Anti-Müllerian Hormone (AMH) and fertility management in agricultural species

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Abstract

A reliable, easy to assess marker for fertility in agricultural species would be highly desirable and Anti-Müllerian Hormone (AMH) is a promising candidate. This review summarizes recent findings concerning AMH and its role in fertility management, mainly in cattle. It focuses on (1) alterations in circulating AMH concentrations from birth to puberty and during estrous cycles; (2) correlation of circulating AMH concentrations with ovarian follicle numbers and ovarian reserve; (3) factors that impact circulating AMH concentrations; (4) use of AMH as a predictor of fertility. Circulating AMH concentrations can be easily and reliably measured with a single blood sample in adult cattle because AMH varies minimally during the estrous cycle and is repeatable across multiple cycles. Circulating AMH concentrations are positively associated with several measures of fertility. Dairy heifers with low compared with higher AMH concentrations subsequently had lower pregnancy rates, higher probability of being culled after birth of their first calf and shorter herd longevity. Also, AMH is predictive of response to superovulation in cattle and sheep. Several factors contribute to the variability in AMH concentrations among individuals; for example, beef cattle have higher AMH than dairy cattle. Nutritional imbalances, disease and endocrine disruptors during fetal life may negatively program the size of the ovarian reserve and consequently serum AMH concentrations and potential fertility in adulthood. We conclude that AMH may be a predictor of fertility and herd longevity in cattle, whereas in sheep and other farm species, the potential association between AMH and reproductive performance remains largely unexplored.

Free Italian abstract: An Italian translation of this abstract is freely available at http://www.reproduction-online.org/content/154/1/R1/suppl/DC1.

Introduction

Anti-Müllerian Hormone (AMH) is a dimeric glycoprotein and a member of the transforming growth factor β (TGF-β) family of growth and differentiation factors (Cate et al. 1986). It is named after its role in male sexual differentiation because it was originally identified in rabbit male fetuses as a testicular factor distinct from testosterone that caused regression of the Müllerian ducts (Jost 1947) and was subsequently found to be produced by Sertoli cells in males (Josso et al. 1993).

More recently, it was discovered that AMH is also released in females and is produced exclusively by granulosa cells of healthy, growing ovarian follicles in women, cattle and sheep (Vigier et al. 1984, Takahashi et al. 1986, Bézard et al. 1987, La Marca & Volpe 2006). AMH expression starts as soon as

follicles are initially recruited (McGee & Hsueh 2000), reaches its highest level in preantral and small antral follicles, whereas it then decreases as the selected, FSH-dependent follicle progresses toward the preovulatory stage and is absent in atretic follicles. This pattern of expression was first assessed in rodents (Ueno et al. 1989) and subsequently in women (Weenen et al. 2004), cattle (Monniaux et al. 2008) and sheep (Veiga-Lopez et al. 2012). In the absence of AMH, follicles are recruited at a faster rate, resulting in an exhausted pool of primordial follicles at a younger age (Durlinger et al. 1999). Further, AMH inhibits FSH-stimulated follicular growth both in vivo and in vitro in mice (Durlinger et al. 2001). Thus, AMH is considered to have two main functional roles: (1) inhibition of primordial follicular growth from the primordial follicle reserve, avoiding premature exhaustion of the ovarian follicular reserve and (2) reduction in the responsiveness to FSH of

preantral and small antral follicles, modulating follicular development (reviewed by Dewailly *et al*. (2014)).

Although its physiological effects have not been completely elucidated, AMH is widely employed in clinical applications in human reproductive medicine. This is because AMH is not produced by primordial or atretic follicles. Rather, it is produced exclusively by healthy growing follicles leading to detectable concentrations of AMH in the blood. Therefore, AMH concentrations are indirectly reflective of the total number of morphologically healthy ovarian follicles in ovaries, and hence, the ovarian reserve (La Marca & Volpe 2006). Consequently, the main application for measurement of circulating AMH concentrations in women is prediction of the relative size of the ovarian reserve and potential response to FSH treatments during assisted reproductive technologies (ART). It may also be used as a marker of ovarian dysfunction, for example, in the diagnosis of premature ovarian failure, menopause and the polycystic ovarian syndrome (Dewailly *et al*. 2014).

In agricultural species, a reliable, cost-effective, easy-to-assess marker for fertility would be highly desirable, and AMH is a promising candidate. This review summarizes recent findings concerning AMH and its role in fertility management in agricultural species, mainly in cattle. Specifically it focuses on (1) alterations in circulating AMH concentrations from birth to puberty and during estrous cycles; (2) correlation of circulating AMH concentrations with ovarian follicle numbers and the ovarian reserve; (3) factors that impact circulating AMH concentrations and (4) use of AMH as a predictor of fertility.

Alterations in circulating AMH concentrations from birth to puberty and during estrous cycles

Understanding the physiological variations in AMH concentrations during life is pivotal to appreciate its potential application as a biomarker for fertility in cattle and other farm species. In women, circulating AMH concentrations rise during infancy (from birth to three months of age), but are stable from childhood to early adulthood (Hagen *et al*. 2011, Kelsey *et al*. 2011). We conducted a study to illustrate the variations of AMH from birth to puberty in Holstein female calves. Results depicted in Fig. 1 show that AMH concentrations increase during the first 2 months of age, decrease at 5 and are stable at 8–9 months of age, around the time of first ovulation. We also described a similar pattern in beef calves. In Maine-Anjou beef heifers, plasma AMH concentrations were found to increase rapidly between 1 and 3 months of age, to remain high at 6 and to decline slowly until 12 months of age, which corresponds to the age of ovulation for this breed (Monniaux *et al*. 2012). These findings are supported by results from
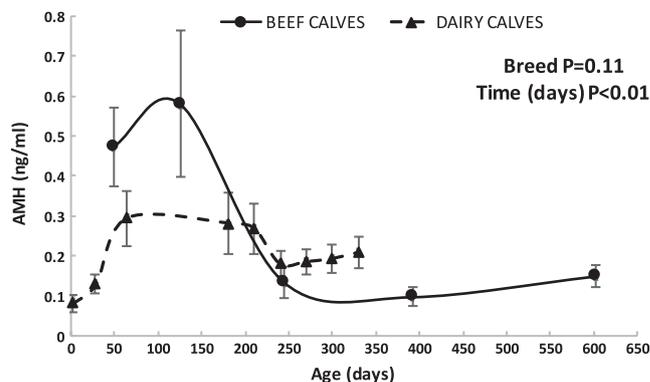
Figure 1 Circulating AMH concentrations (ng/mL) in dairy ($n=9$; unpublished) and cross bred beef ($n=13$, modified from Mossa *et al*. (2013)) female calves. Results of ANOVA indicated that mean AMH concentrations were similar between dairy and beef calves ($P=0.11$), but varied with time ($P<0.01$).

others indicating that 3- to 4-month-old calves have greater AMH levels compared to young adult heifers in both Holstein (14–16 months) and *Bos indicus* Nelore (18–24 months) cattle (Batista *et al*. 2016). It can be assumed that AMH concentrations increase in the first months of life and decrease before puberty in cattle, like women (Hagen *et al*. 2011, Kelsey *et al*. 2011), but the timing of such fluctuations may vary among breeds and genetic groups. Prepubertal heifers experience waves of antral follicular growth like adult cattle and number of follicles increases from 2 to 14 weeks of age (Evans *et al*. 1994). Thus, it is plausible that the variations in AMH concentrations observed before puberty are reflective of changes in growth patterns of small antral follicles. Another possible explanation is that AMH prepubertal variations are due to changes in the ability of granulosa cells to secrete AMH. Nevertheless, if prepubertal concentrations of AMH would be used to predict the future reproductive function in adult cattle, the age at which samples are collected should be considered.

In prepubertal Rasa Aragonesa lambs (mainly bred for meat and wool production), AMH concentrations tended to increase from 3 to 4.5 months and to decline at 6 months of age, but the within-animal repeatability was low (Lahoz *et al*. 2014). In addition, AMH reached its peak at different times among animals, and prepubertal AMH was not correlated to AMH concentrations in adulthood (Lahoz *et al*. 2014). In Sarda ewe lambs (bred for milk production), AMH was not detectable in individuals with a low AFC; and, in those with a high AFC, AMH concentrations increased from 2 to 5 weeks and declined from 6 weeks of age (Torres-Rovira *et al*. 2016). These reports indicate that in sheep, prepubertal AMH concentrations vary considerably among animals and within individuals across age. Therefore, the potential application of prepubertal AMH as a predictor of the reproductive performance in adulthood in sheep appears limited.

In women, AMH concentrations remain relatively constant during the menstrual cycle (Cook *et al*. 2000, Hehenkamp *et al*. 2006). Evidence is also accumulating that AMH concentrations vary minimally during estrous cycles in cattle. For example, we reported that a single AMH measurement in young adult beef heifers was highly correlated ($r = 0.97$) with the average for multiple AMH measurements during different days of the same or multiple estrous cycles (Ireland *et al*. 2011). In Holstein cows, AMH varied minimally during the same estrous cycle (Rico *et al*. 2009, Souza *et al*. 2015) and on different days of two estrous cycles (Rico *et al*. 2009). Also, AMH concentrations were similar within the same individual during natural and synchronized estrous cycles in dairy cows (Pfeiffer *et al*. 2014). Taken together these findings illustrate the static nature of AMH during the estrous cycle and its repeatability across multiple estrous cycles in cattle. This important finding confirms the usefulness of a single blood sample to reliably determine AMH concentrations in adult cattle.

Factors that impact circulating AMH concentrations

Developmental programming: nutrition, disease, lactation and endocrine disruptors

The environment encountered during fetal life exerts a profound influence on development, physiological function and risk of disease in adult mammals (Barker 2007, Langley-Evans & McMullen 2010). A stimulus or an insult at a critical and sensitive period of fetal or perinatal life has permanent effects on the structure, physiology and metabolism of different organs and systems. This process is named 'programming'. Interest is growing on the potential for programming of the reproductive system in mammals (reviewed by Sloboda *et al*. 2011, Evans *et al*. 2012, Mossa *et al*. 2015), albeit studies investigating programming of the size of the ovarian reserve, and correspondingly of AMH production, in cattle are scarce.

Maternal nutritional status is considered a major cause of fetal developmental programming in humans, cattle and sheep (Gluckman & Hanson 2004, McMillen *et al*. 2008, El Hajj *et al*. 2014, Mossa *et al*. 2015). We tested the hypothesis in cattle that dietary nutritional restriction (to 60% of maternal requirements) has permanent effects on the establishment of the ovarian reserve (total number of morphologically healthy follicles and oocytes) in offspring. We imposed the dietary restriction during the first trimester of pregnancy to coincide with the peak in the number of germ cells in fetal ovaries (Erickson 1966). Female calves born to nutritionally restricted mothers had a diminished ovarian reserve (Mossa *et al*. 2013) as assessed by consistently lower circulating AMH concentrations from 4 months to 1.8 years of age, lower antral follicle count (AFC, number of antral follicles growing during follicular waves) from 7 weeks

to 1.6 years of age and increased FSH concentrations, a phenotypic characteristic of cattle with a low AFC (Burns *et al*. 2005, Ireland *et al*. 2007, Jimenez-Krassel *et al*. 2009, Mossa *et al*. 2010). Interestingly, these heifers had similar birth weights, postnatal growth rates and age at puberty compared to offspring from control mothers (Mossa *et al*. 2013). This finding implies that the formation of the ovarian reserve during embryo/fetal development may be very sensitive to diet manipulation during the first trimester of pregnancy.

Another study reported that high levels of protein fed to dams in the second trimester of gestation reduced the number of healthy antral follicles in the offspring of beef heifers, but AMH concentrations were not measured (Sullivan *et al*. 2010). Rats whose mothers were fed a high-fat diet from conception until the end of lactation had reduced AMH signaling as neonates, but an increased number of primordial and transitioning follicles and higher AMH expression levels as adults compared to offspring of control dams (Tsoulis *et al*. 2016). Further, overfed newborn rats showed a trend for decreased AMH expression (Sominsky *et al*. 2016); whereas, in cattle, maternal overnutrition decreased fetal ovarian follicular development (Weller *et al*. 2016). These studies, albeit using different experimental models and different dietary regimes, provide evidence for the programming of ovarian development and hence of AMH secretion in adulthood in response to nutritional imbalances imposed during fetal life. These findings indicate that both maternal undernutrition and overnutrition reduce AMH circulating concentrations in offspring. Because of the potential impact of maternal nutrition on fertility in female offspring, the effect of maternal diet on the development of the ovarian reserve, and in turn, AMH concentrations, clearly warrants further research.

Another aspect of the concomitant lactational and gestational status in dairy cow is the potential impact of mammary inflammation on fetal developmental programming. Many studies have investigated the developmental origins of different reproductive disorders in humans (Ho *et al*. 2017), but experimental evidence on the potential effects of maternal disease during pregnancy on the ovarian development and function is lacking. Dairy cows with a high number of somatic cell count (SCC) in milk, an index of chronic mammary gland infection (Caraviello *et al*. 2005), produced daughters with reduced AMH concentrations as young adults (Ireland *et al*. 2011). These results, albeit preliminary, imply that persistent mammary infection in the dam during gestation may not only impair her milk production but also have a long-term negative impact on the reproductive potential of her female offspring.

Finally, the potential impact of endocrine-disrupting compounds, natural and artificial components as well as environmental chemicals that may interfere with the physiological actions of hormones, on the offspring

health and reproduction need to be considered (reviewed by Padmanabhan and Veiga-Lopez (2014)). In sheep, excess testosterone exposure prenatally from days 30 to 90 of gestation reduced AMH protein expression in granulosa cells of preantral follicles, but it increased AMH expression in antral follicles of young adult ewes compared to controls. In the same study, no effect was detected in prepubertal female lambs (Veiga-Lopez *et al*. 2012). These findings indicate that prenatal testosterone induces changes in AMH expression, implying that testosterone has a role in regulation of the ovarian reserve.

Taken together, these studies provide evidence for the negative impact on AMH concentrations, and in turn, on the establishment of the ovarian reserve, of different factors that may act during fetal life, specifically nutritional imbalances (under and overnutrition), disease, lactation and endocrine disruptors.

Aging

AMH is considered an excellent clinical indicator of ovarian aging in women (Nelson *et al*. 2012), because, like AFC, circulating AMH concentrations show a high correlation with the size of the ovarian reserve that declines with age (Hansen *et al*. 2011). During aging in mice, the decline in serum AMH concentrations correlates positively with the decline in the number of primordial follicles (Kevenaar *et al*. 2006). Investigations on ovarian aging in domestic species are lacking. A study conducted on primiparous and pluriparous Holstein cows reported no correlation between AMH and parity (Souza *et al*. 2015), whereas another study reported higher AMH concentrations in cows on the second and third lactations compared to those on the first and fourth or greater lactations (Ribeiro *et al*. 2014). These observations imply that AMH concentrations do not decline coincident with the first few years of age in cattle.

Breed

Correlation of AMH concentrations and size of the ovarian reserve in different breeds of cattle have not been reported. However, several studies indicate that AMH concentrations and follicle numbers may be lower in dairy compared with beef cattle. In our laboratory, for example, we have summarized circulating AMH concentrations and follicle numbers and ovarian size determined via ovarian ultrasonography approximately 96 h after prostaglandin $F_{2\alpha}$ treatment for 12- to 16-month-old Holstein dairy and crossbred beef (primarily Angus×Charolais) heifers (Jimenez and Ireland, unpublished). Results (Fig. 2) showed that follicle numbers, ovary size and AMH concentrations were lower ($P < 0.01$) in dairy compared with beef heifers. We also measured AMH concentrations in crossbred dairy Holstein and beef prepubertal female
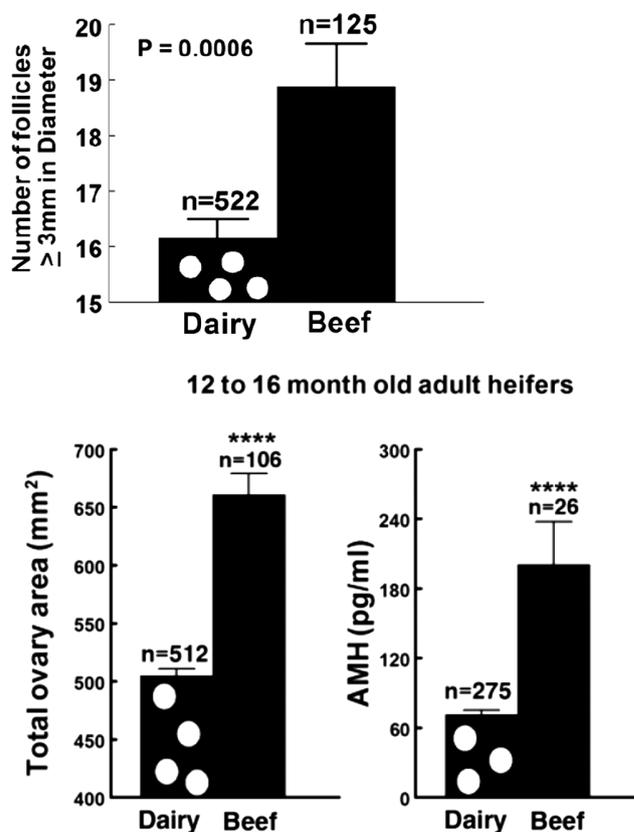
Figure 2 Number of follicles ≥3 mm in diameter (top panel), total ovarian area (mm²) determined using ovarian ultrasonography and circulating AMH concentrations (pg/mL) (bottom panel) approximately 96 h after prostaglandin $F_{2\alpha}$ treatment in 12- to 16-month-old Holstein dairy and crossbred (primarily Angus×Charolais) heifers (Jimenez and Ireland unpublished). Asterisks indicate differences between dairy vs beef (****$P < 0.01$).

calves using the same assay, but we failed to detect a statistically significant difference, possibly because blood samples were collected on different days in dairy and beef calves (Fig. 1). Nevertheless, others report that young adult beef (Angus and Charolais) heifers had increased AMH concentrations compared with dairy (Holstein and Jersey) heifers (Pfeiffer *et al*. 2014). Also, Nelore (*Bos indicus*) zebu beef heifers presented greater plasma AMH concentrations coupled with a larger ovarian antral follicle population than Holstein (*Bos taurus*) heifers (Batista *et al*. 2014).

Whether AMH concentrations differ among dairy breeds, however, is controversial. AMH did not differ between Holstein and Jersey heifers (Pfeiffer *et al*. 2014). Nevertheless, another study conducted on a larger number of animals reports different AMH concentrations among dairy breeds with Jersey cows having the greatest AMH concentrations followed by crossbreds (Holstein×Jersey) and then Holstein (Ribeiro *et al*. 2014). Further, Gyr (*Bos indicus*) dairy zebu heifers had greater AMH concentrations compared

to Murrah buffalo (*Bubalus bubalis*) and Holstein heifers (Baldrighi *et al.* 2014). Thus, it can be assumed that AMH concentrations (1) are higher in beef compared to dairy cattle and (2) vary among genetic groups and breeds among dairy cattle. Whether the relatively low AMH in dairy compared with beef cattle implies they may also have an inherently smaller ovarian reserve, which may contribute to the poorer fertility after calving in dairy compared to beef cows, is unknown.

Granulosa cells

Cattle with a low AFC respond poorly to gonadotropin stimulation during superovulation (Ireland *et al.* 2007); hence, the capacity of granulosa cells to respond to FSH was hypothesized to be diminished in individuals with low vs a high AFC (Scheetz *et al.* 2012). To test this hypothesis, an *in vitro* model was developed to determine whether FSH action on granulosa cells differed between individuals with low compared to high AFC. Concentration of AMH and expression of AMH mRNA were assessed, among a variety of other biomarkers for FSH action, in granulosa cells exposed to different doses of FSH. The basal capacity of untreated granulosa cells to produce AMH was two-fold greater in the high compared to the low AFC group (Fig. 3). Further, granulosa cells from both groups responded in a dose–response fashion to FSH stimulation, but overall AMH concentrations and abundance of AMH mRNA for all FSH doses were lower in the low vs high AFC groups. This finding indicated that granulosa cells from the low AFC group responded minimally to FSH. Cattle with a low AFC have chronically heightened FSH secretion (Burns *et al.* 2005, Ireland *et al.* 2007, Jimenez-Krassel *et al.* 2009, Mossa *et al.* 2010), which may result in the desensitization or uncoupling of FSH receptors from FSH in granulosa cells (Amsterdam *et al.* 2002). This could explain why granulosa cells in cattle with a low AFC were refractory to FSH action and consequently produced less AMH compared to granulosa cells from cattle with a high AFC. In addition, the refractoriness of granulosa cells to FSH could also at least partially explain why cattle (Kawamata 1994, Cushman *et al.* 1999, Taneja *et al.* 2000, Singh *et al.* 2004, Ireland *et al.* 2007) and women (Beckers *et al.* 2002, Broekmans *et al.* 2006, Styer & Toth 2011, Dewailly *et al.* 2014) with a small ovarian reserve and correspondingly chronically high FSH secretion during reproductive cycles respond poorly to FSH stimulation during assisted reproductive technologies.

Correlation of circulating AMH concentrations with ovarian follicle numbers (AFC during follicular waves) and the ovarian reserve

Peripheral AMH concentrations are positively associated with the total number of healthy follicles and oocytes
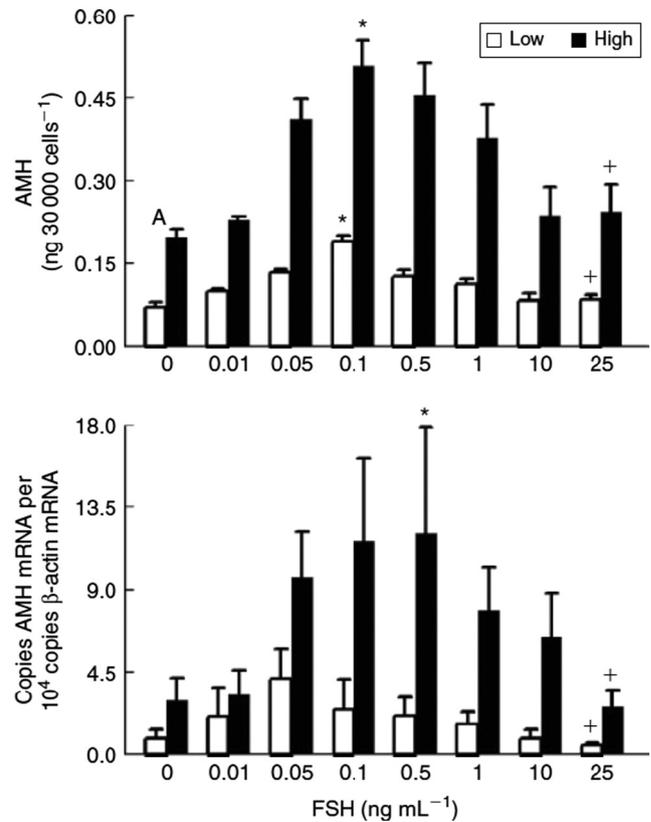
Figure 3 Effect of FSH on AMH production and abundance of AMH mRNA by granulosa cells from cattle with a high vs a low AFC. Granulosa cells were treated *in vitro* with various concentrations of FSH for 6 days. AMH production (top panel) and abundance of AMH mRNA (bottom panel) were measured on Day 6 of culture in the high and low AFC groups. Bars represent the mean±S.E.M. for 3 pools of granulosa cells from 3 to 5 cows per pool. Each pool contained media or cells from 6 culture wells combined. Results of ANOVA indicated that overall AMH concentrations and abundance of AMH mRNA for all FSH doses (0–25 ng/mL) combined were higher ($P < 0.001$) for the high vs the low AFC group. In the top panel, the A above bars at the 0 FSH dose indicates a significant ($P < 0.01$) difference between means. In addition, the asterisk above bars indicates that AMH production increased ($P < 0.001$) linearly in response to FSH doses from 0 to 0.1 ng/mL. The plus symbol indicates that AMH production decreased ($P < 0.05$) linearly in response to doses of FSH >0.1 ng/mL. In the bottom panel, the asterisk above bars in the high AFC group indicates that abundance of AMH mRNA increased ($P < 0.05$) linearly in response to FSH doses from 0 to 0.5 ng/mL, whereas the plus symbol above bars indicates that AMH mRNA abundance decreased ($P < 0.05$) linearly in response to FSH doses >0.5 ng/mL. Also, in the low AFC group, the plus symbol indicated that AMH mRNA decreased ($P < 0.05$) linearly in response to FSH doses >0.05 ng/mL. From Scheetz *et al.* (2012).

in ovaries of mice (Kevenaar *et al.* 2006) and with the number of healthy growing follicles in women (La Marca & Volpe 2006). A high positive correlation ($r > 0.90$) was observed between the variation in AMH, AFC and histological determination of total number of morphologically healthy follicles and oocytes in ovaries of young adult cattle (Ireland *et al.* 2008). In beef heifers,

circulating AMH concentrations were approximately 6- and 2-fold greater in animals with high (≥25 follicles, ≥3 mm in diameter) or intermediate (16–24 follicles) compared with a low (≤15 follicles) AFC during follicular waves. Also, the overall average AMH concentration during ovulatory follicular waves per animal was highly correlated ($r = 0.92$) with average peak AFC during the two or three waves of an estrous cycle (Ireland *et al.* 2008). In another study, AMH plasma concentrations were highly positively correlated with the numbers of 3–7 mm antral follicles detected by ovarian ultrasonography in primiparous dairy cattle (Rico *et al.* 2009). Also, a positive association was detected between the antral follicle population and circulating AMH concentrations in Murrah (*Bubalus bubalus*), Holstein (*Bos taurus*) and Gyr (*Bos indicus*) heifers (Baldrighi *et al.* 2014). It can be concluded, therefore, that AMH and AFC are positively correlated in cattle (Ireland *et al.* 2008, Rico *et al.* 2009, Baldrighi *et al.* 2014) and both AFC and AMH can be used interchangeably and reliably to estimate total number of morphologically healthy follicles and oocytes in the ovaries (ovarian reserve) of an individual (Ireland *et al.* 2008).

Use of AMH as a predictor of fertility

The inherently high variation in the quantity of morphologically healthy follicles and oocytes in the ovarian reserve of individuals may be among the chief factors that contribute to the high variation in fertility among young adults. Thus, reliable biomarkers of the ovarian reserve such as AFC and AMH, which are highly positively correlated with each other, may be used to predict the reproductive potential of an individual. Extensive results have shown that both AFC and AMH are positively associated with several indicators of reproductive efficiency in cattle and sheep.

Fertility

When AMH concentrations were determined in prepubertal ewe lambs, AMH was higher in those animals that subsequently became pregnant after the first mating compared with individuals that became pregnant after the second mating or were not pregnant (Lahoz *et al.* 2012). Although similar studies have not been done in cattle, in our recent work, AMH concentrations were determined in young adult Holstein heifers at 11–12 months of age and a variety of fertility measurements made before and after calving in the same individuals. Results showed that conception rates to first artificial insemination (AI), services per conception and days open after calving until pregnant were similar among individuals in the different AMH quartiles before calving and during the first, second and third lactations. However, the quartile (Q) of cows with the lowest AMH concentrations (Q1) as heifers tended ($P < 0.10$) to be

lower at each lactation and had the lowest overall average for total percentage pregnant compared with cows in Q2 or Q3 but not Q4 AMH quartiles (Jimenez-Krassel *et al.* 2015). These findings contrast somewhat with our other study that examined fertility in dairy cows (up to 8 parities) with low, intermediate or high AFC and presumably corresponding differences in AMH concentrations. In this study, dairy cows with a low AFC had a lower conception rate to first AI, greater number of AI to conceive and higher calving interval compared with cows with an intermediate or high AFC (Mossa *et al.* 2012). Like our finding for dairy cows with low AMH as a heifer (Jimenez-Krassel *et al.* 2015), overall pregnancy rate was lower for the dairy cows with a low compared with a high AFC (Mossa *et al.* 2012). Another study shows that dairy cows with high AMH had greater pregnancy rates and lower incidence of pregnancy loss between days 30 and 65 of gestation (Ribeiro *et al.* 2014). Lower fertility for cattle with a relatively low AFC is further supported by evidence of lower pregnancy rates in beef heifers with a low vs a higher AFC (Cushman *et al.* 2009) and by a study showing that lactating cows with a low AFC had a longer interval from calving to conception and lower pregnancy rates than cows with a high AFC (Martinez *et al.* 2016).

The reasons for the differences between some fertility measurements in the studies that classified cattle based on AMH or AFC are unknown but likely caused by relatively small numbers of cattle in AMH quartiles and some AFC groups coupled with mixed ages of cows in AFC groups. In addition, cross-sectional studies using older cows may be biased by previous removal (culling) of individuals from the herd with a relatively low AFC or AMH. Nevertheless, combined results (Cushman *et al.* 2009, Mossa *et al.* 2012, Jimenez-Krassel *et al.* 2015, Martinez *et al.* 2016) imply that fertility is suboptimal in cows with low AMH concentrations as heifers and in cows with low AMH or a low AFC compared with herd mates with higher AMH concentrations or a higher AFC.

Longevity

In farm species, the ability to conceive with the minimum number of services and, the shortest time after calving and to deliver a healthy offspring, is essential for profitable farming, and this is particularly true for dairy cattle. Thus, we tested the hypothesis that cattle with the lowest AMH concentrations have suboptimal fertility and are removed from a herd for poor reproductive performance at a greater rate and therefore have a shorter productive herd life (time in herd after calving) compared with age-matched herd mates with higher AMH (Jimenez-Krassel *et al.* 2015). A single AMH measurement was made in 281, 11- to 15-month-old Holstein heifers. Records on reproductive performance, level of milk production, health and reasons for culling for each individual were collected. Animals were
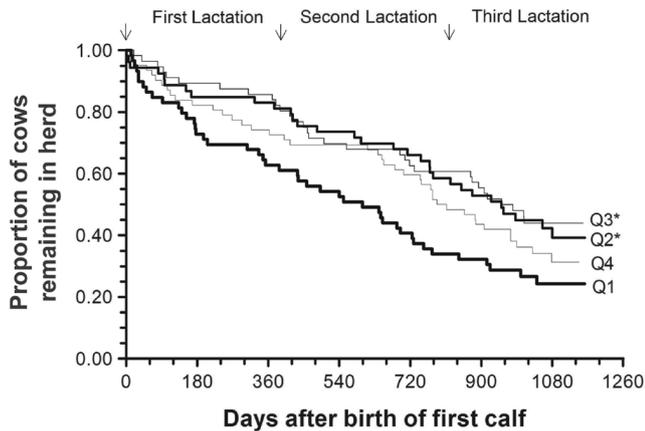
Figure 4 Kaplan–Meier plots of survival curves for proportion of Holstein cows in each AMH quartile (where Q1 = quartile of heifers with the lowest AMH concentration) remaining in the herd after birth of their first calf. Asterisk indicates that survival rate for Q1 differs from that for Q2 ($P < 0.02$) or Q3 ($P < 0.01$); survival rate in Q1 tended ($P = 0.13$) to differ from that in Q4. From Jimenez-Krassel *et al.* (2015).

partitioned into quartiles (Q1, Q2, Q3 and Q4) based on AMH concentrations as heifers and data were analyzed after animals completed three lactations. Q1 cows with the lowest AMH concentrations as heifers completed fewer lactations compared to Q3 cows and had a 180-day average shorter productive herd life compared with Q2 and Q3 cows. By the end of the study 24, 37, 43 and 32% of the cows in Q1, Q2, Q3 and Q4 respectively remained in the herd, but the probability of being culled after birth of the first calf was higher for the Q1 compared with Q2, Q3 and Q4 cows (Fig. 4). Also, removal rate for poor reproductive performance compared with all other reasons for culling was greater for Q1 compared with Q2, Q3 and Q4 cows combined during the first lactation (Jimenez-Krassel *et al.* 2015). This study, albeit conducted on a limited number of animals, indicates that a single determination of AMH concentrations in young adult Holstein heifers is predictive of their future herd longevity. In addition, because level of milk production was not correlated with AMH concentrations (Jimenez-Krassel *et al.* 2015), the potential application of AMH assessment to identify heifers with superior reproductive performance without compromising milk production appears promising.

Superovulation

Both AMH and AFC are used to predict the response to ovarian stimulatory treatments during ART (Broekmans *et al.* 2006). Such responsiveness is negatively associated with aging and is linked to a reduction in number of follicles and oocytes in ovaries in women (Beckers *et al.* 2002, Styer & Toth 2011, Dewailly *et al.* 2014) and in cattle (Kawamata 1994,

Cushman *et al.* 1999, Taneja *et al.* 2000, Singh *et al.* 2004). We documented for the first time that young adult cattle with low AFC have a diminished responsiveness to superovulation (lower number of corpora lutea and of recovered embryos/unfertilized oocytes) and produced fewer high-quality embryos compared to age-matched cattle with high AFC (Ireland *et al.* 2007). Also in *Taurus indicus* Braford cattle (Bhraman × Hereford crossbred animals), AFC assessed before puberty was predictive of the response to superovulation at 24 months of age assessed by higher number of total oocytes and embryos recovered (Silva-Santos *et al.* 2014). Similarly in sheep, a positive association was observed between follicle numbers and responsiveness to superovulation in both adult and prepubertal individuals (Mossa *et al.* 2007, Torres-Rovira *et al.* 2014). In summary, it is clear that AFC represents a reliable index of the ovarian response to stimulation in cattle and sheep, as it is in women (Broekmans *et al.* 2006).

Evidence is now growing to support the use of AMH as a predictor of the responsiveness to ovarian stimulatory treatment in agricultural species. In primiparous dairy cows, AMH concentrations before the superovulatory treatment were positively correlated with the number of follicles before treatment and with the numbers of large follicles and corpora lutea (CL) after treatment (Rico *et al.* 2009). In non-lactating Holstein cows, plasma AMH concentrations before gonadotropin treatments were highly correlated with the numbers of large follicles and oocytes recovered at ovum pick up (OPU), as well as with the number of large follicles at estrus and the number of embryos collected from multiple ovulation and embryo transfer protocols (Rico *et al.* 2012). Further, in Japanese Black beef cattle, AMH concentrations were positively correlated with the number of follicles, number of oocytes/embryos recovered fertilized embryos and transferable embryos (Hirayama *et al.* 2012). In lactating Holstein cows, AMH concentrations for each individual cow were correlated with superovulation response (number of CL on the day of the flush), total oocytes collected and total transferable embryos. Also, when cows were classified into quartiles of circulating AMH, Q4 cows had a >2-fold greater response to superovulation including embryo production compared with cows (Souza *et al.* 2015).

A positive correlation between AMH and OPU coupled with *in vitro* embryo production was established in Holstein (Vernunft *et al.* 2015), beef (Korean Hanwoo) (Ghanem *et al.* 2016) and *Bos Indicus* (Zebu) cattle (Guerreiro *et al.* 2014). In addition, AMH concentrations before treatment were predictive of the response to superovulation in sheep (Lahoz *et al.* 2014), goats (Monniaux *et al.* 2011) and mares (Claes & Ball 2016). These findings confirm the positive association between the response to superovulation and the ovarian reserve and support the use of AMH assessment to select donors for embryo production. In addition, elimination of

recipients with low AMH or low AFC may also improve success of embryo transfer in cattle.

Summary and conclusion

Evidence indicates that AMH concentrations in cattle (1) increases in the first months of age and decreases thereafter until puberty; (2) is repeatable in the same or multiple estrous cycles within individual young adults; (3) can be negatively programmed by factors acting during fetal life (i.e. maternal undernutrition, mastitis, excess testosterone); (4) is higher in dairy than beef breeds and varies among breeds and genetic groups; (5) is positively correlated with AFC; (6) is a reliable indicator of the total number of ovarian follicles and oocytes and (7) is positively associated with measures of fertility (pregnancy rate, herd longevity and response to superovulation). Taken together, these findings support the potential use of AMH as a predictor of fertility and longevity in cattle.

Most reproductive traits are lowly heritable (0.02–0.04) in cattle (Berry *et al*. 2014). However, we have recently shown that AFC is moderately heritable in dairy cows (0.30 ± 0.14) and heifers (0.25 ± 0.13) (Walsh *et al*. 2014). As AFC is highly correlated with AMH concentrations and size of the ovarian reserve (Ireland *et al*. 2008, Rico *et al*. 2009, Baldrighi *et al*. 2014), it is plausible that AMH, like AFC, may be moderately heritable. If true, AMH could be included among the traits used to select males and hence improve animal breeding schemes.

In addition, because levels of milk production were not correlated with AMH concentrations (Jimenez-Krassel *et al*. 2015), the potential application of AMH assessment to identify heifers with a superior reproductive performance without compromising milk production appears promising. In contrast to cattle, the limited number of studies conducted in sheep indicate that AMH concentrations before puberty are not correlated with AMH in adulthood (Lahoz *et al*. 2014) but are positively associated with fertility at first mating. In this and other farm species, the potential association between AMH and reproductive performance remains largely unexplored.

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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