A putative role for anti-Müllerian hormone (AMH) in optimising ovarian reserve expenditure

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Abstract

The mammalian ovary has a finite supply of oocytes, which are contained within primordial follicles where they are arrested in a dormant state. The number of primordial follicles in the ovary at puberty is highly variable between females of the same species. Females that enter puberty with a small ovarian reserve are at risk of a shorter reproductive lifespan, as their ovarian reserve is expected to be depleted faster. One of the roles of anti-Müllerian hormone (AMH) is to inhibit primordial follicle activation, which slows the rate at which the ovarian reserve is depleted. A simple interpretation is that the function of AMH is to conserve ovarian reserve. However, the females with the lowest ovarian reserve and the greatest risk of early reserve depletion have the lowest levels of AMH. In contrast, AMH apparently strongly inhibits primordial follicle activation in females with ample ovarian reserve, for reasons that remain unexplained. The rate of primordial follicle activation determines the size of the developing follicle pool, which in turn, determines how many oocytes are available to be selected for ovulation. This review discusses the evidence that AMH regulates the size of the developing follicle pool by altering the rate of primordial follicle activation in a context-dependent manner. The expression patterns of AMH across life are also consistent with changing requirements for primordial follicle activation in the ageing ovary. A potential role of AMH in the fertility of ageing females is proposed herein.

Key Words

- ▶ anti-Müllerian hormone
- ▶ AMH
- ▶ ovarian reserve
- ▶ primordial follicle
- ▶ ovary
- ▶ female fertility
- ▶ limited oocyte pool hypothesis

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Introduction

The mammalian ovary has a finite number of oocytes that are formed in foetal development (Monniaux *et al.* 2014). During embryonic development, primordial germ cells migrate from the primitive streak through the endoderm to the genital ridge where they differentiate into oogonia while the foetal ovary forms (Richardson & Lehmann 2010). After the initial burst of oogonial proliferation, the cells begin meiosis, but the process is arrested in prophase-I (Jones & Lane 2013). The arrested oocytes initially form clusters and then become encapsulated in pre-granulosa

cells, forming a structure known as the primordial follicle, which represents a dormant, non-growing state (Kerr *et al.* 2013). Primordial follicle activation is the first step in the development and growth phase that eventually leads to the generation of a preovulatory follicle capable of releasing a viable oocyte (McGee & Hsueh 2000). Primordial follicles can become activated soon after their initial formation and it is not known why some follicles become activated early in life, whereas others are able to remain dormant for months, years or decades (Zhang & Liu 2015). The rate

of primordial follicle activation exceeds the rate at which mature oocytes are ovulated, with the excess developing follicles being removed via a process known as atresia (McGee & Hsueh 2000, Monniaux *et al.* 2014).

The size of the primordial follicle pool (the ovarian reserve) declines throughout life, hence, is likely to be a key determinant of the reproductive lifespan. This is particularly true for humans, orca and short-finned pilot whales, all of which experience ovarian reserve depletion and menopause, many years before the end of their natural lifespan (Marsh & Kasuya 1986, Brent *et al.* 2015, Depmann *et al.* 2015). Menopause is rare throughout the animal kingdom, but increasing evidence suggests that reproductive senescence is common (Packer *et al.* 1998, Nussey *et al.* 2013). In humans, female infertility occurs approximately 10 years prior to menopause, with subfertility becoming evident in the early 30s (te Velde & Pearson 2002, Broekmans *et al.* 2009, Eijkemans *et al.* 2014). This suggests that reproductive senescence occurs well in advance of depletion of the ovarian reserve. Little is known about how the ovary regulates the rate at which the primordial follicle reserve declines and the precise mechanisms that determine the length of the reproductive lifespan. This review focuses on an emerging regulator of primordial follicle activation, anti-Müllerian hormone (AMH), which has evolutionarily conserved functions in the mammalian ovary. The possibility that AMH and other primordial follicle activation regulators play a role in regulating female fertility across the lifespan will be discussed.

Anti-Müllerian hormone expression in the ovary

Anti-Müllerian hormone (AMH) is a glycoprotein of the TGF β superfamily, a large and diverse family of growth factors and hormones (Shi & Massague 2003). In the ovary, AMH is primarily produced in the granulosa cells of developing, nonatretic follicles. Granulosa cells do not express AMH in the primordial stage, but expression becomes evident after follicle activation and transition to the primary stage (Baarends *et al.* 1995, Gruijters *et al.* 2003, Weenen *et al.* 2004). Expression of AMH increases as the follicle develops through the preantral and small antral stages in humans (Weenen *et al.* 2004). Similar patterns occur in non-human primates (Modi *et al.* 2006), mice (Gruijters *et al.* 2003), rats (Ueno *et al.* 1989, Hirobe *et al.* 1994, Baarends *et al.* 1995), Siberian hamsters (Shahed & Young 2013), cows (Monniaux *et al.* 2012),

goats (Monniaux *et al.* 2012, Rocha *et al.* 2016), sheep (Bezard *et al.* 1987, Campbell *et al.* 2012) and brushtail possums (Juengel *et al.* 2002). AMH expression declines as follicles progress through the large antral stage of folliculogenesis, with little AMH being produced in preovulatory follicles (Ueno *et al.* 1989, Weenen *et al.* 2004, Jeppesen *et al.* 2013). However, AMH expression remains elevated in the cumulus granulosa cells of large follicles until immediately prior to ovulation (Ueno *et al.* 1989, Hirobe *et al.* 1994, Monniaux *et al.* 2012, Merhi *et al.* 2013). AMH expression is negligible in atretic follicles (Weenen *et al.* 2004).

AMH signalling requires simultaneous binding to one of three type-1 receptors (ACVR1, BMPR1A or BMPR1B) and the AMH type-2 receptor (AMHR2) (Mishina *et al.* 1996, Gouedard *et al.* 2000, Clarke *et al.* 2001, Visser *et al.* 2001, Orvis *et al.* 2008, Sedes *et al.* 2013). AMH is unique among the TGF β superfamily, as it is the only known member that does not share its type 2 receptor with other ligands. AMHR2 in the ovary is expressed in granulosa cells in a pattern that matches AMH; high levels in the early stages of developing follicles and declining expression in large antral stages (Baarends *et al.* 1995). *In situ* hybridisation suggests that *Amhr2* mRNA is not expressed in the granulosa cells of primordial follicles (Baarends *et al.* 1995), but it has been detected by qPCR in the smallest class of follicles isolated from human ovaries, which are likely to contain both primordial and primary follicles (Rice *et al.* 2007, Kristensen *et al.* 2013). The effects of AMH on primordial follicles have been replicated extensively (described below), but the signalling mechanism remains unclear, as there is debate as to whether primordial follicles express low levels of AMHR2 or none at all. A functional experiment suggests that the effect is AMHR2-dependent (Gigli *et al.* 2005), but the mechanism of AMH action on primordial follicles still needs to be elucidated.

AMH expression has been observed in the ovary, brain, placenta and uterus (Wang *et al.* 2005, 2009, Novembri *et al.* 2015, Cimino *et al.* 2016), but serum levels diminish rapidly after oophorectomy indicating that the ovary is the primary contributor of circulating AMH in females (Griesinger *et al.* 2012). AMH levels show minimal diurnal or circadian variation in women (Bungum *et al.* 2011), and variation during the ovarian cycle is subtle (reviewed by La Marca *et al.* 2013, also see Kissell *et al.* 2014, Gnoth *et al.* 2015, Hadlow *et al.* 2016, Lambert-Messerlian *et al.* 2016, Pankhurst & Chong 2016). This contrasts with variation in levels of other ovarian hormones (Groome *et al.* 1996). Longitudinal experiments

suggest that substantive changes in AMH levels only become apparent when examined over multiple years (de Vet *et al.* 2002), with these changes being summarised

in Fig. 1A. Female serum AMH levels are low at birth but slowly increase throughout early life, reaching a peak at about 25 years of age (Hagen *et al.* 2010, Fleming *et al.* 2012). AMH levels subsequently decline, with little or no AMH being detectable after menopause; a time when the ovary is depleted of primordial and developing follicles (Seifer *et al.* 2011, Chong *et al.* 2012, de Kat *et al.* 2016).

The action of hormones and growth factors is determined by their concentration at the target cell's receptors. The function of a hormone or growth factor is often related to the timescale over which concentrations vary. The slow changes in AMH levels suggest that it regulates the long-term processes, across the lifespan. Correlation studies suggest that the size of the developing follicle pool is the primary determinant of AMH concentrations in women (Fanchin *et al.* 2003, Hansen *et al.* 2011, Bentzen *et al.* 2013). In essence, the AMH-responsive cells (outside of early developing follicles) are being regulated by the size of the developing follicle pool. Plasma AMH levels also correlate with primordial follicle numbers in rats (Erbaş *et al.* 2014), which probably occurs due to a strong association between primordial and developing follicle counts (Hansen *et al.* 2011). Women who begin their life with a low antral follicle count/ovarian reserve tend to experience low AMH levels relative to other women of similar age. This relationship is observed in multiple species including mice, cows, goats and horses (Kevenaar *et al.* 2006, Monniaux *et al.* 2012, Batista *et al.* 2014, Claes *et al.* 2015).

It is worth mentioning that AMH has ovarian functions that are unrelated to primordial follicle activation, such as modulation of FSH sensitivity in granulosa cells (reviewed by Visser & Themmen 2014). In this context, AMH signalling is intrafollicular and is not subject to the same age-related changes in concentration that are observed in circulation and the extrafollicular ovarian environment (discussed below). At present, intrafollicular–autocrine AMH signalling does not appear to be essential for reproductive function, as AMH null-mutant (AMH^{-/-}) mice only show altered ovulatory responses under supraphysiological doses of FSH (Visser *et al.* 2007). This review does not discuss the intrafollicular–autocrine functions of AMH further, but research into this area is ongoing.

AMH is a paracrine regulator of primordial follicle activation

Primordial follicles are capable of transitioning to the primary follicle stage soon after their formation; yet, a

Figure 1

Lifelong AMH profiles are consistent with age-related changes in primordial follicle depletion rates in women. The blue band encompasses the time between the initial age at which declining fertility is observed in the population and the average age at menopause. (A) Serum AMH levels in women begin to decline from the mid-twenties which continues until menopause (based on data from Kelsey *et al.* 2011, Seifer *et al.* 2011). (B) The remaining number of primordial follicles declines throughout life with an acceleration in the rate of loss later in reproductive life. The projected trajectory of primordial follicle loss if rate of decline remained constant is displayed by the dashed line (based on data from Faddy *et al.* 1992, Wallace & Kelsey 2010, Depmann *et al.* 2015). (C) The ratio of secondary follicles to primordial follicles increases with age indicating that primordial follicle activation rates increase, relative to the size of the remaining follicle pool (based on data from Faddy and Gosden 1995).

proportion remains quiescent until late in reproductive life (Adhikari & Liu 2009). Numerous regulators that induce follicle activation have been identified including KIT-ligand, epidermal growth factor, fibroblast growth factor 2 and 7, platelet-derived growth factor, bone morphogenetic protein 4 and 7, growth and differentiation factor 9, neurotrophin 3, brain-derived neurotrophic factor, glial-derived neurotrophic factor, insulin, interleukin 16, leukaemia inhibitory factor and gremlin (Dole *et al.* 2008, Adhikari & Liu 2009, McLaughlin & McIver 2009, Nilsson *et al.* 2009, 2014, Feeney *et al.* 2014). The inhibitors of primordial activation that have been described to date include CXCL12, oestradiol, growth hormone, Hippo signalling and AMH (Adhikari & Liu 2009, McLaughlin & McIver 2009, Hsueh *et al.* 2015).

Studies in female AMH^{-/-} mice demonstrate that the loss of AMH accelerates the activation rate of primordial follicles leading to premature depletion of the ovarian reserve, akin to human menopause (Durlinger *et al.* 1999). Accordingly, AMH^{-/-} mice have enlarged pools of preantral and small antral follicles, but concomitant increases in atresia have a correcting influence on large antral follicle counts, which are equivalent to counts in wild-type mice (Durlinger *et al.* 1999, Visser *et al.* 2007). Conservation of the ovarian reserve after injection of recombinant AMH into young mice has also been observed (Hayes *et al.* 2016). Exogenous application of AMH inhibits primordial follicle activation in explant cultures of human, rat, mouse and goat ovary tissue (Durlinger *et al.* 2002, Gigli *et al.* 2005, Carlsson *et al.* 2006, Nilsson *et al.* 2007, 2014, Rocha *et al.* 2016). Similar experiments have shown that positive regulators of primordial follicle activation such as KIT-ligand, fibroblast growth factor 2, 7 or gremlin antagonise the effects of AMH (Nilsson *et al.* 2007, 2014). This suggests that primordial follicle activation involves a balance between activation-promoting and activation-inhibiting factors.

Not all studies support AMH-mediated inhibition of primordial follicle activation. Schmidt and coworkers (Schmidt *et al.* 2005) reported that AMH caused an increase in the rate of primordial activation in human ovarian cortex explant cultures. It has been suggested that this difference occurred due to the culture period of 4 weeks, which is longer than the 2- to 10-day period used in other studies (van Houten *et al.* 2010). A recent report suggested that AMH inhibits primordial follicle assembly in neonatal rat organ cultures (Nilsson *et al.* 2011), which could affect the interpretation of primordial follicle activation experiments involving AMH. However, it was not clear whether AMH affected follicle formation

or short-term survival of oocytes that had failed to assemble into follicles (Nilsson *et al.* 2011). An inherent limitation of ovary explant/organ cultures is the inability to distinguish interactions between primordial follicle activation, survival and assembly. *In vivo*, primordial follicle numbers are similar in AMH^{+/+} and AMH^{-/-} mice prior to puberty (Durlinger *et al.* 1999), which is the phase of life when differences in follicle assembly and survival should be most apparent (Tingen *et al.* 2009). This is the strongest evidence that AMH regulates primordial follicle activation.

In general, primordial follicle activators are produced within the follicles or immediately associated tissue (McLaughlin & McIver 2009). Hence, activation-promoting signals are expected to be largely autocrine (intrafollicular). Paracrine (extrafollicular) signals from adjacent primordial follicles may also have an effect, but extrafollicular signals are expected to be orders of magnitude weaker than intrafollicular autocrine signals due to loss of concentration with diffusion distance. The primordial follicle pool may collectively produce an extrafollicular signal that is correlated to the size of the ovarian reserve, but a mechanism by which primordial follicles can distinguish between a weak extrafollicular, and strong intrafollicular autocrine signal is not known to exist. In contrast, AMH is produced by developing follicles with little or no expression observed in primordial follicles (Bezard *et al.* 1987, Hirobe *et al.* 1994, Baarends *et al.* 1995, Gruijters *et al.* 2003, Weenen *et al.* 2004, Juengel & McNatty 2005, Monniaux *et al.* 2012, Shahed & Young 2013, Rocha *et al.* 2016). Signals such as AMH can correlate with the size of the developing follicle pool and can also act as a surrogate signal for the size of the primordial follicle pool, as these variables are highly correlated (Hansen *et al.* 2011). Furthermore, the AMH signal secreted from developing follicles does not have to compete with a local autocrine signal in primordial follicles. The pattern of AMH expression suggests that it inhibits primordial follicle activation in a manner that is correlated to the size of the ovarian reserve/developing follicle pool.

AMH in the context of ovarian reserve at puberty

A high variability in the initial ovarian reserve and the reserve size at puberty, between individuals, has been observed across multiple mammalian species, and the effect occurs in both genetically diverse and inbred populations

(Myers *et al.* 2004, Ireland *et al.* 2008, Depmann *et al.* 2015, Olcha *et al.* 2016). The efficacy of multiple processes, including primordial germ cell migration, oogonial proliferation, nurse-cell organelle transfer and oogonial incorporation into primordial follicles, all contribute to the initial primordial follicle count (Kerr *et al.* 2013, Lei & Spradling 2016). Subsequent primordial follicle activation, programmed cell death and oocyte extrusion from the ovary are processes that further affect the size of the ovarian reserve at puberty (Wordinger *et al.* 1990, Tingen *et al.* 2009). Variability in ovarian reserve at the beginning of the reproductive phase of life is likely to be an unavoidable consequence of mammalian ovary development. It is possible that females with low ovarian reserve are simply at a reproductive disadvantage. An alternative possibility is that mechanisms have evolved to enable primordial follicles to be recruited at a rate that is optimal for a given ovarian reserve size.

The phenotype of the AMH^{-/-} mouse might suggest that the role of AMH is to prevent the ovarian reserve from being depleted too quickly. A small initial ovarian reserve is postulated to correlate with an early onset of menopause (Faddy & Gosden 1995, Wallace & Kelsey 2010, Depmann *et al.* 2015). Shorter reproductive lifespans present fewer opportunities to produce offspring; hence, conserving the ovarian reserve until later in life has the potential to increase reproductive fitness. However, females born with low ovarian reserve are expected to have the lowest levels of AMH throughout life. Therefore, AMH does little to conserve ovarian reserve in these females. In contrast, females born with high ovarian reserve produce large amounts of AMH in early reproductive life, raising the question; why do females with the largest ovarian reserve have the strongest inhibition of primordial follicle activation? It is possible that conserving the ovarian reserve is only advantageous when the ovarian reserve is large. If this is the case, ovarian reserve-dependent modulation of primordial recruitment rates via AMH may be important for managing lifetime reproductive potential.

AMH expression patterns are consistent with primordial follicle usage

In women, the pool of remaining primordial follicles declines with age leading to progressive reductions in the absolute rate at which primordial follicles are lost from the ovary (Fig. 1B, Wallace & Kelsey 2010, Depmann *et al.* 2015). The absolute rate of activation is a function of

both the size of the remaining ovarian reserve and the proportion of the remaining reserve activated over a given period. The size of the ovarian reserve is determined by past events, but the relative rate of activation is a variable that can be modified by regulatory factors. When the rate of primordial follicle activation is considered as a proportion of the remaining follicle pool, an acceleration in the rate of decline is observed in the 4th and 5th decades of life (Fig. 1C, Faddy *et al.* 1992, Faddy & Gosden 1995). Antral follicle counts also decline throughout life but at a slower rate than primordial follicles, and any age-related acceleration in the rate of decline is subtle, with some evidence suggesting that it remains constant (Rosen *et al.* 2010). Hence, relative increases in primordial follicle activation rates may enable the ageing ovaries to maintain larger antral follicle pools than would be possible otherwise.

The mechanism by which the ageing ovary increases primordial follicle recruitment rates has not been identified, but reduced inhibition of follicle activation is one possibility. Levels of the putative inhibitor oestradiol do not begin to decline until late in the perimenopausal period (Burger *et al.* 1995). However, circulating growth hormone and AMH levels decline progressively with age (Iranmanesh *et al.* 1991, Seifer *et al.* 2011, de Kat *et al.* 2016). Hippo signalling responds to changes in surrounding tissue elasticity (Hsueh *et al.* 2015), which may become altered with age-related fibrosis (Briley *et al.* 2016). Therefore, the age-related increase in primordial follicle activation may arise from a reduction in inhibitory signals rather than an increase in activation-promoting regulators. This is further supported by mutations in the *AMH* and *AMHR2* genes that are associated with primary ovarian insufficiency or decreased age at menopause (Kevenaar *et al.* 2007, Park *et al.* 2014, Alvaro Mercadal *et al.* 2015). Across the lifespan, increased rates of primordial follicle activation tend to coincide with lower levels of inhibitors of primordial follicle activation, including AMH.

The effect of ovarian reserve on declining fertility

The cessation of ovulatory cycles at menopause is sometimes considered to be the absolute end of the reproductive lifespan in women. However, the age at last child-birth occurs approximately 10 years earlier, which signifies the end of fertility in a functional and evolutionary sense (te Velde & Pearson 2002, Eijkemans *et al.* 2014).

The onset of infertility appears to occur gradually, as the time-to-pregnancy for couples attempting to conceive naturally increases with age (Gnoth *et al.* 2003). Oocyte quality appears to be a key factor in age-related infertility, as IVF embryo implantation rates are higher in older women when using oocytes from young donors, rather than their own (Tarin *et al.* 2014).

A combination of oocyte quality and developing oocyte quantity are likely determinants of female fertility (Faddy *et al.* 1992, te Velde & Pearson 2002). The amount of time that oocytes spend suspended in meiosis-I has been proposed to lead to an accumulation of degenerative defects that could explain age-related infertility. Oocyte aneuploidy frequently arises at the resumption of meiosis-I and is embryonically lethal in most cases (Munne *et al.* 2004). Aneuploidy incidence rates increase with age in humans and mice, with evidence suggesting age-related degradation of cohesin proteins in the oocyte nucleus is involved (Chiang *et al.* 2010, Lister *et al.* 2010, Kuliev *et al.* 2011, Duncan *et al.* 2012). Oocyte mitochondrial counts also decline in older females, leading to reduced embryo viability (Wai *et al.* 2010, Kushnir *et al.* 2012, Fragouli *et al.* 2015). Additional factors that contribute to the age-related decline in oocyte quality may yet be discovered, but there is no current evidence to suggest that AMH directly affects oocyte quality. In assisted reproduction, AMH levels are predictive of oocyte yield but not the probability of achieving pregnancy (Fraisie *et al.* 2008, Broer *et al.* 2009, Hamilton *et al.* 2016). However, this does not exclude the possibility that AMH indirectly affects fertility by altering primordial follicle activation rates.

The limited oocyte pool hypothesis postulates that a declining ovarian reserve will lead to higher rates of aneuploidy due to a smaller antral follicle pool (Warburton 1989). In the absence of a suitable follicle, it was proposed that an over- or under-matured follicle with a higher propensity to release an aneuploid oocyte would be selected for ovulation (Warburton 1989). In mice, artificially reducing the ovarian reserve by unilateral ovariectomy causes reduced embryo viability in late reproductive life when compared to age-matched females (Biggers *et al.* 1962, Brook *et al.* 1984). Similarly, a low antral follicle count is associated with reduced pregnancy rates in cows (Mossa *et al.* 2012, Martinez *et al.* 2016). In humans, multiple studies suggest that increased rates of aneuploidy (Kline *et al.* 2000, Haadsma *et al.* 2010, Katz-Jaffe *et al.* 2013, Grande *et al.* 2015) or an inability to achieve pregnancy (Scott *et al.* 1995, El-Toukhy *et al.* 2002, Rosen *et al.* 2011) is associated with low ovarian reserve. Other studies have produced contradictory findings

detecting no association between markers of reduced ovarian reserve and aneuploidy rates (Massie *et al.* 2008, Kline *et al.* 2011, Grande *et al.* 2014) or pregnancy rates (van Rooij *et al.* 2003). This has raised questions about the validity of the limited oocyte pool hypothesis, but human studies often involve women seeking fertility treatment, many of whom would have been considered infertile prior to the advent of assisted reproduction technologies. In the absence of accurate methods to assess fertility and primordial follicle numbers longitudinally, the question remains; what size of ovarian reserve is too small to maintain fertility and does this affect the age at which infertility occurs?

The age-related decline in fertility and the limited oocyte pool effect

The characteristics that determine which follicle is selected to be the dominant or preovulatory follicle are unclear. Presumably, selection is based on a measure of oocyte quality. There is evidence to support this, as oocytes secrete signals to granulosa and theca cells that promote follicle survival (Gilchrist *et al.* 2008). However, in the absence of a high-quality follicle, the hypothalamic–pituitary–gonadal axis appears to select any available follicle. For example, the human historical data suggest that the ovary continues to ovulate for many years after the age of infertility onset (Eijkemans *et al.* 2014). In cows and horses, an ablated dominant follicle can be replaced by a subordinate follicle that would otherwise undergo atresia (Evans *et al.* 2002, Ginther *et al.* 2002a,b).

A simplified model of follicle selection in a polyovulatory species outlines one scenario where a large developing follicle pool is beneficial (Fig. 2). Reducing the size of the developing follicle pool can lead to the selection of a greater number of low-quality (nonviable) oocytes in this system. Age-related increases in the proportion of nonviable oocytes combined with age-related reductions in antral follicle counts exacerbate the problem. Hence, a limited oocyte-pool-like hypothesis is compatible with age-related reductions in oocyte quality, as the two processes are not necessarily mutually exclusive. In theory, this model is not restricted to aneuploidy and could apply to any form of reduced oocyte quality.

A single preovulatory follicle is selected per cycle in humans. The proposed model (Fig. 2) might imply that noticeable effects on oocyte quality in monovulatory species are only observed when the antral follicle count becomes very small (refer to Fig. 2). However, several aspects

Figure 2

A simplified model of quality-based follicle selection in a polyovulatory species. The model assumes that the hypothalamic–pituitary–gonadal axis selects 6 follicles per cycle for ovulation with a preference for viable/high-quality oocytes (blue) over non-viable/low-quality oocytes (red). The model also assumes that there will always be a proportion of oocytes that are inherently low quality or non-viable. When the pool of developing small antral follicles is large (A), there is capacity to choose a high-quality cohort of preovulatory follicles. When the pool of developing small antral follicles is reduced (B), there are fewer high-quality follicles to choose from and the proportion of high-quality preovulatory follicles decreases. When the size and quality of the small antral follicle pool is reduced (C), there is a greater reduction in preovulatory follicle quality. Note that this model has limitations, as it has not been confirmed that high-quality follicles are always selected, and the process is likely to contain an element of error. Similarly, the quality of oocytes in developing follicles has not been described in detail due to a lack of suitable methods. It is worth noting that additional oocyte defects may arise during the final stages of follicle maturation, but this is also proposed to be exacerbated in a limited oocyte pool scenario (Warburton 1989).

of ovarian biology constrain the functional size of the ovarian reserve during reproductive ageing. A substantial proportion of women have low antral follicle counts at the age of 35 years (Scheffer *et al.* 1999, Fanchin *et al.* 2003, Rosen *et al.* 2010). Furthermore, dominant follicle selection occurs over a short time window (a few days in humans) (Schipper *et al.* 1998, Baerwald *et al.* 2012). Only a proportion of the antral follicles are at a suitable stage for selection during the selection window, particularly in older women (Scheffer *et al.* 1999, Baerwald *et al.* 2003a,b, Bentzen *et al.* 2013). Hence, it is feasible that a limited oocyte-pool-like effect occurs at an earlier phase of the age-related fertility decline than originally proposed. In this circumstance, it is feasible that reducing negative regulators such as AMH could promote the formation of larger developing follicle pools and delay the onset of reproductive senescence.

The functions of AMH are conserved across the mammalian taxa but regulating the size of the

developing follicle pool may be more important for certain species. For example, ageing mice maintain a similarly-sized large antral follicle pool to young mice but the older mice recruit from smaller primary follicle pools and have higher rates of aneuploidy (Fu *et al.* 2014). Ovarian reserve, determined by AMH levels, is correlated with litter size in dogs (Hollinshead *et al.* 2016), which could have large consequences for cumulative, lifetime reproductive fitness. In some strains of mice and cows, low ovarian reserve or reproductive ageing is associated with reduced corpus luteum function (Harman & Talbert 1970, Jimenez-Krassel *et al.* 2009). In these cases, the mechanism of infertility may relate to a reduced ability to maintain pregnancy (Mossa *et al.* 2012, Martinez *et al.* 2016), rather than production of low-quality oocytes. Hence, it is possible that multiple selection pressures have preserved systems that generate a comparatively large developing follicle pool when ovarian reserve is low.

A potential biological role for AMH

The largest changes in extrafollicular AMH levels occur across the female lifespan, suggesting that it regulates long-term processes. Any AMH-mediated inhibition of primordial follicle activation can be expected to be strongest early in the reproductive phase of life, with decreasing effects as age advances. In the context of a limited oocyte pool-like hypothesis where oocyte quality and quantity are important factors for fertility, AMH may help generate a developing follicle pool that is optimal for

a given ovarian reserve (Fig. 3). Three possible biological functions for AMH can be hypothesised:

Hypothesis 1: *Declining AMH in late reproductive life stimulates an increase in the relative rate of primordial follicle activation.* Increased activation rates result in faster ovarian reserve depletion but may enable the developing follicle pool to remain large enough to support fertility for longer. In polyovulatory species, the effect may enable females to maintain large litters for longer. Small litters represent a reduced reproductive output relative to other females but carry ongoing opportunity costs as lactational

Figure 3

The putative effects variation in AMH levels when ovarian reserve is large or small in a polyovulatory species model. The pathways coloured black (upper and lower pathways) represent the observed levels of AMH when the ovarian reserve is large or small. The pathways coloured blue (middle pathways) are not observed in normal females but are included for the purpose of demonstration and comparison. Viable/high-quality follicles have oocytes coloured blue and non-viable/low-quality follicles have oocytes coloured red. When the ovarian reserve is large, the small antral follicle pool will be large regardless of AMH levels. However, the small antral follicle pool may be larger than necessary if AMH levels are low with a large ovarian reserve, leading to rapid depletion of the ovarian reserve without additional benefit to fertility. In females with low ovarian reserve, the low AMH levels will increase the relative rate of primordial follicle recruitment leading to a larger small antral follicle pool. This represents a trade-off between rapid ovarian reserve depletion for a moderate increase in fertility. If high AMH levels are present when the ovarian reserve is low, the expected reduction in the size of the small antral follicle pool has the potential to further reduce fertility. The proposed role of AMH is to enable a female to make the most of the ovarian reserve she was endowed with at the beginning of puberty.

infertility delays further attempts to reproduce. In seasonal breeders, reproductive success requires pregnancy to occur over a short period of time and a small number of ovarian cycles. Extending the age of reproductive senescence by mere months could be sufficient to enable one additional breeding season. These effects could be particularly important for reproductive success in short-lived species.

Hypothesis 2: *Females with a small ovarian reserve at puberty have low levels of AMH and proportionately high primordial follicle activation rates over their lifespan.* The absolute rate of primordial follicle activation is still expected to be low, but the reduced levels of AMH may mitigate the effect of low ovarian reserve and allow these females to maintain a relatively large developing follicle pool. The expected cost of this strategy is a reduced reproductive lifespan, but the expected benefit is a lower risk of having a developing follicle pool that is too small to support fertility.

Hypothesis 3: *Females with a large ovarian reserve at puberty have high levels of AMH and proportionately low primordial follicle activation rates in the early phase of the reproductive lifespan.* Past a certain size, larger developing follicle pools may produce diminishing returns on fertility. In this circumstance, females with large ovarian reserve can afford to inhibit primordial follicle activation to extend their reproductive lifespan while still producing a large developing follicle pool that is sufficient to sustain high fertility.

Concluding statements

A fixed rate of primordial follicle activation within a species is unlikely to be optimal for all females. The hypothesis put forward in this review is that AMH alters the relative rate of primordial follicle activation in a context-dependent manner to maximise lifetime reproductive opportunity. Such a system may be necessary to make adjustments for the inherent variability in ovarian reserve that is present when mammalian females reach puberty. The rate of the decline in primordial numbers has been described at the population level with cross-sectional data, but little information is available on rates of decline within individuals. Hence, the development of methods to quantify the ovarian reserve longitudinally will be essential for elucidating the functions of AMH and testing the hypotheses proposed herein. Furthermore, the control of primordial follicle activation is likely to be complex; hence, this putative function of AMH is likely to be part of a larger system with multiple, interacting regulators.

Declaration of interest

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

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