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Anti-Müllerian hormone: a new approach to fertility assessment in cattle – a review

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ABSTRACT

The anti-Müllerian hormone (AMH) enhances fertility in cattle and hence used as a fertility marker. AMH is produced by granulosa cells of all primordial, primary, secondary follicles, and antral follicles up to 4-5 mm diameter, whereas AMH production decreases once antral stage follicles reach the 4-5 mm stage. There is an individual variation in antral follicle count (AFC) and AMH concentration. One-time determination of AMH concentration will help predict the animals' reproductive performance at the heifer stage. In turn, it will help to cull those animals with low reproductive potential. There is no significant fluctuation in the AMH concentration during the estrous cycle, and hence it can be determined at any stage of the estrous cycle. This review explores the potential of AMH as a fertility marker and its association with the antral follicle population (AFP) as AMH can be an effective segregative tool to screen low, average or high fertility future performance in cattle.

Key words: anti-Müllerian hormone; antral follicle count; cattle; endocrine marker; fertility marker; müllerian inhibiting substance.

Anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance (MIS), is a glycoprotein of 140 kDa belonging to the transforming growth factor-beta family, which is only expressed in the gonads (CATE et al., 1986). In contrast to other members of the family, which exert a broad range of functions in multiple tissues, the principal function of AMH is to induce regression of the Müllerian ducts during male sex differentiation. In ovaries, it inhibits the recruitment of primordial follicles into the pool of growing follicles, and it decreases the responsiveness of growing follicles to follicle-stimulating hormones (DURLINGER et al., 2002). The discovery of

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AMH dates back to the middle of the last century when Alfred Jost, a French physiologist, showed that when fetal gonads were removed in utero, the Müllerian ducts developed while the Wolffian ducts regressed. Presently, AMH is one of the endocrine markers of the ovarian follicular reserve in humans; in mice, recent studies have also confirmed it as a potent fertility marker in cows (RICO et al., 2009).

Over the past ten years, attention has been focused on AMH in humans in the context of assisted reproductive technologies (ART). Numerous clinical studies have shown that low plasma AMH concentrations indicate ovarian aging, and conversely, women with polycystic ovary syndrome have high AMH concentrations (FALLAT et al., 1997). AMH is the best predictor of the number of oocytes retrieved in response to an ovarian stimulatory treatment in ART. The development of reliable screening of productive cattle would represent a significant advancement in multiple ovulation and embryo transfer technology (MOET).

Broadly, it can be classified into low, intermediate, or high AFC (MOROTTI et al., 2015). Progesterone production has been linked to the physiological activity of the corpus luteum and the functionality of the ovaries and uterus, with a direct impact on embryonic development and pregnancy in cattle (POHLER et al., 2012). In cattle, circulating AMH concentration can help veterinarians to predict the antral follicular population (AFP) in the ovaries (IRELAND et al., 2008; RICO et al., 2009; BATISTA et al., 2014), and response to superovulation treatments (RICO et al., 2009, MONNIAUX et al., 2010, SOUZA et al., 2015). In addition, studies performed in the last decade have also indicated that cows with a lower number of antral follicle counts have lower fertility (MOSSA et al., 2012). Therefore, since circulating AMH is an indirect measure of ovarian reserve, represented by the size of the ovarian follicle pool, later studies have explored the use of AMH to predict field fertility in cattle (RIBEIRO et al., 2014, JIMENEZ-KRASSEL et al., 2015). The value of AMH for predicting field fertility may vary according to the type of reproductive management employed on the farm since it appears that AMH could not be associated with field fertility in artificially inseminated cows (RIBEIRO et al., 2014).

The anti-Müllerian hormone is produced by granulosa cells of all primordial, primary, secondary follicles, and antral follicles up to 4 to 5 mm diameter. It reflects the total number of healthy follicles within the ovaries. Anti-Müllerian hormone production decreases after antral stage follicles reach the 4 to 5 mm stage, allowing these follicles to regain responsiveness to the follicle-stimulating hormone, and undergo final maturation (VISSER et al., 2006). However, the question arises as to how early in development AMH can be measured as an indicator of fertility. Identifying heifers with low or high fertility at birth or weaning would be advantageous to producers for making management decisions. If the measure of AMH at weaning could predict subsequent fertility, this would reduce replacement heifer costs and identify less fertile heifers at an early age which would allow their marketing as stocker-feeder cattle at a more optimal time.

The potential of AMH as an early fertility marker has grabbed the attention of many researchers, as is evident from recent publications. The main question here is whether the circulating concentration of AMH is correlated with fertility. The present review summarizes current information concerning AFP and its association with AMH, and the possibility of utilizing AMH as a biomarker for reproductive technologies to enhance cattle fertility.

Alterations of AMH from birth to puberty. Understanding the variations of AMH concentrations during life is pivotal to appreciate its potential application as a biomarker for fertility in cattle and other farm species. Many researchers have conducted studies to illustrate AMH changes from birth to puberty in Holstein female calves. The results show that AMH concentrations increase during the first two months of life, decrease at 5 months, and are stable at 8–9 months of age during the first ovulation. In another study of Maine-Anjou beef heifers, plasma AMH concentrations were found to increase rapidly between 1 and 3 months of age, remain high at 6, and decline slowly until 12 months of age, which is in agreement with the period of ovulation for this breed (MONNIAUX et al., 2012). These findings are similar to the results

of other researchers, indicating that 3- to 4-month-old calves have higher AMH concentrations compared to young adult heifers in both Holstein (14–16 months) and Bos indicus Nelore (18–24 months) cattle (BATISTA et al., 2016). In another study of Holstein Friesian crossbred cattle (n=151), the AMH concentrations changed significantly ($P<0.05$) between the related groups of animals. They detected the AMH concentration at the age of 3 months (0.26±0.03 ng/ ml). After that, it increased until 3 years of age and then remained constant (≥ 2 ng/ ml) with slight fluctuations until 8 years of age, and again started a progressive decline in AMH concentration (0.37±0.10 ng/ ml) up to 15 years of age (HALDAR et al., 2019).

However, ALI et al. (2017) investigated AMH concentrations in eleven Japanese Black heifers from birth to the sixth week after puberty. They observed that plasma AMH concentrations were higher ($P<0.001$) in early puberty compared to late puberty (0.69±0.08 vs. 0.37±0.22 ng/ml, respectively). They further concluded that heifers exhibit a characteristic plasma AMH profile during postnatal life. Determining the concentration of AMH at an early prepubertal age could be a biomarker for predicting the age of puberty onset and postpubertal AMH levels associated with future fertility. Other researchers studied the concentration of AMH in males, females, and freemartins from birth to puberty, in Holstein Friesians. They reported that the AMH concentrations are similar in newborn males and freemartins at birth and about sevenfold lower in females as compared to males (ROTA et al., 2002). Prepubertal heifers experience waves of antral follicular growth like adult cattle, and the number of follicles increases at from 2 to 14 weeks of age (EVANS et al., 1994). Thus, it is plausible that the variations in AMH concentrations observed before puberty reflect changes in the growth patterns of small antral follicles. As far as small ruminants are concerned, in prepubertal Rasa Aragonesa lambs AMH concentrations increased from 3 to 4.5 months and declined at six months of age (LAHOZ et al., 2014).

AMH in heifers. Determination of AMH concentrations in young heifers may be a simple diagnostic method to predict herd longevity. AMH may be a useful genetic marker to improve breeding schemes and enhance production longevity (JIMENEZ-KRASSEL et al., 2015). To date, many researchers have proved that the livestock presenting low AMH concentration have corresponding lower fertility/conception rates, viz., LAHOZ et al. (2012) in ewes, and GUERREIRO et al. (2014); BATISTA et al. (2014); PFEIFFER et al. (2014); RIBERIO et al. (2014); CHACHERE (2015); SOUZA et al. (2015); JIMENEZ-KRASSEL et al. (2015); VERNUNFT et al. (2015); STOJSIN-CARTER et al. (2016); NEWBERRY (2016); RORIE et al. (2016); SILVA et al. (2016); HIRAYAMA et al. (2017); ALI et al. (2017); CENTER et al. (2018); BATISTA et al. (2016) and KAVYA et al. (2017) in cattle, respectively. Another recent study in buffaloes by KEKAN et al. (2019a) established significant variations ($P<0.01$) in AMH concentrations, and found that buffaloes with AMH concentrations above 200 pg/ml conceived comparably to low AMH concentration animals (Table 2). They attributed the low AMH concentration in non-pregnant buffaloes to a higher rate of follicular atresia and lower AFC (KAVYA et al., 2017).

In future, the heifers with low AMH concentration can be removed owing to low, suboptimal fertility or poor reproductive performance, as the relationship between AMH concentration and reproductive efficiency has been established in our literature. A single determination of AMH concentration in heifers may be used as an essential diagnostic tool to predict herd longevity and as a phenotypic marker to improve longevity in buffaloes (JIMENEZ-KRASSEL et al., 2015) and cows (HALDAR et al., 2019). Also, AMH measurements can validate the selection of ovum pick-up (OPU) donors for breeding, and accelerate intensive breeding (FUSHIMI et al., 2019).

Determining the AMH concentrations at the heifer stage can confirm fertility, save time and the cost of multiple artificial inseminations (NEWBERRY, 2016; RORIE et al., 2016) and culling unproductive livestock. For example, RICO et al. (2012) suggested that the animals with low AMH concentration, i.e., below 150 pg/ml, remained non-pregnant, and (KEKAN et al., 2019a) found that buffaloes with AMH concentration

above 200 pg/ml conceived successfully. However, further investigations are required to establish the AMH cut-off levels for different livestock species (CHACHERE, 2015).

AMH, AFC and progesterone. Recent studies have indicated that the antral follicle population might be of paramount importance to improve reproductive performance in cows. The antral follicle count (≥3 mm in diameter) is already agreed to be a highly variable trait among animals, with high repeatability and individual variations. Increased variability and repeatability of the maximum numbers of antral follicles >3mm in diameter during follicular waves were recorded during the estrous cycle (STARBUCK-CLEMMER, 2007; CUSHMAN et al., 2009; EVANS et al., 2010) in cattle (WARRIACH and AHMAD, 2009; SHAHZAD et al., 2014; YILMAZ et al., 2014; KEKAN et al., 2018) in buffaloes and Holstein heifers (BURNS et al., 2005). In cattle, the development of a follicular wave is characterized by the recruitment and synchronous growth of many antral follicles, followed by selection and growth of a dominant follicle and regression of subordinates. The presence of a dominant follicle not only suppresses the next follicular wave but regresses subordinate follicles. A typical estrous cycle consists of either one or two waves, with wave emergence detected on day 0 (day of ovulation) and day 10, or days 0, 9, and 16 (GINTHER et. al. 1996; NOSIER, 2003).

Follicular waves are not exclusive to cyclicity but also occur before puberty, during pregnancy, and in anestrus. However, these waves have dominant follicles that produce enough estradiol for ovulation and estrus (CHACHERE, 2015). The dominant follicle attains its maximum diameter on days 7 and 17 in two-wave cycles, whereas in three-wave cycles the second dominant follicle begins to regress on day 19 when it is replaced by a third large dominant follicle, which is the ovulatory follicle in all three wave cycles (TAYLOR and RAJAMAHENDRAN, 1991; NOSIER, 2003). A similar observation was reported in the study by KEKAN et al., (2019b) in Murrah buffaloes (Fig. 1). Several studies have shown the prevalence of 2-wave follicular activity during the estrous cycle in cattle. This could be attributed to the high incidence of 2 or 3 waves of follicular activity, based on the presence of 2 or 3 peaks of gonadotrophic hormones, particularly FSH. The peaks of FSH are also related to lower estrogen concentration, which in turn depends on the regression in follicular size. Genetic predisposition or uncontrolled environmental conditions may also play an important role in regulating the incidence of 2 or 3 follicular waves within one estrous cycle through their influence on follicular development and the concentration of their estrogen secretion (GINTHER et. al. 1996; NOSIER, 2003).

Fig. 1. The dominant follicle developed on day 7th (A) and 17th (B) of the estrous cycle in Murrah buffaloes. Adapted from KEKAN et al. (2019b)

Low progesterone concentrations are associated with high rates of embryonic mortality, less healthy oocytes, and slower growth of the endometrium in females. Low AFC animals showed low concentrations of progesterone during their estrus cycle in comparison with high AFC females. The lower circulating concentrations of progesterone in cows with low AFC were mainly attributed to the decreased function of the corpus luteum, possible changes in the responsiveness of luteal cells to LH, a potential reduction in STAR protein in the corpus luteum, diminished responsiveness of the granulosa and luteal cells to 25-hydroxycholesterol, and the reduced ability of the granulosa cells of the dominant follicles to undergo luteinization in order to produce progesterone (JIMENEZ-KRASSEL et al., 2009). The peripheral plasma progesterone profile in buffalo is similar to that in cattle, and the progesterone concentrations rise and fall in coordination with the growth and regression of the corpus luteum. The peripheral progesterone concentrations are minimal on the day of estrus, then rise to peak concentrations on days 13 to 15 of the cycle, or even on day 17, before declining to the basal concentrations at the onset of the subsequent estrus (Fig. 2). Progesterone concentrations continue to increase in animals that conceive, but drop three days before the subsequent estrus without successful conception (MONDAL et al., 2007). The decline in progesterone concentrations towards the end of the cycle and the sharp rise during luteal development suggest that the functioning of corpus luteum can be monitored by determination of progesterone Similarly, cattle and buffalo exhibited both overt estrus and silent estrus (MONDAL et al., 2010).

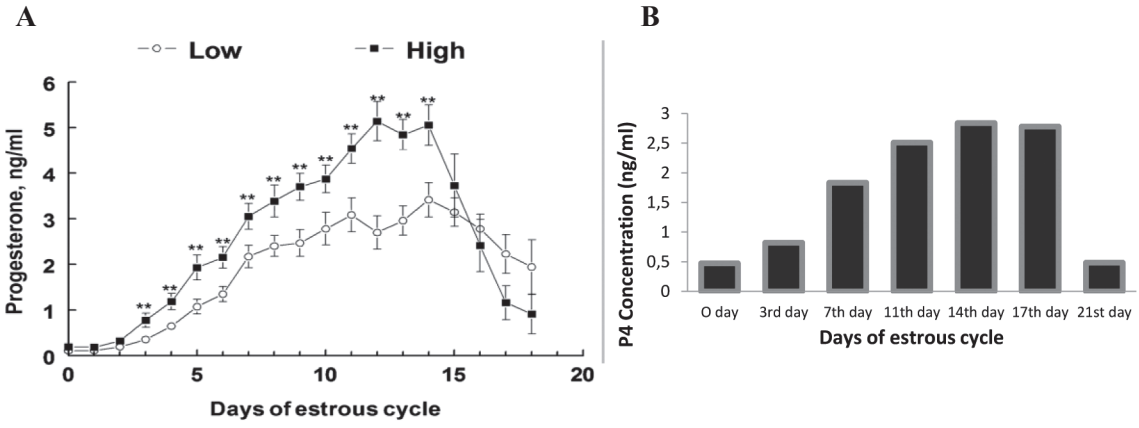

Fig. 2. (A) Alterations in serum concentrations of progesterone during the bovine estrous cycle (day 0 = estrus, day 1 = ovulation)
Blood samples were obtained daily during different days of the estrous cycle for animals in the low vs. high group in study 1 (3- to 5-yr-old Holstein dairy cows, n=3 animals or estrous cycles per group), study 2 (crossbred beef heifers, 19.8 ± 0.7 mo old, n=11 or 14 animals or estrous cycles per group), and study 4 (crossbred beef heifers, 10- to 12-mo-old, n=4 animals or estrous cycles per group). Each symbol represents the daily mean (±SEM) progesterone value for animals with consistently low (≤15 follicles per wave, n=32 estrous cycles for 25 animals) vs. high (≥25 follicles per wave, n=30 cycles for 22 animals)AFC during follicular waves. Asterisks indicate significant differences (**P<0.01) between groups. ANOVA indicated the overall significant effect of group (low vs. high, P<0.02), day of cycle (P<0.001), and group by day interaction (P<0.001; JIMENEZ-KRASSEL et al. 2009). (B) A similar trend of P4 concentration in Murrah buffaloes was reported by KEKAN et al. (2019c) in Murrah buffaloes during the estrous cycle.

Many researchers observed a positive correlation between antral follicular count and fertility. ALVAREZ et al. (2000) and MOSSA et al. (2012) observed that cows with low AFC (>3mm) did not conceive, whereas cattle with higher AFC became pregnant easily. Failure to conceive might be due to an association between low AFC, enhanced FSH secretion, and decreased progesterone production, resulting in an increased embryo mortality rate (EVANS et al., 2010; IRELAND et al., 2011).

This confirmative variation in follicle numbers observed during follicular waves during estrous cycles in young cattle can be used for phenotyping cattle on the basis of antral follicle count as cattle with a relatively low number of follicles have numerous phenotypic characteristics usually associated with infertility (BURNS et al., 2005). Other factors, such as maternal nutrition and disease during pregnancy, may contribute inherently to the high variation in the number of follicles during follicular waves and, correspondingly, the size of the ovarian reserve in their offspring (MOSSA et al., 2009). However, an insignificant number of researchers have reported a lack of association between conception rate with antral follicle count in cattle (STARBUCK- CLEMMER, 2007; SANTOS et al., 2016; CUNHA et al., 2020).

AMH during the estrous cycle. Multiple studies have shown that there is no consistent fluctuation in AMH concentrations during the estrous cycle in cows (RICO et al., 2009; ALI et al., 2013; MONNIAUX et al., 2012; SOUZA et al., 2015; STOJSIN- CARTER et al., 2016; AKBARINEJAD et al., 2017), Murrah buffaloes (PFEIFFER et al., 2014; BATISTA et al., 2016; KEKAN et al., 2019b). In their study, RICO et al. (2011) observed a notable decrease in AMH concentration after estrus, dipping to the lowest concentrations between days 4 and 9 of the estrous cycle, followed by a slow increase until the next estrus (Fig. 3). In a recent study, KEKAN et al. (2019b) observed a similar trend for AMH concentrations (with slightly higher AMH concentrations) in Murrah buffaloes, which confirms the rhythmic AMH secretions during the estrous cycle in cattle.

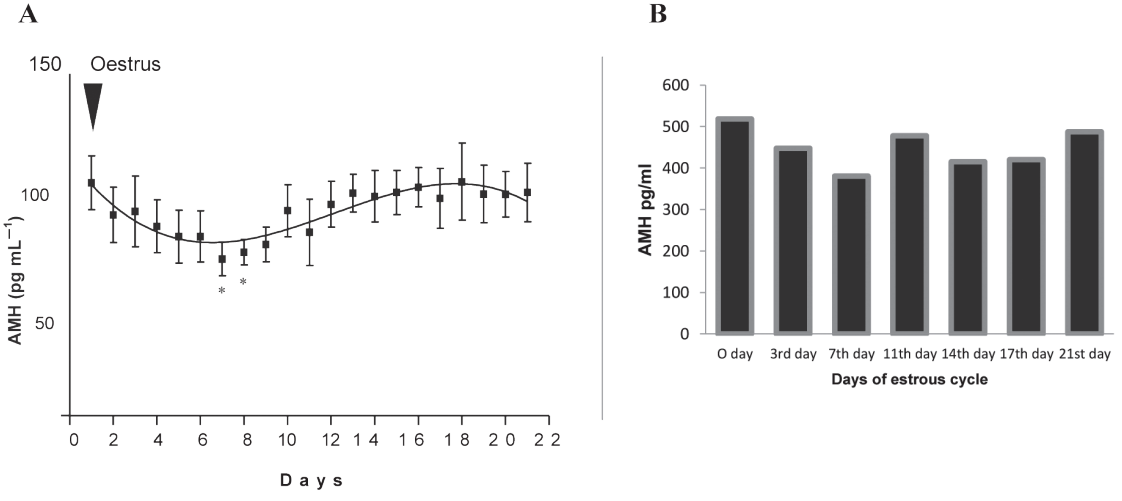

Fig. 3. (A) Daily changes in AMH concentration during the estrous cycle in cows (RICO et al., 2011) and (B) concentration of AMH on 0, 3, 7, 11, 14, 17, and 21 days of the estrous cycle in Murrah buffaloes (KEKAN et al., 2019c)

The expression of AMH within the follicle is dependent on the stage of follicular development. Regarding the ovarian concentration of AMH, the size of the pool of small antral follicles determined ovarian AMH production. AMH followed the specific dynamic profile of the endocrine concentration during the estrous cycle (RICO et al., 2011) which occurred independently of the follicular waves of terminal follicular development. The non-significant decrease in AMH concentration following estrus is not associated with concomitant changes in the number of follicles. However, it results from the FSH inhibition on the granulosa cells of the AMH secreting follicles (MONNIAUX et al., 2012). The inhibitory action of LH, GH, or prolactin on AMH production is still unclear. Nevertheless, the decline in AMH concentration after estrus may be in response to pre-, and periovulatory FSH surges on the granulosa cells of the small antral, high AMH-producing follicles (MONNIAUX et al., 2012).

Bovine granulosa cells with low antral follicle counts are less sensitive to FSH (in terms of FSH induction of in vitro estradiol production) compared with granulosa cells from cows with high antral follicle counts, which is due to the expression of lower FSH-receptor mRNA in granulosa cells (SCHEETZ et al., 2012). In addition, cows with low antral follicle counts have elevated FSH concentrations, which primarily down-regulate follicular FSH sensitivity to exogenous FSH stimulation (IRELAND et al., 2011). In contrast, in other animal models, sensitivity to FSH was generally decreased by higher AMH concentration. Both in vitro and in vivo studies on mouse models revealed that AMH positively inhibited FSH-stimulated growth of preantral follicles (DURLINGER et al., 2001).

Studies during the past decade have established a positive association between AMH and fertility in livestock (IRELAND et al., 2011; RIBERIO et al., 2014; JIMENEZ-KRASSEL et al., 2015; KEKAN et al., 2019b). However, others have reported high, low, or no association of AMH and fertility in cattle, heifers, and equids, respectively. RICO et al. (2009), SCHEETZ, (2010), RICO et al. (2011), ALI et al. (2013), MONNIAUX et al. (2012), SOUZA et al. (2015), BATISTA et al. (2016), IRELAND et al. (2011) highlighted that growing follicle numbers during follicular waves and AMH concentration can be reliably used for phenotyping cattle for fertility. They suggested that cattle with a relatively low number of follicles during follicular waves are associated with infertility. In contrast, CARVALHO et al. (2015) and SILVA et al. (2016) did not observe any interaction between AMH and reproductive performance in lactating cows and heifers, respectively. Although AMH concentrations are highly variable between animals, according to follicle numbers, there are day-to-day alterations in AMH concentrations, which are relatively static during reproductive cycles within individual heifers and cows (IRELAND et al., 2008).

Correlation of AMH and AFC. Multiple studies have indicated a positive correlation between AMH and AFC size, 3-5 mm (EVANS et al., 2010; RICO et al., 2011; IRELAND et al., 2011; HIRAYAMA et al., 2012; BATISTA et al., 2014; BALDRIGHI et al., 2014; RIBERIO et al., 2014; GOBIKRUSHANTH et al., 2016a. and 2016b; MACULAN et al., 2017; CENTER et al., 2018) in cows, JIMENEZ-KRASSEL et al. (2015), BATISTA et al. (2016) in heifers, KEKAN et al. (2019b) in Murrah buffaloes and READHEAD et al. (2018) in water buffaloes. A moderate correlation between AMH and AFC at an unknown stage of the estrous cycle was also reported by GOBIKRUSHANTH et al. (2017). But no correlation was observed between AMH and antral follicle count of 5-8 and >8 mm by MONNIAUX et al. (2011) and KEKAN et al. (2019b). In this context, AMH has been correlated with AFP in Murrah, Holstein, and Gyr cattle (BALDRIGHI et al., 2014). Whereas Batista et al., 2014 correlated AMH and AFP in Holstein heifers and Nelore heifers, where both of them observed significant variations in AMH and AFP between genetic groups (Fig. 4).

Anti-Müllerian hormone concentration and antral follicle populations could be used as an indicator trait in cattle to improve fertility rates genetically, and to identify potent oocyte donors (LAIS et al., 2020). A positive correlation of AFC

with AMH concentrations is a good indicator for high, medium, and low AFC, especially in cattle. AFC could possibly be associated with the fertility predictors that use AMH, without actually analyzing AFC in cattle. A producer can simply look at AMH concentrations before ovulation for effective screening.

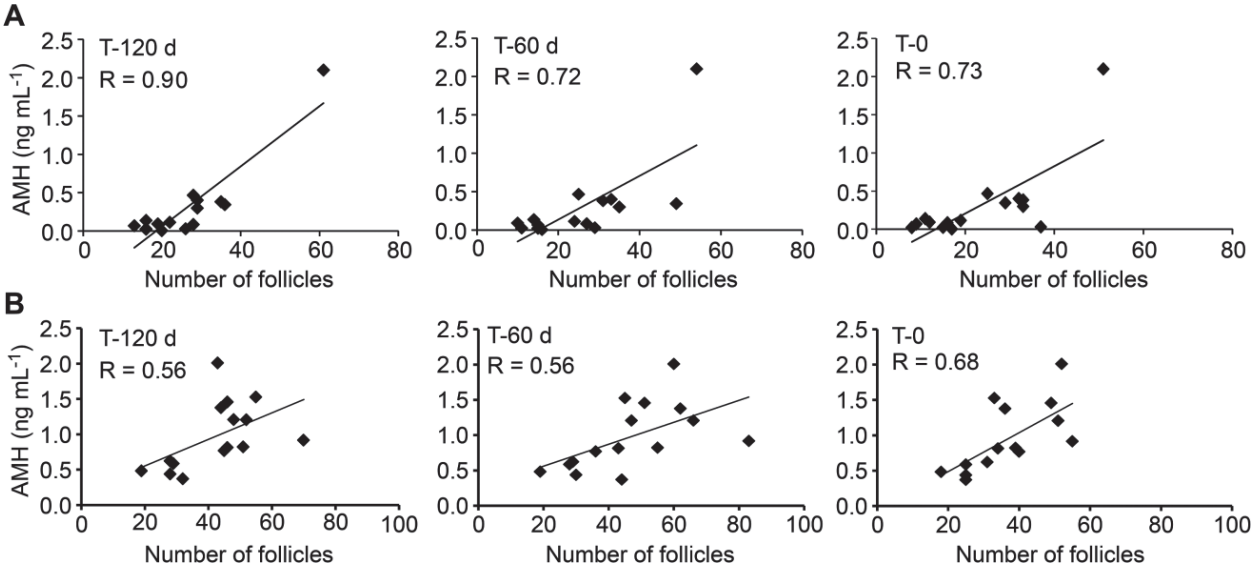

Fig. 4. The relationship between the numbers of follicles counted at T-120, T-60, and T0 and plasma AMH concentration (ng/ml; T0) in Holstein heifers (n=16; A) and Nelore heifers (n=16; B)
The ovarian antral follicular population (AFP) was evaluated three times at 60-day (d) intervals (T-120, 120 days before plasma AMH determination; T-60, 60 days before; and T0, at the time of plasma AMH determination). Blood samples were collected by jugular venipuncture on day T0 of the experimental design. Adapted from BATISTA et al. (2014).

Further, SCHEETZ (2010) stated that concentrations of AMH did not change with AFC groups during 6 to 8 days before ovulation but were ~2 to 6- fold higher in animals in the high and medium AFC groups compared with animals in the low AFC group. In contrast, PFEIFFER et al. (2014), BARUSELLI et al. (2016), and KAVYA (2017) found no correlation between AMH and AFC in cows and buffaloes, respectively. According to PFEIFFER et al. (2014), the correlations amongst gonadotropins, AFC, and AMH during the estrus cycle were complex and unclear, as the capacity of granulosa cells to produce AMH depends on the concentration of FSH, which in turn depends on gonadotropin stimulus. An increase or decrease in FSH surges causes variations in the production of AMH by granulosa cells. A decline in AMH production could be attributed to the luteinization of granulosa cells (VISSER et al., 2006). They further stated that low FSH concentration resulted in the increased production of AMH concomitant with increased production of estradiol. It seems that the effects of gonadotropins on the regulation of ovaries and ovarian endocrine functions will require further basic research and elucidation.

AMH and fertility. Varying AMH concentrations have also been associated with fertility in dairy cows by many researchers (RIBEIRO et al., 2014; JIMENEZ-KRASSEL et al., 2015; KEKAN et al., 2019b; AKBARINEJAD et al., 2020; ALWARD and BOHLEN, 2019). For example, a study from Florida, USA, reported that cows with low AMH

concentrations had a lower conception rate after their first service and more incidence of pregnancy loss between day 30 and 65 of gestation (RIBEIRO et al., 2014; AHMET et al., 2019). Similarly, heifers with low circulating AMH concentrations had lower survival rates than herd mates with greater AMH concentrations (JIMENEZ-KRASSEL et al., 2015). In another study, RIBEIRO et al. (2014) established a positive association between circulating AMH and pregnancy per/AI in inseminated cows. A similar association (r=.80) was also reported between AMH, AFC, and fertility (Table 1) in buffaloes by KEKAN et al. (2019b). These authors concluded that pregnancy rates were significantly higher in buffaloes with higher AMH concentrations and AFC (3-5 mm) than animals with lower AMH concentrations.

Table 1. Average means±SE of individual buffaloes for 3–5, 5–8, >8, total AFC and AMH concentration, and pregnancy status during the estrous cycle. Adapted from KEKAN et al. (2019b)

Buffalo tag No.	3 to 5mm	5 to 8 mm	>8 mm	Total follicle count (>3 mm)	AMH pg/ml	Pregnancy status
27	4.86*±0.51^{b}	1.86±0.34	1.14±0.26	7.86**±0.74	313.57**±15.30^{d}	Pregnant
30	6.71*±0.42	1.29±0.42	0.57±0.20	8.57**±0.57	822.14**±36.00	Pregnant
31	5.00*±0.38^{b}	2.00±0.44	0.86±0.26	7.86**±0.67	535.00**±41.59	Pregnant
32	5.00*±0.31^{b}	2.43±0.48	1.29±0.18	8.71**±0.57	300.00**±23.68^{d}	Pregnant
33	5.43*±0.37^{b}	1.57±0.30	0.71±0.18	7.71**±0.47^{ab}	637.85**±28.05^{b}	Pregnant
34	3.57*±0.30	1.00±0.44	1.14±0.26	5.71**±0.47	256.42**±7.94^{d}	Non pregnant
03	2.86*±0.26	1.86±0.40	1.29±0.42	6.00**±0.79^{bc}	280.00**±9.78^{d}	Non pregnant

Values within a column with no common superscript differed significantly (*P<0.05; **P<0.01)

In contrast, BARUSELLI et al. (2015) observed no correlation between AFC, higher AMH, and conception rates in Nelore cows (n=758) and heifers (n=1,113), following TAI protocols. This finding agrees with a previous study (SANTOS et al., 2014) that reported a strong AFC positive influence on IVEP but not the pregnancy rate of TAI Nelore cattle.

Another recent study involving cows and buffaloes revealed non-statistical differences in AMH concentration between pregnant and non-pregnant animals. Pregnant cattle and buffalo tended to have lower AMH concentrations than non-pregnant animals (1335±670.4 pg/mL vs. 1200±723.1 pg/mL, and 463.5±422.6 pg/mL vs. 322.7±295.1 pg/mL, respectively), reflecting the decrease in ovarian function during pregnancy (BERDUGO et al., 2020). Also, there were no correlations between AMH and the other reproductive parameters in the same study.

AMH in anestrous and repeat breeders. In a recent study (KEKAN et al., 2019a; KEKAN et al., 2020b), the AMH concentration was evaluated in cyclic and repeat breeding buffaloes, and non-significantly lower values of AMH concentration were reported in the repeat breeding group during the estrous cycle (Table 3). The same authors also reported a significantly (P<0.05) higher mean of growing follicles in cyclic buffaloes than anestrus buffaloes (Table 4). At the same time, the AMH concentrations were significantly higher (P<0.05) in cyclic buffaloes (273.50±48.52) than anestrous

buffaloes (79.40±7.80). The current researchers have attributed early postpartum inflammation to be a significant cause of low circulating AMH in cows (OKAWA et al., 2021). The presence of CL in anestrous buffaloes indicates the possibility of silent estrus, where the AMH concentration is high. However, true or seasonal anestrus in buffaloes is characterized by dynamic follicular activity, resulting in a small population of follicles and failure of the large follicle to reach preovulatory size without ovulation, where the AMH concentration is low (ROHILLA et al., 2005). Thus, evaluation of AMH concentrations in anestrus animals can also be utilized as a marker for fertility.

The lower mean of growing follicles in anestrus buffaloes is due to AMH deficiency which inhibits the recruitment of primordial follicles into the pool of growing follicles, and decreases the responsiveness of growing follicles to FSH (VISSER et al., 2006). The size of the follicular pool of AMH-secreting follicles and their responsiveness to intrafollicular and endocrine regulating factors, such as bone morphogenetic proteins (BMP) and FSH, respectively, could account for AMH endocrine concentration. At each estrous cycle, the preovulatory and periovulatory FSH surges would inhibit AMH production by granulosa cells during the days following estrus, leading to a decrease in AMH endocrine concentration. Therefore, the optimal time for a blood test for estimating the size of the pool of gonadotropin responsive follicles through measurement of AMH endocrine concentration should take into account this dynamic profile for each cow to be tested individually (RICO et al., 2011).

Table 2. AMH concentration (mean±SE) and pregnancy status of buffalo heifers. Adapted from KEKAN et al. (2019a)

Buffalo Tag No.	AMH (pg/ml) (n=10)	Pregnancy status
2	286.33 ± 14.91^{c}	Pregnant
3	367.50 ± 17.76^{b}	Pregnant
4	132.00 ± 7.12^{e}	Non pregnant
5	537.50 ± 66.21^{a}	Pregnant
6	214.17 ± 18.71^{d}	Pregnant
7	198.33 ± 9.93^{de}	Non pregnant
8	246.67 ± 22.44^{cd}	Pregnant
9	138.17 ± 12.59^{e}	Non pregnant
11	250.00 ± 5.34^{cd}	Pregnant
14	141.33 ± 15.41^{e}	Non pregnant

Values within a column with no common superscript differed significantly ($P<0.01$)

Table 3. Mean ± SE for AMH concentration in cyclic and repeat breeding buffaloes. Adapted from KEKAN et al. (2020b)

Day	Buffaloes	Mean	t Stat	t table
7th	Cyclic repeat breeder	380.00±78.20 291.00±111.31	0.639 NS	2.20
14th	Cyclic repeat breeder	415.00±68.64 271.66±107.60	1.10 NS	
21st	Cyclic repeat breeder	487.14±95.24 298.33±110.54	1.254 NS	

NS: Non-significant difference.

Table 4. Mean±SE for primordial, antral and growing follicle counts of cyclic and anestrus buffaloes. Adapted from KEKAN et al. (2020a)

Days	Buffaloes	Mean	t Stat	t table
Primordial	Cyclic anestrus	0.42±0.07 0.49±0.02	–1.038^{NS}	2.048
Antral	Cyclic anestrus	0.15±0.03 0.16±0.03	–0.079^{NS}	2.048
Growing	Cyclic anestrus	4.47±0.88 0.41±0.06	5.687**	2.763

**Significant at 1% level, ^{NS}Non-significant difference

Conclusions

It is therefore concluded that AMH is an endocrine marker that can predict the fertility of animals. One-time determination of AMH concentration will help predict the animal's reproductive performance at the heifer stage. Identification of heifers with low or high fertility at birth or weaning would be advantageous for making management decisions as this would reduce replacement heifer costs and identify less fertile heifers at an early age. There is no fluctuation of AMH during the estrous cycle. Therefore, the concentration of AMH in the blood can be determined at any stage of the estrous cycle to discover the reproductive potential of the animal. It will also help to select high potential animals for assisted reproductive technologies, ovum-pick-up, and in vitro embryo production.

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SAŽETAK

Anti-Müllerov hormon (AMH) poboljšava plodnost u goveda zbog čega se upotrebljava kao marker za to važno svojstvo. Proizvode ga granulozne stanice svih primordijalnih, primarnih i sekundarnih folikula te antralnih folikula promjera 4–5 mm. Nakon što folikuli u antralnoj fazi dosegnu 4–5 mm, njihova se proizvodnja smanjuje. Postoje i individualne varijacije u broju antralnih folikula (AFC) i koncentracije AMH-a. Jednokratno određivanje vrijednosti AMH-a pomoći će u predviđanju reproduktivne sposobnosti junica, također i pri izlučivanju životinja s malim reproduktivnim sposobnostima. Kako nema znakovite fluktuacije u vrijednosti AMH-a za vrijeme estrusa, ta se vrijednost može odrediti u bilo kojoj fazi estrusnog ciklusa. U ovom su radu analizirani potencijal AMH-a kao markera plodnosti i njegova povezanost a antralnim folikulima (AFP) s obzirom na to da AMH može biti učinkovit alat u praćenju rezultata niske, prosječne i visoke plodnosti u goveda,

Ključne riječi: anti-Müllerov hormon; broj antralnih folikula; goveda; endokrini marker; marker plodnosti; inhibitor anti-Müllerova hormona