmidt *et al.* 2014). In humans, DNA demethylation occurs much earlier compared with other mammals, from fertilization to the 2-cell stage, at which time, most genes tested have already lost their methylation status (Guo *et al.* 2014, Okae *et al.* 2014). For example, 5' long terminal repeat-containing element is demethylated after fertilization (Smith *et al.* 2014). As embryos develop to the blastocyst stage, repression is slowly reversed in the inner cell mass, and methylation status becomes increased (Smith *et al.* 2012, Guo *et al.* 2014, Okamoto *et al.* 2016).

Epigenetics

A recent review discussed how ARTs influence the epigenetics of early embryos and suggested that gene expression in developing embryos could be altered through the environment in which they interact (Lucas 2013). COH is one of the common hormonal regimens used to induce ovulation, either alone or as part of the IVF/ICSI procedures (Farhi & Orvieto 2010, Berker *et al.* 2011). Studies using *in vitro* matured (IVM) human oocytes (retrieved from gonadotropin-stimulated patients) demonstrate that the widely used oocyte morphological maturation protocol may not necessarily indicate an adequate maturation of gene expression (Jones *et al.* 2008, Virant-Klun *et al.* 2013). These genes are involved in meiosis (*SYCP2*, *SGOL2* and *MSH2*) and are upregulated in the IVM oocytes compared with *in vivo* matured oocytes. Ovarian-stimulated IVM-derived mouse embryos express incomplete DNA demethylation at the 2-cell stage. Aberrant methylation in the mouse embryo can be an indication of failure in embryo development (Shi & Haaf 2002, Wang *et al.* 2010). The evidence showed that *in vitro* pre-implantation mouse embryo culture results in a selective loss of imprinting gene expression of imprinted maternally expressed transcript (*H19*) and small nuclear ribonucleoprotein polypeptide N (*SNRPN*) due to a reduced methylation on their control regions (Mann *et al.* 2004). Moreover, several studies showed that the culture of mouse embryos in different media compositions could lead to epigenetic changes and contribute to developmental defects and aberrant phenotypes in adulthood (Reik *et al.* 1993, Dean *et al.* 1998, Khosla *et al.* 2001). These findings indicated that media composition and COH could contribute to epigenetic alterations in the embryos.

A recent study using cord blood and placentas collected from the children conceived by ART and naturally conceived children showed that the source of alteration in DNA methylation status is a result of ART procedures, rather than the underlying fertility of the parents (Song *et al.* 2015). Hiura and coworkers proposed that imprinting disorders are a combination of heredity, senescent, COH, ART procedures and culture medium that potentiates the early onset of the diseases (Hiura *et al.* 2014). This evidence outlines the important link between ARTs and epigenetic imprinting outcomes in children.

Oxygen tension

The physiological level of O₂ concentration is 8% (Fischer & Bavister 1993). However, IVF embryos are cultured in various oxygen concentrations in different set-ups (5–20%) (Bontekoe *et al.* 2012), which can impact the level of oxidative stress on the embryos. Depends on the culture media composition, the glutathione pool in human oocytes can be depleted, resulting in high ROS and causing plasma membrane damage to the oocytes (Martin-Romero *et al.* 2008). A recent study using post-thawed human embryos found that at 2% O₂ concentration in the culture, embryos

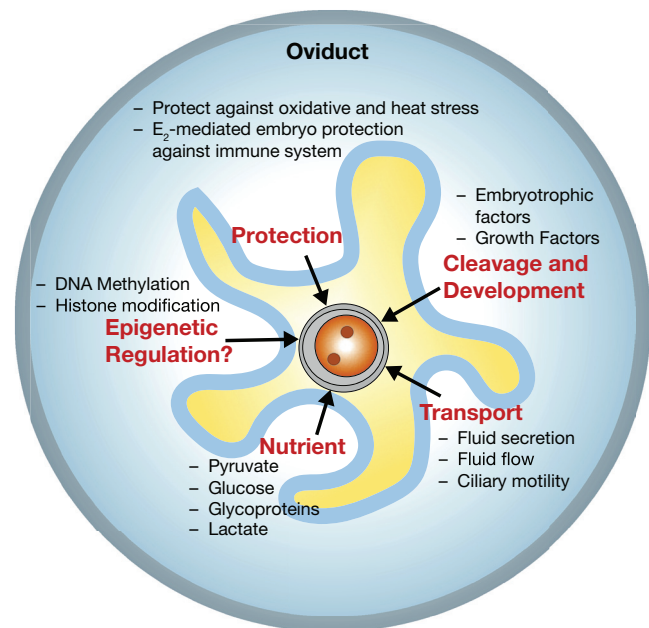


Figure 5 Essential roles of the oviduct in assisting embryo development. Schematic cross-section of the oviduct and the embryo with their interaction regulating embryo development. The interactions are divided into five domains: protection, cleavage and development, transport, nutrients and epigenetic regulation. E₂, estrogen.

Table 1 Recent literatures (published after 2010) regarding molecules and processes required for the fertilization and embryo development in the oviduct.

Reproductive mechanism	Receptors/molecules/pathways	Species studied	Type of publication	References
Oviduct guides sperm to the fertilization site	CatSper	Mouse	Primary research	Ren <i>et al.</i> (2001), Chung <i>et al.</i> (2011), Miki and Clapham (2013)
Rheotaxis				
Cervical microgrooves				
Thermotaxis	Opsins	Bull Human, mouse Human	Primary research Primary research Primary research	Tung <i>et al.</i> (2015) Perez-Cerezales <i>et al.</i> (2015) Bahat <i>et al.</i> (2012)
Thermotaxis				
Temperature gradient in the oviduct				
Chemotaxis	Chemokine receptors	Human, mouse	Review	Hunter (2012)
Chemotaxis	Anandamide	Cow, human	Primary research	Caballero-Campo <i>et al.</i> (2014)
Chemotaxis	TRPV1	Cow	Primary research	Amoako <i>et al.</i> (2013), Gervasi <i>et al.</i> (2013)
Chemotaxis	P ₄	Human	Primary research	Gervasi <i>et al.</i> (2016) Armon <i>et al.</i> (2014)
Oviduct signal in the presence of sperm				
Sperm egg recognition	HSPA2	Human	Primary research	Redgrove <i>et al.</i> (2012, 2013), Bromfield <i>et al.</i> (2015, 2016)
Oviductal muscle regulation	PGE ₂	Horse	Primary research	Ball <i>et al.</i> (2013)
Oviductal muscle regulation	EP2, EP4, and FP	Cow	Primary research	Huang <i>et al.</i> (2015)
Egg entering oviduct				
Egg nutrient supply				
COC protection	Reactive oxygen species	Mouse, cow	Review Primary research	Sutton-McDowall <i>et al.</i> (2010) Shaeib <i>et al.</i> (2013, 2016), Li <i>et al.</i> (2016)
Fertilization and early embryo development				
Fertilization	Ovastacin	Mouse	Primary research	Burkart <i>et al.</i> (2012)
Fertilization	ZP2	Human, mouse	Primary research	Avella <i>et al.</i> (2016)
Fertilization	Juno	Human, mouse, mammals	Primary research	Bianchi <i>et al.</i> (2014), Han <i>et al.</i> (2016)
Oviductal fluid on embryo growth				
Gametes protection	Oviductal fluid	Pig	Primary research	Ballester <i>et al.</i> (2014), Kumaresan <i>et al.</i> (2014)
Metabolism in embryos				
Embryo development	Culture medium	Cow, goat	Review Primary research	Folmes and Terzic (2014) Hammami <i>et al.</i> (2013), Wydooghe <i>et al.</i> (2014), Lopera-Vasquez <i>et al.</i> (2015), Xie <i>et al.</i> (2015), Guimaraes <i>et al.</i> (2016)
Oviductal fluid on embryo stress and pathogen protection				
Embryo stress	Glutathione		Review	Hansen and Harris (2015)
Embryo stress	HSFs, HSP70	Mouse	Primary research	Le Masson and Christians (2011)
Embryo stress	Temperature	Buffalo	Primary research	Ashraf <i>et al.</i> (2014)
Estrogen-mediated embryo protection				
Estrogen-mediated embryo protection	ESR1	Mouse	Primary research	Winuthayanon <i>et al.</i> (2015)
Gas in the oviduct				
Gas regulated embryo transport	Hydrogen sulphide	Mouse	Primary research	Ning <i>et al.</i> (2014)

Gas regulated embryo protection and sperm motility	Nitric oxide synthase	Cow	Primary research	Kobayashi <i>et al.</i> (2016)
Embryo transport	Adrenomedullin	Pig	Primary research	Liao <i>et al.</i> (2013)
Fluid secretion	Prolactin	Mouse	Primary research	Miki and Clapham (2013)
Fluid production and flow	Adrenomedullin	Rat	Primary research	Liao <i>et al.</i> (2011)
Ciliary beat frequency	P ₄	Mouse	Primary research	Bylander <i>et al.</i> (2010, 2013)
Ciliary beat frequency	E ₂ and P ₄	Guinea pig	Primary research	Nakahari <i>et al.</i> (2011)
Ciliary beat frequency	Muscarinic receptors (Chrm1, 3, 4, and 5)	Mouse	Primary research	Noreikat <i>et al.</i> (2012)
Muscle contraction	E ₂ and P ₄	Pig	Primary research	Chen <i>et al.</i> (2013)
Muscle contraction	E ₂	Rat	Primary research	Reuquen <i>et al.</i> (2015)
Recently identified pathways affecting embryo transport	Oviduct morphology and development		Review	Stewart and Behringer (2012)
Oviduct morphology and development	Wnt4	Mouse	Primary research	Prunskaitė-Hyyryläinen <i>et al.</i> (2016)
Oviduct development	Notch	Mouse	Primary research	Ferguson <i>et al.</i> (2016)
Ciliogenesis	Lgr5	Mouse	Review	Choksi <i>et al.</i> (2014)
Ciliogenesis	Notch and WNT	Mouse	Primary research	Ng <i>et al.</i> (2014)
Oviduct stem cell	miRNAs (miR-34b/c and miR-449)	Human	Primary research	Snegovskikh <i>et al.</i> (2014)
Fallopian tube stem cell morphology	Stk36	Mouse	Primary research	Kessler <i>et al.</i> (2015)
Ciliogenesis	Kif19a	Mouse	Primary research	Wu <i>et al.</i> (2014)
Ciliogenesis	Celsr1	Mouse	Primary research	Nozawa <i>et al.</i> (2013)
Cilia length	Lipopolysaccharide	Cow	Primary research	Niwa <i>et al.</i> (2012)
Cilia directionality			Primary research	Shi <i>et al.</i> (2014)
Ciliary beat frequency			Primary research	O'Doherty <i>et al.</i> (2016)
ARTs and embryo development			Bioinformatics and review	Pandey <i>et al.</i> (2012), Pinborg <i>et al.</i> (2013), Mansour <i>et al.</i> (2014), Marino <i>et al.</i> (2014), McLernon <i>et al.</i> (2016)
ARTs statistics and prenatal outcomes		Human	Review	Lazaraviciute <i>et al.</i> (2014), Ventura-Junca <i>et al.</i> (2015)
ARTs and DNA methylation		Human	Bioinformatics	Punamaki <i>et al.</i> (2016)
ARTs and mental health		Human and mammals	Review	Ma <i>et al.</i> (2012), Messerschmidt <i>et al.</i> (2014)
Epigenetics and environmental exposures	Oxygen concentration	Human	Review	Lucas (2013)
DNA methylation and demethylation	Culture medium	Human	Bioinformatics	Bontekoe <i>et al.</i> (2012)
Environmental exposure in ARTs	BPA	Mouse	Bioinformatics	Zandstra <i>et al.</i> (2015)
ARTs		Cow	Primary research	Donjacour <i>et al.</i> (2014)
ARTs			Primary research	Ferris <i>et al.</i> (2016)
Metabolism				
Epigenetics				

have a decreased survival rate and increased apoptotic rate. On the contrary, when the O₂ level is slightly below the physiological level (5–6%), the embryos did not show any significant change in those parameters (Yang *et al.* 2016). The authors suggested that the culture condition at 5–6% O₂ concentration could improve the survival rate of the embryos. However, recent randomized control studies did not find a robust correlation between the culture of human embryos at 5–6% O₂ concentration and the increase in the live birth rate (Nastri *et al.* 2016).

Yang and coworkers also found that cell death genes (*BAX*), antioxidant genes (*MnSOD*) and stress protective genes (*HSP70*) are elevated and apoptosis is increased in human embryos that were cultured at a 20% O₂ level (Yang *et al.* 2016). In addition, mouse embryos cultured in 20% O₂ showed pre-implantation epigenetic changes that altered metabolism later in life (Donjacour *et al.* 2014). Specifically, male mice displayed glucose intolerance, heavier body weight and heart enlargement compared with *in vivo* fertilized embryos. This evidence indicates that the *in vitro* culture conditions during ART procedures, either at low or high O₂ concentration, could potentially alter embryo development and lead to metabolic disease in mammals.

Environmental exposures

The pre-implantation period is critical for embryo epigenetic control; this period normally occurs in the oviduct or Fallopian tube in humans. Factors known to be different between IVF and natural development can cause epigenetic influence, including techniques, embryo culture media and environmental exposures such as tissue culture plastics (Ventura-Junca *et al.* 2015). Bisphenol A (BPA) is known for its action as an endocrine-disrupting compound and a weak estrogen agonist/antagonist. However, BPA is still being used as part of the plastic containers for embryo cultures (Hunt *et al.* 2003, Berger *et al.* 2010, Varayoud *et al.* 2011). Studies indicated a broad range of effects on the embryos upon BPA exposure, such as altered developmental rate and cell death (Ferris *et al.* 2016) and toxicity to the neural progenitor cells (Yin *et al.* 2015). BPA-free replacement products from the industry still diffuse out estrogenic chemicals, such as BPAF (the fluorinated form of BPA) (Bittner *et al.* 2014), which may pose a significant hazard to the embryos.

Together, we need to take extreme precaution to monitor the *in vitro* environment of IVM and IVF/ICSI

procedures and the possible unwanted consequences on the long-term epigenetic imprints.

Developmental factors missing *in vitro*

The most distinct physiological difference between IVF and naturally conceived birth is the artificial fertilization and the omission of development in the *in vivo* environments. IVF procedures cultivate fertilized embryos in the culture conditions until the embryos are ready for uterine implantation. Depending on the procedures and institutional protocols, it can be anywhere between 3 and 7 days of *in vitro* development. The culture media is pre-determined and static compared with a dynamic, interactive Fallopian tube environment. This static environment at the current state cannot provide an interactive response to ROS produced by embryos. Moreover, the viability of the IVF embryos is subjective to institutional procedures.

Of the factors influencing embryo development *in vitro*, the foremost is the culture media used to culture embryos. This media is meant to mimic the oviductal fluid and its nutrient composition to support early cleavage development. A data analysis study suggested that in humans, the embryo culture media could affect the birthweight of IVF babies (Zandstra *et al.* 2015); however, the underlying mechanism is not well understood. The oviductal environment, the fluid and the embryo interaction with the environment are difficult to replicate *in vitro*. This factor could lead to the difference between IVF and natural birth. A known example occurs in very early embryo development; hyaluronan acid synthase 1 (*HAS1*) is highly expressed in the embryo at the 2- to 4-cell stage, but then quickly fades away (Marei *et al.* 2013). The oviduct reacts to this change by expressing hyaluronidase-2 (*HYAL-2*) to degrade excessive hyaluronan acid (*HA*). *In vitro* studies in bovine demonstrated that mimicking this embryo–oviduct interaction by adding *HYAL-2* to the culture media improves embryo quality (Marei *et al.* 2013).

Bovine embryos fertilized *in vitro* have lower quality than those fertilized *in vivo*, as indicated by the difference in the cellular junction, the presence of lipid droplets and other subcellular changes. Co-culture of human embryos with the Fallopian epithelia improved the quality of embryos (Yeung *et al.* 1992, Vlad *et al.* 1996). However, analysis in humans suggested that simply mimicking the *in vivo* environment using an *in vitro* model did not increase the baby delivery rate (Stern *et al.* 2009). This

could be the result of a complex interaction among embryo, tubal epithelia and tubal fluid. An extensive review by Hess and coworkers discussed the important roles of the oviduct in stabilizing the very early stage of embryo development during transit (Hess *et al.* 2013). Therefore, the oviduct–embryo interaction is necessary for the quality of the developing embryo and lacking this interaction could result in negative health effects.

Another difference between IVF and *in vivo* fertilization is the zona pellucida hardening and monospermy during fertilization (Mondejar *et al.* 2013, Anifandis *et al.* 2016, Dadashpour Davachi *et al.* 2016). In a natural pregnancy, the female reproductive tract acts as a passage for sperm selection, by which it minimizes the number of sperm reaching the fertilization site to ensure that polyspermy occurs at a low rate. Current IVF techniques cannot effectively select the most superior sperm, which occurs naturally in the female reproductive tract. To overcome this, one could use a co-culture condition of the egg and oviduct epithelia. An experiment demonstrated that co-culture of eggs and oviductal epithelial cells is significantly better at preventing polyspermic fertilization than the standard IVF counterpart (Dadashpour Davachi *et al.* 2016). This suggests that fertilization in the oviduct is part of a continuing interaction between gametes and oviduct to optimize the fertilization outcome.

Lastly, gas is a factor that we have ignored in most cases. Embryos experience somewhere between 2% and 8% O₂ concentrations in the human Fallopian tube (Bontekoe *et al.* 2012). However, in the IVF procedures, the embryos are incubated at different oxygen levels, from 5% to 20%. The effect of these O₂ percentages in the culture compared with *in vivo* has not been well studied, but it would be wise to take precaution because high oxygen concentration is linked to oxidation stress (Fischer & Bavister 1993, Catt & Henman 2000).

The retrospective on IVF studies suggests that Fallopian tubes not only serve as the passage for the embryo to enter the uterus but also act as a cofactor to cultivate and optimize embryo quality to ensure successful implantation and later normal development.

Conclusion

The oviduct is essential in reproduction. Before fertilization, the oviduct primes the sperm, protects both gametes and guilds the fertilization process through distinct mechanisms, including rheotaxis, thermotaxis and chemotaxis. Increasing evidence indicates that

processes that occur in the oviduct facilitate the path to fertilization, but detailed molecular mechanisms regarding each step are still largely unknown. Most importantly, the oviduct provides the optimized physical site for fertilization to occur.

After fertilization, the oviduct adjusts each of its components to ensure the survival and the normal development of the embryo, summarized in Fig. 5; the current literature regarding these aspects is included in Table 1. The oviductal fluid contains nutrients, growth factors, antioxidants, sex hormones, proteases and many other functional chemicals regulated by the presence of gametes and embryos. The oviduct also transports the embryo from the site of fertilization into the uterus. Defective embryo transport can cause infertility or ectopic pregnancy. Most recent findings suggested that a few new pathways involved in this process, along with ciliated cells, contribute a major role in this transport. Together, the oviduct fine-tunes the oviductal fluid to ensure that the embryos receive proper developmental signals and nutrients as well as helps embryos overcome environmental stress and protects embryos from our own immune system.

The oviduct has been under-appreciated with its ‘non-essential’ role in reproduction since the success of IVF over 30 years ago. However, there have been more studies probing the downside of the ARTs that link to some of the critical functionalities of the oviduct to embryo development. ARTs can be further improved with these findings. At the same time, precautions should be taken, as more research is needed for the roles and functions of the oviduct in fertilization and embryo development to benefit the health of future generations.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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References

- Absalon-Medina VA, Butler WR & Gilbert RO 2014 Preimplantation embryo metabolism and culture systems: experience from domestic animals and clinical implications. *Journal of Assisted Reproduction and Genetics* **31** 393–409. (doi:10.1007/s10815-014-0179-2)
- Adachi K, Kurachi H, Homma H, Adachi H, Imai T, Sakata M, Higashiguchi O, Yamaguchi M, Morishige K, Sakoyama Y, *et al.* 1995 Estrogen induces epidermal growth factor (EGF) receptor

- and its ligands in human fallopian tube: involvement of EGF but not transforming growth factor- α in estrogen-induced tubal cell growth in vitro. *Endocrinology* **136** 2110–2119. (doi:10.1210/endo.136.5.7720660)
- Agbor TA, Demma Z, Msrny RJ, Castillo A, Boll EJ & McCormick BA 2014 The oxido-reductase enzyme glutathione peroxidase 4 (GPX4) governs Salmonella Typhimurium-induced neutrophil transepithelial migration. *Cellular Microbiology* **16** 1339–1353. (doi:10.1111/cmi.12290)
- Al-Alem L, Bridges PJ, Su W, Gong MC, Iglarz M & Ko C 2007 Endothelin-2 induces oviductal contraction via endothelin receptor subtype A in rats. *Journal of Endocrinology* **193** 383–391. (doi:10.1677/JOE-07-0089)
- Alvarez JG & Storey BT 1983 Taurine, hypotaurine, epinephrine and albumin inhibit lipid peroxidation in rabbit spermatozoa and protect against loss of motility. *Biology of Reproduction* **29** 548–555. (doi:10.1095/biolreprod29.3.548)
- Amoako AA, Marczylo TH, Marczylo EL, Elson J, Willets JM, Taylor AH & Konje JC 2013 Anandamide modulates human sperm motility: implications for men with asthenozoospermia and oligoasthenoteratozoospermia. *Human Reproduction* **28** 2058–2066. (doi:10.1093/humrep/det232)
- Anderson RA Jr, Feathergill KA, Rawlins RG, Mack SR & Zaneveld LJ 1995 Atrial natriuretic peptide: a chemoattractant of human spermatozoa by a guanylate cyclase-dependent pathway. *Molecular Reproduction and Development* **40** 371–378. (doi:10.1002/mrd.1080400314)
- Andrade YN, Fernandes J, Vazquez E, Fernandez-Fernandez JM, Arniges M, Sanchez TM, Villalon M & Valverde MA 2005 TRPV4 channel is involved in the coupling of fluid viscosity changes to epithelial ciliary activity. *Journal of Cell Biology* **168** 869–874. (doi:10.1083/jcb.200409070)
- Anifandis G, Messini CI, Dafopoulos K, Daponte A & Messinis IE 2016 Sperm contributions to oocyte activation: more that meets the eye. *Journal of Assisted Reproduction and Genetics* **33** 313–316. (doi:10.1007/s10815-016-0653-0)
- Aquila S, Guido C, Laezza C, Santoro A, Pezzi V, Panza S, Ando S & Bifulco M 2009 A new role of anandamide in human sperm: focus on metabolism. *Journal of Cellular Physiology* **221** 147–153. (doi:10.1002/jcp.21837)
- Aquila S, Guido C, Santoro A, Perrotta I, Laezza C, Bifulco M & Sebastiano A 2010 Human sperm anatomy: ultrastructural localization of the cannabinoid1 receptor and a potential role of anandamide in sperm survival and acrosome reaction. *Anatomical Record* **293** 298–309. (doi:10.1002/ar.21042)
- Ardon F, Markello RD, Hu L, Deutsch ZI, Tung CK, Wu M & Suarez SS 2016 Dynamics of bovine sperm interaction with epithelium differ between oviductal isthmus and ampulla. *Biology of Reproduction* **95** 90. (doi:10.1095/biolreprod.116.140632)
- Armon L, Ben-Ami I, Ron-El R & Eisenbach M 2014 Human oocyte-derived sperm chemoattractant is a hydrophobic molecule associated with a carrier protein. *Fertility and Sterility* **102** 885–890. (doi:10.1016/j.fertnstert.2014.06.011)
- Ashraf S, Shah SM, Saini N, Dhanda S, Kumar A, Goud TS, Singh MK, Chauhan MS & Upadhyay RC 2014 Developmental competence and expression pattern of bubaline (*Bubalus bubalis*) oocytes subjected to elevated temperatures during meiotic maturation in vitro. *Journal of Assisted Reproduction and Genetics* **31** 1349–1360. (doi:10.1007/s10815-014-0275-3)
- Avella MA, Baibakov BA, Jimenez-Movilla M, Sadusky AB & Dean J 2016 ZP2 peptide beads select human sperm in vitro, decoy mouse sperm in vivo, and provide reversible contraception. *Science Translational Medicine* **8** 336ra360. (doi:10.1126/scitranslmed.aad9946)
- Bahat A, Tur-Kaspa I, Gakamsky A, Giojalas LC, Breitbart H & Eisenbach M 2003 Thermotaxis of mammalian sperm cells: a potential navigation mechanism in the female genital tract. *Nature Medicine* **9** 149–150. (doi:10.1038/nm0203-149)
- Bahat A, Eisenbach M & Tur-Kaspa I 2005 Perioovulatory increase in temperature difference within the rabbit oviduct. *Human Reproduction* **20** 2118–2121. (doi:10.1093/humrep/dei006)
- Bahat A, Caplan SR & Eisenbach M 2012 Thermotaxis of human sperm cells in extraordinarily shallow temperature gradients over a wide range. *PLoS ONE* **7** e41915. (doi:10.1371/journal.pone.0041915)
- Ball BA, Scoggin KE, Troedsson MH & Squires EL 2013 Characterization of prostaglandin E2 receptors (EP2, EP4) in the horse oviduct. *Animal Reproduction Science* **142** 35–41. (doi:10.1016/j.anireprosci.2013.07.009)
- Ballester L, Romero-Aguirregomezcorra J, Soriano-Ubeda C, Matas C, Romar R & Coy P 2014 Timing of oviductal fluid collection, steroid concentrations, and sperm preservation method affect porcine in vitro fertilization efficiency. *Fertility and Sterility* **102** 1762.e1761–1768.e1761. (doi:10.1016/j.fertnstert.2014.08.009)
- Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, Cozijnsen M, Haegebarth A, Korving J, Begthel H, Peters PJ, et al. 2007 Identification of stem cells in small intestine and colon by marker gene Lgr5. *Nature* **449** 1003–1007. (doi:10.1038/nature06196)
- Barker N, Huch M, Kujala P, van de Wetering M, Snippert HJ, van Es JH, Sato T, Stange DE, Begthel H, van den Born M, et al. 2010 Lgr5(+ve) stem cells drive self-renewal in the stomach and build long-lived gastric units in vitro. *Cell Stem Cell* **6** 25–36. (doi:10.1016/j.stem.2009.11.013)
- Barker N, Rookmaaker MB, Kujala P, Ng A, Leushacke M, Snippert H, van de Wetering M, Tan S, Van Es JH, Huch M, et al. 2012 Lgr5(+ve) stem/progenitor cells contribute to nephron formation during kidney development. *Cell Reports* **2** 540–552. (doi:10.1016/j.celrep.2012.08.018)
- Basavarajappa BS, Nagre NN, Xie S & Subbanna S 2014 Elevation of endogenous anandamide impairs LTP, learning, and memory through CB1 receptor signaling in mice. *Hippocampus* **24** 808–818. (doi:10.1002/hipo.22272)
- Beier HM 1974 Oviducal and uterine fluids. *Journal of Reproduction and Fertility* **37** 221–237. (doi:10.1530/jrf.0.0370221)
- Berger RG, Foster WG & deCatanzaro D 2010 Bisphenol-A exposure during the period of blastocyst implantation alters uterine morphology and perturbs measures of estrogen and progesterone receptor expression in mice. *Reproductive Toxicology* **30** 393–400. (doi:10.1016/j.reprotox.2010.06.006)
- Berker B, Kahraman K, Taskin S, Sukur YE, Sonmez M & Atabekoglu CS 2011 Recombinant FSH versus clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing intrauterine insemination: a randomized trial. *Archives of Gynecology and Obstetrics* **284** 1561–1566. (doi:10.1007/s00404-011-1997-4)
- Betteridge KJ & Mitchell D 1974 Direct evidence of retention of unfertilized ova in the oviduct of the mare. *Journal of Reproduction and Fertility* **39** 145–148. (doi:10.1530/jrf.0.0390145)
- Bian F, Mao G, Guo M, Mao G, Wang J, Li J, Han Y, Chen X, Zhang M & Xia G 2012 Gradients of natriuretic peptide precursor A (NPPA) in oviduct and of natriuretic peptide receptor 1 (NPR1) in spermatozoon are involved in mouse sperm chemotaxis and fertilization. *Journal of Cellular Physiology* **227** 2230–2239. (doi:10.1002/jcp.22962)
- Bianchi E, Doe B, Goulding D & Wright GJ 2014 Juno is the egg Izumo receptor and is essential for mammalian fertilization. *Nature* **508** 483–487. (doi:10.1038/nature13203)
- Bishop DW 1956 Active secretion in the rabbit oviduct. *American Journal of Physiology* **187** 347–352.
- Bittner GD, Yang CZ & Stoner MA 2014 Estrogenic chemicals often leach from BPA-free plastic products that are replacements for BPA-containing polycarbonate products. *Environmental Health* **13** 41. (doi:10.1186/1476-069X-13-41)
- Bontekoe S, Mantikou E, van Wely M, Seshadri S, Repping S & Mastenbroek S 2012 Low oxygen concentrations for embryo culture

- in assisted reproductive technologies. *Cochrane Database of Systematic Reviews* **7** CD008950. (doi:10.1002/14651858.CD008950.pub2)
- Branes MC, Morales B, Rios M & Villalon MJ 2005 Regulation of the immunoeexpression of aquaporin 9 by ovarian hormones in the rat oviductal epithelium. *American Journal of Physiology: Cell Physiology* **288** C1048–C1057. (doi:10.1152/ajpcell.00420.2003)
- Bromfield EG, Aitken RJ, Anderson AL, McLaughlin EA & Nixon B 2015 The impact of oxidative stress on chaperone-mediated human sperm–egg interaction. *Human Reproduction* **30** 2597–2613. (doi:10.1093/humrep/dev214)
- Bromfield EG, McLaughlin EA, Aitken RJ & Nixon B 2016 Heat Shock Protein member A2 forms a stable complex with angiotensin converting enzyme and protein disulfide isomerase A6 in human spermatozoa. *Molecular Human Reproduction* **22** 93–109. (doi:10.1093/molehr/gav073)
- Burkart AD, Xiong B, Baibakov B, Jimenez-Movilla M & Dean J 2012 Ovastacin, a cortical granule protease, cleaves ZP2 in the zona pellucida to prevent polyspermy. *Journal of Cell Biology* **197** 37–44. (doi:10.1083/jcb.201112094)
- Bylander A, Nutu M, Wellander R, Goksor M, Billig H & Larsson DG 2010 Rapid effects of progesterone on ciliary beat frequency in the mouse fallopian tube. *Reproductive Biology and Endocrinology* **8** 48. (doi:10.1186/1477-7827-8-48)
- Bylander A, Lind K, Goksor M, Billig H & Larsson DG 2013 The classical progesterone receptor mediates the rapid reduction of fallopian tube ciliary beat frequency by progesterone. *Reproductive Biology and Endocrinology* **11** 33. (doi:10.1186/1477-7827-11-33)
- Caballero-Campo P, Buffone MG, Benencia F, Conejo-Garcia JR, Rinaudo PF & Gerton GL 2014 A role for the chemokine receptor CCR6 in mammalian sperm motility and chemotaxis. *Journal of Cellular Physiology* **229** 68–78. (doi:10.1002/jcp.24418)
- Capel B 2014 Ovarian epithelium regeneration by Lgr5(+) cells. *Nature Cell Biology* **16** 743–744. (doi:10.1038/ncb3020)
- Carlsson B, Hillensjo T, Nilsson A, Tornell J & Billig H 1993 Expression of insulin-like growth factor-I (IGF-I) in the rat fallopian tube: possible autocrine and paracrine action of fallopian tube-derived IGF-I on the fallopian tube and on the preimplantation embryo. *Endocrinology* **133** 2031–2039. (doi:10.1210/endo.133.5.8404650)
- Catt JW & Henman M 2000 Toxic effects of oxygen on human embryo development. *Human Reproduction* **15** (Supplement 2) 199–206. (doi:10.1093/humrep/15.suppl_2.199)
- Chang H & Suarez SS 2012 Unexpected flagellar movement patterns and epithelial binding behavior of mouse sperm in the oviduct. *Biology of Reproduction* **86** 140, 141–148. (doi:10.1095/biolreprod.111.096578)
- Chegini N, Zhao Y & McLean FW 1994 Expression of messenger ribonucleic acid and presence of immunoreactive proteins for epidermal growth factor (EGF), transforming growth factor alpha (TGF alpha) and EGF/TGF alpha receptors and 125I-EGF binding sites in human fallopian tube. *Biology of Reproduction* **50** 1049–1058. (doi:10.1095/biolreprod50.5.1049)
- Chen S, Einspanier R & Schoen J 2013 In vitro mimicking of estrous cycle stages in porcine oviduct epithelium cells: estradiol and progesterone regulate differentiation, gene expression, and cellular function. *Biology of Reproduction* **89** 54. (doi:10.1095/biolreprod.113.108829)
- Choksi SP, Lauter G, Swoboda P & Roy S 2014 Switching on cilia: transcriptional networks regulating ciliogenesis. *Development* **141** 1427–1441. (doi:10.1242/dev.074666)
- Christians E, Champion E, Thompson EM & Renard JP 1995 Expression of the HSP 70.1 gene, a landmark of early zygotic activity in the mouse embryo, is restricted to the first burst of transcription. *Development* **121** 113–122.
- Christians E, Michel E & Renard JP 1997 Developmental control of heat shock and chaperone gene expression. Hsp 70 genes and heat shock factors during preimplantation phase of mouse development. *Cellular and Molecular Life Sciences* **53** 168–178. (doi:10.1007/PL00000589)
- Chung JJ, Navarro B, Krapivinsky G, Krapivinsky L & Clapham DE 2011 A novel gene required for male fertility and functional CATSPER channel formation in spermatozoa. *Nature Communications* **2** 153. (doi:10.1038/ncomms1153)
- Conneely OM, Mulac-Jericevic B & Lydon JP 2003 Progesterone-dependent regulation of female reproductive activity by two distinct progesterone receptor isoforms. *Steroids* **68** 771–778. (doi:10.1016/S0039-128X(03)00126-0)
- Couse JF & Korach KS 1999 Estrogen receptor null mice: what have we learned and where will they lead us? *Endocrine Reviews* **20** 358–417. (doi:10.1210/edrv.20.3.0370)
- Cretoiu SM, Cretoiu D, Suciuc L & Popescu LM 2009 Interstitial Cajal-like cells of human Fallopian tube express estrogen and progesterone receptors. *Journal of Molecular Histology* **40** 387–394. (doi:10.1007/s10735-009-9252-z)
- Croxatto HB 2002 Physiology of gamete and embryo transport through the fallopian tube. *Reproductive BioMedicine Online* **4** 160–169. (doi:10.1016/S1472-6483(10)61935-9)
- Dadashpour Davachi N, Zare Shahneh A, Kohram H, Zhandi M, Shamsi H, Hajiyavand AM & Saadat M 2016 Differential influence of ampullary and isthmic derived epithelial cells on zona pellucida hardening and in vitro fertilization in ovine. *Reproductive Biology* **16** 61–69. (doi:10.1016/j.repbio.2015.11.002)
- Daliri M, Rao KB, Kaur G, Garg S, Patil S & Totey SM 1999 Expression of growth factor ligand and receptor genes in preimplantation stage water buffalo (*Bubalus bubalis*) embryos and oviduct epithelial cells. *Journal of Reproduction and Fertility* **117** 61–70. (doi:10.1530/jrf.0.1170061)
- De Blas GA, Darszon A, Ocampo AY, Serrano CJ, Castellano LE, Hernandez-Gonzalez EO, Chirinos M, Larrea F, Beltran C & Trevino CL 2009 TRPM8, a versatile channel in human sperm. *PLoS ONE* **4** e6095. (doi:10.1371/journal.pone.0006095)
- Dean W, Bowden L, Aitchison A, Klose J, Moore T, Meneses JJ, Reik W & Feil R 1998 Altered imprinted gene methylation and expression in completely ES cell-derived mouse fetuses: association with aberrant phenotypes. *Development* **125** 2273–2282.
- Dean W, Santos F, Stojkovic M, Zakhartchenko V, Walter J, Wolf E & Reik W 2001 Conservation of methylation reprogramming in mammalian development: aberrant reprogramming in cloned embryos. *PNAS* **98** 13734–13738. (doi:10.1073/pnas.241522698)
- Dobrinski I, Smith TT, Suarez SS & Ball BA 1997 Membrane contact with oviductal epithelium modulates the intracellular calcium concentration of equine spermatozoa in vitro. *Biology of Reproduction* **56** 861–869. (doi:10.1095/biolreprod56.4.861)
- Donjacour A, Liu X, Lin W, Simbulan R & Rinaudo PF 2014 In vitro fertilization affects growth and glucose metabolism in a sex-specific manner in an outbred mouse model. *Biology of Reproduction* **90** 80. (doi:10.1095/biolreprod.113.113134)
- Dumollard R, Duchon M & Carroll J 2007a The role of mitochondrial function in the oocyte and embryo. *Current Topics in Developmental Biology* **77** 21–49. (doi:10.1016/S0070-2153(06)77002-8)
- Dumollard R, Ward Z, Carroll J & Duchon MR 2007b Regulation of redox metabolism in the mouse oocyte and embryo. *Development* **134** 455–465. (doi:10.1242/dev.02744)
- Ekerhovd E, Brannstrom M, Alexandersson M & Norstrom A 1997 Evidence for nitric oxide mediation of contractile activity in isolated strips of the human Fallopian tube. *Human Reproduction* **12** 301–305. (doi:10.1093/humrep/12.2.301)
- El Mouatassim S, Guerin P & Menezes Y 2000 Mammalian oviduct and protection against free oxygen radicals: expression of genes encoding antioxidant enzymes in human and mouse. *European Journal of Obstetrics and Gynecology and Reproductive Biology* **89** 1–6. (doi:10.1016/S0301-2115(99)00169-4)
- Eyestone WH & First NL 1989 Co-culture of early cattle embryos to the blastocyst stage with oviductal tissue or in conditioned medium.

- Journal of Reproduction and Fertility* **85** 715–720. (doi:10.1530/jrf.0.0850715)
- Farhi J & Orvieto R 2010 Cumulative clinical pregnancy rates after COH and IUI in subfertile couples. *Gynecological Endocrinology* **26** 500–504. (doi:10.3109/09513590903367036)
- Ferguson L, Kaftanovskaya EM, Manresa C, Barbara AM, Poppiti RJ, Tan Y & Agoulnik AI 2016 Constitutive notch signaling causes abnormal development of the oviducts, abnormal angiogenesis, and cyst formation in mouse female reproductive tract. *Biology of Reproduction* **94** 67. (doi:10.1095/biolreprod.115.134569)
- Ferris J, Mahboubi K, MacLusky N, King WA & Favetta LA 2016 BPA exposure during in vitro oocyte maturation results in dose-dependent alterations to embryo development rates, apoptosis rate, sex ratio and gene expression. *Reproductive Toxicology* **59** 128–138. (doi:10.1016/j.reprotox.2015.12.002)
- Fischer B & Bavister BD 1993 Oxygen tension in the oviduct and uterus of rhesus monkeys, hamsters and rabbits. *Journal of Reproduction and Fertility* **99** 673–679. (doi:10.1530/jrf.0.0990673)
- Flood PF, Jong A & Betteridge KJ 1979 The location of eggs retained in the oviducts of mares. *Journal of Reproduction and Fertility* **57** 291–294. (doi:10.1530/jrf.0.0570291)
- Folmes CD & Terzic A 2014 Metabolic determinants of embryonic development and stem cell fate. *Reproduction Fertility and Development* **27** 82–88. (doi:10.1071/RD14383)
- Freeman DA, Woods GL, Vanderwall DK & Weber JA 1992 Embryo-initiated oviductal transport in mares. *Journal of Reproduction and Fertility* **95** 535–538. (doi:10.1530/jrf.0.0950535)
- Gaddum-Rosse P & Blandau RJ 1973 In vitro studies on ciliary activity within the oviducts of the rabbit and pig. *American Journal of Anatomy* **136** 91–104. (doi:10.1002/aja.1001360108)
- Gaddum-Rosse P & Blandau RJ 1976 Comparative observations on ciliary currents in mammalian oviducts. *Biology of Reproduction* **14** 605–609. (doi:10.1095/biolreprod14.5.605)
- Gandolfi F & Moor RM 1987 Stimulation of early embryonic development in the sheep by co-culture with oviduct epithelial cells. *Journal of Reproduction and Fertility* **81** 23–28. (doi:10.1530/jrf.0.0810023)
- Gardiner CS & Reed DJ 1994 Status of glutathione during oxidant-induced oxidative stress in the preimplantation mouse embryo. *Biology of Reproduction* **51** 1307–1314. (doi:10.1095/biolreprod51.6.1307)
- Gardiner CS, Salmen JJ, Brandt CJ & Stover SK 1998 Glutathione is present in reproductive tract secretions and improves development of mouse embryos after chemically induced glutathione depletion. *Biology of Reproduction* **59** 431–436. (doi:10.1095/biolreprod59.2.431)
- Gardner DK & Leese HJ 1990 Concentrations of nutrients in mouse oviduct fluid and their effects on embryo development and metabolism in vitro. *Journal of Reproduction and Fertility* **88** 361–368. (doi:10.1530/jrf.0.0880361)
- Gardner DK, Lane M, Calderon I & Leeton J 1996 Environment of the preimplantation human embryo in vivo: metabolite analysis of oviduct and uterine fluids and metabolism of cumulus cells. *Fertility and Sterility* **65** 349–353. (doi:10.1016/S0015-0282(16)58097-2)
- Ge ZH & Spicer SS 1988 Immunocytochemistry of ion transport mediators in the genital tract of female rodents. *Biology of Reproduction* **38** 439–452. (doi:10.1095/biolreprod38.2.439)
- Georgiou AS, Sostaric E, Wong CH, Sniijders AP, Wright PC, Moore HD & Fazeli A 2005 Gametes alter the oviductal secretory proteome. *Molecular and Cellular Proteomics* **4** 1785–1796. (doi:10.1074/mcp.M500119-MCP200)
- Gervasi MG, Osycka-Salut C, Caballero J, Vazquez-Levin M, Pereyra E, Billi S, Franchi A & Perez-Martinez S 2011 Anandamide capacitates bull spermatozoa through CB1 and TRPV1 activation. *PLoS ONE* **6** e16993. (doi:10.1371/journal.pone.0016993)
- Gervasi MG, Marczylo TH, Lam PM, Rana S, Franchi AM, Konje JC & Perez-Martinez S 2013 Anandamide levels fluctuate in the bovine oviduct during the oestrous cycle. *PLoS ONE* **8** e72521. (doi:10.1371/journal.pone.0072521)
- Gervasi MG, Osycka-Salut C, Sanchez T, Alonso CA, Lladós C, Castellano L, Franchi AM, Villalón M & Perez-Martinez S 2016 Sperm release from the oviductal epithelium depends on Ca(2+) influx upon activation of CB1 and TRPV1 by anandamide. *Journal of Cellular Biochemistry* **117** 320–333. (doi:10.1002/jcb.25273)
- Gomes MV, Gomes CC, Pinto W Jr & Ramos ES 2007 Methylation pattern at the KvDMR in a child with Beckwith–Wiedemann syndrome conceived by ICSI. *American Journal of Medical Genetics Part A* **143A** 625–629. (doi:10.1002/ajmg.a.31628)
- Gonzalez G & Behringer RR 2009 Dicer is required for female reproductive tract development and fertility in the mouse. *Molecular Reproduction and Development* **76** 678–688. (doi:10.1002/mrd.21010)
- Gregoraszcuk EL, Cala M & Witkowska E 2000 Glycogen distribution in porcine fallopian tube epithelium during the estrus cycle. *Folia Biologica* **48** 85–90.
- Griffiths GS, Miller KA, Galileo DS & Martin-DeLeon PA 2008 Murine SPAM1 is secreted by the estrous uterus and oviduct in a form that can bind to sperm during capacitation: acquisition enhances hyaluronic acid-binding ability and cumulus dispersal efficiency. *Reproduction* **135** 293–301. (doi:10.1530/REP-07-0340)
- Grintsted J, Kjer JJ, Blendstrup K & Pedersen JF 1985 Is low temperature of the follicular fluid prior to ovulation necessary for normal oocyte development? *Fertility and Sterility* **43** 34–39. (doi:10.1016/S0015-0282(16)48314-7)
- Groot PC, Mager WH, Henriquez NV, Pronk JC, Arwert F, Planta RJ, Eriksson AW & Frants RR 1990 Evolution of the human alpha-amylase multigene family through unequal, homologous, and inter- and intrachromosomal crossovers. *Genomics* **8** 97–105. (doi:10.1016/0888-7543(90)90230-R)
- Guerin P & Menezo Y 1995 Hypotaurine and taurine in gamete and embryo environments: de novo synthesis via the cysteine sulfinic acid pathway in oviduct cells. *Zygote* **3** 333–343. (doi:10.1017/S0967199400002768)
- Guerin P, Guillaud J & Menezo Y 1995 Hypotaurine in spermatozoa and genital secretions and its production by oviduct epithelial cells in vitro. *Human Reproduction* **10** 866–872.
- Guerin P, El Mouatassim S & Menezo Y 2001 Oxidative stress and protection against reactive oxygen species in the pre-implantation embryo and its surroundings. *Human Reproduction Update* **7** 175–189. (doi:10.1093/humupd/7.2.175)
- Guimaraes AL, Pereira SA, Kussano NR & Dode MA 2016 The effect of pre-maturation culture using phosphodiesterase type 3 inhibitor and insulin, transferrin and selenium on nuclear and cytoplasmic maturation of bovine oocytes. *Zygote* **24** 219–229. (doi:10.1017/S0967199415000064)
- Guo H, Zhu P, Yan L, Li R, Hu B, Lian Y, Yan J, Ren X, Lin S, Li J, et al. 2014 The DNA methylation landscape of human early embryos. *Nature* **511** 606–610. (doi:10.1038/nature13544)
- Guyader-Joly C, Guerin P, Renard JP, Guillaud J, Ponchon S & Menezo Y 1998 Precursors of taurine in female genital tract: effects on developmental capacity of bovine embryo produced in vitro. *Amino Acids* **15** 27–42. (doi:10.1007/BF01345278)
- Haddad SN & Wira CR 2014 Estradiol regulation of constitutive and keratinocyte growth factor-induced CCL20 and CXCL1 secretion by mouse uterine epithelial cells. *American Journal of Reproductive Immunology* **72** 34–44. (doi:10.1111/aji.12260)
- Halbert SA, Tam PY & Blandau RJ 1976 Egg transport in the rabbit oviduct: the roles of cilia and muscle. *Science* **191** 1052–1053. (doi:10.1126/science.1251215)
- Halbert SA, Becker DR & Szal SE 1989 Ovum transport in the rat oviductal ampulla in the absence of muscle contractility. *Biology of Reproduction* **40** 1131–1136. (doi:10.1095/biolreprod40.6.1131)
- Hammami S, Morato R, Romaguera R, Roura M, Catala MG, Paramio MT, Mogas T & Izquierdo D 2013 Developmental competence and

- embryo quality of small oocytes from pre-pubertal goats cultured in IVM medium supplemented with low level of hormones, insulin–transferrin–selenium and ascorbic acid. *Reproduction in Domestic Animals* **48** 339–344. (doi:10.1111/j.1439-0531.2012.02160.x)
- Hamner CE & Fox SB 1968 Effect of oestrogen and progesterone on physical properties of rabbit oviduct fluid. *Journal of Reproduction and Fertility* **16** 121–122. (doi:10.1530/jrf.0.0160121)
- Han L, Nishimura K, Sadat Al Hosseini H, Bianchi E, Wright GJ & Jovine L 2016 Divergent evolution of vitamin B9 binding underlies Juno-mediated adhesion of mammalian gametes. *Current Biology* **26** R100–R101. (doi:10.1016/j.cub.2015.12.034)
- Hansen JM & Harris C 2015 Glutathione during embryonic development. *Biochimica et Biophysica Acta* **1850** 1527–1542. (doi:10.1016/j.bbagen.2014.12.001)
- Harvey MB, Arcellana-Panlilio MY, Zhang X, Schultz GA & Watson AJ 1995 Expression of genes encoding antioxidant enzymes in preimplantation mouse and cow embryos and primary bovine oviduct cultures employed for embryo coculture. *Biology of Reproduction* **53** 532–540. (doi:10.1095/biolreprod53.3.532)
- Hayashi Y, Fukayama M, Koike M & Nakayama T 1986 Amylase in human lungs and the female genital tract. Histochemical and immunohistochemical localization. *Histochemistry* **85** 491–496. (doi:10.1007/BF00508431)
- Hess AP, Talbi S, Hamilton AE, Baston-Buest DM, Nyegaard M, Irwin JC, Barragan F, Kruessel JS, Germeyer A & Giudice LC 2013 The human oviduct transcriptome reveals an anti-inflammatory, anti-angiogenic, secretory and matrix-stable environment during embryo transit. *Reproductive BioMedicine Online* **27** 423–435. (doi:10.1016/j.rbmo.2013.06.013)
- Hiura H, Okae H, Chiba H, Miyauchi N, Sato F, Sato A & Arima T 2014 Imprinting methylation errors in ART. *Reproductive Medicine and Biology* **13** 193–202. (doi:10.1007/s12522-014-0183-3)
- Hochberg CJ 1974 Tubal amylase. *Obstetrics and Gynecology* **43** 129–131.
- Huang Z & Wells D 2010 The human oocyte and cumulus cells relationship: new insights from the cumulus cell transcriptome. *Molecular Human Reproduction* **16** 715–725. (doi:10.1093/molehr/gaq031)
- Huang JC, Goldsby JS, Arbab F, Melhem Z, Aleksic N & Wu KK 2004 Oviduct prostacyclin functions as a paracrine factor to augment the development of embryos. *Human Reproduction* **19** 2907–2912. (doi:10.1093/humrep/deh520)
- Huang N, Liu B, Dong Z, Mao W, Zhang N, Li C & Cao J 2015 Prostanoid receptors EP2, EP4, and FP are regulated by estradiol in bovine oviductal smooth muscle. *Prostaglandins & Other Lipid Mediators* **121** 170–175. (doi:10.1016/j.prostaglandins.2015.08.002)
- Hunt PA, Koehler KE, Susiarjo M, Hodges CA, Ilagan A, Voigt RC, Thomas S, Thomas BF & Hassold TJ 2003 Bisphenol A exposure causes meiotic aneuploidy in the female mouse. *Current Biology* **13** 546–553. (doi:10.1016/S0960-9822(03)00189-1)
- Hunter RH 2012 Temperature gradients in female reproductive tissues. *Reproductive BioMedicine Online* **24** 377–380. (doi:10.1016/j.rbmo.2011.12.007)
- Hunter RH, Bogh IB, Einer-Jensen N, Muller S & Greve T 2000 Pre-ovulatory graafian follicles are cooler than neighbouring stroma in pig ovaries. *Human Reproduction* **15** 273–283. (doi:10.1093/humrep/15.2.273)
- Imai H, Sumi D, Sakamoto H, Hanamoto A, Arai M, Chiba N & Nakagawa Y 1996 Overexpression of phospholipid hydroperoxide glutathione peroxidase suppressed cell death due to oxidative damage in rat basophile leukemia cells (RBL-2H3). *Biochemical and Biophysical Research Communications* **222** 432–438. (doi:10.1006/bbrc.1996.0762)
- Isobe T, Minoura H, Tanaka K, Shibahara T, Hayashi N & Toyoda N 2002 The effect of RANTES on human sperm chemotaxis. *Human Reproduction* **17** 1441–1446. (doi:10.1093/humrep/17.6.1441)
- Jang HY, Ji SJ, Kim YH, Lee HY, Shin JS, Cheong HT, Kim JT, Park IC, Kong HS, Park CK, et al. 2010 Antioxidative effects of astaxanthin against nitric oxide-induced oxidative stress on cell viability and gene expression in bovine oviduct epithelial cell and the developmental competence of bovine IVM/IVF embryos. *Reproduction in Domestic Animals* **45** 967–974. (doi:10.1111/j.1439-0531.2009.01469.x)
- Jankovic SM, Varjacic M & Protic B 2001 Relaxant effect of oxytocin on isolated human oviduct. *Croatian Medical Journal* **42** 511–516.
- Jones GM, Cram DS, Song B, Magli MC, Gianaroli L, Lacham-Kaplan O, Findlay JK, Jenkin G & Trounson AO 2008 Gene expression profiling of human oocytes following in vivo or in vitro maturation. *Human Reproduction* **23** 1138–1144. (doi:10.1093/humrep/den085)
- Kane MT 1975 Bicarbonate requirements for culture of one-cell rabbit ova to blastocysts. *Biology of Reproduction* **12** 552–555. (doi:10.1095/biolreprod12.5.552)
- Kessler M, Hoffmann K, Brinkmann V, Thieck O, Jackisch S, Toelle B, Berger H, Mollenkopf HJ, Mangler M, Sehoul J, et al. 2015 The Notch and Wnt pathways regulate stemness and differentiation in human fallopian tube organoids. *Nature Communications* **6** 8989. (doi:10.1038/ncomms9989)
- Khosla S, Dean W, Brown D, Reik W & Feil R 2001 Culture of preimplantation mouse embryos affects fetal development and the expression of imprinted genes. *Biology of Reproduction* **64** 918–926. (doi:10.1095/biolreprod64.3.918)
- Kim SH, Cho KW, Kim SZ & Koh GY 1997 Characterization of the atrial natriuretic peptide system in the oviduct. *Endocrinology* **138** 2410–2416. (doi:10.1210/endo.138.6.5160)
- Kobayashi Y, Yamamoto Y, Kageyama S, Hirayama H, Kimura K & Okuda K 2016 Regulation of bovine oviductal NO synthesis by follicular steroids and prostaglandins. *Reproduction* **151** 577–587. (doi:10.1530/REP-15-0254)
- Kumaresan A, Gonzalez R, Johannisson A & Berqvist AS 2014 Dynamic quantification of intracellular calcium and protein tyrosine phosphorylation in cryopreserved boar spermatozoa during short-time incubation with oviductal fluid. *Theriogenology* **82** 1145–1153. (doi:10.1016/j.theriogenology.2014.07.029)
- Lam X, Gieseke C, Knoll M & Talbot P 2000 Assay and importance of adhesive interaction between hamster (Mesocricetus auratus) oocyte-cumulus complexes and the oviductal epithelium. *Biology of Reproduction* **62** 579–588. (doi:10.1095/biolreprod62.3.579)
- Lapointe J, Kimmins S, Maclaren LA & Bilodeau JF 2005 Estrogen selectively up-regulates the phospholipid hydroperoxide glutathione peroxidase in the oviducts. *Endocrinology* **146** 2583–2592. (doi:10.1210/en.2004-1373)
- Lazaraviciute G, Kauser M, Bhattacharya S, Haggarty P & Bhattacharya S 2014 A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. *Human Reproduction Update* **20** 840–852. (doi:10.1093/humupd/dmu033)
- Le Masson F & Christians E 2011 HSFs and regulation of Hsp70.1 (Hspa1b) in oocytes and preimplantation embryos: new insights brought by transgenic and knockout mouse models. *Cell Stress and Chaperones* **16** 275–285. (doi:10.1007/s12192-010-0239-1)
- Leese HJ 1988 The formation and function of oviduct fluid. *Journal of Reproduction and Fertility* **82** 843–856. (doi:10.1530/jrf.0.0820843)
- Leese HJ 2012 Metabolism of the preimplantation embryo: 40 years on. *Reproduction* **143** 417–427. (doi:10.1530/REP-11-0484)
- Leese HJ, Conaghan J, Martin KL & Hardy K 1993 Early human embryo metabolism. *Bioessays* **15** 259–264. (doi:10.1002/bies.950150406)
- Li TY, Colley D, Barr KJ, Yee SP & Kidder GM 2007 Rescue of oogenesis in Cx37-null mutant mice by oocyte-specific replacement with Cx43. *Journal of Cell Science* **120** 4117–4125. (doi:10.1242/jcs.03488)
- Li HJ, Sutton-McDowall ML, Wang X, Sugimura S, Thompson JG & Gilchrist RB 2016 Extending prematuration with cAMP modulators enhances the cumulus contribution to oocyte antioxidant defence

- and oocyte quality via gap junctions. *Human Reproduction* **31** 810–821. (doi:10.1093/humrep/dew020)
- Liao SB, Ho JC, Tang F & O WS 2011 Adrenomedullin increases ciliary beat frequency and decreases muscular contraction in the rat oviduct. *Reproduction* **141** 367–372. (doi:10.1530/REP-10-0230)
- Liao SB, Cheung KH, Cheung MP, To YT, O WS & Tang F 2013 Adrenomedullin increased the short-circuit current in the pig oviduct through chloride channels via the CGRP receptor: mediation by cAMP and calcium ions but not by nitric oxide. *Biology of Reproduction* **89** 99. (doi:10.1095/biolreprod.113.109934)
- Lindblom B, Wilhelmsson L, Wikland M, Hamberger L & Wqvist N 1983 Prostaglandins and oviductal function. *Acta Obstetrica et Gynecologica Scandinavica Supplement* **113** 43–46. (doi:10.3109/00016348309155195)
- Lindenbaum ES, Peretz BA & Beach D 1983 Menstrual-cycle-dependent and -independent features of the human Fallopian tube fimbrial epithelium: an ultrastructural and cytochemical study. *Gynecologic and Obstetric Investigation* **16** 76–85. (doi:10.1159/000299227)
- Lippes J, Krasner J, Alfonso LA, Dacalos ED & Lucero R 1981 Human oviductal fluid proteins. *Fertility and Sterility* **36** 623–629. (doi:10.1016/S0015-0282(16)45861-9)
- Lopera-Vasquez R, Hamdi M, Maillo V, Lloreda V, Coy P, Gutierrez-Adan A, Bermejo-Alvarez P & Rizos D 2015 Effect of bovine oviductal fluid on development and quality of bovine embryos produced in vitro. *Reproduction Fertility and Development*. (doi:10.1071/RD15238)
- Lorenzo IM, Liedtke W, Sanderson MJ & Valverde MA 2008 TRPV4 channel participates in receptor-operated calcium entry and ciliary beat frequency regulation in mouse airway epithelial cells. *PNAS* **105** 12611–12616. (doi:10.1073/pnas.0803970105)
- Lu YC, Yang J, Fok KL, Ye YH, Jin L, Chen ZY, Zhang XM, Huang HF & Chan HC 2016 Involvement of Cl⁽⁻⁾/HCO₃⁽⁻⁾ exchanger SLC26A3 and SLC26A6 in preimplantation embryo cleavage. *Scientific Reports* **6** 28402. (doi:10.1038/srep28402)
- Lucas E 2013 Epigenetic effects on the embryo as a result of periconceptual environment and assisted reproduction technology. *Reproductive BioMedicine Online* **27** 477–485. (doi:10.1016/j.rbmo.2013.06.003)
- Luke B, Brown MB, Wantman E, Lederman A, Gibbons W, Schattman GL, Lobo RA, Leach RE & Stern JE 2012 Cumulative birth rates with linked assisted reproductive technology cycles. *New England Journal of Medicine* **366** 2483–2491. (doi:10.1056/NEJMoa1110238)
- Lutwak-Mann C 1955 Carbonic anhydrase in the female reproductive tract; occurrence, distribution and hormonal dependence. *Journal of Endocrinology* **13** 26–38. (doi:10.1677/joe.0.0130026)
- Lyons RA, Saridogan E & Djahanbakhch O 2006 The reproductive significance of human Fallopian tube cilia. *Human Reproduction Update* **12** 363–372. (doi:10.1093/humupd/dml012)
- Ma JY, Liang XW, Schatten H & Sun QY 2012 Active DNA demethylation in mammalian preimplantation embryos: new insights and new perspectives. *Molecular Human Reproduction* **18** 333–340. (doi:10.1093/molehr/gas014)
- Maas DH, Storey BT & Mastroianni L Jr 1977 Hydrogen ion and carbon dioxide content of the oviductal fluid of the rhesus monkey (*Macaca mulatta*). *Fertility and Sterility* **28** 981–985. (doi:10.1016/S0015-0282(16)42801-3)
- Maher ER, Brueton LA, Bowdin SC, Luharia A, Cooper W, Cole TR, Macdonald F, Sampson JR, Barratt CL, Reik W, *et al.* 2003 Beckwith–Wiedemann syndrome and assisted reproduction technology (ART). *Journal of Medical Genetics* **40** 62–64. (doi:10.1136/jmg.40.1.62)
- Mahmood T, Saridogan E, Smutna S, Habib AM & Djahanbakhch O 1998 The effect of ovarian steroids on epithelial ciliary beat frequency in the human Fallopian tube. *Human Reproduction* **13** 2991–2994. (doi:10.1093/humrep/13.11.2991)
- Mann MR, Lee SS, Doherty AS, Verona RI, Nolen LD, Schultz RM & Bartolomei MS 2004 Selective loss of imprinting in the placenta following preimplantation development in culture. *Development* **131** 3727–3735. (doi:10.1242/dev.01241)
- Mansour R, Ishihara O, Adamson GD, Dyer S, de Mouzon J, Nygren KG, Sullivan E & Zegers-Hochschild F 2014 International committee for monitoring assisted reproductive technologies world report: assisted reproductive technology 2006. *Human Reproduction* **29** 1536–1551. (doi:10.1093/humrep/deu084)
- Marei WF, Salavati M & Fouladi-Nashta AA 2013 Critical role of hyaluronidase-2 during preimplantation embryo development. *Molecular Human Reproduction* **19** 590–599. (doi:10.1093/molehr/gat032)
- Mariani ML, Ciocca DR, Gonzalez Jatuff AS & Souto M 2003 Effect of neonatal chronic stress on expression of Hsp70 and oestrogen receptor alpha in the rat oviduct during development and the oestrous cycle. *Reproduction* **126** 801–808. (doi:10.1530/rep.0.1260801)
- Mariani ML, Souto M, Fanelli MA & Ciocca DR 2000 Constitutive expression of heat shock proteins hsp25 and hsp70 in the rat oviduct during neonatal development, the oestrous cycle and early pregnancy. *Journal of Reproduction and Fertility* **120** 217–223. (doi:10.1530/reprod/120.2.217)
- Marino JL, Moore VM, Willson KJ, Rumbold A, Whitrow MJ, Giles LC & Davies MJ 2014 Perinatal outcomes by mode of assisted conception and sub-fertility in an Australian data linkage cohort. *PLoS ONE* **9** e80398. (doi:10.1371/journal.pone.0080398)
- Marquez RT, Baggerly KA, Patterson AP, Liu J, Broadus R, Frumovitz M, Atkinson EN, Smith DI, Hartmann L, Fishman D, *et al.* 2005 Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon. *Clinical Cancer Research* **11** 6116–6126. (doi:10.1158/1078-0432.CCR-04-2509)
- Martin-Romero FJ, Miguel-Lasobras EM, Dominguez-Arroyo JA, Gonzalez-Carrera E & Alvarez IS 2008 Contribution of culture media to oxidative stress and its effect on human oocytes. *Reproductive BioMedicine Online* **17** 652–661. (doi:10.1016/S1472-6483(10)60312-4)
- Mastroianni L Jr & Jones R 1965 Oxygen tension within the rabbit fallopian tube. *Journal of Reproduction and Fertility* **9** 99–102. (doi:10.1530/jrf.0.0090099)
- Mc GR, Hargan LA, Potter BA & Daus AT Jr 1958 Amylase in fallopian tubes. *Proceedings of the Society for Experimental Biology and Medicine* **99** 130–131. (doi:10.3181/00379727-99-24270)
- McDonald MF & Bellve AR 1969 Influence of oestrogen and progesterone on flow of fluid from the Fallopian tube in the ovariectomized ewe. *Journal of Reproduction and Fertility* **20** 51–61. (doi:10.1530/jrf.0.0200051)
- McLernon DJ, Maheshwari A, Lee AJ & Bhattacharya S 2016 Cumulative live birth rates after one or more complete cycles of IVF: a population-based study of linked cycle data from 178,898 women. *Human Reproduction* **31** 572–581. (doi:10.1093/humrep/dev336)
- Messerschmidt DM, Knowles BB & Solter D 2014 DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryos. *Genes and Development* **28** 812–828. (doi:10.1101/gad.234294.113)
- Miki K & Clapham DE 2013 Rheotaxis guides mammalian sperm. *Current Biology* **23** 443–452. (doi:10.1016/j.cub.2013.02.007)
- Mondejar I, Martinez-Martinez I, Aviles M & Coy P 2013 Identification of potential oviductal factors responsible for zona pellucida hardening and monospermy during fertilization in mammals. *Biology of Reproduction* **89** 67. (doi:10.1095/biolreprod.113.111385)
- Morales P, Palma V, Salgado AM & Villalon M 1996 Sperm interaction with human oviductal cells in vitro. *Human Reproduction* **11** 1504–1509. (doi:10.1093/oxfordjournals.humrep.a019426)
- Motta PM, Nottola SA, Makabe S & Heyn R 2000 Mitochondrial morphology in human fetal and adult female germ cells. *Human*

- Reproduction* **15** (Supplement 2) 129–147. (doi:10.1093/humrep/15.suppl_2.129)
- Nagaraja AK, Andreu-Vieyra C, Franco HL, Ma L, Chen R, Han DY, Zhu H, Agno JE, Gunaratne PH, DeMayo FJ, et al. 2008 Deletion of Dicer in somatic cells of the female reproductive tract causes sterility. *Molecular Endocrinology* **22** 2336–2352. (doi:10.1210/me.2008-0142)
- Nakahari T, Nishimura A, Shimamoto C, Sakai A, Kuwabara H, Nakano T, Tanaka S, Kohda Y, Matsumura H & Mori H 2011 The regulation of ciliary beat frequency by ovarian steroids in the guinea pig Fallopian tube: interactions between oestradiol and progesterone. *Biomedical Research* **32** 321–328. (doi:10.2220/biomedres.32.321)
- Nasr-Esfahani MH & Johnson MH 1992 How does transferrin overcome the in vitro block to development of the mouse preimplantation embryo? *Journal of Reproduction and Fertility* **96** 41–48. (doi:10.1530/jrf.0.0960041)
- Nastri CO, Nobrega BN, Teixeira DM, Amorim J, Diniz LM, Barbosa MW, Giorgi VS, Pileggi VN & Martins WP 2016 Low versus atmospheric oxygen tension for embryo culture in assisted reproduction: a systematic review and meta-analysis. *Fertility and Sterility* **106** 95.e117–104.e117. (doi:10.1016/j.fertnstert.2016.02.037)
- Ng A, Tan S, Singh G, Rizk P, Swathi Y, Tan TZ, Huang RY, Leushacke M & Barker N 2014 Lgr5 marks stem/progenitor cells in ovary and tubal epithelia. *Nature Cell Biology* **16** 745–757. (doi:10.1038/ncb3000)
- Nichol R, Hunter RH, Gardner DK, Leese HJ & Cooke GM 1992 Concentrations of energy substrates in oviductal fluid and blood plasma of pigs during the peri-ovulatory period. *Journal of Reproduction and Fertility* **96** 699–707. (doi:10.1530/jrf.0.0960699)
- Nieder GL & Corder CN 1982 Quantitative histochemical measurement of pyruvate and lactate in mouse oviduct during the estrous cycle. *Journal of Histochemistry and Cytochemistry* **30** 1051–1058. (doi:10.1177/30.10.6890080)
- Nieder GL & Corder CN 1983 Pyruvate and lactate levels in oviducts of cycling, pregnant, and pseudopregnant mice. *Biology of Reproduction* **28** 566–574. (doi:10.1095/biolreprod28.3.566)
- Ning N, Zhu J, Du Y, Gao X, Liu C & Li J 2014 Dysregulation of hydrogen sulphide metabolism impairs oviductal transport of embryos. *Nature Communications* **5** 4107. (doi:10.1038/ncomms5107)
- Niwa S, Nakajima K, Miki H, Minato Y, Wang D & Hirokawa N 2012 KIF19A is a microtubule-depolymerizing kinesin for ciliary length control. *Developmental Cell* **23** 1167–1175. (doi:10.1016/j.devcel.2012.10.016)
- Noreikat K, Wolff M, Kummer W & Kolle S 2012 Ciliary activity in the oviduct of cycling, pregnant, and muscarinic receptor knockout mice. *Biology of Reproduction* **86** 120. (doi:10.1095/biolreprod.111.096339)
- Nozawa YI, Yao E, Lin C, Yang JH, Wilson CW, Gacayan R & Chuang PT 2013 Fused (Stk36) is a ciliary protein required for central pair assembly and motile cilia orientation in the mammalian oviduct. *Developmental Dynamics* **242** 1307–1319. (doi:10.1002/dvdy.24024)
- O'Doherty AM, Di Fenza M & Kolle S 2016 Lipopolysaccharide (LPS) disrupts particle transport, cilia function and sperm motility in an ex vivo oviduct model. *Scientific Reports* **6** 24583. (doi:10.1038/srep24583)
- Oberst FW & Plass ED 1936 The hydrogen ion concentration of human vaginal discharge. *American Journal of Obstetrics and Gynecology* **32** 22–35. (doi:10.1016/S0002-9378(15)31872-X)
- Odor DL, Gaddum-Rosse P & Rumery RE 1983 Secretory cells of the oviduct of the pig-tailed monkey, *Macaca nemestrina*, during the menstrual cycle and after estrogen treatment. *American Journal of Anatomy* **166** 149–172. (doi:10.1002/aja.1001660203)
- Okae H, Chiba H, Hiura H, Hamada H, Sato A, Utsunomiya T, Kikuchi H, Yoshida H, Tanaka A, Suyama M, et al. 2014 Genome-wide analysis of DNA methylation dynamics during early human development. *PLoS Genetics* **10** e1004868. (doi:10.1371/journal.pgen.1004868)
- Okamoto Y, Yoshida N, Suzuki T, Shimozaawa N, Asami M, Matsuda T, Kojima N, Perry AC & Takada T 2016 DNA methylation dynamics in mouse preimplantation embryos revealed by mass spectrometry. *Scientific Reports* **6** 19134. (doi:10.1038/srep19134)
- Olson JH & Chandler DE 1999 *Xenopus laevis* egg jelly contains small proteins that are essential to fertilization. *Developmental Biology* **210** 401–410. (doi:10.1006/dbio.1999.9281)
- Olson JH, Xiang X, Ziegert T, Kittelson A, Rawls A, Bieber AL & Chandler DE 2001 Allurin, a 21-kDa sperm chemoattractant from *Xenopus* egg jelly, is related to mammalian sperm-binding proteins. *PNAS* **98** 11205–11210. (doi:10.1073/pnas.211316798)
- Oren-Benaroya R, Orvieto R, Gakamsky A, Pinchasov M & Eisenbach M 2008 The sperm chemoattractant secreted from human cumulus cells is progesterone. *Human Reproduction* **23** 2339–2345. (doi:10.1093/humrep/den265)
- Orihuela PA & Croxatto HB 2001 Acceleration of oviductal transport of oocytes induced by estradiol in cycling rats is mediated by nongenomic stimulation of protein phosphorylation in the oviduct. *Biology of Reproduction* **65** 1238–1245. (doi:10.1095/biolreprod65.4.1238)
- Orihuela PA, Rios M & Croxatto HB 2001 Disparate effects of estradiol on egg transport and oviductal protein synthesis in mated and cyclic rats. *Biology of Reproduction* **65** 1232–1237. (doi:10.1095/biolreprod65.4.1232)
- Orihuela PA, Parada-Bustamante A, Cortes PP, Gatica C & Croxatto HB 2003 Estrogen receptor, cyclic adenosine monophosphate, and protein kinase A are involved in the nongenomic pathway by which estradiol accelerates oviductal oocyte transport in cyclic rats. *Biology of Reproduction* **68** 1225–1231. (doi:10.1095/biolreprod.102.011395)
- Orihuela PA, Parada-Bustamante A, Zuniga LM & Croxatto HB 2006 Inositol triphosphate participates in an oestradiol nongenomic signalling pathway involved in accelerated oviductal transport in cycling rats. *Journal of Endocrinology* **188** 579–588. (doi:10.1677/joe.1.06448)
- Ortiz ME, Bedregal P, Carvajal MI & Croxatto HB 1986 Fertilized and unfertilized ova are transported at different rates by the hamster oviduct. *Biology of Reproduction* **34** 777–781. (doi:10.1095/biolreprod34.4.777)
- Osycka-Salut C, Gervasi MG, Pereyra E, Cella M, Ribeiro ML, Franchi AM & Perez-Martinez S 2012 Anandamide induces sperm release from oviductal epithelia through nitric oxide pathway in bovines. *PLoS ONE* **7** e30671. (doi:10.1371/journal.pone.0030671)
- Overstreet JW & Cooper GW 1978a Sperm transport in the reproductive tract of the female rabbit: I. The rapid transit phase of transport. *Biology of Reproduction* **19** 101–114. (doi:10.1095/biolreprod19.1.101)
- Overstreet JW & Cooper GW 1978b Sperm transport in the reproductive tract of the female rabbit: II. The sustained phase of transport. *Biology of Reproduction* **19** 115–132. (doi:10.1095/biolreprod19.1.115)
- Owen CM & Segars JH Jr 2009 Imprinting disorders and assisted reproductive technology. *Seminars in Reproductive Medicine* **27** 417–428. (doi:10.1055/s-0029-1237430)
- Paik DY, Janzen DM, Schafenacker AM, Velasco VS, Shung MS, Cheng D, Huang J, Witte ON & Memarzadeh S 2012 Stem-like epithelial cells are concentrated in the distal end of the fallopian tube: a site for injury and serous cancer initiation. *Stem Cells* **30** 2487–2497. (doi:10.1002/stem.1207)
- Pandey S, Shetty A, Hamilton M, Bhattacharya S & Maheshwari A 2012 Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Human Reproduction Update* **18** 485–503. (doi:10.1093/humupd/dms018)
- Paria BC & Dey SK 1990 Preimplantation embryo development in vitro: cooperative interactions among embryos and role of growth factors. *PNAS* **87** 4756–4760. (doi:10.1073/pnas.87.12.4756)
- Parr BA & McMahon AP 1998 Sexually dimorphic development of the mammalian reproductive tract requires Wnt-7a. *Nature* **395** 707–710. (doi:10.1038/27221)
- Pelton TA, Bettess MD, Lake J, Rathjen J & Rathjen PD 1998 Developmental complexity of early mammalian pluripotent cell

- populations in vivo and in vitro. *Reproduction Fertility and Development* **10** 535–549. (doi:10.1071/RD98084)
- Perez-Cerezales S, Boryshpolets S, Afanzar O, Brandis A, Nevo R, Kiss V & Eisenbach M 2015 Involvement of opsins in mammalian sperm thermotaxis. *Scientific Reports* **5** 16146. (doi:10.1038/srep16146)
- Pfeifer TL & Chegini N 1994 Immunohistochemical localization of insulin-like growth factor (IGF-I), IGF-I receptor, and IGF binding proteins 1–4 in human fallopian tube at various reproductive stages. *Biology of Reproduction* **50** 281–289. (doi:10.1095/biolreprod50.2.281)
- Pike IL, Murdoch RN & Wales RG 1975 The incorporation of carbon dioxide into the major classes of RNA during culture of the preimplantation mouse embryo. *Journal of Reproduction and Fertility* **45** 211–226. (doi:10.1530/jrf.0.0450211)
- Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Soderstrom-Anttila V, Nygren KG, Hazekamp J & Bergh C 2013 Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Human Reproduction Update* **19** 87–104. (doi:10.1093/humupd/dms044)
- Pollard JW, Plante C, King WA, Hansen PJ, Betteridge KJ & Suarez SS 1991 Fertilizing capacity of bovine sperm may be maintained by binding of oviductal epithelial cells. *Biology of Reproduction* **44** 102–107. (doi:10.1095/biolreprod44.1.102)
- Prunskaitė-Hyyryläinen R, Skovorodkin I, Xu Q, Miinalainen I, Shan J & Vainio SJ 2016 Wnt4 coordinates directional cell migration and extension of the Mullerian duct essential for ontogenesis of the female reproductive tract. *Human Molecular Genetics* **25** 1059–1073. (doi:10.1093/hmg/ddv621)
- Punamaki RL, Tiitinen A, Lindblom J, Unkila-Kallio L, Flykt M, Vanska M, Poikkeus P & Tulppala M 2016 Mental health and developmental outcomes for children born after ART: a comparative prospective study on child gender and treatment type. *Human Reproduction* **31** 100–107. (doi:10.1093/humrep/dev273)
- Quill TA, Sugden SA, Rossi KL, Doolittle LK, Hammer RE & Garbers DL 2003 Hyperactivated sperm motility driven by CatSper2 is required for fertilization. *PNAS* **100** 14869–14874. (doi:10.1073/pnas.2136654100)
- Quinn P & Wales RG 1974 Fixation of carbon dioxide by preimplantation rabbit embryos in vitro. *Journal of Reproduction and Fertility* **36** 29–39. (doi:10.1530/jrf.0.0360029)
- Redgrove KA, Nixon B, Baker MA, Hetherington L, Baker G, Liu DY & Aitken RJ 2012 The molecular chaperone HSPA2 plays a key role in regulating the expression of sperm surface receptors that mediate sperm-egg recognition. *PLoS ONE* **7** e50851. (doi:10.1371/journal.pone.0050851)
- Redgrove KA, Anderson AL, McLaughlin EA, O'Bryan MK, Aitken RJ & Nixon B 2013 Investigation of the mechanisms by which the molecular chaperone HSPA2 regulates the expression of sperm surface receptors involved in human sperm-oocyte recognition. *Molecular Human Reproduction* **19** 120–135. (doi:10.1093/molehr/gas064)
- Reik W, Romer I, Barton SC, Surani MA, Howlett SK & Klose J 1993 Adult phenotype in the mouse can be affected by epigenetic events in the early embryo. *Development* **119** 933–942.
- Reik W, Dean W & Walter J 2001 Epigenetic reprogramming in mammalian development. *Science* **293** 1089–1093. (doi:10.1126/science.1063443)
- Ren D, Navarro B, Perez G, Jackson AC, Hsu S, Shi Q, Tilly JL & Clapham DE 2001 A sperm ion channel required for sperm motility and male fertility. *Nature* **413** 603–609. (doi:10.1038/35098027)
- Reuquen P, Orostica ML, Rojas I, Diaz P, Parada-Bustamante A & Orihuela PA 2015 Estradiol increases IP3 by a nongenomic mechanism in the smooth muscle cells from the rat oviduct. *Reproduction* **150** 331–341. (doi:10.1530/REP-15-0137)
- Rotem R, Zamir N, Keynan N, Barkan D, Breitbart H & Naor Z 1998 Atrial natriuretic peptide induces acrosomal exocytosis of human spermatozoa. *American Journal of Physiology* **274** E218–E223.
- Sakkas D & Trounson AO 1990 Co-culture of mouse embryos with oviduct and uterine cells prepared from mice at different days of pseudopregnancy. *Journal of Reproduction and Fertility* **90** 109–118. (doi:10.1530/jrf.0.0900109)
- Salmen JJ, Skufca F, Matt A, Gushansky G, Mason A & Gardiner CS 2005 Role of glutathione in reproductive tract secretions on mouse preimplantation embryo development. *Biology of Reproduction* **73** 308–314. (doi:10.1095/biolreprod.104.038307)
- Sathananthan AH & Trounson AO 2000 Mitochondrial morphology during preimplantational human embryogenesis. *Human Reproduction* **15** (Supplement 2) 148–159. (doi:10.1093/humrep/15.suppl.2.148)
- Schultka R & Cech S 1989 Demonstration of glycogen in human oviduct epithelium. *Acta Histochemica* **87** 137–139. (doi:10.1016/S0065-1281(89)80016-9)
- Shaieb F, Banerjee J, Maitra D, Diamond MP & Abu-Soud HM 2013 Impact of hydrogen peroxide-driven Fenton reaction on mouse oocyte quality. *Free Radical Biology and Medicine* **58** 154–159. (doi:10.1016/j.freeradbiomed.2012.12.007)
- Shaieb F, Khan SN, Ali I, Thakur M, Saed MG, Dai J, Awonuga AO, Banerjee J & Abu-Soud HM 2016 The defensive role of cumulus cells against reactive oxygen species insult in metaphase II mouse oocytes. *Reproductive Sciences* **23** 498–507. (doi:10.1177/1933719115607993)
- Shi W & Haaf T 2002 Aberrant methylation patterns at the two-cell stage as an indicator of early developmental failure. *Molecular Reproduction and Development* **63** 329–334. (doi:10.1002/mrd.90016)
- Shi D, Komatsu K, Hirao M, Toyooka Y, Koyama H, Tissir F, Goffinet AM, Uemura T & Fujimori T 2014 Celsr1 is required for the generation of polarity at multiple levels of the mouse oviduct. *Development* **141** 4558–4568. (doi:10.1242/dev.115659)
- Simon AM, Goodenough DA, Li E & Paul DL 1997 Female infertility in mice lacking connexin 37. *Nature* **385** 525–529. (doi:10.1038/385525a0)
- Smilnich NJ, Day CD, Fitzpatrick GV, Caldwell GM, Lossie AC, Cooper PR, Smallwood AC, Joyce JA, Schofield PN, Reik W, et al. 1999 A maternally methylated CpG island in KvLQT1 is associated with an antisense paternal transcript and loss of imprinting in Beckwith–Wiedemann syndrome. *PNAS* **96** 8064–8069. (doi:10.1073/pnas.96.14.8064)
- Smith TT & Nothnick WB 1997 Role of direct contact between spermatozoa and oviductal epithelial cells in maintaining rabbit sperm viability. *Biology of Reproduction* **56** 83–89. (doi:10.1095/biolreprod56.1.83)
- Smith ZD, Chan MM, Mikkelsen TS, Gu H, Gnirke A, Regev A & Meissner A 2012 A unique regulatory phase of DNA methylation in the early mammalian embryo. *Nature* **484** 339–344. (doi:10.1038/nature10960)
- Smith ZD, Chan MM, Humm KC, Karnik R, Mekhoubad S, Regev A, Eggan K & Meissner A 2014 DNA methylation dynamics of the human preimplantation embryo. *Nature* **511** 611–615. (doi:10.1038/nature13581)
- Snegovskikh V, Mutlu L, Massasa E & Taylor HS 2014 Identification of putative fallopian tube stem cells. *Reproductive Sciences* **21** 1460–1464. (doi:10.1177/1933719114553448)
- Song S, Ghosh J, Mainigi M, Turan N, Weinerman R, Truongcao M, Coutifaris C & Sapienza C 2015 DNA methylation differences between in vitro- and in vivo-conceived children are associated with ART procedures rather than infertility. *Clinical Epigenetics* **7** 41. (doi:10.1186/s13148-015-0071-7)
- Spilman CH & Harper MJ 1975 Effects of prostaglandins on oviductal motility and egg transport. *Gynecologic and Obstetric Investigation* **6** 186–205. (doi:10.1159/000301516)
- Stern JE, Goldman MB, Hatasaka H, MacKenzie TA, Surrey ES, Racowsky C & Society for Assisted Reproductive Technology Writing Group 2009 Optimizing the number of cleavage stage embryos to transfer on day 3 in women 38 years of age and older: a Society for

- Assisted Reproductive Technology database study. *Fertility and Sterility* **91** 767–776. (doi:10.1016/j.fertnstert.2007.12.051)
- Stewart CA & Behringer RR 2012 Mouse oviduct development. *Results and Problems in Cell Differentiation* **55** 247–262. (doi:10.1007/978-3-642-30406-4_14)
- Sturmeijer RG, Reis A, Leese HJ & McEvoy TG 2009 Role of fatty acids in energy provision during oocyte maturation and early embryo development. *Reproduction in Domestic Animals* **44** (Supplement 3) 50–58. (doi:10.1111/j.1439-0531.2009.01402.x)
- Suarez SS 2016 Mammalian sperm interactions with the female reproductive tract. *Cell and Tissue Research* **363** 185–194. (doi:10.1007/s00441-015-2244-2)
- Suarez SS & Pacey AA 2006 Sperm transport in the female reproductive tract. *Human Reproduction Update* **12** 23–37. (doi:10.1093/humupd/dmi047)
- Suarez SS, Katz DF, Owen DH, Andrew JB & Powell RL 1991 Evidence for the function of hyperactivated motility in sperm. *Biology of Reproduction* **44** 375–381. (doi:10.1095/biolreprod44.2.375)
- Suarez SS, Dai XB, DeMott RP, Redfern K & Mirando MA 1992 Movement characteristics of boar sperm obtained from the oviduct or hyperactivated in vitro. *Journal of Andrology* **13** 75–80.
- Subbanna S, Shivakumar M, Psychoyos D, Xie S & Basavarajappa BS 2013 Anandamide-CB1 receptor signaling contributes to postnatal ethanol-induced neonatal neurodegeneration, adult synaptic, and memory deficits. *Journal of Neuroscience* **33** 6350–6366. (doi:10.1523/JNEUROSCI.3786-12.2013)
- Sun X, Terakawa J, Clevers H, Barker N, Daikoku T & Dey SK 2014 Ovarian LGR5 is critical for successful pregnancy. *FASEB Journal* **28** 2380–2389. (doi:10.1096/fj.13-248344)
- Sutton ML, Gilchrist RB & Thompson JG 2003 Effects of in-vivo and in-vitro environments on the metabolism of the cumulus-oocyte complex and its influence on oocyte developmental capacity. *Human Reproduction Update* **9** 35–48. (doi:10.1093/humupd/dmg009)
- Sutton-McDowall ML, Gilchrist RB & Thompson JG 2010 The pivotal role of glucose metabolism in determining oocyte developmental competence. *Reproduction* **139** 685–695. (doi:10.1530/REP-09-0345)
- Sutton-McDowall ML, Feil D, Robker RL, Thompson JG & Dunning KR 2012 Utilization of endogenous fatty acid stores for energy production in bovine preimplantation embryos. *Theriogenology* **77** 1632–1641. (doi:10.1016/j.theriogenology.2011.12.008)
- Takeuchi K, Nagata Y, Sandow BA & Hodgen GD 1992 Primary culture of human fallopian tube epithelial cells and co-culture of early mouse pre-embryos. *Molecular Reproduction and Development* **32** 236–242. (doi:10.1002/mrd.1080320308)
- Talo A 1991 How the myosalpinx works in gamete and embryo transport. *Archivos de Biología y Medicina Experimentales* **24** 361–375.
- Tanghe S, Van Soom A, Nauwynck H, Coryn M & de Kruijff A 2002 Minireview: functions of the cumulus oophorus during oocyte maturation, ovulation, and fertilization. *Molecular Reproduction and Development* **61** 414–424. (doi:10.1002/mrd.10102)
- Tay JJ, Rutherford AJ, Killick SR, Maguiness SD, Partridge RJ & Leese HJ 1997 Human tubal fluid: production, nutrient composition and response to adrenergic agents. *Human Reproduction* **12** 2451–2456. (doi:10.1093/humrep/12.11.2451)
- Teilmann SC, Byskov AG, Pedersen PA, Wheatley DN, Pazour GJ & Christensen ST 2005 Localization of transient receptor potential ion channels in primary and motile cilia of the female murine reproductive organs. *Molecular Reproduction and Development* **71** 444–452. (doi:10.1002/mrd.20312)
- Teilmann SC, Clement CA, Thorup J, Byskov AG & Christensen ST 2006 Expression and localization of the progesterone receptor in mouse and human reproductive organs. *Journal of Endocrinology* **191** 525–535. (doi:10.1677/joe.1.06565)
- Tenore JL 2000 Ectopic pregnancy. *American Family Physician* **61** 1080–1088.
- Teves ME, Barbano F, Guidobaldi HA, Sanchez R, Miska W & Giojalas LC 2006 Progesterone at the picomolar range is a chemoattractant for mammalian spermatozoa. *Fertility and Sterility* **86** 745–749. (doi:10.1016/j.fertnstert.2006.02.080)
- Tosti E & Menezo Y 2016 Gamete activation: basic knowledge and clinical applications. *Human Reproduction Update* **22** 420–439. (doi:10.1093/humupd/dmw014)
- Trimarchi JR, Liu L, Porterfield DM, Smith PJ & Keefe DL 2000 Oxidative phosphorylation-dependent and -independent oxygen consumption by individual preimplantation mouse embryos. *Biology of Reproduction* **62** 1866–1874. (doi:10.1095/biolreprod62.6.1866)
- Tung CK, Hu L, Fiore AG, Ardon F, Hickman DG, Gilbert RO, Suarez SS & Wu M 2015 Microgrooves and fluid flows provide preferential passageways for sperm over pathogen *Trichomonas foetus*. *PNAS* **112** 5431–5436. (doi:10.1073/pnas.1500541112)
- Varayoud J, Ramos JG, Bosquiaz VL, Lower M, Munoz-de-Toro M & Luque EH 2011 Neonatal exposure to bisphenol A alters rat uterine implantation-associated gene expression and reduces the number of implantation sites. *Endocrinology* **152** 1101–1111. (doi:10.1210/en.2009-1037)
- Ventura-Junca P, Irrarrazaval I, Rolle AJ, Gutierrez JI, Moreno RD & Santos MJ 2015 In vitro fertilization (IVF) in mammals: epigenetic and developmental alterations. Scientific and bioethical implications for IVF in humans. *Biological Research* **48** 68. (doi:10.1186/s40659-015-0059-y)
- Vieira GC, Chockalingam S, Melegh Z, Greenhough A, Malik S, Szemes M, Park JH, Kaidi A, Zhou L, Catchpoole D, et al. 2015 LGR5 regulates pro-survival MEK/ERK and proliferative Wnt/beta-catenin signalling in neuroblastoma. *Oncotarget* **6** 40053–40067. (doi:10.18632/oncotarget.5548)
- Villalon M, Ortiz ME, Aguayo C, Munoz J & Croxatto HB 1982 Differential transport of fertilized and unfertilized ova in the rat. *Biology of Reproduction* **26** 337–341. (doi:10.1095/biolreprod26.2.337)
- Virant-Klun I, Knez K, Tomazevic T & Skutella T 2013 Gene expression profiling of human oocytes developed and matured in vivo or in vitro. *BioMed Research International* **2013** 879489. (doi:10.1155/2013/879489)
- Vishwakarma P 1962 The pH and bicarbonate-ion content of the oviduct and uterine fluids. *Fertility and Sterility* **13** 481–485. (doi:10.1016/S0015-0282(16)34633-7)
- Vitaioi L, Gobbetti A & Baldoni E 1996 Arylsulphatase A activity and sulphatide concentration in the female rabbit oviduct are under physiological hormonal influence. *Histochemical Journal* **28** 149–156. (doi:10.1007/BF02331420)
- Vlad M, Walker D & Kennedy RC 1996 Nuclei number in human embryos co-cultured with human ampullary cells. *Human Reproduction* **11** 1678–1686. (doi:10.1093/oxfordjournals.humrep.a019469)
- Wang H, Guo Y, Wang D, Kingsley PJ, Marnett LJ, Das SK, DuBois RN & Dey SK 2004 Aberrant cannabinoid signaling impairs oviductal transport of embryos. *Nature Medicine* **10** 1074–1080. (doi:10.1038/nm1104)
- Wang N, Le F, Zhan QT, Li L, Dong MY, Ding GL, Xu CM, Jiang SW, Huang HF & Jin F 2010 Effects of in vitro maturation on histone acetylation in metaphase II oocytes and early cleavage embryos. *Obstetrics and Gynecology International* **2010** 989278. (doi:10.1155/2010/989278)
- Wangren K, Lalitkumar PG, Stavreus-Evers A, Stabi B & Gemzell-Danielsson K 2006 Prostaglandin E2 and F2alpha receptors in the human Fallopian tube before and after mifepristone treatment. *Molecular Human Reproduction* **12** 577–585. (doi:10.1093/molehr/gal058)
- Wangren K, Stavreus-Evers A, Olsson C, Andersson E & Gemzell-Danielsson K 2008 Regulation of muscular contractions in the human Fallopian tube through prostaglandins and prostaglandins. *Human Reproduction* **23** 2359–2368. (doi:10.1093/humrep/den260)

- Ward GE, Brokaw CJ, Garbers DL & Vacquier VD 1985 Chemotaxis of *Arbacia punctulata* spermatozoa to resact, a peptide from the egg jelly layer. *Journal of Cell Biology* **101** 2324–2329. (doi:10.1083/jcb.101.6.2324)
- Weber JA, Freeman DA, Vanderwall DK & Woods GL 1991a Prostaglandin E2 hastens oviductal transport of equine embryos. *Biology of Reproduction* **45** 544–546. (doi:10.1095/biolreprod45.4.544)
- Weber JA, Freeman DA, Vanderwall DK & Woods GL 1991b Prostaglandin E2 secretion by oviductal transport-stage equine embryos. *Biology of Reproduction* **45** 540–543. (doi:10.1095/biolreprod45.4.540)
- Wen S, Cao G, Bao T, Cheng L, Li H, Du C, Tu Y, Li Q, Jian R, Zhao P, et al. 2012 Modulation of ovine SBD-1 expression by 17beta-estradiol in ovine oviduct epithelial cells. *BMC Veterinary Research* **8** 143. (doi:10.1186/1746-6148-8-143)
- White KL, Hehnke K, Rickords LF, Southern LL, Thompson DL Jr & Wood TC 1989 Early embryonic development in vitro by coculture with oviductal epithelial cells in pigs. *Biology of Reproduction* **41** 425–430. (doi:10.1095/biolreprod41.3.425)
- Wijayagunawardane MP, Miyamoto A, Taquahashi Y, Gabler C, Acosta TJ, Nishimura M, Killian G & Sato K 2001 In vitro regulation of local secretion and contraction of the bovine oviduct: stimulation by luteinizing hormone, endothelin-1 and prostaglandins, and inhibition by oxytocin. *Journal of Endocrinology* **168** 117–130. (doi:10.1677/joe.0.1680117)
- Winuthayanon W, Bernhardt ML, Padilla-Banks E, Myers PH, Edin ML, Hewitt SC, Korach KS & Williams CJ 2015 Oviductal estrogen receptor alpha signaling prevents protease-mediated embryo death. *eLife* **4** e10453. (doi:10.7554/eLife.10453)
- Wira CR, Fahey JV, Sentman CL, Pioli PA & Shen L 2005 Innate and adaptive immunity in female genital tract: cellular responses and interactions. *Immunological Reviews* **206** 306–335. (doi:10.1111/j.0105-2896.2005.00287.x)
- Wu J, Bao J, Kim M, Yuan S, Tang C, Zheng H, Mastick GS, Xu C & Yan W 2014 Two miRNA clusters, miR-34b/c and miR-449, are essential for normal brain development, motile ciliogenesis, and spermatogenesis. *PNAS* **111** E2851–E2857. (doi:10.1073/pnas.1407777111)
- Wydooghe E, Heras S, Dewulf J, Piepers S, Van den Abbeel E, De Sutter P, Vandaele L & Van Soom A 2014 Replacing serum in culture medium with albumin and insulin, transferrin and selenium is the key to successful bovine embryo development in individual culture. *Reproduction Fertility and Development* **26** 717–724. (doi:10.1071/RD13043)
- Xie M, McCoski SR, Johnson SE, Rhoads ML & Ealy AD 2015 Combinatorial effects of epidermal growth factor, fibroblast growth factor 2 and insulin-like growth factor 1 on trophoblast cell proliferation and embryogenesis in cattle. *Reproduction Fertility and Development*. (doi:10.1071/RD15226)
- Xu JS, Lee YL, Lee KF, Kwok KL, Lee WM, Luk JM & Yeung WS 2004 Embryotrophic factor-3 from human oviductal cells enhances proliferation, suppresses apoptosis and stimulates the expression of the beta1 subunit of sodium–potassium ATPase in mouse embryos. *Human Reproduction* **19** 2919–2926. (doi:10.1093/humrep/deh497)
- Yang Y, Xu Y, Ding C, Khoudja RY, Lin M, Awonuga AO, Dai J, Puscheck EE, Rappolee DA & Zhou C 2016 Comparison of 2, 5, and 20% O₂ on the development of post-thaw human embryos. *Journal of Assisted Reproduction and Genetics* **33** 919–927. (doi:10.1007/s10815-016-0693-5)
- Ye J, Coleman J, Hunter MG, Craigon J, Campbell KH & Luck MR 2007 Physiological temperature variants and culture media modify meiotic progression and developmental potential of pig oocytes in vitro. *Reproduction* **133** 877–886. (doi:10.1530/REP-06-0318)
- Yedwab GA, Paz G, Homonnai TZ, David MP & Kraicer PF 1976 The temperature, pH, and partial pressure of oxygen in the cervix and uterus of women and uterus of rats during the cycle. *Fertility and Sterility* **27** 304–309. (doi:10.1016/S0015-0282(16)41722-X)
- Yeung WS, Ho PC, Lau EY & Chan ST 1992 Improved development of human embryos in vitro by a human oviductal cell co-culture system. *Human Reproduction* **7** 1144–1149.
- Yin N, Yao X, Qin Z, Wang YL & Faiola F 2015 Assessment of Bisphenol A (BPA) neurotoxicity in vitro with mouse embryonic stem cells. *Journal of Environmental Sciences* **36** 181–187. (doi:10.1016/j.jes.2015.06.004)
- Zamir N, Riven-Kreitman R, Manor M, Makler A, Blumberg S, Ralt D & Eisenbach M 1993 Atrial natriuretic peptide attracts human spermatozoa in vitro. *Biochemical and Biophysical Research Communications* **197** 116–122. (doi:10.1006/bbrc.1993.2449)
- Zamir N, Barkan D, Keynan N, Naor Z & Breitbart H 1995 Atrial natriuretic peptide induces acrosomal exocytosis in bovine spermatozoa. *American Journal of Physiology* **269** E216–E221.
- Zandstra H, Van Montfoort AP & Dumoulin JC 2015 Does the type of culture medium used influence birthweight of children born after IVF? *Human Reproduction* **30** 530–542. (doi:10.1093/humrep/deu346)
- Zhang M, Hong H, Zhou B, Jin S, Wang C, Fu M, Wang S & Xia G 2006 The expression of atrial natriuretic peptide in the oviduct and its functions in pig spermatozoa. *Journal of Endocrinology* **189** 493–507. (doi:10.1677/joe.1.06483)

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