Roles of steroid hormones in oviductal function

Brooke E Barton^{1,*}, Gerardo G Herrera^{1,*}, Prashanth Anamthathmakula^{1,2}, Jenna K Rock¹, Anna M Willie¹, Emily A Harris^{1,2}, Ken-Ichi Takemaru³ and Wipawee Winuthayanon^{1,2}

¹School of Molecular Biosciences, Washington State University, Pullman, Washington, USA, ²Center for Reproductive Biology, College of Veterinary Medicine, Washington State University, Pullman, Washington, USA and

³Department of Pharmacological Sciences, Stony Brook University, Stony Brook, New York, USA

Correspondence should be addressed to W Winuthayanon; Email: w.winuthayanon@wsu.edu

*(B E Barton and G G Herrera contributed equally to this work)

Abstract

The oviduct (known as the fallopian tube in humans) is the site for fertilization and pre-implantation embryo development. Female steroid hormones, estrogen and progesterone, are known to modulate the morphology and function of cells in the oviduct. In this review, we focus on the actions of estrogen and progesterone on secretory, ciliated, and muscle cell functions and morphologies during fertilization, pre-implantation embryo development, and embryo transport in humans, laboratory rodents and farm animals. We review some aspects of oviductal anatomy and histology and discuss current assisted reproductive technologies (ARTs) that bypass the oviduct and their effects on embryo quality. Lastly, we review the causes of alterations in secretory, ciliated, and muscle cell functions that could result in embryo transport defects.

Reproduction (2020) **159** R125–R137

Gross anatomy and cell physiology of the oviduct

The oviduct is a tubular organ that connects the ovary and the uterus. In humans, the oviduct is referred to as the fallopian tube. We will use the term ‘the oviduct’ hereafter for continuity. In humans, the oviduct is curved, whereas in some mammals, especially in rodents, is coiled. The oviduct is the site of fertilization, pre-implantation embryo development and is made up of five main regions: the fimbria, the infundibulum, the ampulla, the isthmus, and the uterotubal junction (Fig. 1). The fimbria, a fringe of finger-like structures projecting from the infundibulum, is responsible for egg ‘pick-up’ into the oviduct after ovulation. The fimbria and infundibulum are adjacent to the ampulla, where fertilization occurs. The isthmus and uterotubal junction (UTJ) are the proximal regions of the oviduct. The UTJ then exits into the uterine cavity. The isthmus functions as a sperm reservoir and is also thought to limit polyspermy by allowing only a gradual entry of sperm into the ampulla (reviewed by Suarez 2002).

The primary regions of the oviduct are joined by distinct segments. First, the ampullary–isthmus junction (AIJ) separates the ampulla from the isthmus. At the AIJ, there is a transition from tall and branching mucosal folds in the ampulla, to shorter and simpler folds in the isthmus. The smooth muscle transitions from a thin layer in the ampulla to a thick layer in the

isthmus. Lastly, the UTJ (also known as the intramural portion of the oviduct in humans) joins the isthmus to the uterus. In numerous species (such as rats, mice, pigs and cows), the UTJ facilitates the regulation of sperm entering the oviduct (reviewed by Holt & Fazeli 2010).

Recent findings using transgenic mice with sperm expressing fluorescent proteins showed that the majority of the sperm accumulates around the opening of the UTJ 15 min after coitus (Muro *et al.* 2016). Additionally, there are at least 13 proteins expressed on sperm that are required for passage through the UTJ (reviewed by Okabe 2015). For example, proteins in a disintegrin and metalloproteinase (ADAM) family (necessary for cell migration, cell adhesion, and cell interactions) are required for sperm migration to the oviduct. Specifically, ADAM1B and ADAM2 dimerize and form fertilin. The presence of fertilin in the endoplasmic reticulum of spermatids then subsequently leads to a localization of ADAM3 on the mature sperm surface. Male mice with a global deletion of *Adam3* are completely sterile due to an impairment of sperm transport through the UTJ (reviewed by Fujihara *et al.* 2018). However, the precise mechanism of ADAM3-mediated sperm migration is still unclear. These data suggest that normal sperm motility is an important factor, but protein–protein interactions between the sperm surface and UTJ are also essential for successful sperm entry into the oviduct.

Figure 1 Gross and histological morphologies of human and mouse oviducts. (A) Human oviduct. Top panel: a drawing for gross anatomy of the oviduct. Purple and orange layers represent myosalpinx and endosalpinx layers, respectively. Middle and bottom left panels: Hematoxylin and Eosin (H&E) staining of the ampulla and the isthmus regions of the oviduct demonstrating three tissue layers: endosalpinx, myosalpinx, and mesosalpinx. Middle and bottom right panels: Ampulla and isthmus at higher magnification. (B) Mouse oviduct. Top panel: gross anatomy of the female reproductive tract including ovaries, oviducts, and the uterus. Middle and bottom left panels: the cross section of the ovary and the whole oviduct indicating three different regions; the infundibulum, the ampulla, and the isthmus. Middle and bottom right panels: Ampulla and isthmus at higher magnification. CC, ciliated epithelial cells; non-CC, non-ciliated (secretory) epithelial cells.

The oviduct is made up of three structural components (Fig. 1A). The outside layer is the mesosalpinx, which surrounds the myosalpinx and the inner mucosal endosalpinx.

Mesosalpinx

The mesosalpinx, a part of the broad ligament, anchors the oviduct to the body wall. The outermost layer of the oviduct is the serosa (Fig. 1A). The mesosalpinx also supplies the oviduct, and the uterine and ovarian arteries, with the vascular system through the serous membrane and into the muscle layer underneath (Hunter 1988). These veins and arteries allow for circulation throughout the organ, which is partly responsible for the generation and maintenance of tubal fluid via transudation. The mesosalpinx also connects the oviduct to the lymphatic system. The interconnection of vascular, nervous, and lymphatic systems allows for the oviduct to receive all necessary nutrients as well as to eliminate waste products into lymphatic drainage.

Myosalpinx

The myosalpinx is the muscular layer of the oviduct, consisting of an outer longitudinal and an inner circular layer of smooth muscle. The use of scanning electron microscopy after tissue maceration showed that the myosalpinx contains complex networks of smooth muscle cells (SMCs) (reviewed by Muglia & Motta 2001). Muglia and Motta demonstrated that the histoarchitecture of the myosalpinx in the oviduct varies between regions and among species. For the UTJ, the muscular layer can be classified as either a barrier-like or a sphincter-like structure depending on the species (Fig. 2A and B). Barrier-like structures are characterized by robust musculature, rich in densely packed SMC fibers (in rats and pigs). Sphincter-like structures are classified by geometrically organized independent muscle fibers, called sphincter-like type a (in rabbits and sheep). Sphincter-like type b structures show loosely interwoven plexiforms, which are characterized by uneven distributions and alignments of muscle fibers (in cows and humans). In the isthmus, bundles of SMC also orient in an intermingled fashion

Figure 2 Scanning electron microscopy (SEM) images of the myosalpinx and the inner endosalpinx. (A, B, C and D) SEM images of the myosalpinx in the uterotubal junction (UTJ) and isthmic regions after tissue maceration techniques (adapted from (Muglia & Motta 2001) with permission with original scale bars shown). (A) Barrier-like salpinx in rat UTJ, bar=25 μ m. (B) Sphincter-like type a salpinx in ewe UTJ, bar=5 μ m. (C) Plexiform arrangement of myosalpinx in the isthmus in (C) human (bar=100 μ m) and (D) rabbit (bar=50 μ m). (E and F) SEM images of inner endosalpinx at the ampulla region including ciliated and non-ciliated (or secretory) epithelial cells from (E) human oviduct ($\times 7810$ magnification, modified with permission from (Seki *et al.* 1978)) and (F) mouse oviduct ($\times 9000$ magnification, modified with permission from (Dirksen & Satir 1972)). Motile cilia are present at the apical membrane of ciliated cells and microvilli are present on the apical surface of secretory cells.

which gives rise to a plexiform musculature (Fig. 2C and D). In humans, the myosalpinx in the ampulla is comprised of bundles of inner and outer SMC arranged into clockwise and counter-clockwise spiral fibers that also intermingle into a plexiform.

Muscle contractions in the oviduct facilitate sperm transport to the fertilization site and oocyte transport to the uterus. In mice, a specialized network of pacemaker cells called interstitial cells of Cajal generate slow electric waves that underlie myosalpinx contractions (Dixon *et al.* 2010). In humans, similar cells have been identified and are referred to as interstitial cells of Cajal-like cells (Popescu *et al.* 2005). The myosalpinx contracts and relaxes depending on different levels of steroid hormones, which will be discussed in a later section. Muscle contractions create a back-and-forth motion of the oocytes/embryos within the oviduct before arrival to the uterus. In rodents, peristaltic contractions of the myosalpinx result in movement of tubal fluid that is crucial for sperm transport from the isthmus to the ampulla (Hino & Yanagimachi 2019). As shown in Fig. 1A, the myosalpinx is thicker in the isthmus than in the ampulla or infundibulum.

Endosalpinx

The endosalpinx is the inner mucosal layer of the oviduct and is comprised of epithelial cells and lamina

propria mucosa (Castro *et al.* 2019). The lamina propria mucosa is a network of connective tissues containing fibroblasts (or stromal cells) and other mononuclear cell populations (Pauerstein & Eddy 1979). In mammals, the oviductal epithelium is made-up of secretory (or non-ciliated) and ciliated epithelial cells (Fig. 2E and F). Secretory epithelial cells are characterized by the presence of microvilli on the apical surface. In contrast, ciliated epithelial cells have motile cilia at the apical surface.

Functions of epithelial and muscle cells of the oviduct

The fine-tuning of tubal fluid flow aids in the fertilization of eggs and congruent transport of embryos from the oviduct into the uterus. Approximate duration of embryo transport varies between species. In pigs, embryos do not enter the uterus until 2 days post fertilization. In other species, this embryo transport takes longer, with embryos exiting the oviduct closer to 3 days in mice and cows, and ~3.5 days in humans (reviewed by Croxatto 2002). Recently developed optical coherence microscopy for *in vivo* imaging in mice showed that zygotes are located in the ampulla at 0.5 days post-coitus (dpc) (Moore *et al.* 2018). Furthermore, at 1.5 dpc, two-cell embryos are in the isthmus and at day 3, embryos are generally located in the UTJ.

Secretory cells

Secretory cells are abundant in the proximal region of the oviduct, specifically throughout the isthmus (Fig. 3). Recent findings using lineage tracing showed that some secretory cells in mouse neonatal oviducts act as epithelial progenitors, giving rise and differentiating into both secretory and ciliated epithelial cells (Ghosh *et al.* 2017). Using *in vivo* ligation in mice, it was found that secretory cells in the isthmus continuously secrete fluid into the oviductal lumen (Hino & Yanagimachi 2019), in addition to the transudation mechanism previously described. Tubal fluid is comprised of ions, energy substrates (such as glucose, pyruvate and lactate), amino acids, prostaglandins (PGs), steroid hormones (E_2 and P_4) as well as various proteins (such as albumin, glycoproteins and lipoproteins) and growth factors (including EGF, fibroblast growth factor (FGF), transforming growth factor (TGF), insulin-like growth factor (IGF), and IGF-binding protein (IGFBP)) (reviewed by Aguilar & Reyley 2005). There are several secreted proteins in tubal fluid that contribute to embryo development and transport (reviewed by Coy & Yanagimachi 2015).

One factor from secretory cells is oviductal glycoprotein 1 (OVGP1, encoded by *Muc9* gene). OVGP1 is involved in sperm capacitation, sperm–oocyte binding, oocyte penetration, modification of the zona pellucida (ZP), and regulation of polyspermy (Avilés *et al.* 2010). In pigs and cows, incubation of oviductal fluid-containing OVGP1 significantly reduces sperm–ZP binding and subsequently prevents polyspermy (Coy *et al.* 2008), potentially through increased resistance of proteolytic digestion of ZP and decreased affinity for sperm binding due to modified ZP proteins. Recent studies showed that the presence of recombinant porcine OVGP1 improves fertilization rates (Algarra *et al.* 2016) but does not affect developmental rates of bovine embryos (Algarra *et al.* 2018). In mice, OVGP1 is localized to perivitelline space but does not bind to the ZP (Kapur & Johnson 1986). However, in a subsequent study, OVGP1 was shown to be associated with the ZP of the ovulated oocyte and facilitates sperm–ZP adhesion (Lyng & Shur 2009). Nevertheless, global deletion of *Ovgp1* in mice has no fertility defect (Araki *et al.* 2003). Moreover, *Ovgp1* is a pseudogene in rats and horses (Avilés *et al.* 2010). These findings suggest that the functional significance of OVGP1 in female fertility varies among species.

Another important protein is fetuin B, a liver-derived plasma protein that is also expressed locally in the oviduct in response to estrogen signaling (Winuthayanon *et al.* 2015). In mice, fetuin B is essential for fertilization, as global deletion of *Fetub* causes female infertility (Dietzel *et al.* 2013). Therefore, it is likely that secretory cells of the oviduct facilitate fertilization and pre-implantation embryo development by secreting necessary factors into the oviductal lumen.

Figure 3 Ciliated epithelial cells (CC) are more abundant in the distal part of the oviduct (including infundibulum and ampulla), whereas the secretory epithelial cells (SC) are more prominent in the proximal part including the isthmus. Muscle cell (MC) layer is also thickest in the proximal compared to the distal region of the oviduct (as also seen in the histological analysis in Fig. 1). Lamina propria (LP) represents fibroblasts underneath epithelial cells in the mucosal folds. Zygote, two-cell, four- to eight-cell, morula, and blastocyst stage embryo develops within the oviducts before the transport into the uterine cavity.

Ciliated cells

Ciliated cells are most abundant in the infundibulum and ampulla (Figs 1 and 3). There are two proposed functions of oviductal cilia in reproduction: (1) to facilitate movement of tubal fluid and embryos toward the uterus and (2) to create a rheotaxis signal for sperm to reach the ampulla (Miki & Clapham 2013). However, recent *in vivo* studies by Hino and Yanagimachi showed that rheotaxis does not seem to play a role in sperm movement in mice (Hino & Yanagimachi 2019). Therefore, the function of unidirectional flow generated by ciliated epithelial cells is still under controversy. Nevertheless, a genetic study in mice showed that cilia of appropriate length are essential for oviductal function as a global loss of *Kif19* gene (kinesin family member 19) has significantly longer cilia in the oviduct compared to controls (Niwa *et al.* 2012). These elongated cilia in *Kif19*^{−/−} females led to an ineffective fluid flow causing an obstruction of cell debris and an occluded lumen, resulting in complete sterility. In contrast, conditional deletion of *Cep164*, encoding a key ciliary protein and central regulator of primary ciliogenesis, in ciliated cells caused a reduction in both length and number of multicilia compared to control mice (Siller *et al.* 2017). Surprisingly, these female mice lacking *Cep164* in ciliated cells are fertile, indicating that if the oviductal lumen is not occluded, eggs and embryos are able to transport to the uterus and that shortening cilia has no overt effect on fertility in mice.

In mice, ciliary beat frequency (CBF) cycles at 7–10 Hertz (Hz) at 0.5 dpc and decreases significantly to ~2.5–5.0 Hz at 2.5 dpc (Wang *et al.* 2015, Li *et al.* 2017). It is likely that this reduction in CBF at 2.5 dpc decelerates the luminal fluid flow and helps retain the

embryo within the oviduct to prevent the premature arrival of the embryos into the uterus before 3.5 dpc.

Muscle cells

The layer of smooth muscle cells is thicker in the isthmus than in the ampulla (Figs 1 and 3). Contraction of smooth muscle cells results in an increased velocity of fluid flow. As mentioned earlier, muscle contraction is a major contributor to adovarian tubal fluid flow, supporting sperm transport from the isthmus to the ampulla (Hino & Yanagimachi 2019). It is also postulated that muscle contraction facilitates the embryo transport process, in addition to the function of cilia. Studies in rats and rabbits showed that in the absence of smooth muscle contraction after treatment with isoproterenol, a β -adrenergic agonist, ciliated cells were able to make up most of the tubal flow and egg transport was not affected (Halbert *et al.* 1976, 1989). However, a study in mice showed that disruption of cannabinoid receptor (*Cnr1*^{-/-}) resulted in impaired embryo transport due to an alteration of smooth muscle contraction and relaxation (Wang *et al.* 2004). In mouse oviducts, one of the Ca²⁺-activated Cl⁻ channels protein called anoctamin-1, encoded by *Tmem16a* gene, in the interstitial cells of Cajal in the myosalpinx, is responsible for the generation of spontaneous slow electrical wave and may be involved in egg transport (Dixon *et al.* 2012). Dixon *et al.* showed that the oviduct from *Tmem16a*^{-/-} females completely lack their slow wave activity. However, whether this slow wave generated by interstitial cells of Cajal is required for female fertility remains unclear as *Tmem16a*^{-/-} mice die before puberty. Overall, oviductal muscle contraction does plays a crucial role in female reproduction but appears to vary among species and therefore must be the subject of future investigations as the mechanisms are widely unknown.

Roles of estrogen and progesterone in oviductal function

Estrogen (E₂) and progesterone (P₄) are female steroid hormones that act through nuclear and membrane receptors. E₂ is produced by granulosa cells in the ovary and exhibits its activity through estrogen receptor α and β (encoded by *Esr1* and *Esr2* genes) (Hewitt *et al.* 2016). P₄ is secreted from peri-ovulatory granulosa and luteal cells and acts through progesterone receptors (encoded by *Pgr* gene) (Conneely *et al.* 2003, Mulac-Jericevic *et al.* 2003). In mice and rats, ESR1 is expressed in epithelial, stromal, and muscle cells of the oviduct (Okada *et al.* 2003, Winuthayanon *et al.* 2015) (Fig. 4). Comparatively, immunohistochemical analysis of PGR showed higher expression in stromal and muscle cells compared to epithelial cells in the infundibulum and ampulla, respectively, while PGR expression is observed in all three

Figure 4 Expression of estrogen and progesterone receptor (ESR1 and PGR) proteins in the mouse oviduct at the infundibulum, the ampulla, and the isthmus. Oviducts were randomly collected from female mice at different stages of the estrus cycle. E, epithelium; M, muscle cells; S, stroma.

cell types in the isthmus of mouse oviducts (Fig. 4). In addition to classical nuclear receptors, P₄ also functions through membrane progesterone receptors (mPRs) and their expression is tissue specific (Kowalik *et al.* 2013). Nutu *et al.* showed that mPR β protein is detected in the cilia, whereas the mPR γ is localized at the apical plasma membrane of ciliated cells in mouse oviducts and human oviducts (Nutu *et al.* 2009).

Classical studies from the 1950s–1990s in several species have described that both secretory and ciliated cells change their morphology in response to changes in levels of E₂ and P₄ (reviewed by Abe 1996). As shown in rhesus monkeys (Brenner 1969), epithelial cells of the oviduct in the fimbria are cuboidal at day 2 of the menstrual cycle (Fig. 5). At days 5–6 (follicular phase, high levels of circulating E₂), epithelial cell height drastically increases and ciliation is observed. At day 15 (early luteal phase, E₂ level declines while P₄ level rises), the epithelial cells regress and atrophy (decreased cell height and underwent partial de-ciliation as ciliary apparatus pinched off and shed into the lumen). At the end of the menstrual cycle, in which both E₂ and P₄ are at basal levels (day 27), the epithelial cells return to cuboidal morphology and cilia are rarely present. Unlike the fimbria and ampulla, ciliated and secretory cells in the isthmus do not drastically regress during luteal phase (Steffl *et al.* 2008). Whether or not these

Figure 5 Images from light microscopy of epithelial cell layer of oviducts collected from the fimbria region at different days of the menstrual cycle in Rhesus monkeys. Days 2, 5–6, 15, and 27 represent days after menstruation. All images are taken at $\times 1200$ magnification (adapted from Brenner 1969 with permission).

ciliated cells undergo apoptotic cell death and renew each cycle is still debatable and appears to vary among species (Steffl *et al.* 2008). As mentioned earlier, secretory cells in neonatal mouse oviducts could give rise to the ciliated cell population, driven by Wnt/ β -catenin signaling pathway, due to its pluripotency during development (Ghosh *et al.* 2017). However, it is unlikely that these terminally differentiated de-ciliated epithelial cells could become secretory cells during luteal phase.

In the oviduct, both E_2 and P_4 have also been shown to modulate sperm function in the female reproductive tract. In humans, P_4 , secreted from cumulus cells, was shown to be a chemoattractant for sperm (Oren-Benaroya *et al.* 2008). The presence of P_4 increased intracellular Ca^{2+} in sperm flagella through the potentiation of CatSper, a pH-dependent Ca^{2+} channel in human sperm (Lishko *et al.* 2011). The effect of P_4 on sperm motility appears to be mediated by mPR α (Tan *et al.* 2019), not classical PGRs (Lishko *et al.* 2011). These data are supported by the finding that global deletion of *Pgr* (*Pgr*^{−/−}) has no effect on male fertility in mice (Lydon *et al.* 1995). Inhibition of mPR activity also significantly decreases acrosome reactions in human sperm (Sabeur *et al.* 1996). These findings indicate that P_4 acts as a chemotactic cue and stimulates capacitation-related events in human sperm. In contrast, the mechanism and effects of E_2 on sperm capacitation and motility are less defined. ESR1 and ESR2 are expressed in the head and midpiece of human sperm, respectively (Solakidi *et al.* 2005). In mice, treatment of sperm with E_2 significantly increases capacitation and acrosome reactions (Adeoya-Osiguwa *et al.* 2003). Additionally, studies using a global *Esr1*-knockout mouse model (*Esr1*^{−/−}) showed a severe reduction in sperm motility

and sperm count, leading to an inability to fertilize eggs *in vitro* (Eddy *et al.* 1996). However, the defect in *Esr1*^{−/−} mice appears to be due to a disruption of spermatogenesis and seminiferous tubule development.

Steroid action in secretory epithelial cells

Tubal fluid is produced not only by transudation of fluid from capillaries, as mentioned above, but also by the secretory cells that line the oviduct. Oviducts are filled with this tubal fluid that not only nourishes and protects the egg and embryo but also maintains sperm motility, viability and storage and aids in embryo transport to the implantation site. In rats and pigs, expression of aquaporins (water channels encoded by *Aqp* genes; including *Aqp5*, *Aqp8*, and *Aqp9*, on the apical plasma membrane along the oviduct) is regulated by both E_2 and P_4 (Brañes *et al.* 2005, Skowronski *et al.* 2011). In mice the expression of *Aqp5*, specific to secretory cells, is highest during estrus when E_2 levels peak (Nah *et al.* 2017). As such, these aquaporins may contribute to the regulation of fluid within the oviductal lumen. Accordingly, Hino and Yanagimachi showed that, at estrus, the isthmus region produced approximately 2.2 μ L of fluid per hour in mice (Hino & Yanagimachi 2019). In cows, sheep and rabbits, oviductal fluid volume drastically increases after E_2 treatment or at estrus (McDonald & Bellve 1969, Roberts *et al.* 1975, Gott *et al.* 1988). Therefore, E_2 is a positive regulator for secretory function in the oviduct.

In addition to fluid production, E_2 also increases oviductal protein production. Some of these secreted proteins, called embryotrophic factors, are postulated to be involved in embryo development (Avilés *et al.* 2010). These factors include OVGP1 (Buhi *et al.* 1992, Chen *et al.* 2013), demilune cell and parotid protein (DCPP) (Lee *et al.* 2006), insulin-like growth factor-binding proteins (IGFBP) (Lai *et al.* 1996), among others (Bauersachs *et al.* 2003). In addition to positive regulation of embryo development, our group also found that E_2 through ESR1 in oviductal epithelial cells is necessary for *in vivo* embryo protection, as deletion of *Esr1* in these cells leads to embryo death prior to the two-cell stage (Winuthayanon *et al.* 2015). This defect is mainly due to excess protease activity in the oviductal lumen, resulting in a disruption of embryonic plasma membranes.

P_4 has the opposite effect of E_2 . When P_4 levels are high, such as during the luteal phase, aquaporin expression and fluid secretions decrease (McDonald & Bellve 1969, Skowronski *et al.* 2011). In rabbits, oviductal fluid production is attenuated when P_4 is administered alone or co-administered with E_2 (Bishop 1956), suggesting that P_4 opposes E_2 -induced fluid secretion. It was also found that rabbits treated with P_4 have higher protein content in the oviductal fluid when compared to non-treated controls, suggesting that P_4 increases protein concentration and alters the viscosity of the oviductal fluid (Hamner & Fox 1968). In primary

porcine oviductal epithelial cells, treatment with P_4 is correlated with a decrease in OVGP1 expression (Chen *et al.* 2013). A combination of decreasing fluid production and increasing protein content characterizes the negative regulatory effects of P_4 on oviductal fluid. Therefore, E_2 and P_4 oppositely affect the production of tubal fluid and work in a balanced unison throughout the estrous/menstrual cycle to maintain appropriate fluid levels and protein content.

Steroid actions in ciliated epithelial cells

The function of ciliated epithelial cells is crucial for recruiting the released egg to the ampulla. Ciliated cells, in addition to muscle cells, create tubal fluid flow in the oviduct. As shown in Fig. 5, the length of cilia in rhesus monkey is increased in the presence of E_2 and decreased by P_4 (Brenner 1969). Normal cilia formation in female mice with a global loss of *Esr1* (*Esr1*^{-/-}) suggests that ESR1 is not required for ciliogenesis in the oviduct (Okada *et al.* 2004). However, E_2 induces the differentiation of ciliated epithelial cells in rats by neonatal day 5, leading to the conclusion that E_2 facilitates but is not required for cilia development (Okada *et al.* 2004). Additionally, Okada *et al.* showed that inhibition of ESR activity using ESR antagonist, ICI182,780, hinders ciliary differentiation in neonatal rat oviducts. Our recent studies showed that loss of ESR1 in oviductal epithelial cells (*Esr1*^{d/d}) causes an increase in ciliary length and decrease in CBF compared to control littermates, resulting in complete embryo retention in the oviduct and failed implantation (Li *et al.* 2017). Although ESR2 is exclusively expressed in the cilia of oviductal ciliated epithelial cells, thea global deletion of *Esr2* (*Esr2*^{-/-}) does not affect embryo transport (Li *et al.* 2017). These findings indicate that E_2 signaling through ESR1 is crucial for the regulation of length and function of cilia in mouse oviduct and that signaling through ESR2 may be secondary.

P_4 has the opposite effect of E_2 in regard to ciliation. High circulating level of P_4 causes de-ciliation and decreases CBF (Brenner 1969, Mahmood *et al.* 1998). In mice, cows and humans, treatment with P_4 causes a rapid decrease in CBF in the oviduct (Mahmood *et al.* 1998, Wessel *et al.* 2004, Bylander *et al.* 2010). However, global deletion of *Pgr* in mice has no effect on ciliogenesis as cilia remain present in the oviductal epithelial cells of *Pgr*^{-/-} females (Akison *et al.* 2014). Treatment with RU486, a PGR antagonist, suppresses P_4 -mediated actions on CBF (Bylander *et al.* 2013) suggesting a requirement of classical PGR regulation for ciliated cell activity in the oviduct.

Transient receptor potential cation channel subfamily V member 4 (or TRPV4) was shown to regulate Ca^{2+} intracellular influx and the beating of ciliated epithelial cells (Lorenzo *et al.* 2008). In hamsters, activation of TRPV4 caused an increase in oviductal CBF (Andrade *et al.* 2005). Expression of TRPV4 protein in

both human airways and mammary gland epithelial cells, as well as in vascular smooth muscle cells, is suppressed by P_4 treatment (Jung *et al.* 2009). As such, the action of P_4 on decreasing CBF may also result from a suppression of TRPV4 expression in ciliated epithelial cells in addition to classical steroid hormone regulation of oviductal CBF.

Steroid action in muscle cells

Both ESR1 and PGR proteins are detected in the muscle cell layers of the oviduct in rodents (Okada *et al.* 2003, Winuthayanon *et al.* 2015) as shown in Fig. 4. In rats, E_2 increases contraction of primary smooth muscle cells through a non-genomic mechanism via the induction of inositol trisphosphate production (Reuquén *et al.* 2015). In cows, rabbits and rats, E_2 and P_4 are involved in the production of PGs (especially PGE_2 and $PGF_{2\alpha}$) and endothelins (EDNs) in oviductal epithelial cells, which are crucial for oviductal muscle contractility (Spilman 1974, Rosselli *et al.* 1994a,b, Wijayagunawardane *et al.* 1999, Al-Alem *et al.* 2007, Parada-Bustamante *et al.* 2012).

In rats, E_2 upregulates the expression of cyclooxygenase-2 (COX2; enzyme responsible for biosynthesis of PG precursor) in oviductal epithelial cells, leading to an increase in the production of PGs in the whole oviductal tissue (Pérez Martínez *et al.* 2006). Therefore, it is possible that oviductal epithelial cells are a source of PGs production in rats that subsequently acts on muscle cells. However, direct evidence to support this speculation has not been evaluated. In cows, treatment with E_2 increased the expression of PG synthetases and prostanoid receptors (EP2, EP4, and FP) within the smooth muscle cells of the oviduct (Huang *et al.* 2015, 2018). When bound to PGs, EP2 and FP increase contraction and EP4 decreases contraction (Huang *et al.* 2015), therefore resulting in an increased rate of oviductal contraction. Overall, E_2 acts through PGs and EDNs to increase tubal contractility.

P_4 , on the other hand, decreases muscle contractility in the oviduct to induce relaxation. In cows, *EDN1* mRNA in epithelial cells and the production of PGE_2 and $PGF_{2\alpha}$ are lowest during the luteal phase, at which circulating P_4 is elevated (Wijayagunawardane *et al.* 2001, Priyadarsana *et al.* 2004). Corresponding to levels of EDN1, PGE_2 and $PGF_{2\alpha}$, tubal contraction is also significantly lower during the luteal phase compared to the follicular or post-ovulatory phases (Wijayagunawardane *et al.* 2001).

In summary, a fine-tuned balance of E_2 and P_4 action plays a crucial role in secretory and ciliated epithelial cells as well as muscle cells in the oviduct during sperm transport, fertilization, embryo transport, and embryo development. Collectively, E_2 and P_4 have direct and opposing effects on ciliated, secretory, and muscle cell types to prepare the microenvironment in the oviduct for successful establishment of early pregnancy (summarized in Fig. 6).

Figure 6 Actions of estrogen and progesterone in the oviductal cells in the oviducts. Estrogen and progesterone exhibit different effects on secretory, ciliated, and muscle cells in the oviduct. Estrogen- and progesterone-mediated signals are represented with green and red lines, respectively. The overall summation of estrogen and progesterone action is to increase and decrease the embryo transport rate, respectively, within the oviduct. CBF, ciliary beat frequency.

Defective oviductal function

Potential negative effects of assisted reproductive technologies (ARTs) when the oviduct is bypassed

Assisted reproductive technologies (ARTs) are fertility treatments that include artificial insemination, ovarian stimulation, gamete intra-fallopian transfer (GIFT), zygote intra-fallopian transfer (ZIFT), intrauterine insemination, *in vitro* fertilization (IVF) and embryo transfer (ET). GIFT and ZIFT procedures allow gametes to fertilize or embryos to develop inside the oviduct. IVF procedures, however, require fertilization to occur in a culture dish. Fertilized eggs are developed in culture to cleavage or blastocyst stages, when the embryos are then transferred into the uterine cavity. IVF includes a specialized procedure in which sperm are injected directly into the oocyte's cytoplasm, called intracytoplasmic sperm injection (ICSI). Eggs fertilized by ICSI are also developed to blastocyst stage. As such, we will refer to 'IVF' for both IVF and ICSI techniques. As a result, IVF bypasses the entire oviduct, whereas GIFT and ZIFT utilize the oviduct for fertilization and/or pre-implantation embryos to develop *in vivo*. In the United States, more than 99% of all ARTs performed are IVF procedures (Sunderam *et al.* 2017) compared to 65% in Europe (De Geyter *et al.* 2018).

The Developmental Origins of Health and Disease (DoHaD) hypothesis argues that the environment with which a fetus interacts *in utero* can have lasting effects on the health of the offspring (reviewed by Wadhwa *et al.* 2009); yet, it is less conclusive concerning the effect of the oviductal environment on the embryo prior to uterine implantation. Because human embryos undergo

genome activation (i.e., activation of transcription) during day 3 of development (at 4–8-cell stage) while traveling through the oviduct (Braude *et al.* 1988), it is crucial that the embryo is subjected to the optimal microenvironment within the oviduct to support proper embryonic genome activation. As GIFT and ZIFT are less common in comparison to IVF (Sunderam *et al.* 2017), it is difficult to accurately compare the incidence of diseases in babies-conceived and developed in the presence (GIFT and ZIFT) or the absence (IVF and ICSI) of oviducts. Nevertheless, ARTs have been shown to alter the epigenome of resulting offspring in mice and humans as well as to increase the frequency of epigenetic disorders such as Angelman or Beckwith–Wiedemann syndromes (reviewed by Uyar & Seli 2014).

Early studies showed that co-culturing gametes or fertilized eggs with epithelial cells improved both fertilization rates and embryo quality (Bongso *et al.* 1989, White *et al.* 1989). In mice and cows, introduction of oviductal fluid extracellular vesicles (oEVs) have been shown to improve embryo development, cryoresistance (Almiñana *et al.* 2017, Lopera-Vasquez *et al.* 2017) and increase ARTs birth rates in mice (Qu *et al.* 2019). In cows, oEVs secreted from oviductal epithelial cells *in vivo* (obtained by flushing oviducts) compared to oEVs obtained from *in vitro* primary oviductal epithelial cell culture presented different proteins, among which notably, OVGP1 was present only in oEVs from *in vivo* origin (Almiñana *et al.* 2017). Furthermore, oEVs produced *in vivo* were found to be under the hormonal regulatory effects of the estrous cycle (Alminana *et al.* 2018). Lopera-Vasquez *et al.* also demonstrated that addition of oEVs collected from the isthmus improved the developmental competence and quality of bovine embryos (Lopera-Vasquez *et al.* 2017).

In addition to oEVs, optimal culture media for the development of embryos to the blastocyst stage in IVF settings have been developed. There are two approaches, including one-step (monophasic) media and sequential media tailored for metabolically changing embryos during different stages. However, a recent meta-analysis showed that the superiority of sequential over monophasic media for several pregnancy outcomes was still inconclusive (Sfontouris *et al.* 2016), suggesting a need for further studies. Efforts have also been made to improve embryo quality in ARTs by providing a simulated oviductal environment for fertilization and early embryo development *ex vivo*. Ferraz *et al.* developed a three-dimensional microfluidic model of bovine oviduct epithelial cells, called an oviduct-on-a-chip, which has been shown to produce bovine embryos with epigenetic patterning more similar to that of *in vivo*-derived embryos compared to embryos derived using current optimized IVF protocols (Ferraz *et al.* 2017). Recently, pig blastocysts produced *in vitro* in the presence of natural reproductive fluids (follicular, oviductal and uterine fluids) showed higher quality in terms of cell

number and hatching ability, with gene expression and methylation patterns closer to naturally conceived embryos than blastocysts produced in non-supplemented ARTs liquids (Canovas *et al.* 2017). Similarly, bovine blastocysts cultured in the presence of oviductal and uterine fluids supported embryo development and improved blastocyst cryosurvival, DNA methylation and antioxidant activity (Hamdi *et al.* 2018).

Ectopic pregnancy

If embryo transport in the oviduct does not properly occur (i.e.- if the embryo travels too slowly due to improper regulation of ciliary beating, muscle contractions, or fluid flow), the embryo may implant itself outside of the uterus, known as an ectopic pregnancy. Implantation of embryos in the oviduct (known as a tubal pregnancy) accounts for 90% of all ectopic pregnancies; the remaining 10% of ectopic pregnancies occur in the abdominal cavity, interstitial, ovary, and cervix (Panelli *et al.* 2015). A recent retrospective population-based longitudinal cohort study showed that women with ectopic first pregnancies had an increased risk of adverse birth outcomes (such as preterm birth, low birth weight and placental abruption) during subsequent intrauterine pregnancies. Furthermore, 10% of these women had subsequent ectopic pregnancies (Chouinard *et al.* 2019). Ectopic pregnancy accounts for 5% of maternal deaths in developed countries and less than 1% in developing countries (Khan *et al.* 2006). This is mainly due to ruptures at the site of implantation leading to internal bleeding. Many factors may contribute to increasing the likelihood of ectopic pregnancies, including mal-developed oviducts (infection-induced or anatomical defect), ARTs procedures (due to increased uterine peristalsis in the cervix-to-fundus direction following embryo transfer), as well as improper regulation of oviductal mechanisms (Shaw *et al.* 2010, Perkins *et al.* 2015, Rombauts *et al.* 2015). Interestingly, tubal pregnancies appear to be restricted to primates and this could be due to anatomical differences at the uterotubal junction, known as the intramural segment in humans. Compared to laboratory and farm animals, there is no clear-cut distinction between the endometrium and endosalpinx in primates, leading to mixing of oviductal and uterine fluids and environments which could result in tubal pregnancies (reviewed by Corpa 2006).

Disruption of estrogen signaling from exposure to endocrine disruptors such as bisphenol A (BPA), used for manufacturing plastics, has been shown to increase the incidence of embryo retention in mouse oviducts (Xiao *et al.* 2011). Some plastics used for ARTs have been found to contain BPA (Gatimel *et al.* 2016). Although the levels are low in these products, BPA could negatively impact embryo quality and implantation (Ehrlich *et al.* 2012).

As discussed previously, oviductal microenvironments play a role in transporting and nurturing developing embryos before implantation through fluid secretions, ciliary beating, and tubal muscle contractions. Ji *et al.* showed that expression of AQP9 is decreased in oviduct tissues collected from patients who had ectopic pregnancies (Ji *et al.* 2013). In addition to AQP, the presence of MUC1, a glycoprotein expressed in epithelial cells of the upper reproductive tract, inhibits embryo implantation by acting as an anti-adhesive molecule (Aplin *et al.* 2001). MUC1 expression on the apical membrane of uterine epithelial cells is lost shortly before embryo attachment (Aplin *et al.* 2001). Aplin *et al.* also showed that MUC1 protein was detected on the epithelial surface of ampulla in both humans and monkeys, suggesting that the presence of MUC1 may provide anti-adhesive activity against embryo attachment in the oviduct preventing ectopic pregnancy. Accordingly, ectopic pregnancy is associated with low MUC1 expression (Al-Azemi *et al.* 2009). These data together demonstrate that secretory cells are necessary for normal embryo transport in the oviduct.

In addition to the secretory cells, ciliated epithelial cells in the oviduct also facilitate proper embryo transport. In rats, levonorgestrel (a synthetic P₄ analog used in plan B contraceptive pills) decreases CBF in the oviduct (Zhao *et al.* 2015). In humans, increased circulating levels of levonorgestrel have also been associated with ectopic pregnancies (Sheffer-Mimouni *et al.* 2003, Graner *et al.* 2019). Recently Li *et al.* demonstrated that levonorgestrel decreases expression of TRPV4 channels in human fallopian tubal epithelial cell line OE-E6/E7 (Li *et al.* 2019). Cultured primary ciliated epithelial cells of human oviducts treated with levonorgestrel showed a significant reduction of CBF in a TRPV4-dependent manner (Li *et al.* 2019). In fact, oviducts from patients with ectopic pregnancies have significantly lower levels of TRPV4 protein expression (Li *et al.* 2019).

In addition to the effect of high levels of P₄, cigarette smoking also increases risk of ectopic pregnancies (1.6–3.5 times higher in smokers vs non-smokers) (Saraiya *et al.* 1998). Exposure to cigarette smoke significantly decreases CBF of ciliated epithelial cells in hamster oviducts (Knoll *et al.* 1995). Inhalation of cigarette smoke not only affects ciliary function, but it also slows muscle contractions in hamster oviducts (DiCarantonio & Talbot 1999). Together these findings suggest that excess exposure to P₄ (or synthetic P₄) as well as cigarette smoking can cause a disruption in ciliated epithelial and muscle cell functions in the oviduct and could result in ectopic pregnancies.

Conclusion

Regulation of the mechanical processes in the oviduct including the physiological function of secretory,

ciliated, and muscle cells is crucial for maintaining proper embryo quality and transport within the oviduct, along with supporting various sperm functions. Alterations in steroid hormone signaling can result in the disruption of normal embryo development and can also lead to ectopic pregnancies or infertility.

Declaration of interest

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

Funding

This work was supported by grants from the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health (award number R01HD097087) and the start-up fund from Washington State University, College of Veterinary Medicine to W W and the National Heart, Lung, and Blood Institute (award number R01HL139643) to K-I T.

Author contribution statement

B E B, G G H, P A, J K R, A M W, and E A H wrote and edited the paper. G G H, A M W and E A H performed histological staining, immunostaining and analyzed data. K-I T provided human oviduct samples, wrote and edited the paper. W W conceived the study, analyzed data, wrote and edited the paper.

Acknowledgements

The authors thank Lana Lim for an initial contribution of the manuscript and acknowledge the Stony Brook University Medicine (SBUM) BioBank, a Department of Pathology and Cancer Center Core Facility at the Stony Brook University School of Medicine for human oviduct specimens.

References

- Abe H 1996 The mammalian oviductal epithelium: regional variations in cytological and functional aspects of the oviductal secretory cells. *Histology and Histopathology* **11** 743–768.
- Adeoya-Osiguwa SA, Markoulaki S, Pocock V, Milligan SR & Fraser LR 2003 17 β -Estradiol and environmental estrogens significantly affect mammalian sperm function. *Human Reproduction* **18** 100–107. (<https://doi.org/10.1093/humrep/deg037>)
- Aguilar J & Reyley M 2005 The uterine tubal fluid: secretion, composition and biological effects. *Animal Reproduction* **2** 91–105.
- Akison LK, Boden MJ, Kennaway DJ, Russell DL & Robker RL 2014 Progesterone receptor-dependent regulation of genes in the oviducts of female mice. *Physiological Genomics* **46** 583–592. (<https://doi.org/10.1152/physiolgenomics.00044.2014>)
- 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. (<https://doi.org/10.1677/JOE-07-0089>)
- Al-Azemi M, Refaat B, Aplin J & Ledger W 2009 The expression of muc1 in human fallopian tube during the menstrual cycle and in ectopic pregnancy. *Human Reproduction* **24** 2582–2587. (<https://doi.org/10.1093/humrep/dep233>)
- Algarra B, Han L, Soriano-Ubeda C, Aviles M, Coy P, Jovine L & Jimenez-Movilla M 2016 The C-terminal region of ovpg1 remodels the zona pellucida and modifies fertility parameters. *Scientific Reports* **6** 32556. (<https://doi.org/10.1038/srep32556>)
- Algarra B, Maillo V, Aviles M, Gutierrez-Adan A, Rijos D & Jimenez-Movilla M 2018 Effects of recombinant OVGP1 protein on in vitro bovine embryo development. *Journal of Reproduction and Development* **64** 433–443. (<https://doi.org/10.1262/jrd.2018-058>)
- Almiñana C, Corbin E, Tsikis G, Alcántara-Neto AS, Labas V, Reynaud K, Galio L, Uzbekov R, Garanina AS, Druart X *et al.* 2017 Oviduct extracellular vesicles protein content and their role during oviduct-embryo cross-talk. *Reproduction* **154** 153–168. (<https://doi.org/10.1530/REP-17-0054>)
- Alminana C, Tsikis G, Labas V, Uzbekov R, Da Silveira JC, Bauersachs S & Mermillod P 2018 Deciphering the oviductal extracellular vesicles content across the estrous cycle: implications for the gametes-oviduct interactions and the environment of the potential embryo. *BMC Genomics* **19** 622. (<https://doi.org/10.1186/s12864-018-4982-5>)
- 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. (<https://doi.org/10.1083/jcb.200409070>)
- Aplin JD, Meseguer M, Simon C, Ortiz ME, Croxatto H & Jones CJP 2001 MUC1, glycans and the cell-surface barrier to embryo implantation. *Biochemical Society Transactions* **29** 153–156. (<https://doi.org/10.1042/0300-5127:0290153>)
- Araki Y, Nohara M, Yoshida-Komiya H, Kuramochi T, Ito M, Hoshi H, Shinkai Y & Sendai Y 2003 Effect of a null mutation of the oviduct-specific glycoprotein gene on mouse fertilization. *Biochemical Journal* **374** 551–557. (<https://doi.org/10.1042/BJ20030466>)
- Avilés M, Gutiérrez-Adán A & Coy P 2010 Oviductal secretions: will they be key factors for the future arts? *Molecular Human Reproduction* **16** 896–906. (<https://doi.org/10.1093/molehr/gaq056>)
- Bauersachs S, Blum H, Mallok S, Wenigerkind H, Rief S, Prella K & Wolf E 2003 Regulation of ipsilateral and contralateral bovine oviduct epithelial cell function in the postovulation period: a transcriptomics approach. *Biology of Reproduction* **68** 1170–1177. (<https://doi.org/10.1095/biolreprod.102.010660>)
- Bishop DW 1956 Active secretion in the rabbit oviduct. *American Journal of Physiology* **187** 347–352. (<https://doi.org/10.1152/ajplegacy.1956.187.2.347>)
- Bongso A, Soon-Chye N, Sathananthan H, Lian NP, Rauff M & Ratnam S 1989 Improved quality of human embryos when co-cultured with human ampullary cells. *Human Reproduction* **4** 706–713. (<https://doi.org/10.1093/oxfordjournals.humrep.a136971>)
- Brañes MC, Morales B, Ríos M & Villalón MJ 2005 Regulation of the immunorepression of aquaporin 9 by ovarian hormones in the rat oviductal epithelium. *American Journal of Physiology: Cell Physiology* **288** C1048–C1057. (<https://doi.org/10.1152/ajpcell.00420.2003>)
- Braude P, Bolton V & Moore S 1988 Human gene expression first occurs between the four- and eight-cell stages of preimplantation development. *Nature* **332** 459–461. (<https://doi.org/10.1038/332459a0>)
- Brenner RM 1969 Renewal of oviduct cilia during the menstrual cycle of the rhesus monkey. *Fertility and Sterility* **20** 599–611. ([https://doi.org/10.1016/s0015-0282\(16\)37086-8](https://doi.org/10.1016/s0015-0282(16)37086-8))
- Buhi WC, Ashworth CJ, Bazer FW & Alvarez IM 1992 In vitro synthesis of oviductal secretory proteins by estrogen-treated ovariectomized gilts. *Journal of Experimental Zoology* **262** 426–435. (<https://doi.org/10.1002/jez.1402620409>)
- 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. (<https://doi.org/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. (<https://doi.org/10.1186/1477-7827-11-33>)
- Canovas S, Ivanova E, Romar R, Garcia-Martinez S, Soriano-Ubeda C, Garcia-Vazquez FA, Saadeh H, Andrews S, Kelsey G & Coy P 2017 DNA methylation and gene expression changes derived from assisted reproductive technologies can be decreased by reproductive fluids. *eLife* **6** e23670. (<https://doi.org/10.7554/eLife.23670>)

- Castro PT, Aranda OL, Matos APP, Marchiori E, De Araujo LFB, Alves HDL, Machado AS, Lopes RT, Werner H & Junior EA 2019 The human endosalpinx: anatomical three-dimensional study and reconstruction using confocal microtomography. *Polish Journal of Radiology* **84** e281–e288. (<https://doi.org/10.5114/pjr.2019.86824>)
- Chen S, Einspanier R & Schoen J 2013 Long-term culture of primary porcine oviduct epithelial cells: validation of a comprehensive in vitro model for reproductive science. *Theriogenology* **80** 862–869. (<https://doi.org/10.1016/j.theriogenology.2013.07.011>)
- Chouinard M, Mayrand MH, Ayoub A, Healy-Profitts J & Auger N 2019 Ectopic pregnancy and outcomes of future intrauterine pregnancy. *Fertility and Sterility* **112** 112–119. (<https://doi.org/10.1016/j.fertnstert.2019.03.019>)
- 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. ([https://doi.org/10.1016/S0039-128X\(03\)00126-0](https://doi.org/10.1016/S0039-128X(03)00126-0))
- Corpa JM 2006 Ectopic pregnancy in animals and humans. *Reproduction* **131** 631–640. (<https://doi.org/10.1530/rep.1.00606>)
- Coy P & Yanagimachi R 2015 The common and species-specific roles of oviductal proteins in mammalian fertilization and embryo development. *BioScience* **65** 973–984. (<https://doi.org/10.1093/biosci/biv119>)
- Coy P, Cánovas S, Mondéjar I, Saavedra MD, Romar R, Grullón L, Matás C & Avilés M 2008 Oviduct-specific glycoprotein and heparin modulate sperm–zona pellucida interaction during fertilization and contribute to the control of polyspermy. *PNAS* **105** 15809–15814. (<https://doi.org/10.1073/pnas.0804422105>)
- Croxatto HB 2002 Physiology of gamete and embryo transport through the Fallopian tube. *Reproductive Biomedicine Online* **4** 160–169. ([https://doi.org/10.1016/S1472-6483\(10\)61935-9](https://doi.org/10.1016/S1472-6483(10)61935-9))
- De Geyter C, Calhaz-Jorge C, Kupka MS, Wyns C, Mocanu E, Motrenko T, Scaravelli G, Smeenk J, Vidakovic S, Goossens V *et al.* 2018 ART in Europe, 2014: results generated from European registries by eshre: the European IVF-monitoring consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). *Human Reproduction* **33** 1586–1601. (<https://doi.org/10.1093/humrep/dey242>)
- Dicarlantonio G & Talbot P 1999 Inhalation of mainstream and sidestream cigarette smoke retards embryo transport and slows muscle contraction in oviducts of hamsters (*Mesocricetus auratus*). *Biology of Reproduction* **61** 651–656. (<https://doi.org/10.1095/biolreprod61.3.651>)
- Dietzel E, Wessling J, Floehr J, Schäfer C, Ensslen S, Denecke B, Rösing B, Neulen J, Veitinger T, Spehr M *et al.* 2013 Fetuin-b, a liver-derived plasma protein is essential for fertilization. *Developmental Cell* **25** 106–112. (<https://doi.org/10.1016/j.devcel.2013.03.001>)
- Dirksen ER & Satir P 1972 Ciliary activity in the mouse oviduct as studied by transmission and scanning electron microscopy. *Tissue and Cell* **4** 389–403. ([https://doi.org/10.1016/S0040-8166\(72\)80017-X](https://doi.org/10.1016/S0040-8166(72)80017-X))
- Dixon RE, Ramsey KH, Schripsema JH, Sanders KM & Ward SM 2010 Time-dependent disruption of oviduct pacemaker cells by chlamydia infection in mice. *Biology of Reproduction* **83** 244–253. (<https://doi.org/10.1095/biolreprod.110.083808>)
- Dixon RE, Hennig GW, Baker SA, Britton FC, Harfe BD, Rock JR, Sanders KM & Ward SM 2012 Electrical slow waves in the mouse oviduct are dependent upon a calcium activated chloride conductance encoded by *Tmem16a*. *Biology of Reproduction* **86** 1–7. (<https://doi.org/10.1095/biolreprod.111.095554>)
- Eddy EM, Washburn TF, Bunch DO, Goulding EH, Gladen BC, Lubahn DB & Korach KS 1996 Targeted disruption of the estrogen receptor gene in male mice causes alteration of spermatogenesis and infertility. *Endocrinology* **137** 4796–4805. (<https://doi.org/10.1210/endo.137.11.8895349>)
- Ehrlich S, Williams PL, Missmer SA, Flaws JA, Berry KF, Calafat AM, Ye X, Petrozza JC, Wright D & Hauser R 2012 Urinary bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. *Environmental Health Perspectives* **120** 978–983. (<https://doi.org/10.1289/ehp.1104307>)
- Ferraz MAMM, Henning HHW, Stout TAE, Vos PLAM & Gadella BM 2017 Designing 3-dimensional in vitro oviduct culture systems to study mammalian fertilization and embryo production. *Annals of Biomedical Engineering* **45** 1731–1744. (<https://doi.org/10.1007/s10439-016-1760-x>)
- Fujihara Y, Miyata H & Ikawa M 2018 Factors controlling sperm migration through the oviduct revealed by gene-modified mouse models. *Experimental Animals* **67** 91–104. (<https://doi.org/10.1538/expanim.17-0153>)
- Gatimel N, Lacroix MZ, Chanthavisouk S, Picard-Hagen N, Gayraud V, Parinaud J & Léandri RD 2016 Bisphenol A in culture media and plastic consumables used for art. *Human Reproduction* **31** 1436–1444. (<https://doi.org/10.1093/humrep/dew116>)
- Ghosh A, Syed SM & Tanwar PS 2017 In vivo genetic cell lineage tracing reveals that oviductal secretory cells self-renew and give rise to ciliated cells. *Development* **144** 3031–3041. (<https://doi.org/10.1242/dev.149989>)
- Gott AL, Gray SM, James AF & Leese HJ 1988 The mechanism and control of rabbit oviduct fluid formation. *Biology of Reproduction* **39** 758–763. (<https://doi.org/10.1095/biolreprod39.4.758>)
- Graner S, Mc Taggart J, Nordström F, Melander E, Widenberg J & Kopp Kallner H 2019 Levonorgestrel intrauterine contraceptive systems (13.5 mg and 52 mg) and risk of ectopic pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* **98** 937–943. (<https://doi.org/10.1111/aogs.13564>)
- Halbert SA, Tam PY & Blandau RJ 1976 Egg transport in the rabbit oviduct: the roles of cilia and muscle. *Science* **191** 1052–1053. (<https://doi.org/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. (<https://doi.org/10.1095/biolreprod40.6.1131>)
- Hamdi M, Lopera-Vasquez R, Maillou V, Sanchez-Calabuig MJ, Nunez C, Gutierrez-Adan A & Rizos D 2018 Bovine oviductal and uterine fluid support in vitro embryo development. *Reproduction Fertility and Development* **30** 935–945. (<https://doi.org/10.1071/RD17286>)
- Hammer CE & Fox SB 1968 Effect of oestrogen and progesterone on physical properties of rabbit oviduct fluid. *Journal of Reproduction and Fertility* **16** 121–122. (<https://doi.org/10.1530/jrf.0.0160121>)
- Hewitt SC, Winuthayanon W & Korach KS 2016 What's new in estrogen receptor action in the female reproductive tract. *Journal of Molecular Endocrinology* **56** R55–R71. (<https://doi.org/10.1530/JME-15-0254>)
- Hino T & Yanagimachi R 2019 Active peristaltic movements and fluid production of the mouse oviduct: their roles in fluid and sperm transport and fertilization. *Biology of Reproduction* **101** 40–49. (<https://doi.org/10.1093/biolre/iox061>)
- Holt WV & Fazeli A 2010 The oviduct as a complex mediator of mammalian sperm function and selection. *Molecular Reproduction and Development* **77** 934–943. (<https://doi.org/10.1002/mrd.21234>)
- 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 and Other Lipid Mediators* **121** 170–175. (<https://doi.org/10.1016/j.prostaglandins.2015.08.002>)
- Huang N, Wang C, Zhang N, Mao W, Liu B, Shen Y, Gao Y, Zhao Y & Cao J 2018 Effect of estrogen on prostaglandin synthetase in bovine oviduct smooth muscle. *European Journal of Pharmacology* **818** 287–293. (<https://doi.org/10.1016/j.ejphar.2017.10.058>)
- Hunter RHF 1988 Development of the fallopian tubes and their functional anatomy. In *The Fallopian Tubes: Their Role in Fertility and Infertility*, pp 12–29. Ed RHF Hunter. Berlin, Germany: Springer-Verlag.
- Ji YF, Chen LY, Xu KH, Yao JF, Shi YF & Shanguan XJ 2013 Reduced expression of aquaporin 9 in tubal ectopic pregnancy. *Journal of Molecular Histology* **44** 167–173. (<https://doi.org/10.1007/s10735-012-9471-6>)
- Jung C, Fandos C, Lorenzo IM, Plata C, Fernandes J, Gene GG, Vazquez E & Valverde MA 2009 The progesterone receptor regulates the expression of TRPV4 channel. *Pflügers Archiv* **459** 105–113. (<https://doi.org/10.1007/s00424-009-0706-7>)
- Kapur RP & Johnson LV 1986 Selective sequestration of an oviductal fluid glycoprotein in the perivitelline space of mouse oocytes and embryos. *Journal of Experimental Zoology* **238** 249–260. (<https://doi.org/10.1002/jez.1402380215>)
- Khan KS, Wojdyla D, Say L, Gülmezoglu AM & Van Look PF 2006 Who analysis of causes of maternal death: a systematic review. *Lancet* **367** 1066–1074. ([https://doi.org/10.1016/S0140-6736\(06\)68397-9](https://doi.org/10.1016/S0140-6736(06)68397-9))
- Knoll M, Shaoulain R, Magers T & Talbot P 1995 Ciliary beat frequency of hamster oviducts is decreased in vitro by exposure to solutions of mainstream and sidestream cigarette smoke. *Biology of Reproduction* **53** 29–37. (<https://doi.org/10.1095/biolreprod53.1.29>)
- Kowalik MK, Slonina D, Rekawiecki R & Kotwica J 2013 Expression of progesterone receptor membrane component (PGRMC) 1 and 2, serpine mRNA binding protein 1 (SERBP1) and nuclear progesterone receptor (pgr) in the bovine endometrium during the estrous cycle and the first

- trimester of pregnancy. *Reproductive Biology* **13** 15–23. (<https://doi.org/10.1016/j.repbio.2013.01.170>)
- Lai YM, Wang HS, Lee CL, Lee JD, Huang HY, Chang FH, Lee JF & Soong YK 1996 Insulin-like growth factor-binding proteins produced by vero cells, human oviductal cells and human endometrial cells, and the role of insulin-like growth factor-binding protein-3 in mouse embryo co-culture systems. *Human Reproduction* **11** 1281–1286. (<https://doi.org/10.1093/oxfordjournals.humrep.a019372>)
- Lee KF, Xu JS, Lee YL & Yeung WS 2006 Demilune cell and parotid protein from murine oviductal epithelium stimulates preimplantation embryo development. *Endocrinology* **147** 79–87. (<https://doi.org/10.1210/en.2005-0596>)
- Li S, O'Neill SRS, Zhang Y, Holtzman MJ, Takemaru KI, Korach KS & Winuthayanon W 2017 Estrogen receptor α is required for oviductal transport of embryos. *FASEB Journal* **31** 1595–1607. (<https://doi.org/10.1096/fj.201601128R>)
- Li C, Wu YT, Zhu Q, Zhang HY, Huang Z, Zhang D, Qi H, Liang GL, He XQ, Wang XF *et al.* 2019 TRPV4 is involved in levonorgestrel-induced reduction in oviduct ciliary beating. *Journal of Pathology* **248** 77–87. (<https://doi.org/10.1002/path.5233>)
- Lishko PV, Botchkina IL & Kirichok Y 2011 Progesterone activates the principal Ca^{2+} channel of human sperm. *Nature* **471** 387–391. (<https://doi.org/10.1038/nature09767>)
- Lopera-Vasquez R, Hamdi M, Maillou V, Gutierrez-Adan A, Bermejo-Alvarez P, Ramirez MÁ, Yanez-Mo M & Rijos D 2017 Effect of bovine oviductal extracellular vesicles on embryo development and quality in vitro. *Reproduction* **153** 461–470. (<https://doi.org/10.1530/REP-16-0384>)
- 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. (<https://doi.org/10.1073/pnas.0803970105>)
- Lydon JP, Demayo FJ, Funk CR, Mani SK, Hughes AR, Montgomery Jr CA, Shyamala G, Conneely OM & O'Malley BW 1995 Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. *Genes and Development* **9** 2266–2278. (<https://doi.org/10.1101/gad.9.18.2266>)
- Lyng R & Shur BD 2009 Mouse oviduct-specific glycoprotein is an egg-associated ZP3-independent sperm-adhesion ligand. *Journal of Cell Science* **122** 3894–3906. (<https://doi.org/10.1242/jcs.058776>)
- 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. (<https://doi.org/10.1093/humrep/13.11.2991>)
- 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. (<https://doi.org/10.1530/jrf.0.0200051>)
- Miki K & Clapham DE 2013 Rheotaxis guides mammalian sperm. *Current Biology* **23** 443–452. (<https://doi.org/10.1016/j.cub.2013.02.007>)
- Moore EL, Wang S & Larina IV 2018 Staging mouse preimplantation development in vivo using optical coherence microscopy. *Journal of Biophotonics* **12** e201800364.
- Muglia U & Motta PM 2001 A new morpho-functional classification of the fallopian tube based on its three-dimensional myoarchitecture. *Histology and Histopathology* **16** 227–237.
- Mulac-Jericevic B, Lydon JP, Demayo FJ & Conneely OM 2003 Defective mammary gland morphogenesis in mice lacking the progesterone receptor b isoform. *PNAS* **100** 9744–9749. (<https://doi.org/10.1073/pnas.1732707100>)
- Muro Y, Hasuwa H, Isotani A, Miyata H, Yamagata K, Ikawa M, Yanagimachi R & Okabe M 2016 Behavior of mouse spermatozoa in the female reproductive tract from soon after mating to the beginning of fertilization. *Biology of Reproduction* **94** 80. (<https://doi.org/10.1095/biolreprod.115.135368>)
- Nah WH, Oh YS, Hwang JH & Gye MC 2017 Changes in aquaporin 5 in the non-ciliated cells of mouse oviduct according to sexual maturation and oestrous cycle. *Reproduction Fertility and Development* **29** 336–344. (<https://doi.org/10.1071/RD15186>)
- 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. (<https://doi.org/10.1016/j.devcel.2012.10.016>)
- Nutu M, Weijdegard B, Thomas P, Thurin-Kjellberg A, Billig H & Larsson DG 2009 Distribution and hormonal regulation of membrane progesterone receptors beta and gamma in ciliated epithelial cells of mouse and human fallopian tubes. *Reproductive Biology and Endocrinology* **7** 89. (<https://doi.org/10.1186/1477-7827-7-89>)
- Okabe M 2015 Mechanisms of fertilization elucidated by gene-manipulated animals. *Asian Journal of Andrology* **17** 646–652. (<https://doi.org/10.4103/1008-682X.153299>)
- Okada A, Ohta Y, Inoue S, Hiroi H, Muramatsu M & Iguchi T 2003 Expression of estrogen, progesterone and androgen receptors in the oviduct of developing, cycling and pre-implantation rats. *Journal of Molecular Endocrinology* **30** 301–315. (<https://doi.org/10.1677/jme.0.0300301>)
- Okada A, Ohta Y, Brody SL, Watanabe H, Krust A, Chambon P & Iguchi T 2004 Role of FOXJ1 and estrogen receptor alpha in ciliated epithelial cell differentiation of the neonatal oviduct. *Journal of Molecular Endocrinology* **32** 615–625. (<https://doi.org/10.1677/jme.0.0320615>)
- 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. (<https://doi.org/10.1093/humrep/den265>)
- Panelli DM, Phillips CH & Brady PC 2015 Incidence, diagnosis and management of tubal and nontubal ectopic pregnancies: a review. *Fertility Research and Practice* **1** 15. (<https://doi.org/10.1186/s40738-015-0008-z>)
- Parada-Bustamante A, Croxatto HB, Cárdenas H & Orihuela PA 2012 Differential participation of endothelin receptors in estradiol-induced oviductal egg transport acceleration in unmated and mated rats. *Asian Pacific Journal of Reproduction* **1** 22–26. ([https://doi.org/10.1016/S2305-0500\(13\)60042-1](https://doi.org/10.1016/S2305-0500(13)60042-1))
- Pauerstein CJ & Eddy CA 1979 Morphology of the Fallopian tube. In *The Biology of the Fluids of the Female Reproductive Tract*, pp 299–317. Eds FK Beller & GFB Schumacher. Amsterdam: Elsevier.
- Pérez Martínez S, Hermoso M, Farina M, Ribeiro ML, Rapanelli M, Espinosa M, Villalón M & Franchi A 2006 17- β -Estradiol upregulates COX-2 in the rat oviduct. *Prostaglandins and Other Lipid Mediators* **80** 155–164. (<https://doi.org/10.1016/j.prostaglandins.2006.06.002>)
- Perkins KM, Boulet SL, Kissin DM, Jamieson DJ & National ART Surveillance (NASS) Group 2015 Risk of ectopic pregnancy associated with assisted reproductive technology in the United States, 2001–2011. *Obstetrics and Gynecology* **125** 70–78. (<https://doi.org/10.1097/AOG.0000000000000584>)
- Popescu LM, Ciontea SM, Cretoiu D, Hinescu ME, Radu E, Ionescu N, Ceausu M, Gherghiceanu M, Braga RI, Vasilescu F *et al.* 2005 Novel type of interstitial cell (Cajal-like) in human Fallopian tube. *Journal of Cellular and Molecular Medicine* **9** 479–523. (<https://doi.org/10.1111/j.1582-4934.2005.tb00376.x>)
- Priyadarsana M, Wijayagunawardane B & Miyamoto A 2004 Endothelin-1 system in the bovine oviduct: a regulator of local contraction and gamete transport. *Journal of Cardiovascular Pharmacology* **44** (Supplement 1) S248–S251. (<https://doi.org/10.1097/01.fjc.0000166253.66486.4f>)
- Qu P, Zhao Y, Wang R, Zhang Y, Li L, Fan J & Liu E 2019 Extracellular vesicles derived from donor oviduct fluid improved birth rates after embryo transfer in mice. *Reproduction Fertility and Development* **31** 324–332. (<https://doi.org/10.1071/RD18203>)
- Reuquén P, Oróstica 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. (<https://doi.org/10.1530/REP-15-0137>)
- Roberts GP, Parker JM & Symonds HW 1975 Proteins in the luminal fluid from the bovine oviduct. *Journal of Reproduction and Fertility* **45** 301–313. (<https://doi.org/10.1530/jrf.0.0450301>)
- Rombauts L, McMaster R, Motteram C & Fernando S 2015 Risk of ectopic pregnancy is linked to endometrial thickness in a retrospective cohort study of 8120 assisted reproduction technology cycles. *Human Reproduction* **30** 2846–2852. (<https://doi.org/10.1093/humrep/dev249>)
- Rosselli M, Imthurn B, Macas E & Keller PJ 1994a Endothelin production by bovine oviduct epithelial cells. *Journal of Reproduction and Fertility* **101** 27–30. (<https://doi.org/10.1530/jrf.0.1010027>)
- Rosselli M, Imthurn B, Macas E, Keller PJ & Dubey RK 1994b Endogenous nitric oxide modulates endothelin-1 induced contraction of bovine

- oviduct. *Biochemical and Biophysical Research Communications* **201** 143–148. (<https://doi.org/10.1006/bbrc.1994.1680>)
- Sabeur K, Edwards DP & Meizel S 1996 Human sperm plasma membrane progesterone receptor(s) and the acrosome reaction. *Biology of Reproduction* **54** 993–1001. (<https://doi.org/10.1095/biolreprod54.5.993>)
- Saraiya M, Berg CJ, Kendrick JS, Strauss LT, Atrash HK & Ahn YW 1998 Cigarette smoking as a risk factor for ectopic pregnancy. *American Journal of Obstetrics and Gynecology* **178** 493–498. ([https://doi.org/10.1016/s0002-9378\(98\)70427-2](https://doi.org/10.1016/s0002-9378(98)70427-2))
- Seki K, Rawson J, Eddy CA, Smith NK & Pauerstein CJ 1978 Deciliation in the puerperal Fallopian tube. *Fertility and Sterility* **29** 75–83. ([https://doi.org/10.1016/S0015-0282\(16\)43042-6](https://doi.org/10.1016/S0015-0282(16)43042-6))
- Sfontouris IA, Martins WP, Nastri CO, Viana IGR, Navarro PA, Raine-Fenning N, Van Der Poel S, Rienzi L & Racowsky C 2016 Blastocyst culture using single versus sequential media in clinical IVF: a systematic review and meta-analysis of randomized controlled trials. *Journal of Assisted Reproduction and Genetics* **33** 1261–1272. (<https://doi.org/10.1007/s10815-016-0774-5>)
- Shaw JL, Dey SK, Critchley HO & Horne AW 2010 Current knowledge of the aetiology of human tubal ectopic pregnancy. *Human Reproduction Update* **16** 432–444. (<https://doi.org/10.1093/humupd/dmp057>)
- Sheffer-Mimouni G, Pauzner D, Maslovitch S, Lessing JB & Gamzu R 2003 Ectopic pregnancies following emergency levonorgestrel contraception. *Contraception* **67** 267–269. ([https://doi.org/10.1016/s0010-7824\(02\)00539-5](https://doi.org/10.1016/s0010-7824(02)00539-5))
- Siller SS, Sharma H, Li S, Yang J, Zhang Y, Holtzman MJ, Winuthayanon W, Colognato H, Holdener BC, Li FQ *et al.* 2017 Conditional knockout mice for the distal appendage protein CEP164 reveal its essential roles in airway multiciliated cell differentiation. *PLoS Genetics* **13** e1007128. (<https://doi.org/10.1371/journal.pgen.1007128>)
- Skowronski MT, Skowronska A & Nielsen S 2011 Fluctuation of aquaporin 1, 5, and 9 expression in the pig oviduct during the estrous cycle and early pregnancy. *Journal of Histochemistry and Cytochemistry* **59** 419–427. (<https://doi.org/10.1369/0022155411400874>)
- Solkadi S, Psarra AM, Nikolaropoulos S & Sekeris CE 2005 Estrogen receptors alpha and beta (ER α and ER β) and androgen receptor (AR) in human sperm: localization of ER β and AR in mitochondria of the midpiece. *Human Reproduction* **20** 3481–3487. (<https://doi.org/10.1093/humrep/dei267>)
- Spilman CH 1974 Oviduct response to prostaglandins: influence of estradiol and progesterone. *Prostaglandins* **7** 465–472. ([https://doi.org/10.1016/0090-6980\(74\)90091-4](https://doi.org/10.1016/0090-6980(74)90091-4))
- Steffl M, Schweiger M, Sugiyama T & Amselgruber WM 2008 Review of apoptotic and non-apoptotic events in non-ciliated cells of the mammalian oviduct. *Annals of Anatomy* **190** 46–52. (<https://doi.org/10.1016/j.aanat.2007.04.003>)
- Suarez SS 2002 Formation of a reservoir of sperm in the oviduct. *Reproduction in Domestic Animals* **37** 140–143. (<https://doi.org/10.1046/j.1439-0531.2002.00346.x>)
- Sunderam S, Kissin DM, Crawford SB, Folger SG, Jamieson DJ, Warner L & Barfield WD 2017 Assisted reproductive technology surveillance – United States, 2014. *MMWR: Surveillance Summaries* **66** 1–24. (<https://doi.org/10.15585/mmwr.ss6606a1>)
- Tan W, Pang Y, Tubbs C & Thomas P 2019 Induction of sperm hypermotility through membrane progesterin receptor alpha (mPR α): a teleost model of rapid, multifaceted, nongenomic progesterin signaling. *General and Comparative Endocrinology* **279** 60–66. (<https://doi.org/10.1016/j.ygcen.2018.12.002>)
- Uyar A & Seli E 2014 The impact of assisted reproductive technologies on genomic imprinting and imprinting disorders. *Current Opinion in Obstetrics and Gynecology* **26** 210–221. (<https://doi.org/10.1097/GCO.0000000000000071>)
- Wadhwa PD, Buss C, Entringer S & Swanson JM 2009 Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Seminars in Reproductive Medicine* **27** 358–368. (<https://doi.org/10.1055/s-0029-1237424>)
- 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. (<https://doi.org/10.1038/nm1104>)
- Wang S, Burton JC, Behringer RR & Larina IV 2015 In vivo micro-scale tomography of ciliary behavior in the mammalian oviduct. *Scientific Reports* **5** 13216. (<https://doi.org/10.1038/srep13216>)
- Wessel T, Schuchter U & Walt H 2004 Ciliary motility in bovine oviducts for sensing rapid non-genomic reactions upon exposure to progesterone. *Hormone and Metabolic Research* **36** 136–141. (<https://doi.org/10.1055/s-2004-814336>)
- White KL, Hehnke K, Rickards LF, Southern LL, Thompson Jr DL & Wood TC 1989 Early embryonic development in vitro by coculture with oviductal epithelial cells in pigs. *Biology of Reproduction* **41** 425–430. (<https://doi.org/10.1095/biolreprod41.3.425>)
- Wijayagunawardane MP, Choi YH, Miyamoto A, Kamishita H, Fujimoto S, Takagi M & Sato K 1999 Effect of ovarian steroids and oxytocin on the production of prostaglandin E₂, prostaglandin F_{2 α} and endothelin-1 from cow oviductal epithelial cell monolayers in vitro. *Animal Reproduction Science* **56** 11–17. ([https://doi.org/10.1016/S0378-4320\(99\)00021-4](https://doi.org/10.1016/S0378-4320(99)00021-4))
- 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. (<https://doi.org/10.1677/joe.0.1680117>)
- Winuthayanon W, Bernhardt ML, Padilla-Banks E, Myers PH, Edin ML, Lih FB, Hewitt SC, Korach KS & Williams CJ 2015 Oviductal estrogen receptor alpha signaling prevents protease-mediated embryo death. *eLife* **4** e10453. (<https://doi.org/10.7554/eLife.10453>)
- Xiao S, Diao H, Smith MA, Song X & Ye X 2011 Preimplantation exposure to bisphenol A (BPA) affects embryo transport, preimplantation embryo development, and uterine receptivity in mice. *Reproductive Toxicology* **32** 434–441. (<https://doi.org/10.1016/j.reprotox.2011.08.010>)
- Zhao W, Zhu Q, Yan M, Li C, Yuan J, Qin G & Zhang J 2015 Levonorgestrel decreases cilia beat frequency of human fallopian tubes and rat oviducts without changing morphological structure. *Clinical and Experimental Pharmacology and Physiology* **42** 171–178. (<https://doi.org/10.1111/1440-1681.12337>)

Received 24 April 2019

First decision 28 May 2019

Revised manuscript received 10 October 2019

Accepted 18 October 2019