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Anti-Mullerian Hormone (AMH): Current perspective and future application in fertility management in farm animals: A review

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Abstract
AMH is a gonadospecific hormone that is a member of the Transforming Growth Factor-ß super family and its molecular weight is140 killo Dalton. All growing follicles in animals exhibit anti-Mullerian hormone (AMH) expression; however the level is highest in healthy antral follicle. AMH is a reliable endocrine marker and plasma AMH concentrations are unique to individual animals. Throughout the prepubertal age, the oestrous cycle, and the transition from the gestation to the postpartum period in the cow, plasma AMH concentrations follow certain dynamic patterns. These variations most likely reflect numerical changes in the population of high AMH generating follicles. AMH can also be used for a diagnosis of Sertoli cell tumors and in female dogs used as a potential predictor of litter size. Follicle-stimulating hormone decreased granulosa cell AMH production whereas bone morphogenetic proteins increased it. The expression of AMH in the follicle at the follicular level was influenced by the stage of follicular development. The amount of tiny antral developing follicles in an ovary's pool impacted how much AMH was produced there.

Keywords: AMH, antral foliicles, ovarian follicle reserve, endocrine marker, antral foliicle count

1. Introduction
The anti-Mullerian hormone (AMH) is also known as Mullerian inhibiting substance (MIS) and it is responsible for regression of Mullerian ducts in male foetuses (Jost *et al.*, 1973) [32]. According to Di Clemente *et al.* (1994) [11] and Durlinger *et al.* (2002) [12], AMH plays a crucial role in the ovary because it prevents the recruitment of primordial follicles into the pool of growing follicles and reduces the responsiveness of growing follicles to follicle-stimulating hormone. AMH is the best endocrine marker of the ovarian follicular reserve in women (Van Rooij *et al.*, 2002 and Visser *et al.*, 2006) [63, 68] and in mouse (Kevenaar *et al.*, 2006) [34]. Rico *et al.* (2009) [52] reported that AMH is also a reliable endocrine marker of the population of small antral gonadotropin responsive follicles in the cow.
Rico *et al.* (2011) [53] found that AMH play crucial role in multiple ovulation and embryo transfer (MOET) technology, in cattle it improve the genetic selection strategies because plasma AMH concentrations of individuals before treatment have been found to be characteristic of each animal over a long-term period and predictive of the number of ovulations and embryos produced in response to ovarian super-ovulatory treatments (Rico *et al.*, 2009 and Monniauex *et al.*, 2010) [52].

History and structure
AMH is a dimeric glycoprotein hormone and its molecular weight is 140 Killo Dalton and it belongs to member of the transforming growth factor β (TGF-β) family of growth and differentiation factors (Cate *et al.*, 1986) [9]. AMH has been also play a role in male sexual differentiation. A testicular component other than testosterone was responsible for the regression of the Mullerian ducts during male fetal sex differentiation, which is Mullerian inhibiting substance (MIS) according to Jost (1947) [31], who demonstrated castration trials in the fetal rabbit. Josso *et al* (1993) [29] later research revealed that Sertoli cells in the testis

produce this substance.

Ovarian AMH production in domestic animals

The cow ovary's cumulus oophorous, preantral, and tiny antral follicles are where AMH is found, however primordial follicles before growth activation lack the protein. Immunohistochemistry or in situ hybridization has been used to support these findings (Bezard *et al.*, 1987; Baarends *et al.*, 1995; Juengel *et al.*, 2002; Weenen *et al.*, 2004 and Sadeu *et al.*, 2008) [7, 2, 33, 69, 56]. In healthy antral follicles in the cow, AMH expression is predominately strong in the cumulus cells and outer layers of granulosa cells close to the theca.

AMH concentrations are highest in small antral follicles of cows, goats, and sheep and significantly decrease when follicles grow to preovulatory size. Cysts, which do not ovulate or regress, have lowest AMH concentrations. Monniaux *et al.* (2008) [38] identified a negative connection between progesterone and AMH concentrations, demonstrating that low AMH concentrations in cysts are related to luteinization.

The roles of AMH in ovarian physiology

The functional roles of AMH in ovarian folliculogenesis were discovered by Durlinger *et al.* (1999) [14], they studies the follicle pool in the ovaries of AMH-deficient animals at various ages. The reservoir of primordial follicles is exhausted at a younger age without AMH because primordial follicles are recruited more quickly. Nilsson *et al.* (2010) [45] reported that neonatal ovaries and ovarian cortical strips of several animals, including humans, shown that AMH suppresses the conversion of primordial to primary follicles.

AMH-deficient mice have a normal ovulation rate, despite the fact that their ovaries produce more developing follicles when AMH is absent. Increased oocyte degradation and follicular atresia suggest that AMH may be a factor in small developing follicle survival (Visser *et al.*, 2007) [67]. AMH reduces FSH-induced pre-antral follicle growth by lowering both *in vivo* and *in vitro* follicle sensitivity to FSH, according to Durlinger *et al.* (2001) [13]. Therefore, it is clear that AMH is involved in regulating the FSH sensitivity threshold and the start of follicle growth.

Factors affecting AMH concentrations

Nutrition

In humans, cattle, and sheep, the nutritional state of the mother is significant during the development of the fetus (Mossa *et al.*, 2015) [43]. According to a study by Mossa *et al.* (2017) [41], calves' ovarian reserves (the total number of morphologically healthy follicles and oocytes) are permanently impacted by dietary caloric restriction (to 60% of maternal requirements). He claimed that the peak in the number of germ cells in fetal ovaries coincided with dietary restriction during the first trimester of pregnancy.

According to Mossa *et al.* (2015) [43], female calves born to nutritionally restricted mothers had less ovarian reserve when circulating AMH concentrations decreased from 4 months to 1.8 years of age, lower antral follicle count (AFC) from 7 weeks to 1.6 years of age, and higher FSH concentrations, a phenotypic trait of cattle with a low AFC (Jimenez- Krassel *et al.*, 2009 and Mossa *et al.* 2010) [42, 25].

Lactation and Endocrine disruptors

High somatic cell counts in dairy cow milk, indicate the sign of persistent mammary gland infection, these infection are also transmit to daughters which have lower levels of AMH as adults (Ireland *et al.*, 2011) [22]. While it increased the expression of the AMH protein in antral follicles of young adult ewes relative to controls, prenatal exposure to high testosterone from days 30 to 90 of gestation decreased the expression of the AMH protein in granulosa cells of preantral follicles in sheep. The identical experiment, carried out on ewe lambs at the prepubertal stage, produced no effects (Veiga-Lopez *et al.*, 2012) [64]. These findings imply that prenatal testosterone causes changes in AMH expression, indicating that testosterone regulates the ovarian reserve.

Aging

AMH is regarded as a good clinical indicator of ovarian aging in women, according to Nelson *et al.* (2012) [44], since, like AFC, circulating AMH concentrations show a high correlation with the amount of ovarian reserve, which decreases with age (Hansen *et al.*, 2011) [18]. While Ribeiro *et al.* (2014) [51] discovered that cows on the second and third lactations had higher AMH concentrations than those on the first and fourth or greater lactations, Souza *et al.* (2015) [60] reported that there is no correlation between AMH and parity in studies on primiparous and pluriparous Holstein cows.

Age specific alterations of AMH level

AMH is a crucial component in sexual differentiation and Mullerian duct regression, according to Josso *et al.* (2001) [30]. Because they show Sertoli cell function, serum AMH concentrations have been shown to provide novel diagnostic criteria for male infertility in humans. Changes in AMH secretion have been linked to the emergence of anorchia and hypogonadism, two aberrant illnesses in males (Rey *et al.*, 2000) [50]. AMH release from Sertoli cells peaked in adolescence and then abruptly decreased after spermatogenesis began (Josso *et al.*, 2001) [30].

According to Rajpert-De *et al.* (1999) [48], the production of AMH in males after puberty, indicate that the Sertoli cell maturation process has failed. Although the concentrations of AMH in peripheral blood plasma have been examined in relation to ovarian follicular reserve and ovarian function in women (La Marca *et al.*, 2010) [35], cows (Batista *et al.*, 2014 and Vernunft *et al.*, 2015) [6, 65], and mares (Vernunft *et al.*, 2011) [65, 66], the expression of the AMH gene and peripheral concentrations have not been thoroughly investigated in bulls. Information on AMH concentrations during a pre-pubertal and pubertal phase is few, but information on AMH concentrations during the period of sexual differentiation of the fetus is available (Rota *et al.*, 2002) [55].

AMH as a predictor of fertility

Anti-Müllerian hormone (AMH) is the best endocrine indicator of the ovarian follicular reserve of developing follicles and is used to predict the ovarian response to gonadotropins in human, mouse, and bovine (Rico *et al.*, 2009) [52] species. According to Rico *et al.* (2009) [52], the number of antral follicles measuring 3 to 7 mm in diameter, the primary targets of superovulation treatments, is substantially associated with the concentration of AMH in plasma in cows.

AMH measurements can also be used to forecast a cow's ability to produce repeatable and perhaps heritable traits, such as high or low embryo production rates after superovulation. AMH may be a predictor of the number of follicles available in a follicle aspiration program, according to recent research by Venunft *et al.* (2011) [65] who also reported comparable results in mares.

The ability of a cow to produce repeatable and perhaps heritable features, such as high or low embryo production rates following superovulation, can also be predicted using AMH data. According to recent research by Venunft *et al.* (2011) [65], who also showed comparable results in mares, AMH may be a predictor of the number of follicles available in a follicle aspiration program.

Plasma anti-mullerian hormone: An endocrine marker for *in vitro* embryo production from cows

In vitro embryo performance of B. taurus (Holstein) and B. Indicus (Nelore) donors may be predicted using plasma AMH content, according to Guerreiro *et al.* (2014) [17]. All quantitative factors analyzed during the OPU-IVP procedures, such as total follicles aspirated, total COCs retrieved, number of COCs cultured, and number of embryos produced per OPU, showed a positive correlation with plasma AMH concentration, with the exception of factors relating to *in vitro* development competence (such as cleavage and blastocyst rates).

Anti-mullerian hormone use in female dogs as a potential predictor of litter size

Additionally, Hollinshead *et al.* (2017) [20] discovered that compared to female dogs under 4 years of age, older female dogs had a reduced whelping rate and mean AMH concentration. He failed to notice a connection between the AMH concentration and the female dogs' whelping rate, however, or a commensurate drop in the whelping rate at any age. This result is consistent with a large body of human research that found that age is the most reliable predictor of pregnancy (Revelli *et al.*, 2016) [49] and that there is little link between AMH and pregnancy outcomes (Zarek *et al.*, 2015) [70].

According to Visser *et al.* (2006) [68], the granulosa cells of female small antral developing follicles specifically express AMH. This unique property of AMH makes it a reliable tool for estimating the quantity of ovarian gonadotrophin-responsive follicles in the cow (Rico *et al.*, 2012) [54] and an endocrine marker of ovarian reserve in females of various animals (Monniaux *et al.*, 2013) [39]. Therefore, it makes sense that AMH could also be a possible indicator of litter size in female dogs.

The selection of more fertile female dogs for insemination with genetically valuable and irreplaceable frozen semen may greatly facilitate improved reproductive performance and accelerated genetic gain in canine breeding programs by combining the measurement of AMH concentration with other breeding management tools.

Anti- Mullerian hormone and its relationship with superovulation

The effectiveness of ovarian stimulatory therapies during ART is predicted using both AMH and AFC (Broekmans *et al.*, 2006) [8]. Such responsiveness is adversely correlated with aging and is connected to a decrease in the number of follicles and oocytes in the ovaries of humans (Dewailly *et al.*, 2014) [10] as well as cattle (Singh *et al.*, 2004) [58]. Ireland *et al.* (2007) [23] provided the first evidence of young adult cattle with low AFC having reduced responsiveness to super ovulation (lower number of corpora lutea and of recovered embryos/unfertilized oocytes), as well as producing fewer high-quality embryos than age-matched cattle with high AFC.

Silva-Santos *et al.* (2014) [57] conducted research on Taurus indicus Braford cattle (crossbred Bhraman and Hereford animals), and they found that AFC measured before puberty was predictive of the response to super ovulation at 24 months of age as measured by a larger number of total oocytes and embryos recovered. Similarly, in sheep, both adult and prepubertal individuals showed favorable associations between follicle counts and reactivity to superovulation (Mossa *et al.*, 2007; Torres-Rovira *et al.*, 2014) [40, 62]. According to Broekmans *et al.* (2006) [8], AFC functions similarly to AFC in women as a reliable indicator of the ovarian response to stimulation in cattle and sheep.

Anti-Mullerian hormone useful biomarker for diagnosis of canine Sertoli cell tumors

The main effect of high AMH production in animals, which occurs from the time of testicular development to puberty, is the regression of the müllerian ducts during the start of male sex differentiation (Josso *et al.*, 2015) [27]. According to Banco *et al.* (2012) [5], dogs' sertoli cells from fetuses and pups up to day 45 expressed AMH. Analysis of serum AMH concentrations has been shown to be useful for identifying SCT, according to Holst and Dreimanis (2015) [67].

As a result, AMH analysis may be helpful as a diagnostic tool for individuals with skin conditions and bone marrow suppression. Sertoli cells are essential for spermatogenesis, and changes to their function may cause spermatogenesis to be compromised causing male infertility. Dog infertility has been linked to non-palpable SCT. AMH expression is enhanced in testicular degeneration and AMH concentrations are elevated in dogs with SCT (Giudice *et al.*, 2014). AMH is a biomarker for canine SCT and can be helpful in the diagnosis of male canines exhibiting feminization, hyperpigmentation, alopecia, subfertility, infertility, and bone marrow suppression, among other symptoms.

Conclusion

AMH can only be produced in small and developing antral and pre-antral follicles in the mammalian ovary. The amount of this pool is tightly correlated with plasma AMH values. Although AMH levels in adult cows and goats vary greatly from person to person, they are indicative of each animal over the course of several months. The opposition between immature and highly differentiated granulosa cells during terminal follicular development is amply demonstrated by the negative association between AMH and CYP19A1 expression in granulosa cells. Due to its ability to decrease AMH expression, induce CYP19A1 expression in granulosa cells of all species, stimulate CYP19A1 expression in granulosa cells of all species, and neutralize the stimulatory effects of BMP at high doses in granulosa cells of cattle, FSH may be able to influence these alterations.

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