

Oviductal response to gametes and early embryos in mammals

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Abstract

The oviduct is a complex and organized thin tubular structure connecting the ovary with the uterus. It is the site of final sperm capacitation, oocyte fertilization and, in most species, the first 3–4 days of early embryo development. The oviductal epithelium is made up of ciliary and secretory cells responsible for the secretion of proteins and other factors which contribute to the formation of the oviductal fluid. Despite significant research, most of the pathways and oviductal factors implicated in the crosstalk between gametes/early embryo and the oviduct remain unknown. Therefore, studying the oviductal environment is crucial to improve our understanding of the regulatory mechanisms controlling fertilization and embryo development. *In vitro* systems are a valuable tool to study *in vivo* pathways and mechanisms, particularly those in the oviducts which in livestock species are challenging to access. In studies of gamete and embryo interaction with the reproductive tract, oviductal epithelial cells, oviductal fluid and microvesicles co-cultured with gametes/embryos represent the most appropriate *in vitro* models to mimic the physiological conditions *in vivo*.

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Introduction

The oviducts (or fallopian tubes, uterine tubes) were described for the first time by the 16th century Italian anatomist, Gabriele Falloppio (1523–1562). However, it was not until a century later when Regnier de Graaf (1641–1673) asserted that the human egg transits through the fallopian tubes. At this time, the fallopian tubes were viewed as ‘chimneys enabling the smoke to rise from the matrix into the abdominal cavity’ (Alexandre 2001). The oviduct, a seromuscular organ connecting the ovary to the uterus, is the place where life begins in most mammalian species. It is the site of final sperm capacitation, oocyte fertilization and, in most species, the first 3–4 days of embryo development. While embryos can be produced in the absence of exposure to the oviductal environment, it is clear that the oviduct plays an important function in fertilization and early embryo development. Several studies have demonstrated that embryos cultured in the oviducts of sheep (Lazzari *et al.* 2002, Rizos *et al.* 2002), cattle (Fair *et al.* 2001, Tesfaye *et al.* 2007) or mice (Rizos *et al.* 2007) are of superior quality than those produced *in vitro*, in terms of morphology, gene expression, cryotolerance and pregnancy rate after transfer, indicating that the oviduct is not merely an organ through which gametes and embryos transit.

Despite significant research, most of the pathways and oviductal factors implicated in the crosstalk between the gametes/early embryo(s) and the oviduct remain unknown. In this review, we bring together knowledge related to the oviductal response to gametes and the early embryo, and the impact of the oviductal environment on embryo development *in vitro*.

Anatomy and physiology of the oviduct

The oviduct is a complex and organized thin tubular structure connecting the ovary with the uterus in which the earliest reproductive events occur. It can be divided into three main regions: the infundibulum, the ampulla and the isthmus (Fig. 1). Histologically, the oviduct contains four distinct cell layers: the outer ‘serosa’, a single cell layer of squamous (flattened) cells that simply cover the surface; the ‘muscularis’, usually a double layer of smooth muscle consisting of an outer longitudinal layer and an inner circular layer providing the ability to contract (i.e. transport of secretory products, gametes and early embryo); the ‘submucosa’, a layer housing blood vessels, nerves and lymphatics; and the ‘mucosa’, a secretory layer of epithelium lined with a mixture of ciliated and nonciliated simple columnar cells, which produce fluids and also move materials along the

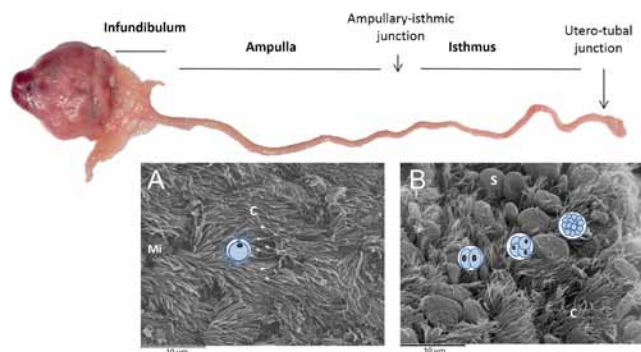


Figure 1 Illustration of the bovine oviduct. Top: Gross anatomy of the oviduct. Bottom: Scanning electron microscopy of the ampulla (A) and isthmus (B) epithelium. Note the difference in cell morphology and population between the two regions. See text for more details. C, cilia; Mi, microvilli; S, secretory cells.

oviduct because of ciliary action (Hunter 1988). At the ovarian extremity, the infundibulum contains finger-like mucosal folds; in the ampulla, the mucosa forms numerous elaborated branched folds, while in the isthmus, the longitudinal folds are less extensive and less branched and the muscle layer is well developed (Abe 1996).

As mentioned above, the oviductal epithelium is made up of ciliary and secretory cells (Fig. 1), the latter responsible for the secretion of proteins and other factors that, together with constituents derived from plasma, contribute to the formation of the oviductal fluid (OF) (Buhi *et al.* 2000, Leese *et al.* 2008). The relative proportions of ciliated and secretory cells as well as their morphology change markedly during the oestrous cycle, i.e. under hormonal control. During the follicular phase, there are more ciliated cells in the infundibulum and ampulla while secretory cells predominate during the luteal phase. In contrast, the proportion of secretory and ciliated cells in the isthmus remain similar between the follicular and the luteal phase (Abe 1996).

After ovulation, the fimbria of the infundibulum that surrounds the ovary allows the passage of the ovulated oocyte into the oviduct. At this point, both muscle layers and ciliated cells mechanically guide the oocyte into the lumen of the ampulla (Hunter 1988). During this time, sperm progress in a counter-current fashion from the distal portion of the oviduct, the uterotubal junction, following two different pathways. A small proportion migrate to the ampulla while the vast majority remain in the isthmus, adhered to epithelial cells establishing a sperm reservoir where capacitation is delayed until ovulation occurs (Coy *et al.* 2012a). Fertilization takes place around the ampullary-isthmic junction (Croxatto 2002) and after that, ciliary activity facilitates zygote transportation through the isthmus (Kölle *et al.* 2009) until entry into the uterus which occurs at about the 16-cell stage on Day 4 in cattle.

The mammalian oviduct undergoes significant endocrine-induced morphological, biochemical and

physiological changes during the oestrous cycle. The processes that take place in the oviduct are dependent on activities of the ciliated and secretory epithelia of the oviduct microenvironment, which are controlled by the ovarian steroids, oestrogen (E_2) and progesterone (P_4) (Buhi 2002). Larger preovulatory follicles, associated with greater proestrus E_2 concentrations and early diestrus P_4 concentrations, lead to different oviductal gene expression profiles compared with small preovulatory follicles, which could modify the oviductal environment and impact on embryo development and survival (Gonella-Díaz *et al.* 2015).

Components of the oviduct contributing to fertilization and early embryo development

Epithelial cells

The epithelial mucosa consists of ciliated and secretory simple columnar epithelial cells (Yániz *et al.* 2000), the ratio of which is regulated by steroid hormones, facilitating sperm binding and release, capacitation and hyperactivation (Hunter 2008). Epithelial cells are an active site of biosynthesis and secretion of amino acids, energy substances and ions (Hugentobler *et al.* 2007a,b, 2008). Thus, steroid-regulated epithelial cell secretions can be considered important mediators of the microenvironment that facilitates gamete and zygote health and early development. Winuthayanon and coworkers (2015) demonstrated that conditional knockout mice (cKO) lacking the oestrogen-epithelial receptor α exhibited impaired fertilization due to a reduction in sperm migration and the death of fertilized eggs before the 2-cell stage due to persistence of secreted proteases. This elevated protease activity caused premature degradation of the zona pellucida (ZP) and embryo lysis and wild-type embryos transferred into cKO oviduct failed to develop normally unless rescued by concomitant transfer of protease inhibitors. It was concluded that oestrogen-epithelial receptor α is necessary to suppress oviductal protease activity, which is required for a successful fertilization and preimplantation embryo development (Winuthayanon *et al.* 2015). Epithelial cells also play a role in the transport of the oocyte to the site of fertilization; whereas, during early embryo development, they contribute to creating an optimal environment. Growth factors such as IGFs (insulin-like growth factors), EGF (epidermal growth factor), PDGF (platelet-derived growth factor) and FGFs (fibroblast growth factors) have been implicated in the maternal support of embryonic growth and development (Gandolfi 1995).

Transcriptomic analysis of bovine oviduct epithelial cells have identified different functional groups of genes involved in the regulation of the oviduct during the oestrous cycle (Bauersachs *et al.* 2004). Cerny and coworkers (2015) identified a large number of

differentially expressed genes (DEGs) in bovine oviductal epithelial cells between the follicular and luteal phase of the oestrous cycle many of which were exclusive to either the ampulla or the isthmus (a list of differentially expressed genes in the oviduct related with oocyte, sperm and embryo interaction in different species is shown in [Table 1](#)). However, the physiological relevance of changes in oviduct physiology during the luteal phase (at Day 12 in those experiments), when gametes or embryos are no longer present, is unclear. Recently, we identified DEGs between the oviductal epithelial cells from the ampulla and isthmus of pregnant heifers collected on Day 3 after oestrus, which may reflect morphological and functional differences between those regions ([Maillo et al. 2016](#)). In that study, the main biological processes overrepresented in the ampulla were cell motion, motility and migration, DNA repair, calcium ion homeostasis, carbohydrate biosynthesis and regulation of cilium movement and beat frequency. In the isthmus, synthesis of compounds such as nitrogen, lipids, nucleotides, steroids and cholesterol, as well as vesicle-mediated transport, cell cycle, apoptosis, endocytosis and exocytosis were overrepresented ([Maillo et al. 2016](#)). In addition, the co-culture of ampulla cells and cumulus oocyte complexes (COCs) *in vitro* increased the duration of ZP digestion, the number of penetrated oocytes and monospermic penetration rate compared with isthmus cells and control COCs without oviduct cells ([Dadashpour Davachi et al. 2016](#)). Therefore, it seems that the epithelial cells of each part of the oviduct, ampulla and isthmus are specifically prepared to support fertilization and early embryo development.

Oviductal fluid

Oviductal fluid contains simple and complex carbohydrates, ions, lipids, phospholipids and proteins ([Aviles et al. 2010](#)). Some of these components are energy substrates, such as lactate, pyruvate and glucose, as well as amino acids, the concentration of which differs between OF, uterine fluid and serum ([Hugentobler et al. 2007a, 2008](#)).

Among the proteins present in OF, glycodefins and lactoferrin are involved in gamete interaction ([Ghersevich et al. 2015](#)) and oviductin, osteopontins and the complement protein C3 contribute to early embryo development ([Tse et al. 2008](#)). Glycodefins, highly evolutionary conserved proteins, have been detected in the human oviduct at least in four isoforms (glycodefin S, A, F and C) based on the differences in glycosylation ([Ghersevich et al. 2015](#)). The use of recombinant glycodefin A was shown to inhibit capacitation of human and hamster sperm ([Dutta et al. 2001](#)). Lactoferrin, an oestrogen-regulated glycoprotein, was first identified in human OF. Depending on the sperm capacitation status, this protein exhibited different binding patterns,

suggesting its involvement in gamete interaction ([Zumoffen et al. 2013](#)). Oviductin, or oviduct-specific glycoprotein (OVGP1), is an oestrus-associated protein that has been demonstrated to be highly conserved in all species studied ([Aviles et al. 2010](#)). Analyses of *de novo* synthesized and secreted proteins from the oviduct epithelia have identified OVGP1 as the major secretory product ([Buhi 2002](#)). In pigs and cows, OVGP1 and heparin-like glycosaminoglycans, from the OF, participate in the functional modification of the ZP, which before fertilization makes it more resistant to enzymatic digestion and sperm penetration, contributing to the control of polyspermy ([Coy et al. 2008](#)). Moreover, OVGP1 promotes sperm capacitation while maintaining motility and viability ([Coy et al. 2012a](#)). Oviductin has been localized in the perivitelline space and the membrane of embryos from different species before implantation, potentially acting as a protective ‘shield’ around the early embryo ([Ghersevich et al. 2015](#)). Embryo culture in the presence of oviductin increased embryo development *in vitro* in pigs ([McCauley et al. 2003](#)) and sheep ([Pradeep et al. 2011](#)).

Identification and role of proteins present in the OF is currently the target of many studies because of the potential benefits for *in vitro* embryo culture. Proteomic analysis of OF have reported significant differences in the protein content between the different phases of the oestrous cycle ([Seytanoglu et al. 2008](#)). In that study, seven proteins were highly abundant during the follicular phase (endoplasmin precursor, tumour rejection antigen gp96, ezrin, heat-shock 70 kDa protein 5, calreticulin precursor, actin, cytoplasmic 1, creatine kinase B-type), while six proteins were highly abundant during the luteal phase (gelsolin precursor, serum albumin precursor, myo-inositol 1-phosphate synthase A1, adenosylhomocysteinase, keratin, type II cytoskeletal 8, keratin, type I cytoskeletal 19) ([Seytanoglu et al. 2008](#)). Moreover, the presence of gametes in the oviduct also alters the pattern of protein secretion of the epithelial cells ([Georgiou et al. 2007](#)). Such changes in the composition of OF reflect the ability of the oviduct to adapt the environment to the different events from fertilization to early embryo development. Oviductal proteomic changes in different species are shown in [Table 2](#).

Microvesicles

The role of microvesicles (MVs) as mediators of intercellular communication ([Raposo & Stoorvogel 2013](#)) is based on the transport of proteins, lipids, nucleic acids, ligands and receptors from their cell of origin to a recipient cell ([Cocucci et al. 2009](#)). Their potential role in reproduction has been discovered relatively recently. [Da Silveira and coworkers \(2012\)](#) proposed that isolated MV and exosomes are involved in mediating cell communication within the mammalian ovarian follicle.

Table 1 Summary of data relating to oviductal transcriptomic changes.

Source	Species	Studied effect	Sample	Day after estrus	Method used	Total upregulated genes/top ten upregulated genes	Total downregulated genes/top ten downregulated genes
Lee et al. (2002)	Murine	Embryo vs oocyte (transferred into the same animal but different oviducts)	Oviduct epithelial cells	48 h after the transfer	SSH	6 <i>Rpl41</i> ; transient receptor protein 2; <i>Tmsb4x</i> ; <i>Myf6</i> ; <i>Acta2</i> ; <i>Rab1a</i>	
Fazeli et al. (2004)	Murine	Sperm (mated vs no mated)	Oviduct epithelial cells	D0 vs 6 h after mating	Microarray	58 <i>Anp32a</i> ; <i>Ptgs2</i> ; <i>Slc9a1</i> ; <i>Cxcl1</i> <i>Cyp11a1</i> ; <i>Spp1</i> ; <i>Serpine1</i> ; <i>Mela</i> ; <i>Adm</i> ; <i>Ndrg1</i>	156 <i>Eda</i> ; <i>Adfp-ps</i> ; <i>Gas2</i> ; <i>Kifap3</i> ; <i>Arid1a</i> ; <i>Ph3b1</i> ; <i>Ssr4</i> ; <i>Crygb</i> ; <i>Ckmt2</i> ; <i>Scg3</i>
Bauersachs et al. (2003)	Bovine	Ipsilateral vs contralateral	Oviduct epithelial cells	D3.5	SSH	27 <i>TM4SF2</i> ; <i>MAP17</i> ; <i>LTF</i> ; <i>SCP2</i> ; <i>THY1</i> ; <i>CAAF1</i> ; <i>DD96</i> ; <i>NP</i> ; <i>PHGPx</i> ; <i>WFDC</i> ;	8 Pol. IG Receptor; component C4; fibrillin; <i>ORF1</i> ; neurotrimin (<i>HNT</i>); <i>OVGP1</i> ; human DNA sequence from clone RP11-552M11 on chromosome 1; 1Ru19C11.ab <i>B. taurus</i> rumen
Bauersachs et al. (2004)	Bovine	Estrus vs diestrus	Oviduct epithelial cells	D1 vs D12	SSH	37 <i>OVGP1</i> ; <i>HSPA5</i> ; <i>AGR2</i> ; <i>GRP</i> ; <i>RARREST1</i> ; <i>DMTBT1</i> ; <i>TRAI</i> ; <i>ERP70</i> ; <i>TRA1</i> ; <i>SDF2L1</i>	40 C3; <i>CCND1</i> ; <i>FKBP1A</i> ; <i>NT5E</i> ; <i>PKD4</i> ; <i>MTND1</i> ; <i>OGT</i> ; <i>RPL5</i> ; <i>ZNF36</i> ; <i>NPCI</i>
Cerny et al. (2015)	Bovine	Follicular phase vs luteal phase	Ipsilateral ampulla epithelial cells	36 h after PGF _{2α} vs D11–12	Microarray	972 NTS; <i>PRND</i> ; <i>CDC20B</i> ; <i>BTIRAPPIN-5</i> ; <i>TMEM45A</i> ; <i>CRELD2</i> ; <i>SLC2A10</i> ; <i>SDF2L1</i> ; <i>MIR449C</i> ; <i>KRT23</i>	597 <i>EGR1</i> ; <i>FOS</i> ; <i>VCAM1</i> ; <i>GABRP</i> ; ; <i>GPR174</i> ; <i>ZBTB16</i> <i>BMP4</i> ; <i>LOC777601</i> ; <i>FIGF</i> ; <i>KLRK1</i>
	"	"	Ipsilateral isthmus epithelial cells	"	"	946 <i>KRT23</i> ; <i>NTS</i> ; <i>PRND</i> ; <i>STRA6</i> ; <i>TMEM45A</i> ; <i>PKHD1L1</i> ; <i>LPL</i> ; <i>SLC7A11</i> ; <i>CLEC3A</i> ; <i>GFAP</i>	817 <i>KLF17</i> ; <i>KSR2</i> ; <i>LOC100337391</i> ; <i>BSP3</i> ; <i>OR9Q2</i> ; <i>ZBTB16</i> ; <i>EGR1</i> ; <i>LOC522479</i> ; <i>CWH43</i> ; <i>TFF3</i>
Conella-Díaz et al. (2015)	Bovine	Large vs small preovulatory follicle	Ipsilateral ampulla epithelial cells	D4	RNAseq	325 <i>CADM3</i> ; <i>KIF5C</i> ; <i>S100A8</i> ; <i>BPIFA1</i> ; <i>GRIN3A</i> ; <i>NLRP13</i> ; <i>FOLR1</i> ; <i>MYH7</i> ; <i>FIGF</i> ; <i>NXPH3</i>	367 <i>CT2orf74</i> ; <i>PLEKHG7</i> ; <i>F5</i> ; <i>GPRIN3</i> ; <i>CAV2.3</i> ; <i>HPCD</i> ; <i>MMP7</i> ; <i>KCNQ4</i> ; <i>SNAP25</i> ; <i>KIF19</i>
	"	"	Ipsilateral isthmus epithelial cells	"	"	274 <i>EDAR</i> ; <i>LRRN4</i> ; <i>LRP2</i> ; <i>JAKMIP2</i> ; <i>SLC25A48</i> ; <i>HNFA1</i> ; <i>TF</i> ; <i>ACT</i> ; <i>CHRNA1</i> ; <i>DEGS2</i>	316 <i>MGC133804</i> ; <i>BNIP1</i> ; <i>CLEC4E</i> ; <i>LRRC18</i> ; <i>HMGCL1</i> ; <i>BCL2L14</i> ; <i>MSLN</i> ; <i>OSTN</i> ; <i>FCCB9</i> ; <i>C3H1orf189</i>
Maillo et al. (2015)	Bovine	Embryo vs oocyte (pregnant vs cyclic)	Ipsilateral isthmus epithelial cells	D3	Microarray	0	0

"	Embryos vs oocyte (pregnant with multiple embryo transfer vs cyclic)	"	"	RNAseq	123 STK32A; SLC26A3; KERA; QREPR; MCTP1; MMRN1; SLC24A4; USP44; CHRNA1; PIP	155 MUC12; RPS3A; CA5A; CCL20; SOCS3; CXCL2; VATIL; PRELP; BGN; ECSOD
Maillo et al. (2016)	Bovine	Isthmus vs ampulla (pregnant heifers)	D3 Ipsilateral ampulla and isthmus epithelial cells	Microarray	1132 GRP; LRP2; RNASE1; NETO1; SLC13A5; GPM6B; CTGF; AKR1B1; CCNB1; LYZ1	1155 GATA6; FMO2; PLEKHG7; PTGDS; UPK1B; PGA5; PPP2R2B; HPGD; KDR; MEF2C
Almiñana et al. (2012)	Porcine	Embryos vs oocytes (transferred into the same animal but different oviducts)	D2, 3, 4, 5, 6 after laparoscopic AI	Microarray	1 TICAM2 (when the embryo migrated from the oviduct to the uterus TICAM2 was downregulated in the oviduct and the uterus)	
Almiñana et al. (2014)	Porcine	Sperm (Y- vs X-chromosome spermatozoa)	24 h after laparoscopic insemination	Microarray	230 SDS; SLC23A1; SLC16A12; C6orf103; TGFB1; TCA; SLIT3; PDE1A; FAM135A; C15ORF48	271 CLSPN; RCL1; FAM82A1; PPP2R5C; DDX46; PMCHL1; HHAT; WDR51B; GPN3; OXR1
Lopez-Ubeda et al. (2015)	Porcine	Sperm (inseminated vs not inseminated)	D1-2	Microarray	17 TOR3A; RAB1B; SAA2; CCDC149; ALOX12; GSTA1; MSC; SLA-3; C3; IGHG1	9 CYP51; PTH1R; TMOD3; SIX1; C8orf74; RPP40; SLC5A5; NEURL1; DLX5
Smits et al. (2016)	Equine	Embryo vs oocyte (pregnant vs cyclic mares)	D4	RNAseq	253 C18orf63; ELAVL3; RPL7_2; BTLA; ACTA1; FITM1; FAM83A; PSORS1C2; CORIN; TMEM150B	108 B4GALNT2; EQUCABV1R919; SEC14L5; EQUCABV1R924; EQUCABV1R920; HPGD; EQUCABV1R921; FOXI3; TREM1; FIGF
"	Embryo (pregnant mares)	Ipsilateral vs contralateral AIJ cells	"	"	143 GRXCR2; PITX2; CELF3; CLDND2; NRXN2; RFX8; MCHRT; SF-2; PHOX2A; GLP1R	21 HOXD13; SNCA; TREM1; ADAM11; JPH2; CXorf36; HPGD; CCM2L; FCN3; ADRA2A
"	Oocyte (cyclic mares)	"	"	"	40 CXCL11; CLIC3; TUSC5; PZP; GPR174; TALI; SAA_1; SLFN14; C2CD4D; E2F2	37 KRT17; ADGRG3; GREM2; WSCD1; PCP4; CLDND2; EMX1; SCUBE1; DLK1; GABRA1

Table 2 Summary of data relating to oviductal proteomic changes.

Source	Species	Studied effect	Sample	Day after oestrus	Method used	Total proteins increased/top ten proteins increased	Total proteins decreased/top ten proteins decreased
Wang <i>et al.</i> (2016)	Human	Oviductal proteome	Ampullary fallopian tube	Follicular phase	Filter aided sample preparation + HPLC + triple TOF MS/MS	Proteins identified: mucins, oviduct specific glycoprotein 1, β -tubulin IV, progesterone receptor, membrane-associated progesterone receptor component 1 and 2, oestrogen-related receptor γ , inhibin α chain, β A chain, endothelial nitric oxide synthase, nitric oxide synthase-interacting protein and epidermal growth factor receptor	
Mondejar <i>et al.</i> (2012)	Bovine and porcine	To detect plasminogen in the oviduct and clarify its role during fertilization	Oviductal fluid (oviducts from slaughterhouse)	Early and late follicular phase and early and late luteal phase	Chromogenic, a chromogenic substrate for determination of plasmin and streptokinase-activated plasminogen	Protein identified: presence of plasminogen in both species which regulate the sperm entry into the oocyte	
Mondejar <i>et al.</i> (2013)	Bovine	ZP hardening and reduced polyspermy <i>in vitro</i>	Oviductal fluid (oviducts from slaughterhouse)	Ovaries with one large dominant follicle or close to ovulation	Heparin affinity chromatography + on-chip electrophoresis + HPLC-MS/MS	Proteins identified: OVGPI and members of the HSP and PDI families as potential proteins responsible for ZP hardening	
Georgiou <i>et al.</i> (2005)	Porcine	Sperm (ex vivo) incubation of sperm and oocytes in different oviducts	Oviductal fluid	18 h after coincubation	2D-PAGE + LC-ESI-MS/MS	9 Nucleophosmin; CCT8 protein; cytoskeleton-associated protein 1a; triose-phosphate isomerase; heat shock 70-kDa protein 1A; elongation factor 1- β ; heat shock 70-kDa protein 1A; protein CutA precursor; thioredoxin	10 λ chain C; osmotic stress protein 94; phosphoglycerate mutase; α enolase; 40-kDa peptidyl-prolyl cis-trans isomerase; lamin A/C; cathepsin D; osteoclast-stimulating factor; non-selenium phospholipid-hydroperoxide glutathione peroxidase; ribonuclease UK114c
	"	Oocytes (ex vivo) incubation of sperm and oocytes in different oviducts	"	"	"	3 Apolipoprotein A-I precursor; haptoglobin precursor; dimethylarginine dimethylaminohydrolyase 2	1 Transgelin 2
	"	Sperm vs oocytes (ex vivo) incubation of sperm and oocytes in different oviducts	"	"	"	6 Heat shock 70-kDa protein 1A; esterase D; lamin B1; triose-phosphate isomerase; protein carboxyl-O-methyltransferase; ribonuclease UK114	3 FAM10A5; FAM10A5; Peroxiredoxin 2
Sostaric <i>et al.</i> (2006)	Porcine	Oestrus (surface proteome of the oviductal epithelium)	Oviductal epithelium	Large follicle or recent ovulation (oviducts from slaughterhouse)	<i>In situ</i> biotinylation + isolation + identification by 2D-PAGE or 1D-PAGE MudPIT + Nano-LC-MS/MS	Proteins identified combining these two different techniques of identification: 287, among them oviduct specific glycoprotein, triosephosphate isomerase 1, heat-shock 70 kDa protein 1, elongation factor 1- β , non-selenium glutathione phospholipid hydroperoxide peroxidase, dimethylarginine dimethylaminohydrolyase 2, and peroxiredoxin 2	
Georgiou <i>et al.</i> (2007)	Porcine	Sperm	Oviductal fluid	24 h after AI	SDS-PAGE + LC-ESI-MS/MS	8 α -1 acid glycoprotein; fibrinogen A- α -chain; fibrinogen β chain precursor; hemoglobin α chain; inter- α -trypsin inhibitor; oviduct-specific glycoprotein; retinol-binding protein; Vitamin D-binding protein precursor	
	"	Oocytes	Oviductal fluid	24 h after ovulation	"	1 Ig κ light chain	

Carrasco <i>et al.</i> (2008)	Porcine	Glycosidase activity to understand sperm-oocyte binding and gamete-oviductal epithelium	Oviductal fluid (oviducts from slaughterhouse)	Early and late follicular phase and early and late luteal phase	4-methylumbelliferyl-glucopyranosides as substrates to measure the activity of 7 glycosidases	Proteins identified: β -D-galactosidase, α -D-mannosidase, and β -N-acetyl-galactosaminidase higher activity at the early follicular phase α -L-fucosidase and β -N-acetyl-glucosaminidase maximum activity at the late follicular phase
Seytanoglu <i>et al.</i> (2008)	Porcine	Follicular vs luteal phase	Oviductal fluid (oviducts from slaughterhouse)	Large dominant follicle vs corpora lutea	2D-PAGE + LC-ESI-MS/MS	27 Only 6 were characterized: gelsolin precursor; serum albumin precursor; Myo-inositol 1-phosphate synthase A1; adenosylhomocysteinase; keratin, type II cytoskeletal 8; keratin, type I cytoskeletal 19 α -2-macroglobulin; ceruloplasmin; gelsolin; transferrin; complement factor B; lactoferrin; membrane primary amine oxidase; complement C4; Ig λ chain V-I region HA; hemopexin
Soleilhavoup <i>et al.</i> (2016)	Ovine	Oestrus vs luteal phase	Oviductal fluid	D0 vs D10	SDS + NanoLC-MS/MS	12 Oviduct-specific glycoprotein; isocitrate dehydrogenase; heat shock cognate 71 kDa protein; elongation factor 1- α 1; 14-3-3 protein epsilon; retinal dehydrogenase 1; tubulin β -4B chain; fatty acid-binding protein, epidermal; malate dehydrogenase; transaldolase
Artemenko <i>et al.</i> (2015)	Lapine	Sperm (surface proteome of the oviductal epithelium) (not inseminated vs inseminated)	Oviductal epithelium	0 h vs 1 h after endoscopic intrauterine AI	<i>In situ</i> biotinylation + isolation of these proteins + SDS-PAGE + differential labelling + LC-MS/MS	12 ATP synthase, H+ transporting, mitochondrial F1 complex, β polypeptide; prohibitin; ATP synthase, H+ transporting, mitochondrial F1 complex, α subunit 1, cardiac muscle; keratin 13; keratin 8; SH3-domain kinase binding protein 1; α -hemoglobin; oviductal glycoprotein 1; tubulin, α 1b; isocitrate dehydrogenase 2 (NADP+), mitochondrial
		Sperm (surface proteome of the oviductal epithelium) (not inseminated vs inseminated)	Oviductal epithelium	1 h vs 2 h after endoscopic intrauterine AI	"	12 Protein disulfide isomerase family A, member 3; lamin A/C; histidine triad nucleotide binding protein 2; clusterin; actin γ 1; lamin B1; keratin 7; keratin 19; dipeptidyl-peptidase 4; α -hemoglobin
		"	"	0 h vs 2 h after endoscopic intrauterine AI	"	14 ATP synthase, H+ transporting, mitochondrial F1 complex, β polypeptide; aldehyde dehydrogenase 2 family (mitochondrial); keratin 13; keratin 8; SH3-domain kinase binding protein 1; tubulin, α 1b; sirtuin 5; myeloid leukemia factor 1; ATP synthase, H+ transporting, mitochondrial F1 complex, α subunit 1, cardiac muscle; oviductal glycoprotein 1
		"	"	"	"	16 ATP synthase, H+ transporting, mitochondrial F1 complex, β polypeptide; prohibitin; α -hemoglobin; ATP synthase, H+ transporting, mitochondrial F1 complex, α subunit 1, cardiac muscle; oviductal glycoprotein 1; radial spoke head 9 homolog (Chlamydomonas); dipeptidyl-peptidase 4; isocitrate dehydrogenase 2 (NADP+), mitochondrial; ribophorin 1; keratin 19
		"	"	"	"	13 Lamin B1; myeloid leukemia factor 1; aldehyde dehydrogenase 2 family (mitochondrial); hydroxacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), α subunit; phosphoglycerate dehydrogenase; peroxiredoxin 1; keratin 7; thiosulfate sulfurtransferase (rhodanese); tubulin, β class I; Tu translation elongation factor, mitochondrial

Indeed, the presence of an exosome-mediated transport of miRNAs in the bovine follicle has been already demonstrated (Sohel *et al.* 2013). Oviductosomes (exosomes and microvesicles present in the oviductal fluid) have been identified in murine and bovine species although studies are needed to determine their interaction with gametes/early embryo(s) (Al-Dossary & Martin-Deleon 2016). The expression and secretion via oviductal exosomes of PMCA4a (Ca²⁺ homeostasis) in female reproductive tissues and luminal fluids during oestrus, and uptake by sperm, suggest possible roles in sperm viability during storage in the oviduct and during capacitation and the acrosome reaction (Al-Dossary *et al.* 2013).

The study of MV and exosome-specific miRNA in the uterus has enabled the identification of pathways that could be influenced if the exosomes are taken up by trophoblast or epithelial cells during implantation, or transferred to sperm during transit through the uterus cavity (Ng *et al.* 2013). Recent evidence from Burns and coworkers (2014) indicates that MV present in uterine fluid of pregnant and cyclic ewes contain specific proteins, miRNAs and mRNAs, capable of delivering their content *in vitro*. Furthermore, in that study, the differences in molecular content by pregnancy status suggested a differential MV source (endometrial epithelia-conceptus trophoblast) (Burns *et al.* 2014). This was demonstrated recently by the same group who described extracellular vesicles emanating from both the conceptus trophoblast and uterine epithelia supporting the notion that MV in uterine fluid have a biological role in conceptus–endometrial interactions, which may be important for the establishment and maintenance of pregnancy (Burns *et al.* 2016).

Oviductal response to gametes/embryo(s)

Oviductal response to sperm

Physiologically, sperm transiently adhere to the epithelial cells lining of the caudal isthmus (sperm reservoir) and this interaction lengthens the fertile lifespan of sperm, regulates capacitation and also controls the number of sperm present at the site of fertilization to limit the opportunity for polyspermy (Miller 2015). In human and mouse oviducts, presence of sperm increased the expression of adrenomedullin (*Adm*), a transcript which stimulates ciliary motility (Li *et al.* 2010). This was also described by Fazeli and coworkers (2004) who reported that the arrival of sperm in the oviduct increased the expression of *Adm* and prostaglandin endoperoxidase synthase 2 (*Ptgs2*), involved in smooth muscle contraction/relaxation. Indeed, it seems that X- and Y-chromosome bearing spermatozoa may elicit a sex-specific transcriptomic response in the oviductal cells; 60–70% of the genes upregulated in the presence of Y-spermatozoa were related to signal transduction

and immune system, compared with the X-spermatozoa (Almiñana *et al.* 2014). Moreover, Lopez-Ubeda and coworkers (2015) recently showed that the main pathways affected by insemination were related to inflammatory response and immune system, molecular transport, protein trafficking and cell-to-cell signalling (Table 1).

In relation to the oviductal proteome, alterations have been associated with the presence of oocytes or sperm (Table 2). Georgiou and coworkers (2007) showed that although the sperm and the oocyte were able to modulate similar proteins (complement component C3, Ig κ variable region and haemoglobin β chain), they also had a specific effect on the oviductal proteome. Thus, sperm influenced the expression of 20 proteins (among them α-1 acid glycoprotein, fibrinogen A-α-chain and fibrinogen β chain precursor), whereas the oocyte influenced only one (Ig κ light chain). In addition, the protein secretion of complement C3 was increased in the presence of sperm but decreased when the oocyte was present. It is likely that some of these activated genes and secreted proteins play a role in maintaining the viability of sperm while others may be involved in preparing the oviduct for the future embryo (Holt & Fazeli 2016).

Seminal plasma is a mixture of components originating from male accessory glands which provide nutrients and metabolites, essential for sperm motility, and proteins that modify sperm membrane surface to prevent spontaneous acrosome reaction (Kuo *et al.* 2016). The role of seminal plasma in successful pregnancy establishment is controversial considering that embryos produced *in vitro* can establish pregnancy following transfer into recipients not previously exposed to seminal plasma. However, the impact of seminal plasma on embryo development has been addressed in several experiments. Studies in mice show that at conception, seminal fluid elicits molecular and cellular changes in the oviduct and endometrium that directly promote embryo development and implantation competence (Schjenken & Robertson 2015). In particular, seminal fluid initiates female immune adaptation processes required to tolerate male antigens present in seminal fluid (Robertson *et al.* 2009). In a very comprehensive study carried out by the same group in mice, it was shown that paternal seminal fluid had an impact on periconception environment through an indirect effect on preimplantation embryos via oviduct expression of embryotrophic cytokines, as well as affected the growth and health of male offspring (Bromfield *et al.* 2014). Intrauterine infusion of seminal plasma in gilts induced the expression of the cytokines, granulocyte macrophage colony-stimulating factor, interleukin-6 and monocyte chemoattractant protein-1, and the eicosanoid-synthesizing enzyme cyclo-oxygenase-2, accompanied by altered dynamics in preimplantation embryo development with an increase

in the number of embryos and their viability (O’Leary *et al.* 2004). Furthermore, cows and heifers mounted with a vasectomized bull at oestrus had an increased pregnancy rate following artificial insemination compared with those not mounted (60 vs 35.6% respectively) (Rodriguez & Rivera 1999). However, in another study, females exposed to a vasectomized bull or not exposed to a bull had similar pregnancy rates (42.2 vs 49.5% respectively) (Pfeiffer *et al.* 2012).

Oviductal response to oocyte(s)

The oviduct is typically presented with a fully mature oocyte surrounded by an expanded cumulus cell mass that depends on the oviduct to facilitate successful fertilization. According to Hunter (1988), the cilia of the infundibulum move the COC into the oviduct and the spontaneous contraction of the oviduct transport the COC to the site of fertilization. In addition, during its transit through the oviduct, the COC starts to lose the cumulus cells and thereby the ZP becomes more exposed to the OF that prepares the oocyte for fertilization and minimizes polyspermy (Coy *et al.* 2008, 2012b).

Using a videomicroscopic system, Kölle and coworkers (2009) studied the interaction of gametes/embryo(s) with the oviduct in an *ex vivo* model in cows. They observed that when a COC entered the ampulla, it immediately firmly attached to the oviductal epithelium while a degenerated COC floated in the oviductal lumen. After reaching the oviduct, the sperm formed a sperm reservoir in the isthmus bounding their heads to ciliated cells. As soon as a vital COC was in the ampulla, the sperm were hyperactivated, released and went to the ampulla helped by contractions of the oviductal smooth muscles to successfully move against the current caused by ciliary beating. Finally, after fertilization and in the presence of an embryo, the speed of transport was reduced and the vascularization of the oviduct was modified.

Oviductal response to the early embryo(s)

Some of the earliest evidence demonstrating that the oviduct may have an effect on the embryo comes from investigations carried out in mares, hamsters and rats in the 1960s. In mares, it was found that nonfertilized oocytes were retained in the oviduct (Van Niekerk & Gerneke 1966) while the fertilized embryos that produced prostaglandin E₂ were transported to the uterus (Weber *et al.* 1991). In hamsters, it was shown that embryos were transported to the uterus 1 day earlier than nonfertilized oocytes (Ortiz *et al.* 1986). In rats, when 1-cell embryos were transferred into the oviducts of recipients, 3 days later, they had reached the morula stage and remained in the oviduct; while when 4-cell embryos were transferred, 3 days later, a significant proportion of those embryos at the blastocyst stage

were located in the uterus (Ortiz *et al.* 1989). It is well known that maternal recognition of pregnancy occurs in the uterus; however, these studies showed that even in the oviduct, the embryo was able to secrete ‘a signal’ that the mother recognized and to which the oviduct responded specifically according to the presence or not of an embryo.

While more than 30 years have passed since those initial experiments, the oviductal response to the presence of embryos has not been fully elucidated. Lee and coworkers (2002) showed that the presence of embryos in the oviduct upregulated the expression of specific genes in mice like thymosin β 4, ribosomal protein L41 and nonmuscle myosin light chain 3. In pigs, it was found that most of the newly expressed genes were detected at the 4-cell stage and beyond and three of them were identified as porcine transforming growth factor- α , porcine transforming growth factor- β -binding protein II and porcine astral natriuretic factor receptor-like (Chang *et al.* 2000). In another study in pigs, Almiñana and coworkers (2012) found that the presence of embryos downregulated the expression of genes related with the immune system. Presumably, any embryo-derived signals would be magnified in litter-bearing species compared with mono-ovulatory species which may explain why data demonstrating an effect of the embryo on the oviduct *in vivo* are scarce (Maillo *et al.* 2015, Smits *et al.* 2016). In a recent study from our group, it was necessary to transfer multiple embryos (up to 50) into the oviduct of heifers to detect differences in the transcriptome, while when a single embryo was present in the oviduct (pregnant vs cyclic heifers), no differences were found, suggesting a local effect of the embryo (Maillo *et al.* 2015). More recently, Smits and coworkers (2016) reported a local influence of the embryo on the transcriptome of the equine oviduct epithelium.

In the studies mentioned above, in cattle, horses and pigs, the presence of an embryo induces subtle changes in the oviductal expression of genes related to immune function. This decrease in the reactivity of the immune system is not that surprising given the semiallogenic nature of the embryo/foetus. Without the appropriate control of the maternal immune system, the embryo will be rejected (Schjenken *et al.* 2012). However, the semiallogenic foetus that expresses paternal antigens is able to avoid immunological rejection (Billington 2003). In our study in cattle, the genes downregulated were related to: (i) the complement system, which helps to the antibodies and phagocytic cells to clear pathogens; (ii) inflammation, one of the first reactions against a foreign body; and (iii) the major histocompatibility complex, which binds the antigens and present them to T cells (Maillo *et al.* 2015). In addition, results of immunological studies shown that circulating progesterone blocks the capacity of antigen-presenting cells to present the embryo antigen to Th lymphocytes and creates maternal

immunological tolerance (Krzymowski & Stefanczyk-Krzymowska 2012) (Table 1).

***In vitro* models to study oviduct function**

Studying the oviductal environment is crucial to improving our understanding of the regulatory mechanisms controlling fertilization and embryo development (Aviles *et al.* 2015). *In vitro* systems are a valuable tool to study pathways and mechanisms, which are difficult to study *in vivo*, particularly those in the oviduct in which livestock species are challenging to access (Besenfelder *et al.* 2012). Nonetheless, while *in vitro* models provide a simple and defined context to study maternal interactions with gametes and embryos, their advantages are not limited to their simplicity. As Van Soom and coworkers (2010) pointed out, when choosing an *in vitro* model, the aim of the experiment is an important consideration. In studies of gamete and embryo interaction with the reproductive tract, the use of oviductal epithelial cells, OF and microvesicles may be considered as the most appropriate *in vitro* models to mimic the physiological conditions pertaining *in vivo*.

Fertilization models

Many groups have used *in vitro* models to study sperm-oviduct binding (Suarez 2008, Miller 2015). Two-dimensional bovine oviduct epithelial cell (BOEC) monolayers have been used to study the role of the oviduct in sperm selection, viability and release (Talevi & Gualtieri 2010). One criticism of such models is that oviduct epithelial cells lose their cilia *in vitro* and therefore interpretation of such data from a physiological perspective is challenging. Therefore, other methods have been developed to mimic as close as possible the *in vivo* conditions. The same research group demonstrated that a three-dimensional culture of the oviductal epithelium is a more reliable model for highly sophisticated and expensive studies aimed to understand the maternal crosstalk with gametes and embryos at the molecular level (Gualtieri *et al.* 2012). Jordaens and coworkers (2015) compared three different BOEC culture systems: monolayer, explants and monolayers in hanging inserts to keep the cells polarized. More recently, a promising system to mimic the *in vivo* oviduct epithelial cells niche has been developed consisting of a transwell cell culture combined with U-shape inserts that are able to create a tube-like surface, in which bovine oviductal cells can be cultured to confluence and thereafter repolarize (Ferraz *et al.* 2016).

In relation to OF, Coy and coworkers (2008) demonstrated that preincubation of pig and cow oocytes with periovarian OF from sows and heifers increased the resistance of the ZP to digestion with pronase (a parameter commonly used to measure the

block to polyspermy) and increased the incidence of monospermy after *in vitro* fertilization.

Embryo development models

Evolution of techniques using oviduct components for *in vitro* embryo culture is presented in Fig. 2. BOEC co-culture has been widely used to study early embryonic events (Ulbrich *et al.* 2010). Embryo co-culture with BOEC has been successfully used since the late 1980s in sheep (Gandolfi & Moor 1987) and cattle (Eyestone & First 1989) and later as an *in vitro* model to identify embryo-maternal signals (Rief *et al.* 2002). A recent study by Cordova and coworkers (2014) showed that embryo co-culture with BOEC during the first 4 days of embryo development accelerated the kinetics of blastocyst development and improved the expression of genes related with apoptosis and oxidative stress in the developed embryos. Schmalz-Panneau and coworkers (2014) used BOEC monolayers as *in vitro* models to demonstrate differences in their gene expression in the presence of bovine blastocysts. In this experiment, those genes upregulated by the presence of the embryos were related with antiviral and immune response (Schmalz-Panneau *et al.* 2014).

The positive effects of BOEC on embryos are attributed to embryotrophic substances, such as growth factors secreted by the cells (Tse *et al.* 2008).

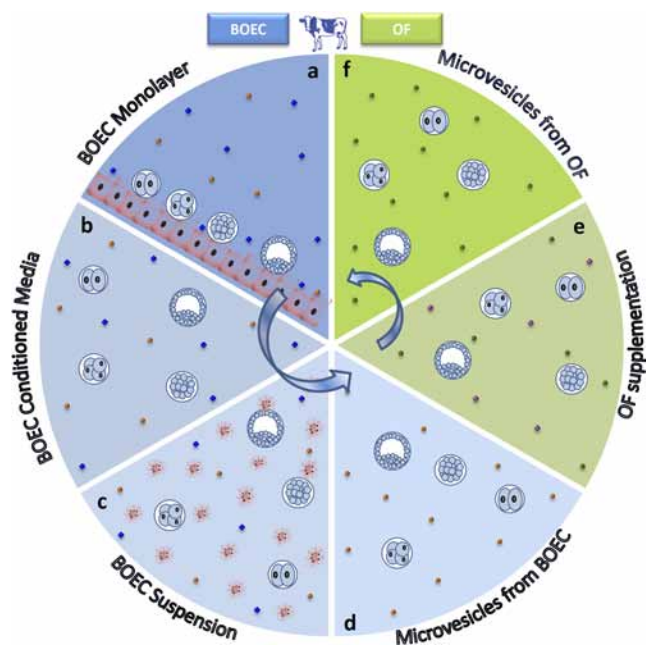


Figure 2 Evolution of techniques for *in vitro* embryo culture using oviduct components in cattle going anticlockwise. (a) Bovine oviduct epithelial cell (BOEC) monolayer (■); (b) BOEC conditioned media; (c) BOEC suspension (■); (d) microvesicles purified from BOEC conditioned media (●); (e) oviduct fluid (OF) supplementation; (f) microvesicles purified from OF (●). ◆ Embryotrophic factors released from BOEC; ◆ Proteins, ions, energy substances from OF.

However, co-culture systems have been associated with methodological complexity, lack of repeatability and biosanitary risk. Moreover, when cells are cultured in monolayers, they dedifferentiate with the concomitant loss of important morphological characteristics including reduction in cell height, loss of cilia and loss of secretory granules and bulbous protrusions (Ulbrich *et al.* 2010). An alternative may be the use of BOEC in suspension: nonproliferated BOEC clumps, which remain polarized and viable for longer time than BOEC rapidly proliferating monolayers (Xu *et al.* 1992). Recently, Yamamoto and coworkers (2014) demonstrated that suspension cells seem to mimic more faithfully *in vivo* cellular conditions and thereby would be more valuable for studying embryo–maternal interactions. Nevertheless, to avoid primary cultures, established cell lines may constitute an alternative co-culture system by providing a continuous supply of cells that are easily cultured *in vitro*, cryopreserved and screened for pathogens. We recently reported that an established BOEC line can be used successfully after freezing and thawing, avoiding the lack of reproducibility between replicates, as an *in vitro* embryo co-culture system and did not differ from BOEC in suspension in terms of embryo development (Lopera-Vasquez *et al.* 2016a).

An alternative to embryo co-culture with BOEC is the use of their conditioned media (BOEC-CM) (Eyestone & First 1989). The advantages of BOEC-CM over monolayer co-culture are that no additional cells are required for the culture and the media can be frozen, stored and used when needed (Ramos-Ibeas *et al.* 2014). This would potentially reduce the variation in embryo development often noted in monolayer culture systems. The BOEC-CM is able to support embryo development to the blastocyst stage and improve embryo quality (Lopera-Vasquez *et al.* 2016a) through secreted embryotrophic components such as OVGPI (Britton-Jones *et al.* 2004), ET-1 (Reinhart *et al.* 2003), IGF (Xia *et al.* 1996), VEGF, EGF, IGF1, TGF β 2 and IL4 (Okada *et al.* 2005) that have been properly identified.

OF has also been used during *in vitro* embryo culture in an attempt to mimic the *in vivo* environment. A short exposure of matured porcine oocytes to bovine OF for 30 min before fertilization increases the blastocyst rate and quality in terms of morphology, cell number and gene expression patterns of apoptotic and developmentally related genes (Lloyd *et al.* 2009). In bovine matured oocytes, a short incubation with bovine OF before fertilization did not affect embryo development but altered expression of gene transcripts such as *G6PD* and *SOD32* (Cebrian-Serrano *et al.* 2013). However, in a recent study, we observed that the culture of bovine zygotes with low concentrations of OF (1.25–0.62%) increased embryo development and the quality of bovine blastocysts (Lopera-Vasquez *et al.* 2015). Coy and Yanagimachi (2015) affirmed that the inclusion of reproductive fluids in the human- and

animal-assisted reproductive technologies may improve the periconceptual environment for *in vitro* derived embryos, and improve the efficiency of the current systems for *in vitro* embryo.

The role of MV as mediators of intercellular communication between their cell of origin to the recipient cell and their action in reproduction has been described above. However, the effect of these MV on *in vitro* embryo production is unknown. Saadeldin and coworkers (2015) showed that *in vitro* derived embryos secrete MV in their conditioned media. Thus, there is a need to investigate the effect of MV on early stages of embryo development *in vivo* and *in vitro*. By trying to mimic the intercellular communications between oviductal tissue and embryo *in vitro*, in a recent study, we provided evidence that MV from conditioned media of an extended culture BOEC monolayer can be isolated, morphologically characterized and successfully used for *in vitro* embryo culture, improving the quality of the produced blastocysts (Lopera-Vasquez *et al.* 2016a). Furthermore, research in progress from our group shows also that MV from bovine isthmic OF can be isolated and their supplementation in *in vitro* embryo culture has a positive effect on the expression patterns of developmental related genes (Lopera-Vasquez *et al.* 2016b). Future studies on reproductive fluids and their content will identify the molecular mechanisms behind this maternal–embryo communication that affects embryo development and quality *in vitro*.

Concluding remarks

While it is possible to fertilize oocytes and grow embryos *in vitro* in synthetic media, nonetheless, spending time in the oviduct has demonstrable positive effects on the quality of the embryo in terms of morphology, cryotolerance and ability to establish a pregnancy. Despite significant advances in our understanding of early reproductive events, there is still limited evidence for effects of the gametes or embryos on oviduct function (gene expression and protein abundance). However, when one considers the lack of evidence for an effect of the embryo on the uterus up until at least Day 15/16, the time of maternal recognition of pregnancy in cattle, it is not difficult to accept that embryo-induced changes in the oviduct, if any, are probably of limited biological significance. Given the difficulty of study the oviduct–gametes–embryos(s) interaction *in vivo*, the challenge is to continue to develop and optimize systems of *in vitro* culture to maximize embryo quality.

Declaration of interest

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

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