Oviduct: roles in fertilization and early embryo development

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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

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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 isthmic region of the oviduct, the sperm heads attach to the oviductal epithelial cells. The studies using scanning electron micrographs of

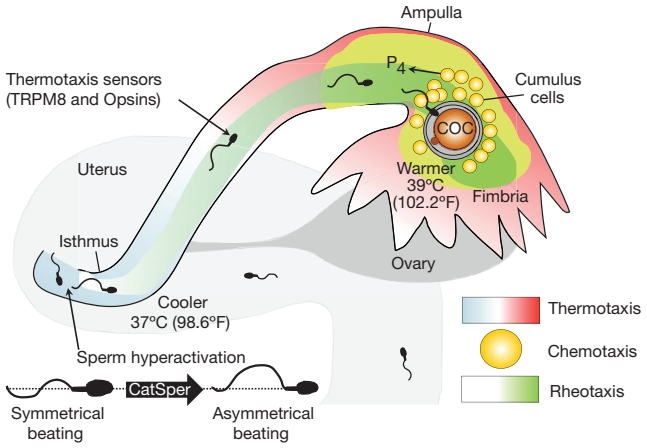

Figure 1
Oviduct-guided fertilization. The oviduct regulates fertilization through sperm guidance and sperm hyperactivation. The sperm guidance is achieved through rheotaxis, thermotaxis and chemotaxis. Rheotaxis is created by tubal fluid, which generates a current flow from the ampulla toward the isthmus 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°C (Bahat *et al.* 2012). Temperatures depicted (37°C vs 39°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 (Dobrinski *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 isthmic 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

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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 Ca^{2+}-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 (Grinsted *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 (P_4) 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 Ca^{2+} 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

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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 viscose, 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). PGE_2 and $PGF_{2\alpha}$ increase muscle contraction, whereas PGE_1 decreases muscle contraction (Wanggren *et al.* 2008). Evidence indicates that the contraction is possibly regulated by both E_2 and P_4, 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 1978*a*). 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 1978*a*,*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

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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, immunoglobin, 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.* 2007*a*,*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.* 2007*a*). 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 (Sturmey *et al.* 2009,

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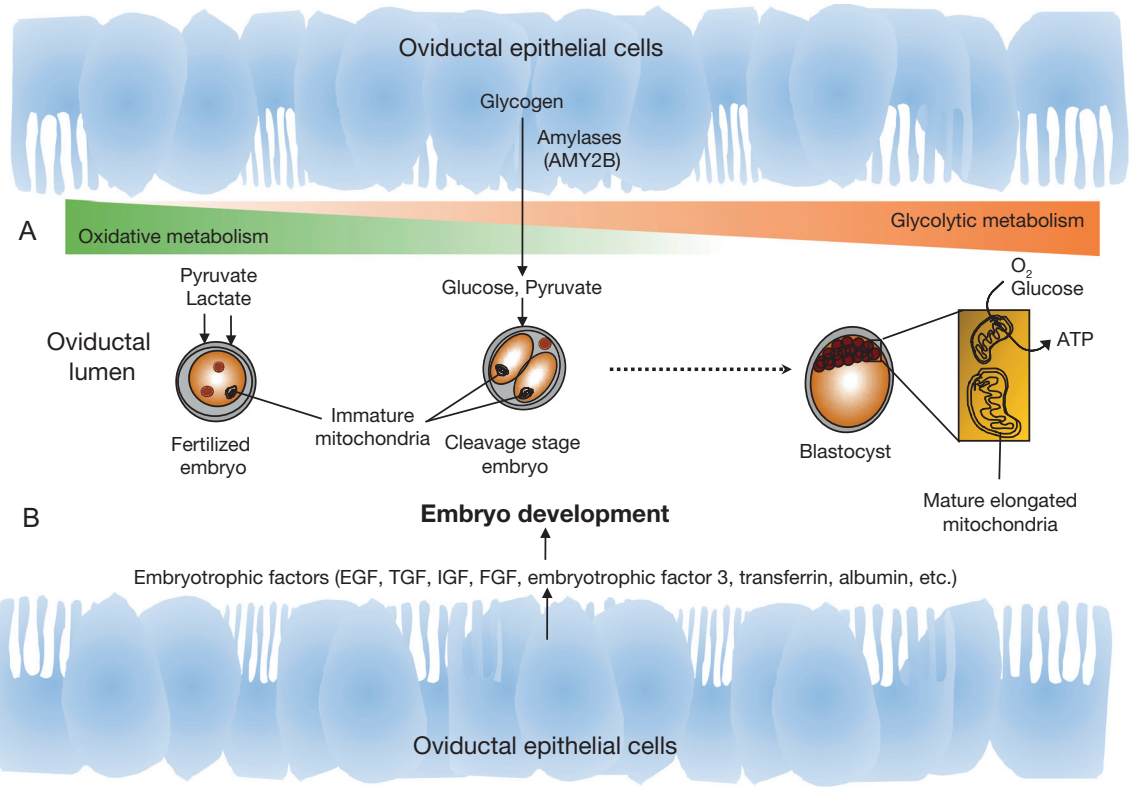

Figure 2
The influence of the oviduct on embryo development. (A) The main energy supply for the embryos is pyruvate and lactate. During the very early stage of embryo development, pyruvate and lactate are provided by the oviductal fluid as energy sources for oxidative metabolism. The oviduct can also 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, Gregoraszczuk *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).

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In addition to energy substrates, CO_2 also serves as a carbon source for RNA synthesis (Quinn & Wales 1974, Pike *et al.* 1975). In mouse and rabbit, CO_2 fixation has been demonstrated in early developing embryos (Quinn & Wales 1974, Pike *et al.* 1975). The level of CO_2 is inversely proportional the HCO_3^- 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^-/HCO_3^- exchanger (solute carrier family 26) expressed in pre-implantation embryos (Lu *et al.* 2016). The HCO_3^- level in the oviduct is relatively high compared with other tissues (Vishwakarma 1962, Maas *et al.* 1977), and it has been previously shown that HCO_3^- is indispensable for the cleavage of pre-implantation embryos (Kane 1975). These studies indicate that a balance of CO_2 and HCO_3^- 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 I_2 (PGI_2) at day 2 than day 4 after coitus (Huang *et al.* 2004). The spiked production of PGI_2 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 PGI_2 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

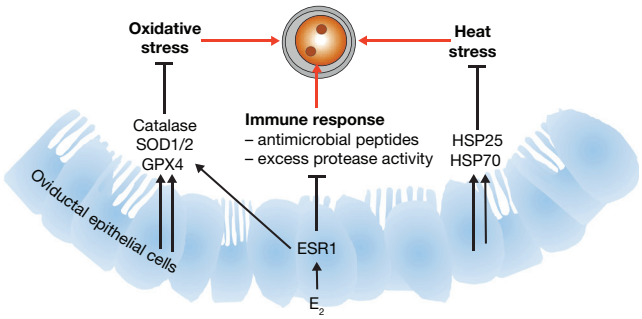

Figure 3
Oviduct-mediated embryo protection against stress and immune responses. Oviductal epithelial cells produce heat shock protein family (HSP25 and HSP70) to handle heat stress. Oviductal fluid also contains catalase, superoxide dismutases (SOD1/2) and glutathione peroxidase (GPX4) to reduce stress 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 E_2/ESR1 signaling, by inhibiting the production of antimicrobial peptides and excess protease activity. ESR1, estrogen receptor α.

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present in the secretions of the female reproductive tract (Guyader-Joly *et al.* 1998) and is proposed to act through the hydroxyl radical ($OH^{\bullet}$) scavenging pathway (Guerin *et al.* 2001). The $OH^{\bullet}$ scavenging pathway may also covert CSH into hypotaurine, a sulfinic acid neutralizing $OH^{\bullet}$ 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 $OH^{\bullet}$ from Fe^{2+} 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 H_2O and O_2 (Harvey *et al.* 1995). Similarly, SOD1 and SOD2 bind to ROS byproducts and turn the byproducts into O_2 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 E_2 induces the GPX4 production in bovine oviduct (Lapointe *et al.* 2005). This evidence indicates that E_2 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 *Hsfs* 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

E_2 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 E_2 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 E_2 in regulating the immune functions in the oviduct are unclear. Recently, a study indicated another important property that E_2 possesses—embryo protection. E_2 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 E_2 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 E_2 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,

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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 H_2S gas in the Fallopian tubes has been linked to impaired embryo transport in humans. H_2S 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, H_2S 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 E_2 (PGE_2), which mediates an acceleration of the transit to the uterus (Weber *et al.* 1991*a*,*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).

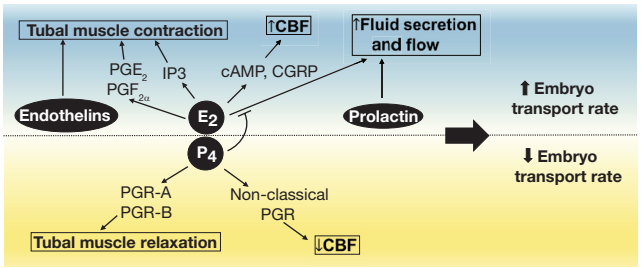

Figure 4
Roles of the oviduct during embryo transport. Embryo transport is composed of tubal muscle contraction and the motility of ciliated epithelial cells. Estrogen (E_2) generally increases the tubal muscle contraction, tubal fluid secretion, and ciliary beat frequency (CBF), which accelerate the embryo transport rate. Opposite to E_2, progesterone (P_4) causes muscle relaxation and decreases CBF to reduce the embryo transport rate. In addition, P_4 also inhibits E_2-induced tubal fluid production. Prostaglandins (PGs) can be produced in the oviductal epithelial cells or induced by E_2 treatment. PGE_2 and $PGF_{2\alpha}$ stimulate muscle contraction in both human and bovine oviducts. Endothelin 1 and 2 are expressed and contribute to the oviduct contraction. IP3, inositol triphosphate; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin F_2; 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.

P_4 and E_2 are the key players in regulating ciliary beat frequency (CBF). P_4 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 P_4 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 P_4 without involving a long-delayed genomic regulation may be the cause of direct CBF regulation.

E_2 is required to accelerate the transport of the eggs (Orihuela *et al.* 2001). E_2 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, E_2 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).

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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, P_4, PGs and nitric oxide participate in the tubal muscle relaxation and contraction (Ekerhovd *et al.* 1997, Jankovic *et al.* 2001, Wanggren *et al.* 2008). P_4, through PGR-A and PGR-B relaxes muscle contraction in mice (Conneely *et al.* 2003). Administration of P_4 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 P_4 is involved in directing muscle relaxation remains unclear.

E_2 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, E_2, P_4 and endothelin-1 stimulate the release of PGs (PGE_2 and $PGF_{2\alpha}$) in bovine oviduct (Wijayagunawardane *et al.* 2001). Both PGE_2 and $PGF_{2\alpha}$ 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 E_2 (Hamner & Fox 1968, McDonald & Bellve 1969). The fluid production is attenuated when P_4 is co-administered with E_2, suggesting that P_4 opposes E_2-induced fluid secretion (Fig. 4). In rabbits, ovariectomy causes decreased secreted fluid in the oviduct, and this fluid level can be restored by E_2 treatment (Bishop 1956), suggesting that E_2 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 E_2 and P_4 (Branes *et al.* 2005). These findings indicate that E_2, P_4 and prolactin play a major role in fluid production in the oviduct. In summary, an overall action of E_2 is to increase the embryo transport rate by stimulating muscle contraction, inducing fluid production and flow, and increasing the CBF, whereas P_4 has an opposite effect of E_2 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.

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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 (Prunskaite-Hyyrylainen *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 & McMahon 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 kinesis 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.

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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 section (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 (Smilinich *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,

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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* maturated (IVM) human oocytes (retrieved from gonadotropin-stimulated patients) demonstrate that the wildly 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* maturated 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 O_2 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% O_2 concentration in the culture, embryos

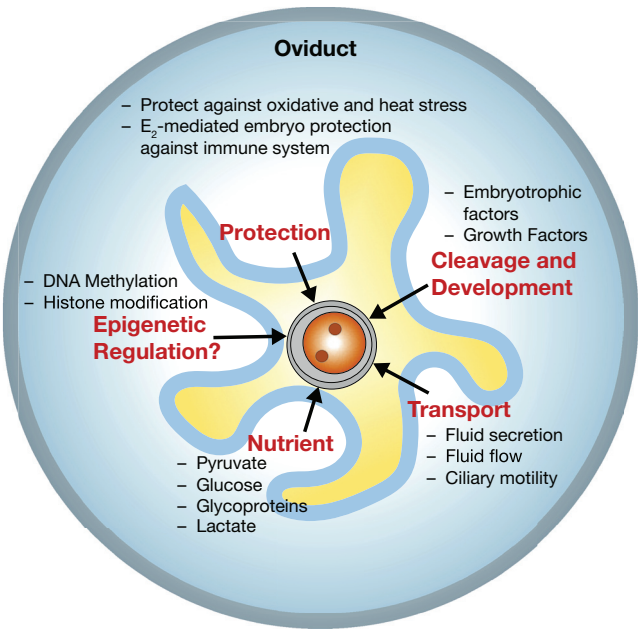

Figure 5
Essential roles of the oviduct in assisting embryo development. Schematic cross-section of the oviduct and the embryo with their interaction regulating embryo development. The interactions are divided into five domains: protection, cleavage and development, transport, nutrients and epigenetic regulation. E_2, estrogen.

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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				
Rheotaxis	CatSper	Mouse	Primary research	Ren *et al.* (2001), Chung *et al.* (2011), Miki and Clapham (2013)
Cervical microgrooves		Bull	Primary research	Tung *et al.* (2015)
Thermotaxis	Opsins	Human, mouse	Primary research	Perez-Cerezales *et al.* (2015)
Thermotaxis		Human	Primary research	Bahat *et al.* (2012)
Temperature gradient in the oviduct			Review	Hunter (2012)
Chemotaxis	Chemokine receptors	Human, mouse	Primary research	Caballero-Campo *et al.* (2014)
Chemotaxis	Anandamide	Cow, human	Primary research	Amoako *et al.* (2013), Gervasi *et al.* (2013)
Chemotaxis	TRPV1	Cow	Primary research	Gervasi *et al.* (2016)
Chemotaxis	P_4	Human	Primary research	Armon *et al.* (2014)
Oviduct signal in the presence of sperm				
Sperm egg recognition	HSPA2	Human	Primary research	Redgrove *et al.* (2012, 2013), Bromfield *et al.* (2015, 2016)
Oviductal muscle regulation	PGE_2	Horse	Primary research	Ball *et al.* (2013)
Oviductal muscle regulation	EP2, EP4, and FP	Cow	Primary research	Huang *et al.* (2015)
Egg entering oviduct				
Egg nutrient supply			Review	Sutton-McDowall *et al.* (2010)
COC protection	Reactive oxygen species	Mouse, cow	Primary research	Shaeib *et al.* (2013, 2016), Li *et al.* (2016)
Fertilization and early embryo development				
Fertilization	Ovastacin	Mouse	Primary research	Burkart *et al.* (2012)
Fertilization	ZP2	Human, mouse	Primary research	Avella *et al.* (2016)
Fertilization	Juno	Human, mouse, mammals	Primary research	Bianchi *et al.* (2014), Han *et al.* (2016)
Oviductal fluid on embryo growth				
Gametes protection	Oviductal fluid	Pig	Primary research	Ballester *et al.* (2014), Kumaresan *et al.* (2014)
Metabolism in embryos			Review	Folmes and Terzic (2014)
Embryo development	Culture medium	Cow, goat	Primary research	Hammami *et al.* (2013), Wydooghe *et al.* (2014), Lopera-Vasquez *et al.* (2015), Xie *et al.* (2015), Guimaraes *et al.* (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 *et al.* (2014)
Estrogen-mediated embryo protection				
Estrogen-mediated embryo protection	ESR1	Mouse	Primary research	Winuthayanon *et al.* (2015)
Gas in the oviduct				
Gas regulated embryo transport	Hydrogen sulphide	Mouse	Primary research	Ning *et al.* (2014)

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Gas regulated embryo protection and sperm motility	Nitric oxide synthase	Cow	Primary research	Kobayashi *et al.* (2016)
Embryo transport				
Fluid secretion	Adrenomedullin	Pig	Primary research	Liao *et al.* (2013)
Fluid production and flow	Prolactin	Mouse	Primary research	Miki and Clapham (2013)
Ciliary beat frequency	Adrenomedullin	Rat	Primary research	Liao *et al.* (2011)
Ciliary beat frequency	P_4	Mouse	Primary research	Bylander *et al.* (2010, 2013)
Ciliary beat frequency	E_2 and P_4	Guinea pig	Primary research	Nakahari *et al.* (2011)
Ciliary beat frequency	Muscarinic receptors (Chrm1, 3, 4, and 5)	Mouse	Primary research	Noreikat *et al.* (2012)
Muscle contraction	E_2 and P_4	Pig	Primary research	Chen *et al.* (2013)
Muscle contraction	E_2	Rat	Primary research	Reuquen *et al.* (2015)
Recently identified pathways affecting embryo transport				
Oviduct morphology and development			Review	Stewart and Behringer (2012)
Oviduct development	Wnt4	Mouse	Primary research	Prunskaite-Hyyrylainen *et al.* (2016)
Oviduct development	Notch	Mouse	Primary research	Ferguson *et al.* (2016)
Ciliogenesis			Review	Choksi *et al.* (2014)
Ciliogenesis	Lgr5	Mouse	Primary research	Ng *et al.* (2014)
Oviduct stem cell		Mouse	Primary research	Snegovskikh *et al.* (2014)
Fallopian tube stem cell morphology	Notch and WNT	Human	Primary research	Kessler *et al.* (2015)
Ciliogenesis	miRNAs (miR-34b/c and miR-449)	Mouse	Primary research	Wu *et al.* (2014)
Ciliogenesis	Stk36	Mouse	Primary research	Nozawa *et al.* (2013)
Cilia length	Kif19a	Mouse	Primary research	Niwa *et al.* (2012)
Cilia directionality	Celsr1	Mouse	Primary research	Shi *et al.* (2014)
Ciliary beat frequency	Lipopolysaccharide	Cow	Primary research	O'Doherty *et al.* (2016)
ARTs and embryo development				
ARTs statistics and prenatal outcomes		Human	Bioinformatics and review	Pandey *et al.* (2012), Pinborg *et al.* (2013), Mansour *et al.* (2014), Marino *et al.* (2014), McLernon *et al.* (2016)
ARTs and DNA methylation		Human	Review	Lazaraviciute *et al.* (2014), Ventura-Junca *et al.* (2015)
ARTs and mental health		Human	Bioinformatics	Punamaki *et al.* (2016)
Epigenetics and environmental exposures				
DNA methylation and demethylation		Human and mammals	Review	Ma *et al.* (2012), Messerschmidt *et al.* (2014)
Environmental exposure in ARTs		Human	Review	Lucas (2013)
ARTs	Oxygen concentration	Human	Bioinformatics	Bontekoe *et al.* (2012)
ARTs	Culture medium	Human	Bioinformatics	Zandstra *et al.* (2015)
Metabolism		Mouse	Primary research	Donjacour *et al.* (2014)
Epigenetics	BPA	Cow	Primary research	Ferris *et al.* (2016)

have a decreased survival rate and increased apoptotic rate. On the contrary, when the O_2 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% O_2 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% O_2 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% O_2 level (Yang *et al.* 2016). In addition, mouse embryos cultured in 20% O_2 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 O_2 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

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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% O_2 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 O_2 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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