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The ovarian follicle of ruminants: the path from conceptus to adult

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Abstract. This review resulted from an international workshop and presents a consensus view of critical advances over the past decade in our understanding of follicle function in ruminants. The major concepts covered include: (1) the value of major genes; (2) the dynamics of fetal ovarian development and its sensitivity to nutritional and environmental influences; (3) the concept of an ovarian follicle reserve, aligned with the rise of anti-Müllerian hormone as a controller of ovarian processes; (4) renewed recognition of the diverse and important roles of theca cells; (5) the importance of follicular fluid as a microenvironment that determines oocyte quality; (6) the 'adipokine' as a key concept linking metabolic inputs with follicle development; and (7) the contribution of follicle development to the success of conception. These concepts are important because, in sheep and cattle, ovulation rate is tightly regulated and, as the primary determinant of litter size, it is a major component of reproductive efficiency and therefore productivity. Nowadays, reproductive efficiency is also a target for improving the 'methane efficiency' of livestock enterprises, increasing the need to understand the processes of ovarian development and folliculogenesis, while avoiding detrimental trade-offs as greater performance is sought.

Keywords: fetal programming, genetics, granulosa cell, nutrition, oocyte, theca cell.

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Dedication: David T. Armstrong

A theme of this series of workshops, and thus the reviews, is an appreciation of the intricate interactions among cell types within the ovary, as well as between the ovary and other tissues.

The fine-tuning of follicle development by adipose tissue has become accepted, and there is a growing recognition that, within the follicle wall, the well-established interactions between theca and granulosa cells are accompanied by functional relationships

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with other follicular cells, including endothelial and immune system cells. The ‘two cell theory’ of follicle development has thus expanded into a ‘multicell hypothesis’ since the original ‘two gonadotrophin, two cell theory’ was pioneered by Dr David T. Armstrong in the 1960s. In his publications in *Nature* (Armstrong 1967) and in *Endocrinology* (Armstrong and Papkoff 1976), he identified granulosa and theca cells as targets of FSH and LH, respectively. He followed this up in the 1970s with numerous studies demonstrating that both gonadotrophins and both cell types were absolutely required for follicular oestradiol secretion (International Embryo Technology Society 2018). This body of work essentially defined our understanding of follicle development. Armstrong was so excited about the two cell theory that he was known to pull over to the side of the road and stop the car to explain it to students! Remarkably, this was not his only groundbreaking contribution: in the 1950s, while at Cornell University with William Hansel, he was the first to describe the luteolytic action of oxytocin (Armstrong and Hansel 1959) and, later, in the 1970s, his laboratory discovered the role that prostaglandins play in ovulation (Armstrong and Grinwich 1972). These discoveries, and his purification of FSH, paved the way to many practical applications in assisted reproduction, including oestrus synchronisation and superovulation in farm animals.

Although a scientific giant, Armstrong was quite unpretentious and insisted that everyone call him ‘Dave’. Dave’s home base was in his native Canada at the University of Western Ontario (now named Western University) and, in the late 1970s, he took up a post as visiting professor at the University of Adelaide, Australia. His main hobby was sailing, either on Lake Huron, Ontario, or around Hindmarsh Island, South Australia. He was well known to spend northern summers in Canada and northern winters in Australia, the ultimate snowbird practising a ‘two country, two summer’ theory.

Dave’s illustrious career led him to the Presidency of the Society for the Study of Reproduction (SSR) and of the International Embryo Transfer Society (now the International Embryo Technology Society), and to numerous awards and recognitions, including the SSR’s Carl Hartman Award and Fellowship of the Royal Society of Canada. Although Dave retired in 2012 and passed away in 2016, the mark that he left on our field lives on.

Introduction

In ruminants, the number of oocytes released at ovulation (ovulation rate) is tightly regulated, seldom exceeds three and is the outcome of complex processes of follicle development and differentiation. These processes are of major interest in farm animals because they determine litter size, a major component of reproductive efficiency and thus productivity. Litter size has always been important but, these days, it has also become a focus in our plans to reduce the environmental impact of ruminant industries because fecundity and fertility are determinants of the greenhouse gas emissions efficiency of a livestock enterprise.

For investigating folliculogenesis, the ewe has proven to be an excellent experimental model because its ovulation rate is affected by the classical gene \times environment interaction. Environmental factors, especially photoperiod and nutrition, have been researched for over 100 years but, in recent decades, our

understanding of the genetic component of the phenotype has been reinvigorated by the discoveries of critical major genes. The roles of these genes have transformed our understanding of the molecular and cellular processes that control follicle development and function. The cow has also been useful because the processes leading to ovulation in this species are even more tightly controlled, so multiple ovulations are rare. In other words, the differences between the ovine and bovine models have been informative, if perhaps a little frustrating for those interested in reproductive efficiency in cattle. Moreover, as well as being a determinant of litter size, the processes controlling follicle development and differentiation are critical for an animal’s ability to conceive. Considering these issues, it is no surprise that improving our understanding of the process of folliculogenesis is still seen as essential for all ruminant-based industries worldwide.

Progress in this field over the past 30 years has been marked by international workshops that produced a series of consensus views of the state of knowledge. The first was held in 1991 in Australia and focused mostly on the mechanisms in sheep that caused variation in ovulation rate with breed and with environmental or experimental conditions (Scaramuzzi *et al.* 1993). The second workshop, held in 2008 in France, updated the scientific consensus and extended the scope to include bovine folliculogenesis. Among the major leaps since the 1993 publication was a revolution in our understanding of the role of the oocyte: it had been transformed from passive passenger into an active controller of its own destiny. We also started to understand the development of ovarian follicles in the fetus, as well as how metabolic factors directly affect the processes leading to ovulation (Scaramuzzi *et al.* 2011).

The third workshop, the foundation of the present paper, was held in 2020 in New Zealand and was timely, in terms of both scientific advances and global industry context. With respect to the science, another wave of technical advances has led to profound improvements in our understanding of the cellular and molecular processes that underpin follicle development, in particular: (1) the dynamics of development in the fetal ovary (represented as a black box in the 1993 paper!), with inevitable links to environmental influences and the concept of ‘programming’; (2) new perspectives of the value of the major genes; (3) the concept of the ‘ovarian follicle reserve’, aligned with the rise of anti-Müllerian hormone (AMH) as a player in ovarian function and in diagnosis of dysfunction; (4) the resurrection of the theca and its various cell types as important participants in follicular processes; (5) recognition of normal antral fluid as a regulatory environment for the oocyte; and (6) the arrival of the ‘adipokinome’ as a major metabolic input. The 2020 workshop covered these issues and the consensus of those discussions forms the body of this review.

The period 2010–20 has also seen a marked upheaval in societal attitudes to ruminant production systems. Specifically, issues such as climate change, pollution, animal welfare, food safety and the role of animal products in the human diet came to the fore. The view that ruminant industries cause rather than solve problems was predominant in 2010, but it subsequently became clear that we needed to consider all options to ensure human food security. To this conversation, ruminants bring their ‘superpower’: they can digest grass to produce human food (Eisler *et al.* 2014). Nevertheless, considering this contextual change, we need to develop new visions and goals for our

research programs in reproduction. For example, a deeper understanding of metabolic inputs into folliculogenesis is fundamental for 'clean, green and ethical' management systems, and ovulation rate now needs to be considered as an avenue for improving the 'methane efficiency' of cattle, sheep and goat enterprises (Martin *et al.* 2009).

Over the three decades between the first and present reviews, there has been a changing of the guard – all except one of the original workshop participants has left the field, although Rex Scaramuzzi instigated the 2020 workshop and contributed to planning the program. The authors of the present review take pleasure in acknowledging the contributions of our predecessors and were pleased to retain a similar scope for the workshop. In particular, the mechanisms at various levels of analysis, from molecular and cellular to whole organism, were considered as we readdressed the functional model of folliculogenesis and the control of ovulation rate, and suggested primary foci for future research.

This paper therefore highlights key advances in our understanding of ovarian function over the past decade. Discoveries of new genes controlling ovulation rate continue to provide new insights into factors controlling follicle development and remain a driver of our changing perspectives in the field. Integrating findings from multiple perspectives has highlighted a potential central role of AMH in ovarian follicle development, and thereby fertility. This review embraces the entire process, from the very beginning (i.e. the formation of primordial follicles during fetal ovary development) through to the mechanisms that underpin the growth and selection of a healthy ovulatory follicle(s) during adult life.

Genetic determination of ovarian function

Studies on the genetic determination of ovulation rate and litter size in sheep have led to very important discoveries about the control of folliculogenesis. For reference, the broad overview of the process from Scaramuzzi *et al.* (2011) is presented in Fig. 1. In addition, understanding of the concept of ovarian follicular waves and hierarchical follicle development has also added to our understanding of the dynamics of follicle development and its role in the control of reproductive cycles. However, these topics are outside of the scope of this review and so, for further information on them, readers are directed to McNatty *et al.* (2010), Bartlewski *et al.* (2011), Forde *et al.* (2011) and García-Guerra *et al.* (2018c). Although prolificacy is a lowly heritable trait ($h^2 = 0.1\text{--}0.2$; Van Vleck *et al.* 1991; Árnason and Jónmundsson 2008; Borg *et al.* 2009), and determined mainly by polygenic processes, numerous major mutations play critical roles. In cattle, genetic mapping studies of animals selected for multiple ovulation or twinning have revealed quantitative trait loci on chromosome 5 (Allan *et al.* 2009) and identified the insulin-like growth factor (IGF) pathway as a potential regulator of multiple ovulations (Echternkamp *et al.* 1990, 2004; Aad *et al.* 2013). Further information on the role of the IGF pathway in follicle development can be found in reviews by Webb and Campbell (2007) and Shimizu (2016). In sheep, there has been particular interest in three major fecundity (*Fec*) genes, namely bone morphogenetic protein receptor type 1B (*BMPR1B*), bone morphogenetic protein

15 (*BMP15*) and growth differentiation factor 9 (*GDF9*), that control the bone morphogenetic protein (BMP) signalling pathway and have major effects on ovulation rate (for a review, see Fabre *et al.* 2006; Juengel *et al.* 2013).

Recently, a new major mutation, *FecL*, has been added to the list of those associated with high ovulation rate and hyperprolificacy. Most importantly, as a mutation of beta-1,4-*N*-acetyl-galactosaminyltransferase 2 (*B4GALNT2*), it has provoked new questions about the control of ovarian function because it brings into play a pathway that is not related *a priori* to the BMP signalling system (Drouilhet *et al.* 2013). *B4GALNT2* encodes a β -1,4-*N*-acetyl-galactosaminyltransferase, which catalyses a terminal step of glycosylation by adding an *N*-acetylgalactosamine residue to a subterminal galactose residue of glycosylated target proteins (Montiel *et al.* 2003). In Lacaune sheep, increased ovulation rate is associated with the ectopic over-expression of *B4GALNT2* in granulosa cells (where it is not normally expressed), but only in follicles from the secondary to preovulatory stages. The search for intraovarian targets of *B4GALNT2* activity has led to elements of the extracellular matrix and, more interestingly, to the two subunits of inhibin A, INHA and INHBA (Drouilhet *et al.* 2013). Indeed, differential subunit association, leading to either inhibin A (INHA/INHBA) or activin A (INHBA/INHBA), depends on glycosylation events (Antenos *et al.* 2007) and it has long been known that immunisation against inhibin can increase ovulation rate and prolificacy in ruminants (O'Shea *et al.* 1994).

In *FecL* carrier ewes, the high ovulation rate is associated with an increase in the number of gonadotrophin-dependent follicles, as well as a reduction in the size of the preovulatory follicles (Drouilhet *et al.* 2010). These relationships are consistently observed with major genes that control ovulation rate in sheep and cattle (Fabre *et al.* 2006; García-Guerra *et al.* 2018a). However, compared with non-carrier ewes, *FecL* carriers have greater circulating concentrations of oestradiol during the follicular phase, leading to an increase in LH pulse frequency followed by an earlier preovulatory LH surge. In the luteal phase, circulating progesterone concentrations are also increased, probably due to the increased number of corpora lutea. More importantly, inhibin A concentrations are consistently decreased, possibly due to atypical glycosylation by *B4GALNT2*. Only the circulating concentrations of FSH and activin A are unaffected by *FecL* (Drouilhet *et al.* 2010; C. Mansanet and S. Fabre, unpubl. data). Apart from FSH, this endocrine scenario contrasts strongly with those for mutations in *BMP15*, *GDF9* or *BMPR1B*, in which the concentrations of LH, inhibin, oestradiol or progesterone did not differ from those in wild types, as also observed in the *Trio* model in cattle (Juengel *et al.* 2013; García-Guerra *et al.* 2018b).

Conversely, one notable endocrine observation could reconcile, at least in part, the prolific sheep models: circulating AMH concentrations are low in *B4GALNT2/FecL* ewes, as well as in *BMPR1B/FecB*, *GDF9/FecG* and *BMP15/FecX^R* ewes (Lahoz *et al.* 2014; Estienne *et al.* 2015; Chantepie *et al.* 2018; Pinto *et al.* 2018). Circulating AMH may not be affected by other *BMP15* mutations (*FecX^L* and *FecX^{Gr}*), but ovarian AMH signalling is altered by a decrease in the expression of the AMH receptor type 2 (*AMHR2*) gene, probably through direct

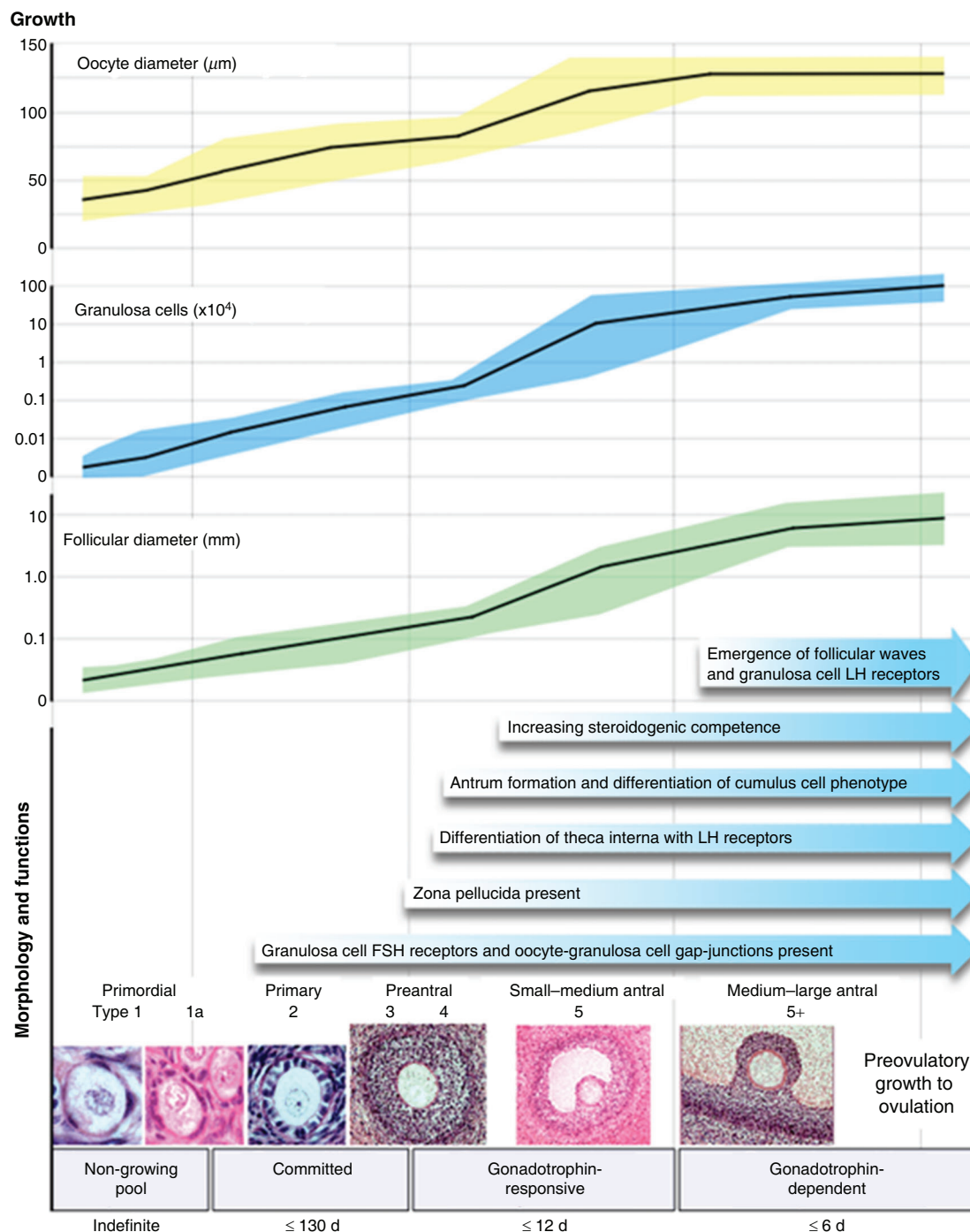


Fig. 1. Summary of folliculogenesis in the ewe, reproduced with permission from Scaramuzzi *et al.* (2011). The upper panel shows the mean (central line) and range (shaded band) timelines of growth of the follicle and oocyte, and the number of granulosa cells, from primordial to ovulatory stages. The lower panel shows the progressive emergence of several critical functional and morphological characteristics of follicles as they develop. The stages of development have been defined by two different systems, one based on morphology and the other on the functional characteristics of follicles.

action of BMP molecules on *AMH* and *AMHR2* gene expression in granulosa cells (Estienne *et al.* 2015; Pierre *et al.* 2016). These findings raise the intriguing possibility that AMH plays a role in

the control of ovulation rate and prolificacy, at least in sheep. Notably, this relationship is not obvious in prolific cattle (García-Guerra *et al.* 2017).

Use of major genes to improve reproductive efficiency

Over the past 40 years, sheep and cattle models of major genes for prolificacy have been crucial in deciphering mechanisms that control ovarian function. However, with respect to reproductive efficiency, major genes for prolificacy can have a much broader impact than simply increasing litter size because, compared with non-carriers, female carriers of prolific mutations (when not homozygous sterile) show several advantages in assisted reproductive technologies. For instance, *FecL*^L carrier Lacaune ewes exhibit precocious puberty, a higher fertility rate to AI and increased responsiveness to equine chorionic gonadotrophin (eCG; Martin *et al.* 2014; L. Chantepie and S. Fabre, unpubl. data, 2021). In *FecB*^B carrier ewes from the short-tailed Han breed, lambing rate after AI was also improved (Qi *et al.* 2020). In *FecX*^R carrier Rasa Aragonesa sheep, responsiveness to eCG was increased, as was the recovery of oocytes competent for *in vitro* development and the rate of embryo survival after transfer (Lahoz *et al.* 2011, 2013). For double-heterozygous mutant *FecG*^V/*FecB*^B ewes during the breeding season, there is also an increase in responsiveness to eCG but, more interestingly, eCG is not needed during seasonal anoestrus when these ewes continue to produce twin ovulations naturally (Moraes and Souza 2017). Together, these observations strongly suggest that the major genes for prolificacy could also deliver a reduction in the use of hormones in livestock herd management.

Rise of AMH

The major genes have revealed a variety of critical processes in follicle development and function, including the role of AMH. In fact, for sheep and cattle, the importance of AMH produced by granulosa cells was pioneered in the 1980s (Vigier *et al.* 1984), but was then largely ignored for 20 years until it gained recognition as an endocrine marker of growing follicles in the human in the context of assisted reproductive technologies. Completing the cycle, we now have a greatly renewed interest for ruminant reproduction, where AMH has now been recognised for its role in activating primordial follicles and limiting the growth of activated follicles (Campbell *et al.* 2012; Yang *et al.* 2017). This perspective was accompanied by the development of assays allowing accurate measurement of AMH in blood and follicular fluid, and thus the precise delineation of the spatiotemporal expression, regulation and production of AMH within the ovary.

Regulation of AMH production by granulosa cells

In the ruminant ovary, expression of the *AMH* gene is restricted to granulosa cells, where the rate of expression increases with the transition of the follicle from primary through to early antral stages, before declining through to the preovulatory stage (for a review, see Monniaux *et al.* 2012). In healthy antral follicles in cattle and sheep, the *AMH* gene is mostly expressed in the cumulus cells and the outer layers of granulosa cells, close to the theca. Moreover, *AMH* gene expression in the granulosa cells is accompanied by accumulation of AMH protein in follicular fluid to the point where it becomes easily measurable by using immunoassays. In cattle, sheep and goats, follicular fluid AMH concentrations are greatest in small antral follicles

(~300–500 ng mL⁻¹) and then decrease markedly as follicles grow to the preovulatory stage (Monniaux *et al.* 2012). In atretic follicles, *AMH* expression is greatly diminished, except for the cumulus cells surrounding the oocyte. These observations suggest that, generally, the oocyte and the theca both produce paracrine factors that support *AMH* expression in growing follicles.

The pattern of *AMH* expression (i.e. switching on in primary follicles, maximum production in granulosa cells of preantral and small antral follicles, switching off during atresia or in preovulatory follicles (except cumulus cells)), raises important questions about AMH regulation during the process of folliculogenesis. As indicated above, AMH activity is probably regulated by signals from both the oocyte and the theca cells, and BMPs are likely candidates (Fig. 2). In particular, oocyte-derived BMP15 upregulates *AMH* gene expression in ruminants (Pierre *et al.* 2016; Poole *et al.* 2016; Zhao *et al.* 2018) and the temporal sequence of *BMP15* expression in oocytes parallels that of *AMH* expression, beginning during primary follicle development and increasing until the antral stages (Bonnet *et al.* 2011). Moreover, BMP2, BMP4 and BMP6, produced by granulosa or theca cells, stimulate *AMH* expression and could even sustain AMH production during follicle development in ruminants (Rico *et al.* 2011; Estienne *et al.* 2015; Poole *et al.* 2016). By contrast, activin A and transforming growth factor- β 1 (TGFB1), members of the TGFB family, play no role (Monniaux *et al.* 2012).

In the developing antral follicle, steroid hormones and FSH are also thought to affect *AMH* expression in granulosa cells, although there are differences among species: (1) androgens inhibit *AMH* expression in cattle and humans, but stimulate it in mouse granulosa cells (Crisosto *et al.* 2009); (2) oestradiol inhibits *AMH* expression in granulosa cells of humans, but not cattle (Crisosto *et al.* 2009; Grynberg *et al.* 2012); and (3) in cattle, FSH regulates *AMH* gene expression in a bimodal, dose-dependent manner, being stimulatory at low concentrations and inhibitory at high concentrations (Scheetz *et al.* 2012; Umer *et al.* 2019), yet has no effect in ovine granulosa cells (Monniaux *et al.* 2012). This complexity could be due to inconsistent methodologies and incomplete control of experimental variables, so it will be difficult to develop a universal theory until such issues are resolved.

AMH in the peripheral circulation

Circulating AMH concentrations have been measured in cattle, sheep and goats, and vary greatly among individuals within species (Ireland *et al.* 2008; Rico *et al.* 2009; Monniaux *et al.* 2011; Lahoz *et al.* 2014; Torres-Rovira *et al.* 2014; Gobikrushanth *et al.* 2018). Conversely, within individuals, circulating AMH concentrations are stable over months or even years (Monniaux *et al.* 2011; Evans *et al.* 2012) because the population of growing small antral follicles, where the greatest amounts of AMH are produced, is itself quite stable (Scaramuzzi *et al.* 2011). A degree of uncertainty has been introduced by the recent discovery that, in cattle, AMH is synthesised and secreted by epithelial cells in the oviduct and endometrium (Ferdousy *et al.* 2020), suggesting that we can expect changes in plasma

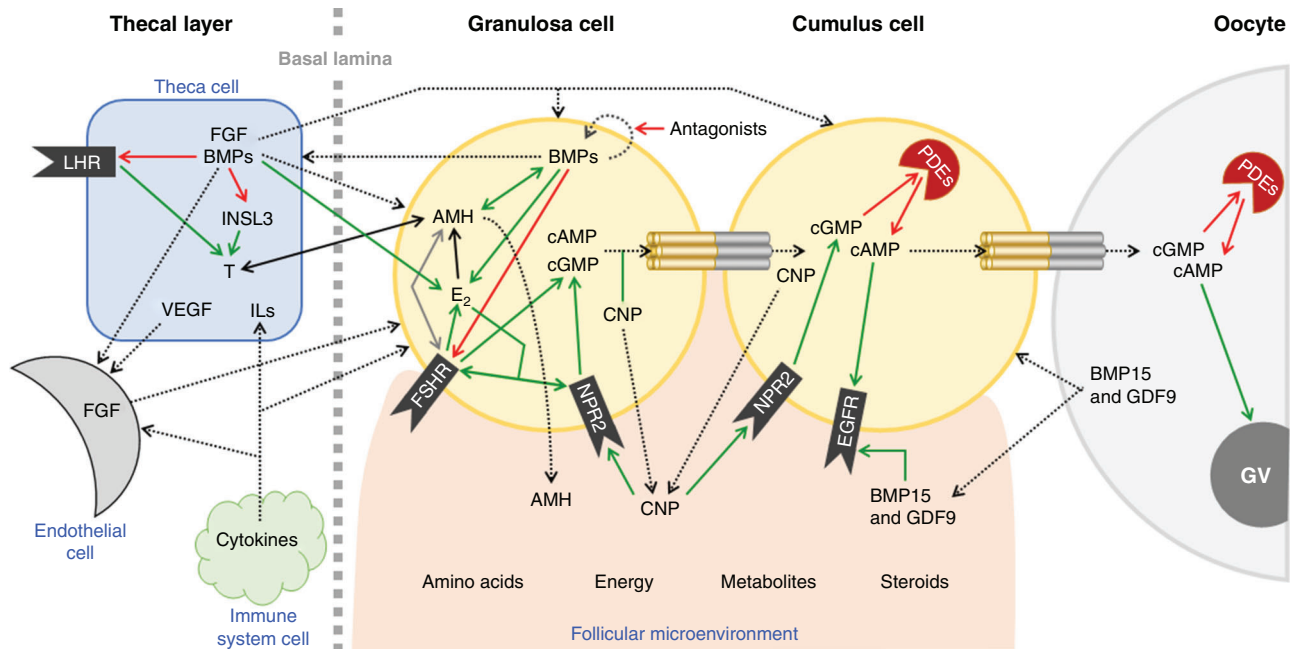


Fig. 2. The microcosm of the antral ovarian follicle comprises an oocyte hosting the germinal vesicle (GV) surrounded by various layers of follicular cells. The cumulus cells have direct contact with the oocyte and, along with the granulosa cells, bathe in a follicular microenvironment that is rich in locally produced hormones and growth factors, as well as extrafollicular signalling molecules (e.g. energy metabolites from the ‘adipokinome’). The basal lamina, comprising various extracellular matrix elements, separates granulosa cells from the thecal layer that contains steroidogenic cells, capillary endothelial cells and immune cells. Multidirectional communications between the cellular compartments are represented by arrows with information, when available, on the positive (green) or negative (red) effect of the main molecules (metabolites, ligands, hormones, receptors) highlighted in this review. Solid black lines indicate functional interactions between molecules where the literature is inconsistent. Broken lines represent either the transport of a molecule between the cellular compartments or the action of a molecule on differentiation, proliferation or apoptosis of the target cells. The intrafollicular communications include bone morphogenetic protein (BMP) 15/growth differentiation factor (GDF) 9 signalling from the oocyte to cumulus cells, and C-type natriuretic peptide (CNP) signalling from granulosa to cumulus cells. Granulosa cells also send growth factors, such as BMPs, to the theca layer, and various types of cell within the theca layer secrete growth factors, such as fibroblast growth factors (FGFs) and cytokines, that, in turn, affect the steroidogenic cells (theca and granulosa). AA, amino-acid; AMH, anti-Müllerian hormone; Antagonists, chordin, follistatin, gremlin and noggin; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; E₂, oestradiol; EGFR, epidermal growth factor receptor; FSHR, FSH receptor; GDF, growth differentiation factor; IL, interleukin; INSL3, insulin-like factor 3; LHR, LH receptor; NPR2, natriuretic peptide receptor 2; PDE, phosphodiesterase; T, testosterone; VEGF, vascular endothelial growth factor.

AMH concentrations as animals progress through major stages of reproductive life, such as puberty.

In heifers, circulating AMH is almost undetectable at birth, increases markedly by 2–3 months of age, declines but remains quite high until 5–6 months of age, then declines markedly to a stable baseline at puberty (8–9 months of age for dairy cattle; 12 months for beef cattle; Monniaux *et al.* 2012; Mossa *et al.* 2017). Similar dynamics have been observed in ewe lambs, with peak concentrations also at age 2–3 months (Lahoz *et al.* 2014; Torres-Rovira *et al.* 2014). Interestingly, in both species, the prepubertal peak is preceded by a rise in plasma FSH concentration (Torres-Rovira *et al.* 2014; El-Sheikh Ali *et al.* 2017) that probably drives the postnatal increase in the number of antral follicles (Rawlings *et al.* 2003) and thus the rise in AMH concentrations. Thereafter, FSH concentrations fall to their lowest levels as AMH concentrations reach peak values. As puberty approaches, these changes are reversed, with AMH concentrations decreasing to reach adult values and FSH concentrations rising (Monniaux *et al.* 2012; El-Sheikh Ali *et al.* 2017).

Plasma AMH concentration varies little in cattle during the oestrous cycle or between successive cycles. In heifers, it

remains quite static around ovulation (Ireland *et al.* 2008). In adult cows, particularly those with high average values, it does vary slightly within the oestrous cycle, with maximum values at the time of oestrus and minimum values around Days 7–8 after ovulation (Monniaux *et al.* 2012; Gobikrushanth *et al.* 2018). The same patterns are seen in natural and synchronised oestrous cycles in dairy cows (Pfeiffer *et al.* 2014) unless superovulation is induced by exogenous FSH, a treatment that increases plasma AMH concentrations at oestrus but, curiously, decreases it in goats (Rico *et al.* 2009; Monniaux *et al.* 2011). There are also significant changes in circulating AMH concentrations during gestation; in cows, for example, levels increase during the two first trimesters and then decline until calving, when basal postpartum concentrations are reached (Monniaux *et al.* 2012).

Development of the ovary and establishment of the ovarian reserve

Arguably, the establishment of the ovarian reserve is the key outcome of ovarian development in the fetus. Here, we briefly describe the current dogma on the development of the ovary,

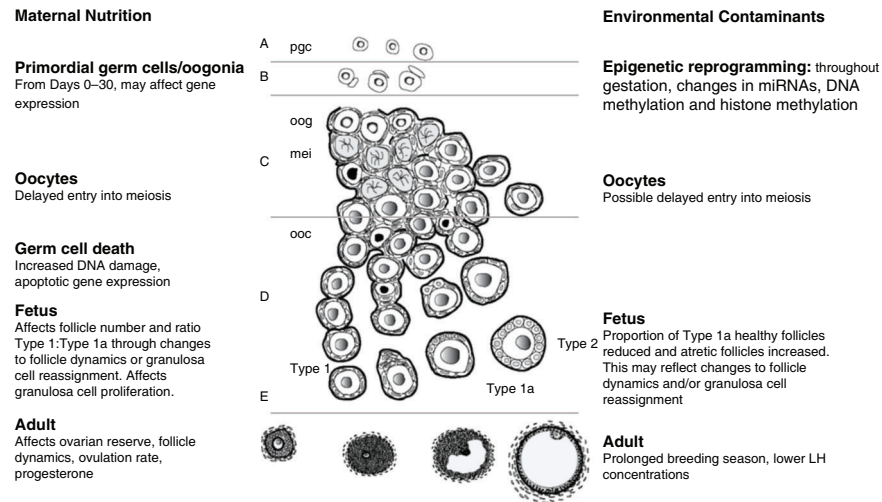


Fig. 3. Fetal ovary development. The basic pattern is common to most mammals and comprises five key developmental stages (A–E), all potentially affected by maternal nutrition (left) and environmental stressors (right). In Stage A, primordial germ cells (pgc) migrate along the hindgut to the developing gonad. In Stage B, following arrival at the gonad, germ cells make contact with somatic cells that are later destined to become granulosa cells; throughout Stages A and B, germ cells proliferate. In Stage C, there is ovigerous cord development, with clusters of germ cells (oogonia (oog)) and pregranulosa cells becoming enclosed within a basement membrane; the cords remain open to the surface epithelium, but isolate the germ cells/pregranulosa cells from the somatic cells of the ovary. Within the cords, proliferation slows markedly; at this time, there is further ‘recruitment’ of pregranulosa cells, probably from cells derived from the ovarian surface epithelium. Germ cells undergo the first stage of meiosis (mei), ultimately being arrested in prophase of meiosis I. At the same time, some germ cells die, predominantly but not exclusively by apoptosis, and, as they do so, the pregranulosa cells associated with them remain viable and are ‘reassigned’ to adjacent healthy germ cells. In Stage D, dissolution of the ovigerous cords results in the emergence of isolated, fully formed follicles with encapsulated oocytes (ooc) that vary markedly in their appearance, depending largely on the number of granulosa cells (and thus ‘reassigned’ granulosa cells). In some instances, newly formed follicles can appear with Type 1a morphology (multiple layers of cells on some aspects and a mixture of cuboidal and flattened granulosa cells). In Stage E, there is initiation of follicle growth that, in ruminants, begins during fetal life; by birth, relatively large antral follicles can be present, and the number and size of follicles can also vary markedly from year to year.

emphasising processes that are susceptible to disruption by environmental factors with potential long-term consequences on postnatal fertility (Fig. 3). There have been numerous studies, and the results have varied markedly, probably because they differed in the levels and windows of exposure, the species studied and the methodologies used. Moreover, both *Lea et al. (2016)* and *Smith et al. (2019b)* have highlighted that, during the period of fetal development, changes in exposure to environmental contaminants or nutritional treatments may perturb development more potently than long periods of consistent exposure. It appears that, given time to adapt, compensatory mechanisms are activated to allow development to cope with at least some level of environmental challenge.

Maternal nutrition

Effects of maternal nutrition during the periconception period on fetal ovarian development are associated with changes in oocyte health and the survival and growth of early embryos, potentially mediated by epigenetic alterations to gene expression (*Sinclair et al. 2016*). The effects of maternal nutrition during early gestation in sheep had been clearly demonstrated by the study of

Rae et al. (2001), who underfed ewes during the first 30 days of gestation and observed changes in follicle populations in the fetal ovary on Day 100 of gestation. These outcomes were known to be associated with a delayed germ cell meiosis (*Borwick et al. 1997*). Importantly, the period of germ cell meiosis overlaps the periods of germ cell mitosis and germ cell death. Germ cell death is particularly significant because, in most mammalian species, 80–90% of germ cells are lost during a brief window (Days 75–90 of gestation in sheep; Days 130–170 of gestation in cattle). Therefore, delayed entry into meiosis alters the dynamics of germ cell death and potentially reduces reproductive performance in adult animals (*Borwick et al. 1997*).

The loss of germ cells is often attributed to apoptosis, but non-apoptotic pathways have long been recognised (*Wartenberg et al. 2001; McClellan et al. 2003*). Autophagy plays a role (*Zhang et al. 2012; Smith et al. 2019a*) but, before follicle formation, autophagy proteins are thought to be more important for germ cell survival, with their role in germ cell death only becoming dominant after follicle formation. During this particularly active period, the classical gradient of germ cell development has been observed in most species, with the least

developed cells (oogonia) at the ovarian periphery and the more developed (oocytes and subsequently follicles) located in the inner regions of the ovarian cortex. At a simplistic level, the three developmental processes (mitosis, meiosis, cell death) program the ovarian reserve, and several studies implicate them in environment-induced changes in ovary development (Lea *et al.* 2006; Smith *et al.* 2014).

Germ cell meiosis is known to be susceptible to environmental disruptors such as nutrition and infection. Murdoch *et al.* (2003) proposed that germ cells entering meiosis are susceptible to oxidative DNA damage, with undernutrition leading up to and during meiosis being critically important. Recent gene expression studies by Smith *et al.* (2019a) have expanded on this concept and suggest that the damage may be caused by an increase in the production of nitric oxide by the germ cells.

The effects of restricted nutrition on the size of the ovarian reserve are not limited to germ cell death. As germ cells die, the associated pregranulosa cells appear to remain healthy and are subsequently redistributed among the remaining germ cells, leading to the formation of follicles with a lopsided appearance, often containing multiple granulosa cell layers on one side (Sawyer *et al.* 2002). This 'granulosa cell reassignment hypothesis' suggests that environmental challenges affecting germ cell proliferation, cell death and meiosis affect the number of germ cells that are available to form follicles, in turn dictating the number of granulosa cells associated with each newly formed primordial follicle. Further, this outcome raises the possibility that, in late-fetal or neonatal animals, an altered ratio of Type 1 to Type 1a follicles, often interpreted as a change in early follicle dynamics, actually reflects variation in granulosa cell reassignment resulting from differences in the numbers of germ cells present in the fetal ovary when follicles are formed. Thus, in addition to influencing the size of the ovarian reserve, environmental challenges have the potential to affect the structure and therefore the function of the follicles in the reserve, including follicle dynamics and granulosa cell expression of proliferation and apoptosis genes (Lea *et al.* 2006).

Environmental contaminants

In addition to the effects of nutrition on fetal ovarian development, our understanding of the effects of chemical contaminants on fetal ovaries, particularly on primordial germ cells, has increased greatly over the past decade. We have seen the emergence of an ovine model for exploring exposure to a mixture of chemicals during pregnancy, with relevance to human real-life exposure. The model is based on the common global agricultural practice of grazing pregnant ewes on pastures that have been treated with processed human sewage sludge (biosolids) as a fertiliser (Sharma *et al.* 2017). The biosolids and the treated soil contain a variety of types of chemicals from a variety of sources, including plasticizers (phthalates, bisphenol A (BPA)), industrial surfactants and coolants (polychlorinated biphenyls (PCBs)), flame retardants (polybrominated diphenyl ethers), combustion products (polyaromatic hydrocarbons), pesticides and various pharmaceuticals (Rhind *et al.* 2002; Rhind *et al.* 2013). Notably, our understanding of such exposures is complicated by additive, synergistic or antagonistic interactions among the chemicals, reflecting the role of the

fundamentally synergistic interaction between oestrogen and progesterone in negative feedback in the ewe (Martin *et al.* 1983). In addition, both the contaminants and their breakdown products may exhibit androgenic, anti-androgenic and/or oestrogenic activities.

Worryingly, many of the chemicals listed above have been detected in both maternal and fetal tissues collected from mid- and late-gestation pregnant ewes (Rhind *et al.* 2005, 2009, 2010), and many of the pollutants exhibit endocrine-disrupting activity, leading to concerns about their effects on reproductive development in the fetal and prepubertal lamb.

Ovary development in fetuses, in both mid- and late gestation, that have been exposed *in utero* to biosolids (via the ewe) is perturbed compared with control non-exposed fetuses (ewes grazed on pastures treated with inorganic fertiliser), and there is a striking reduction in the number of healthy early stage Type 1a transitional follicles (Fowler *et al.* 2008; Bellingham *et al.* 2013; Lea *et al.* 2016). This observation is consistent with that of Fowler *et al.* (2008) who reported that exposure to biosolids from mating to Day 110 reduced follicle density. Bellingham *et al.* (2013) compared two periods of exposure, the first from preconception to Day 110 of gestation and the second from mating through to Day 110 of gestation, and included additional ewe cohorts that were switched between treated and control pastures at mating. Intriguingly, ewes that were transferred from treated to control pastures had fewer Type 1a follicles than ewes exposed from before mating through to the end of gestation. Moreover, ovarian proteomics revealed that more protein changes were induced in ewes switched from control to treated pastures at mating than in the other exposure groups (Bellingham *et al.* 2013). Again, consistent, long-term exposure appears to activate compensatory mechanisms, whereas a change in exposure seems to be more potent in perturbing development.

When examining the effects of exposure of the fetus via the mother consuming the chemical contaminants contained in biosolids, Lea *et al.* (2016) compared the effects of a period of continuous exposure from mating to exposure limited to 80-day periods during either early, mid- or late gestation. In all exposure groups, regardless of the timing or duration of exposure, there was a reduced percentage of healthy Type 1a follicles in Day 140 fetal ovaries. It is not clear whether this outcome reflects changes in follicle formation mediated through pregranulosa reassignment or changes in the initiation of follicle growth. Again, compared with continuous exposure, exposure during mid- or late gestation had a greater effect on the number of fetal genes and proteins that were altered (Lea *et al.* 2016). Most of the genes were downregulated, suggesting an underlying epigenetic mechanism, a hypothesis supported by bioinformatic analysis showing that 14 of the differentially expressed genes were regulators of histone methylation (Lea *et al.* 2016).

The differences in outcome between continuous and short-term exposure raise fundamental questions about both the mechanisms and the biological advantages of the different responses. One possibility centres on a group of differentially expressed genes that code for drug-metabolising enzymes, raising the possibility that changes in these enzymes during early development are an adaptation to counter the effects of the

abnormal environment later in gestation. This adaptation would allow logical and biologically advantageous responses to changes in the follicular environment and may also explain the more deleterious effects of subsequent environmental challenges, such as transitory exposure to biosolids. Indeed, this same concept seems to be applicable to pregnant ewes grazing high-salt fodder (Tay *et al.* 2012). Thus, being able to adapt to changes in the maternal environment would enable the developing fetus to prepare for postnatal life, on the expectation that the maternal and postnatal environments are similar.

Additional insights regarding the long-term effects of environmental contaminants on the developing ovary have been provided by examination of key compounds in isolation or as mixtures of a few defined compounds. Given that the intrauterine endocrine milieu is critical for fetal development, and that many environmental contaminants act as endocrine disruptors, it became essential to characterise the effects of supplementary androgen and oestrogen in pregnant ruminants. In sheep, exposure of the developing lamb to androgens during mid-pregnancy induces an adult ovarian, metabolic and hormonal phenotype that is similar to that seen in women with polycystic ovarian syndrome (Padmanabhan and Veiga-Lopez 2013; Monniaux *et al.* 2020; Siemienowicz *et al.* 2020). Smith *et al.* (2009) focused on the androgen effect and, in 10-month-old neonates, demonstrated an increase in late-gestation early growing follicles but a decrease in primordial follicles. Intriguingly, the decrease in primordial follicles was attributed to oestrogen derived from aromatisation of testosterone propionate. Together, these studies suggest that anthropogenic chemicals with androgenic or oestrogenic activity would cause similar effects. In support of this hypothesis, mid-gestation exposure of the developing female lamb to BPA prolonged the first breeding season and delayed and dampened the preovulatory LH surge (Savabieasfahani *et al.* 2006). Moreover, in lambs exposed to BPA or diethylstilbestrol from Day 1 to Day 14 after birth, the reserve of primordial follicles was reduced and the transition to primary follicles was increased by Day 30 (Rivera *et al.* 2011). This outcome was accompanied by a greater rate of proliferation of granulosa and theca cells, and an increased incidence of multi-ovular follicles, suggesting that one or more key processes in early follicle development had been perturbed.

It is now clear that primordial germ cell biology often affects ovary development through changes in DNA methylation. Migrating germ cells begin with a high level of DNA methylation, then undergo demethylation until around birth, followed by a period of remethylation, although the temporal sequence varies with sex and species (Zeng and Chen 2019). In the mouse, for example, male germ cells undergo remethylation *in utero*, whereas remethylation in female germ cells begins postnatally and continues as the oocytes develop and follicles are recruited. Therefore, environmental changes have more opportunity to alter imprinting patterns in females than in males.

It should be noted that DNA methylation is only one of the three main epigenetic mechanisms underpinning changes in gene action without needing a change in DNA sequence; the other two are modification of histones, including acetylation and methylation, and the production of non-coding RNAs that inhibit gene expression. All three mechanisms regulate the

development of the follicle in the fetal, postnatal and adult ovary (for reviews, see Pan *et al.* 2012; Cruz *et al.* 2014). For example, in pregnant ewes, the expression of fetal ovarian microRNAs is modified by exposure to BPA from Days 30 to 90 of gestation, leading to changes in developmental and functional insulin-related genes (Veiga-Lopez *et al.* 2013). This observation builds on extensive literature suggesting that the prenatal fetal ovary is particularly sensitive to BPA, in both human and animal models, and that low BPA concentrations affect the epigenome of female germ cells in rodents (Eichenlaub-Ritter and Pacchierotti 2015; Chianese *et al.* 2018; Mathew and Mahalingaiah 2019; Huang and Zeng 2021). The effects of environmental contaminants can also be transgenerational, although to date the most emphatic demonstration has been with rodent models. Exposure of the pregnant rat clearly results in exposure of the F1 fetus, with the F2 generation generated from the exposed F1 germline. By definition, the F3 generation has not been exposed, so any effects observed in the third or fourth generations are truly transgenerational. In 2005, a landmark paper showed that exposure of pregnant rats to the endocrine disruptor vinclozolin results in transgenerational effects on male fertility that are accompanied by alterations in DNA methylation patterns in the germ line (Anway *et al.* 2005). More recently, in a study of gestating rats exposed to the pesticide methoxychlor (a contaminant known to affect fetal ovarian development and postnatal fertility), there was an increased incidence of disease in both male and female F3 offspring (Manikkam *et al.* 2014). Remarkably, the increase in disease in the reverse outcross F4 female (but not male) offspring provides strong evidence of transgenerational inheritance through the female germline.

Transgenerational effects in sheep or cattle following maternal exposure to environmental contaminants, or even to natural phytoestrogens, have yet to be reported. Interestingly, differences in ovarian genomic DNA methylation have been reported in high- and low-prolificacy sheep, with lower levels of DNA methyltransferase genes in the high-prolificacy group (Zhang *et al.* 2017b). The authors of that study also reported differential methylation of genes associated with prolificacy, including *BMP7*, *BMPR1B*, FSH receptor (*FSHR*), LH/choriogonadotrophin receptor (*LHCGR*), *TGFB2* and *TGFB3*, providing a potential mechanism by which maternal exposure to environmental contaminants or nutritional restriction could alter follicle growth and the ovulation rate in future generations.

Oocyte exposure to environmental contaminants has been associated with perturbations in meiosis. For example, *in vitro* exposure of cattle oocytes to BPA and to mixtures of PCBs is reported to delay meiotic progression (Pocar *et al.* 2001; Ferris *et al.* 2016; Campen *et al.* 2018); similar observations have been reported in mice (Susiarjo *et al.* 2007). Therefore, it would appear that meiotic progression in the oocyte is sensitive to both chemical exposure and altered nutrition, as discussed above.

Relationships among ovarian reserve, fertility and AMH

The size of the ovarian reserve varies greatly among young females (Erickson 1966), and there have been several attempts to dissect the relationship between variation in ovarian reserve and

fertility. In cattle, phenotypic studies have mostly been positive, showing that a greater number of follicles is associated with: (1) earlier conception in the breeding season (Mossa *et al.* 2012; Cushman *et al.* 2014; McNeel and Cushman 2015); (2) greater uterine luminal protein concentrations (McNeel *et al.* 2017); (3) greater circulating progesterone concentrations (Jimenez-Krassel *et al.* 2009; Santa Cruz *et al.* 2018); and (4) a shorter interval from calving to oestrus (Martinez *et al.* 2016).

Genetic selection for ovarian reserve traits to improve fertility

In cattle, the heritability of most female reproductive traits is usually less than 0.05. In contrast, the genomic heritability of traits linked to ovarian reserve are moderate, thus more responsive to selection. The heritability of circulating AMH concentration is 0.36–0.46 (Gobikrushanth *et al.* 2018; Nawaz *et al.* 2018), similar to a heritability of 0.14–0.21 for the number of embryos collected after superovulation (Jaton *et al.* 2016) and a heritability of 0.31–0.44 for antral follicle count by ultrasonography (Snelling *et al.* 2012; Walsh *et al.* 2014). Therefore, fertility may be enhanced by genetic selection to increase the ovarian reserve, with phenotype measured directly by antral follicle count or indirectly by AMH concentration. In Holsteins, it seems likely that we can select based on strongly associated molecular markers on chromosomes 7 and 11, as well as positional candidates for the *AMH* gene itself on chromosome 11 (Gobikrushanth *et al.* 2018, 2019; Nawaz *et al.* 2018). Conversely, the adoption of ultrasonography for assessing reproductive efficiency in cattle has been hindered by the reports of antagonistic genomic relationships between antral follicle number and heifer pregnancy rate, as well as between antral follicle number and age at puberty (Snelling *et al.* 2012; Oliveira Júnior *et al.* 2017). The disagreement between phenotypic data and genomic correlations can be explained by the presumption that the relationship is linear in the genomic models, whereas, in fact, it may be quadratic. For example, reproductive longevity increases as the circulating concentrations of AMH increase, but the response is bimodal, with reproductive longevity being shorter in heifers with very high circulating concentrations of AMH (Mossa and Ireland 2019). In sheep, similar studies have not been done and we know only that greater prepubertal plasma AMH concentrations are associated with earlier puberty and greater fertility at first lambing (Lahoz *et al.* 2012; Torres-Rovira *et al.* 2014).

Altering the size of the ovarian reserve by management and nutrition

In beef cows, underfeeding during the first 110 days of the first pregnancy resulted in daughters with fewer antral follicles during the first 1.5 years of life (Mossa *et al.* 2013). It is not known whether fewer antral follicles has consequences for reproductive efficiency. In contrast, in ewes, underfeeding during the first 55 days of gestation followed by *ad libitum* feeding throughout the remainder of pregnancy resulted in daughters with more antral follicles and a higher ovulation rate at 20 months of age (Smith *et al.* 2019b). Moreover, at 75 days of gestation, germ cell number and ovarian volume were also increased in the daughters of the feed-restricted ewes

(Smith *et al.* 2019a). For cattle, a comparable histological analysis has not yet been done.

The age of the dam also affects follicle number in daughters, with heifers born to heifers having fewer antral follicles than herd mates born to mature cows (Walsh *et al.* 2014; McNeel *et al.* 2017; Tenley *et al.* 2019). This observation may reflect the effects of nutritional restriction described above (Mossa *et al.* 2013), because heifers may be less efficient at providing nutrients to their daughters *in utero*.

With peripubertal heifers, a decrease in energy intake causes an increase in the number of primordial follicles in the ovaries at the time of breeding, a counterintuitive response that is probably explained by a slowing of the rate of activation of primordial follicles (Freetly *et al.* 2014; Amundson *et al.* 2015). Whether this increase in primordial follicle number truly improves reproductive function remains unclear, but a large production-setting study recently demonstrated that herd survival, largely influenced by reproductive longevity, is greater in heifers developed at a slower rate of gain (Freetly *et al.* 2021).

Applications of developmental programming of the ovarian reserve

If nutrition during fetal development or the peripubertal period really does alter primordial follicle numbers (for better or worse), then it may be possible to use nutritional interventions to alter the size of the ovarian reserve and the fertility of replacement females. It will be important to determine whether nutrition-induced changes in primordial follicle number also alter fertility endpoints in the same way that natural increases in ovarian reserve improve uterine luminal protein concentrations, progesterone concentrations and reproductive performance. Until these important questions are answered, we cannot know whether there is any value in manipulating developmental programming to alter the size of the ovarian reserve.

Answering such questions is difficult while various methods are used to estimate the ovarian reserve. Histological counts of primordial follicle number undertaken with stereological principals are the gold standard but are not practical for a production system where less direct indicators would need to be used, such as ultrasound counts of antral follicles or measurements of circulating AMH concentrations. Strong correlations between AMH and the number of growing follicles support the widely held view that AMH is a reliable marker of the ovarian reserve of growing follicles (Ireland *et al.* 2008; Rico *et al.* 2011; Monniaux *et al.* 2012; Baruselli *et al.* 2015; Mossa *et al.* 2017). Strong relationships between the numbers of primordial follicles and antral follicle counts (Ireland *et al.* 2008; Monniaux *et al.* 2014) have been observed, but the assumption that relationships among these three variables are universally valid may be false. For instance, changes in circulating AMH in relation to the major genes affecting prolificacy could challenge AMH as a marker of growing follicles in the context of assisted reproductive technologies in ovine genotypes where these prolificacy mutations are segregating. Moreover, research questions and practical application often have different endpoints. If the concept of the follicle reserve is to be transferred to production systems, the basic research must always return to histological results to ensure that conclusions based on ultrasound or AMH concentrations are challenged.

In addition to nutrition and environmental contaminants, other environmental factors may affect ovary development and thus postnatal fertility. Among the current gaps in our knowledge are the effects of maternal disease status and heat stress, both of which warrant more attention given the effects of global climate change on disease vectors and thermoregulation. Recently, it has been shown that dairy heifers conceived in the summer, with their mothers having been exposed to a high temperature–humidity index, had lower antral follicle counts and AMH concentrations than those conceived in the winter (Succu *et al.* 2020), although there appeared to be no association between season and conception or fertility at first conception.

Over the past decade, our understanding of the mechanisms linking environment and fetal development has increased greatly. Over the next decade, our challenge is to put this knowledge to use by determining whether we can reprogram ovary development to produce a desired fertility outcome for livestock, as well as pest animals and companion animals. We also need to test whether we can mitigate negative impacts and maintain fertility in the face of environmental challenges.

Resurrection of the theca

Interactions between granulosa/cumulus cells and the oocyte have received a great deal of attention in the past decade, and the layer of theca cells seems to have been neglected. Indeed, when Young and McNeilly (2010) reviewed our scant knowledge of the development and endocrine activity of the theca cell, they referred to it as ‘the forgotten cell’. According to the dogma at the time, the theca provided physical support for the follicle and had only one essential role, namely the secretion of androgens as a precursor for granulosa cells to synthesise and secrete oestradiol, the basis of the ‘two-cell theory’ originally presented by Armstrong *et al.* (1979). The only other functional aspect being explored was the effect of members of the TGFB family on thecal androgen secretion (for a review, see Juengel *et al.* 2018). It has now become clear that this tissue layer plays a more important role in the development and health of the follicle.

The primary endocrine function of theca cells is bidirectional signalling with granulosa cells (Fig. 2), although other cell types are also involved, as discussed below. Theca cells secrete several growth factors, including members of the BMP family, specifically BMP4 and BMP7, that act on granulosa cells to enhance oestradiol secretion and cell proliferation, and are considered to be inhibitors of luteinisation and apoptosis (Glister *et al.* 2004; Chang *et al.* 2016a). The signals from granulosa cells to theca cells include BMP6, which, in cultured bovine cells, inhibits androgen production (Glister *et al.* 2005). Following BMP6 treatment, the strongest downregulation was seen with insulin-like factor 3 (INSL3) protein and mRNA abundance (Glister *et al.* 2013); INSL3 is a theca-derived protein involved in the paracrine control of theca function that enhances theca androgen secretion, thereby increasing the availability of precursors for oestradiol production by granulosa cells (Glister *et al.* 2013). Androstenedione and oestradiol stimulate INSL3 secretion from theca cells (Dai *et al.* 2017), apparently establishing a positive feedback loop that enhances the ability of a growing follicle to produce oestradiol.

The inhibition of androgen secretion by BMP6 may involve the inhibition of INSL3 secretion.

The action of BMPs is regulated by four secreted proteins, namely noggin (NOG), gremlin (GREM1), follistatin (FST) and chordin (CHRD). These proteins are produced mainly by the granulosa cell layer, at least in cattle (Glister *et al.* 2011). In bovine theca cells *in vitro*, GREM1 and NOG attenuate the inhibition of androgen secretion by granulosa- and theca-derived BMPs (Glister *et al.* 2019), suggesting that granulosa cells may modulate paracrine and/or autocrine signalling within the theca layer, as well as modulating the bioactivity of their own BMP output.

Several members of the fibroblast growth factor (FGF) family, including FGF2, FGF7 and FGF18, are produced mainly, if not exclusively, by the theca layer, at least in cattle (for a review, see Price 2016), and exert a variety of effects on granulosa and theca cells. It has long been known that FGF7 from the bovine theca increases granulosa cell proliferation without affecting theca cells themselves (Parrott and Skinner 1998). Most interesting is theca-derived FGF18, because, unlike the other FGFs, it stimulates apoptosis in granulosa cells without activating the typical FGF signalling pathways (Jiang *et al.* 2013; Portela *et al.* 2015). In contrast, FGF18 acts as a typical growth factor in theca cells by reducing apoptosis and activating typical signalling pathways (Han *et al.* 2018). Adverse effects on follicle health may not be limited to those caused by FGF18; in cattle, *FGF10* mRNA in the theca layer is more abundant in subordinate than dominant follicles (Castilho *et al.* 2017) and, as seen with FGF18, FGF10 does not elicit the typical cellular response to growth factors in granulosa cells (Jiang and Price 2012).

As a follicle undergoes atresia, apoptosis begins with the granulosa cells and oocyte, and then the theca cells, although the theca layer does seem to be disrupted early in smaller follicles (<5 mm in cattle; Irving-Rodgers *et al.* 2001). In atretic follicles, theca cells do not show increased expression of genes related to apoptosis, but rather show a decrease in genes involved in the cell cycle and proliferation, such as cyclin B1 (*CCNB1*) and centromere protein F (*CENPF*; Hatzirodos *et al.* 2014). However, theca cells can be affected by environmental factors. For example, prenatal exposure to testosterone impairs androgen production in the theca of small follicles during adult life (Monniaux *et al.* 2020). In addition, theca cells appear surprisingly susceptible to the mycotoxin metabolite deoxynivalenol, showing increased apoptosis and levels of mRNAs that encode apoptosis-related genes, including BH3 interacting domain death agonist (*BID*) and Fas ligand (*FASLG*; Guerrero-Netro *et al.* 2017). Clearly, the theca cell should not be overlooked when assessing the effects of environmental toxins and endocrine disruptors on ovarian function.

It is important to remember that the theca cell layer is complex, containing vascular cells, immune cells and fibroblasts, all of which are gaining recognition for their roles in follicle function. The thecal vasculature is well developed in healthy follicles and breaks down in atretic follicles. The major proangiogenic factors, FGF2 and vascular endothelial growth factor (VEGF), are expressed in follicles and are under endocrine or paracrine control, as demonstrated by the ability of BMP4 to stimulate *VEGFA* mRNA levels *in vitro* in the bovine theca (Nichols *et al.*

2019). In a bovine theca–endothelial cell coculture system, endothelial tubes form during culture, and angiogenesis is inhibited by TGFB1 or BMP6 and stimulated by a combination of VEGF and FGF2 (Mattar *et al.* 2020). In these studies, some observations do not agree, perhaps due to differences among the various BMPs in intracellular signalling, the potential for confounding effects with coculture in contrast to monoculture and variations in the additives to the culture media. There is still a lot to be learned about the roles of thecal vascular cells.

Immune cells within the thecal layer may also be involved in follicle development. For example, in the mouse, depletion of macrophages from the ovary causes haemorrhage and loss of vascular integrity in the theca layer (Turner *et al.* 2011). In cattle, mRNA encoding the macrophage-specific markers CD68 and CD14 is upregulated in the theca layer during atresia (Hatzirodos *et al.* 2014), suggesting an influx of macrophages, and coculture of theca cells with macrophages suppresses thecal androgen secretion (Samir *et al.* 2017). Macrophages secrete FGF2 and VEGF, so there are likely to be complex and stage-specific interactions among steroidogenic cells, endothelial cells and immune cells. The challenge now is to determine the local concentrations of these paracrine factors, and to dissect out the degree of cross-talk between the various cell types in a physiological model.

Follicular microenvironment and oocyte maturation

The follicular microenvironment has long been recognised as important for the oocyte to attain developmental competency. However, many of the recent advances in our understanding of key events in the later stages of follicle development have arisen from *in vitro* experiments, and we are now realising that it is additionally helpful when such experiments simulate, as best they can, physiologically relevant conditions. We appreciate the importance of a whole-follicle setting for supporting key physiological pathways that promote oocyte development, but then often ignore the issue during the commercial production of embryos *in vitro*.

Follicular fluid contains a myriad of factors obtained from the circulation, the cells of the theca, mural granulosa and cumulus layers, and the oocyte (Fig. 2). Assessment of follicular fluid constituents at each stage of follicle development has revealed changes in the microenvironment, including substrates, energy and metabolites, as the oocyte matures (Murray 2019; Clark *et al.* 2020). These changes may be essential for enabling each follicle cell type to perform the many critical processes for successful oocyte maturation.

One such process is the active maintenance of meiotic arrest; in all mammals studied to date, inhibiting the resumption of meiosis involves preventing the activation of maturation-promoting factor (MPF), a cyclin-dependent kinase (CDK) 1–cyclin B complex. Activation of MPF is inhibited by high intraoocyte concentrations of cyclic adenosine monophosphate (cAMP) that sustain activation of protein kinase A, which, in turn, phosphorylates nuclear kinase WEE2 oocyte meiosis inhibiting kinase (WEE2) and cell division cycle 25B (CDC25B) phosphatase. The phosphorylated forms of WEE2 and CDC25B phosphatase inhibit MPF activity (Eppig 1993; Tsafirri and Dekel 1994; Han and Conti 2006). The intra-oocyte cAMP concentration is the sum of its production in the

oocyte by adenylate cyclase and its degradation by phosphodiesterases (PDEs). Hydrolysis of cAMP by species-specific isoforms of PDEs, as well as the conserved PDE3a isoform, is regulated by the presence of cyclic guanosine monophosphate (cGMP), which enters the oocyte via gap junctions from cumulus cells and then competitively binds the catalytic site of PDEs (Franciosi *et al.* 2014). The production of cGMP in granulosa and cumulus cells is stimulated by the action of granulosa cell-derived C-type natriuretic peptide, via natriuretic peptide receptor (NPR2) on cumulus cells (Zhang *et al.* 2010; Hiradate *et al.* 2014). As the follicle matures, this pathway is increasingly supported by gonadotrophin-induced cGMP production, as well as oestradiol, which upregulates NPR2 (Zhang *et al.* 2011; Wigglesworth *et al.* 2013).

Other critical factors present within the follicular fluid include the oocyte-secreted factors GDF9 and BMP15. These two growth factors are key mediators of follicle growth, affecting both granulosa and theca cell function, and are critical for the attainment of developmental competency in the ruminant oocyte (Gilchrist *et al.* 2008; Spicer *et al.* 2008; Juengel 2018; Juengel *et al.* 2018; D'Occhio *et al.* 2020). In other species, GDF9 and BMP15 have been reported to suppress expression of *Lhcgr* (Eppig *et al.* 1997) and activate numerous key metabolic genes, such as those controlling the enzymes for glycolysis and cholesterol biosynthesis (Su *et al.* 2008), which aid cumulus cell-specific functions. Recently, GDF9 and BMP15 have also been implicated in the signalling events required for ovulation. Ovulation is triggered when the preovulatory LH surge initiates a cascade of events, resulting in gap junction closure and an immediate decline in intraoocyte cGMP and cAMP levels, allowing meiosis to resume. In contrast with mural granulosa cells, where the expression of LH receptors increases during selection of the dominant follicle (Webb and Campbell 2007; Scaramuzzi *et al.* 2011), cumulus cells lose LH receptors as the follicle grows (Baltar *et al.* 2000). Thus, the effect of the LH surge signal is facilitated through the production of epidermal growth-factor-like peptides (EGF-p) from granulosa cells. The EGF-p bind onto epidermal growth factor receptors (EGFR) on cumulus cells to promote the final events in maturation, such as cumulus cell expansion (Sela-Abramovich *et al.* 2006; Norris *et al.* 2008; Vaccari *et al.* 2009). The functionality of EGFRs on cumulus cells is promoted through the cooperation of cAMP, GDF9 and BMP15 (Sugimura *et al.* 2015).

Clearly, this new understanding of the regulation of oocyte maturation must be used to revise our methodologies if we are to further improve the production of embryos *in vitro*. For example, we know that the addition of BMP15 and GDF9 to IVM media improves the blastocyst rate following IVF (Hussein *et al.* 2006). Similarly, we would expect the addition of C-type natriuretic peptide in place of pharmacological agents, such as PDE inhibitors or exogenous cAMP (Gilchrist *et al.* 2016), to prevent precocious resumption of meiosis and improve oocyte quality (Santiquet *et al.* 2017; Zhang *et al.* 2017a). This approach has led to the development of a physiologically relevant IVM system (PR-IVM) that mimics the intrafollicular microenvironment of bovine follicles with respect to the concentrations of amino acids, energy substrates, steroids, hormones, growth factors and metabolites (Murray 2019). With bovine cumulus cell–oocyte complexes, PR-IVM did not improve the blastocyst rate of

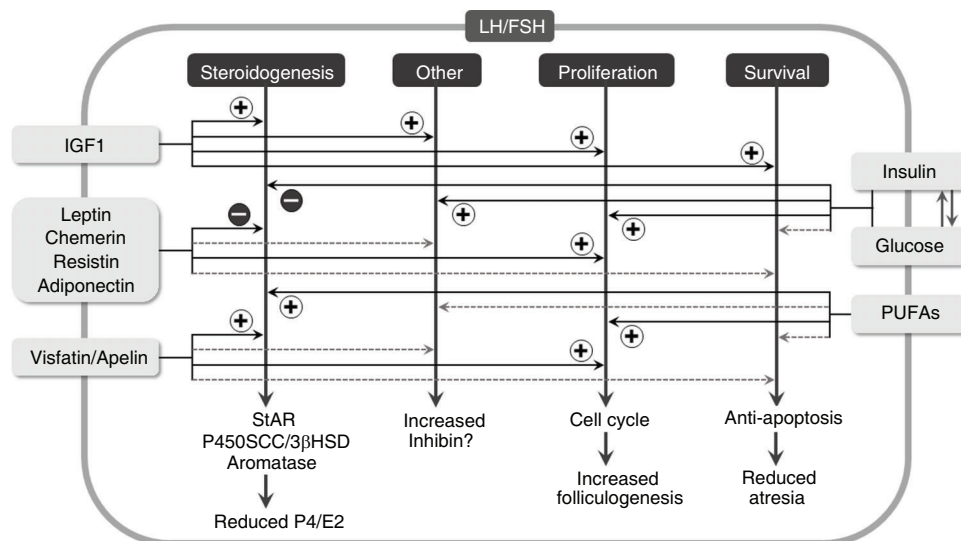


Fig. 4. Effects of metabolic factors, including adipokines, in bovine ovarian cells. As with insulin-like growth factor (IGF) 1, visfatin and apelin increase *in vitro* granulosa cell steroidogenesis and cell proliferation when given alone and in response to gonadotrophin (FSH and LH). Similar effects are described in response to polyunsaturated fatty acids (PUFA). The effects of insulin are largely dependent on stimulation of glucose uptake by cells and result in stimulation of cell proliferation, although some inhibitory effects have been reported in the presence of gonadotrophins. Conversely, *in vitro* studies have suggested that leptin, chemerin, resistin and adiponectin inhibit basal and FSH-induced steroid secretion. In contrast, other adipokines stimulate cell growth. These effects are associated with variations in protein levels for steroidogenesis enzymes (cholesterol side-chain cleavage enzyme, mitochondrial (P450SCC); 3 beta-hydroxysteroid dehydrogenase/isomerase (3βHSD); aromatase), the cholesterol carrier steroidogenic acute regulatory protein (StAR) and cell cycle components at the protein level. IGF1 is anti-apoptotic and stimulates inhibin production, whereas the effects of adipokines on apoptosis and inhibin production are unknown. +, stimulatory effects; -, inhibitory effects; E2, oestradiol; P4, progesterone. Modified from Scaramuzzi *et al.* (2011).

abattoir-sourced cumulus cell–oocyte complexes after IVF; however, it did decrease the number of pyknotic cells in both the inner cell mass and trophoblast compartments of the resultant embryos, suggesting an improvement in embryo quality (Murray 2019). It is becoming increasingly clear that careful scrutiny of changes in the follicular microenvironment will provide new insights into the regulation of oocyte maturation, better IVM media and greater success in artificial reproductive technologies in any species.

Adipokines as mediators of nutritional and metabolic input to the follicle: the adipokinome

The effects of metabolic state on reproduction and fertility are well documented. In cattle, for example, poor nutritional status, as reflected by a low body condition score, together with offspring presence or suckling, is associated with long postpartum anoestrus, early embryo death and reduced pregnancy and weaning rates (Diskin and Morris 2008). Body condition is related to fertility, especially in the peripartum period, when underfed cows mobilise their lipid reserves, increasing the concentrations of non-esterified fatty acids, reflecting their negative energy balance (Cardoso *et al.* 2020). The key roles of metabolic hormones, produced by various peripheral tissues, including growth hormone (GH), insulin-like growth factor 1 (IGF1), insulin, ghrelin, tri-iodothyronine, thyroxine and leptin, as well as metabolic factors (glucose, fatty acids, amino acids), that affect each component of the hypothalamic–pituitary–ovarian axis in female

cattle have been reviewed many times (Butler 2000; Wettemann *et al.* 2003; Chagas *et al.* 2007; Hernandez-Medrano *et al.* 2012; Dupont *et al.* 2014; D’Occhio *et al.* 2019). Body condition score is largely related to the amount of white adipose tissue, which, in addition to playing a key role in energy storage, is an active endocrine tissue that senses metabolic status and secretes numerous biologically active adipokines. For many years, the leptin concentration was viewed as an index of metabolic status, as well as a metabolic signal to the reproductive system. However, studies over the past 10 years have demonstrated the importance of other adipokines produced by adipose tissue, such as adiponectin, resistin, chemerin, visfatin and apelin, in the regulation of bovine ovarian function (Fig. 4; Kurowska *et al.* 2021).

Adiponectin plays important roles in the control of lipid metabolism, glucose homeostasis and insulin sensitivity, and evidence is slowly accumulating for its position as a systemic endocrine communicator between metabolism and reproduction. For example, during the normal oestrous cycle of the cow, circulating adiponectin concentrations gradually decrease after ovulation and then increase before the next ovulation (Kafi *et al.* 2015). Moreover, normal luteal activity starts earlier in high-producing dairy cows that have high postpartum adiponectin concentrations (Kafi *et al.* 2015).

In addition to their endocrine roles, adipokines can act locally within reproductive tissues; follicles, corpora lutea, oocytes, granulosa cells, theca cells and cumulus cells all have adiponectin and its two receptors, AdipoR1 and AdipoR2

(Lagaly *et al.* 2008; Maillard *et al.* 2010; Tabandeh *et al.* 2010). Similarly, all types of ovarian cells have chemerin and its three G-protein-coupled receptors, chemokine receptor-like 1 (CMKLR1), G-protein-coupled receptor 1 (GPR1) and C-C chemokine receptor-like 2 (CCRL2), apelin and its receptor GPR1, and resistin and visfatin, whose receptors are yet to be identified (Maillard *et al.* 2011; Spicer *et al.* 2011; Reverchon *et al.* 2014, 2016; Roche *et al.* 2017). *In vitro* studies with bovine granulosa cells have shown that, like leptin, adiponectin, chemerin and resistin decrease FSH-induced steroidogenesis (Lagaly *et al.* 2008; Maillard *et al.* 2010, 2011; Spicer *et al.* 2011; Reverchon *et al.* 2014), as illustrated in Fig. 4. Moreover, *in vitro* studies with bovine theca cells have shown that adiponectin decreases insulin-induced production of androgen and progesterone (Lagaly *et al.* 2008). Conversely, visfatin and apelin increase steroid secretion by granulosa cells (Reverchon *et al.* 2016; Roche *et al.* 2017), as illustrated in Fig. 4. Omentin and asprosin have also been identified as adipokines that may regulate ovarian follicle development in polycystic ovarian disease (Bongrani *et al.* 2019; Deniz *et al.* 2021). It is important to recognise that monogastrics typically achieve average body fat percentages that are greater than those achieved by ruminants, so the roles of the adipokines could differ significantly between these two types of animals. However, recent research with heifer tissues has shown strong expression of the precursor of asprosin (fibrillin 1 (*FBN1*)) in theca cells, with regulation by TGFB1, epidermal growth factor and FGFs; furthermore, asprosin inhibits IGF1-stimulated proliferation and enhances LH-induced androstenedione production (Maylem *et al.* 2021).

Thus, we have strong indications that adipokines play significant paracrine or autocrine roles within the ovary, but these roles are complex. First, most adipokines are produced in more than one variant (e.g. adiponectin, chemerin) and, to date, it has not proven possible to detect all forms in cattle. Second, most of our knowledge comes from *in vitro* experiments. *In vivo* studies are limited; for chemerin, for example, some recombinant forms have been synthesised and specific ELISAs have been developed, but only for humans and mice, not cattle (Chang *et al.* 2016b). Third, many studies report the effects of one or two adipokines, but it is probably important to evaluate the roles of all adipokines simultaneously because additive, antagonistic or synergistic effects are possible. Indeed, during early lactation in cattle, the various adipokines have different circulatory profiles (Mellouk *et al.* 2017), clearly indicating the need to consider the full 'adipokinome' rather than individual adipokines if we are to understand endocrine effects on reproductive function.

Big data and massive complexity: a return to mathematical modelling?

In the first workshop 30 years ago, a critical part of the vision was a functional model of follicle development, follicle selection and the determination of ovulation rate, based on quantitative knowledge of physiological processes rather than anatomical changes (Scaramuzzi *et al.* 1993). That change in perspective, from descriptive to functional and quantitative, has since been a foundation for hypothesis development in this field. The intention had been to translate the conceptual models into

mathematical models that could be used to define knowledge gaps, and to rank research areas based on sensitivity, and therefore importance, for the outcomes of folliculogenesis. That translation did not eventuate, but it is now time to reinvigorate the idea. The past decade has seen the rise of 'big data' and bioinformatics, and the development of vast arrays of transcriptomic, proteomic, metabolomic and genomic techniques, all generating massive volumes of information. We need to meet the challenge of translating that information into a useable form that can drive our understanding of follicle development and create new opportunities for managing ovarian development and function for livestock industries, as well as human health.

Conclusion

Over the past decade we continued our journey towards an understanding of the regulation of ovarian follicle development and ovulation rate in domestic ruminants. Finally, we are coming to grips with the origins of the process: the events during fetal life that can determine, for better or worse, the structure of the ovary and therefore act as the foundation of the future fertility of an animal. Having developed, the ovary contains follicles with two major layers of cells, one of which, the theca, was largely forgotten but is now being recognised as critically important. We have also started to recognise the antrum of the mature follicle, a fluid-filled cavity bathing the oocyte and its cumulus cells, as providing a microenvironment that nurtures the oocyte as it prepares for fertilisation and transformation into a healthy embryo. Achieving this first goal in reproduction involves complex interactions among many genes, including major genes that exert profound effects on, for example, the number of follicles that ovulate. These genes continue to provide novel insights into the processes that affect fecundity and fertility. Among the most important changes in our perspective has been a deeper understanding of the role of AMH as a biomarker for the ovarian reserve and as a regulator of fertility. AMH has already provided a breakthrough to the next level of efficiency in assisted reproductive technologies. Gaining a better understanding of the role AMH plays in determining fertility in natural cycles is a challenge that we are just beginning to confront.

The series of follicle workshops leading to this review were originally driven by the need to understand how nutrition affects ovarian follicle development and ovulation rate in sheep. The past four decades have seen an explosion in the variety of metabolic factors, and the intricacy of nutrition–reproduction relationships, that regulate the development of the fetal ovary and folliculogenesis. This revolution is exemplified by the realisation that there is an 'adipokinome' and that it is far more important than any single adipokine as a determinant of ovarian activity. Our need to understand the complexity of these systems is further accentuated by the arrival of human-made environmental pollutants that interfere with the very mechanisms that we need to control.

The major new foci of his review, namely AMH, follicle reserve, theca function, the adipokinome and environmental influences, have arisen primarily as a consequence of an ever-expanding variety of new tools and methodologies, bringing with them an explosion of data. Inevitably, one of the big challenges for the next decade will be the synthesis of the resulting massive

datasets into a better understanding of the factors that regulate female fertility. It is difficult to see how we can achieve this goal without continued mathematical modelling.

In addition to the changes flowing through our investigative technologies, changes are flowing through society. The world's population is growing, putting pressure on food security, the planetary environment and the way food is produced. We now have a focus on sustainability, leading inevitably to questions about food-producing animals: questions about food safety, the environmental footprint of food animals and animal welfare. Given this situation, improvements in reproductive efficiency become even more significant. Clearly, sheep or cows that fail to become pregnant effectively only produce methane, and females that wean single rather than twin offspring increase the environmental impact per unit of product. We must continue investigating the processes that link ovarian development in the fetus to folliculogenesis in the adult to the development of a healthy oocyte to the delivery and growth of healthy offspring.

Conflicts of interest

Graeme Martin is the Editor-in-Chief of *Reproduction, Fertility and Development*, but was blinded from the peer-review process for this paper. Rex Scaramuzzi is an Associate Editor of *Reproduction, Fertility and Development* and contributed to the organisation of the workshop from which this review was derived.

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