Differences of the Fertility Potential between Buffaloes (*Bubalus bubalis*) and Cattle (*Bos indicus*): The Role of Antimullerian Hormone (AMH)

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Abstract: For years the study of the differences in reproduction between bovines have been restricted to describe the consequences not the causes, it is very easy to find differences in parameters such as embryo/oocyte morphology, metabolism, cleavage rate, but it is quite difficult to find papers trying to explain the reason of this differences and it is not possible to identify their influence in the reproductive parameters and answer to reproductive biotechnologies. The idea that the quantity of follicles and oocytes in ovaries impacts on fertility is a long-held tenet in reproductive biology Follicle formation occurs during fetal life in ruminants and primates. The establishment of the pool of primordial follicles is critical to a female's reproductive success, but very little is known about how this important developmental process is regulated. It has been reported is has been reported in buffaloes the effect of season in the gene expression of oocytes and follicles However, until now very few studies has been attempted to evaluate this fundamental hypothesis, it is possible to think that animals with low follicle count such buffaloes has lower fertility than cattle but this must be demonstrated. The aim of this review is to present evidence related to the differences in reproductive potential in two closely related bovines: buffaloes (*Bubalus bubalis*) and cattle (*Bos taurus* and *Bos indicus*), with special emphasis in the role of antimullerian hormone (AMH) and discuss their possible role in the application of reproductive biotechnologies.

Keywords: AMH, Ovarian reserve, AFC, markers.

1. FERTILITY POTENTIAL

The fertility potential of a given individual or specie, is a concept developed to define the capacity to reproduce themselves through its reproductive behavior and gamete content, it has been long time used in bull in the breeding soundness evaluation [1], but with the information obtained to date it is very difficult to have an absolute way for calculation. In the case of the females, the term has been applied to define the possibility of a given female to have oocytes and follicles, ovulate, forms an embryo, became pregnant and produce a live birth.

While it is well established that size of testes is a moderately to highly heritable trait [2-4] and that it is positively associated with fertility in bulls [5, 6], it is not very difficult to think that this concept could be not applied to the female. The idea that the quantity of follicles and oocytes in ovaries impacts on fertility is a long-held tenet in reproductive biology [7, 8]; however, this fundamental hypothesis has heretofore never been tested or almost quantified.

In spite of being difficult to quantify the fertility potential, it is true that it could be preserved or altered some authors have been suggested that could be parameterized. Today, it has been developed many forms to evaluate the fertility potential, such as comparing the number of follicles at a given moment during reproductive life, or measuring the antimullerian hormone (AMH) levels.

It is very difficult to define numerically the best ovulatory follicle or the more competent oocyte in female mammals, but it is accepted that the concept of ovarian reserve define the fertility potential, and it is possible to be quantified. Also it is well established that the limit of the ovarian follicles is the number of primordial follicles defined during gestation development or early after birth, and that, the number of primordial follicles at puberty is positively correlated with the number of growing follicles and their response to gonadotropin treatments, that could be converted in the fertility potential. The size of this ovarian reserve depends on genes involved in germ cell proliferation and differentiation, sexual differentiation, meiosis, germ cell degeneration, formation of primordial follicles, and on a potential mechanism of self-renewal of germ stem cells [9].

But nevertheless, it is possible to demonstrate that between species or individuals there are differences in reproductive potential, using markers or analyzing their performance in reproductive biotechnologies.

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2. FOLLICULAR DEVELOPMENT

For years researchers have focused their attention to the follicle development through oestrus cycle, showing the interaction between hormones, mainly gonadotropins, but today there are enough evidence that the process before preantral follicle recruitment are very important as part of the fertility potential of the females. It seems that exist two different steps for follicular development, gonadotropin dependent and independent.

A plausible general hypothesis for how the initiation of follicular growth is regulated *in vivo* is that, it is the results of the balance of stimulatory and inhibitory factors in the immediate environment of a primordial follicle [10]. Until, 15 years ago there were no candidates for potential activation inhibitors. In 1999, anti-Mullerian hormone (AMH), best known for its role in the development of the male reproductive tract, became such a candidate [11]. Although mice null mutant for AMH are fertile, careful analysis of their ovaries showed that more primordial follicles leave the resting pool and thus the ovaries become depleted of follicles earlier in life, compared with wild-type Mice [12].

Soon after oocytes enter a prolonged diplotene, the dictyate stage, the precursors to the follicular somatic cells encompass the oocyte in a single squamous layer to form the primordial follice [13]. The large population of non-growing primordial follicles serves as the source of developing follicles and oocytes until the end of a female's reproductive life. Until that time, there is a continuous recruitment of follicles from the pool, beginning with the formation of primary follicles [14]. The oocyte in a primary follicle begins its extensive growth phase, and the surrounding granulosa cells become cuboidal and proliferative. When the growing oocytes are surrounded by more than one layer of granulosa cells, the follicle is called a secondary follicle. Although primary and secondary follicular development can take place in the absence of gonadotropins, these follicles are responsive to gonadotropins and therefore optimal development of preantral follicles may require these hormones [15]. In addition, around the time of transition from preantral to antral follicles, a critical developmental change takes place in the oocyte. Before antrum formation, oocytes are unable to progress beyond the diplotene stage of meiosis I, they stay in germinal vesicle stage (GV), these oocytes are therefore referred to as meiotically incompetent, a state that is attributable to an insufficiency in regulatory molecules necessary to drive meiotic progression [16].

Functional gap junctions between surface membranes of the oocyte and their surrounding granullosa cells has been described from the primordial stage in mice and secondary follicles in cattle [17]. Gap junctions facilitate the transfer of amino acids, glucose metabolites and nucleotides to the growing oocyte. Gap junctions are composed by proteins known as connexins. Connexins 32, 37, 43, 45 and 57 have been reported within growing and mature mouse follicles [18]. In cattle, the connexins expression appears to be stage specific; for example, Cx26 is expressed in oocytes of primordial, primary and secondary follicles, and in the granulosa of healthy antral follicles [19]. Other important gene for primordial follicle formation is FIGa gene, FIGa-knockout mice are devoid of primordial follicle [20].

The majority of follicles in mammalian ovaries are in a resting state known as the primordial follicle stage. Follicles continually leave this resting pool to activate and become primary follicles [21].

In humans, Wallace & Kelsey [22] using mathematical modeling estimated that at birth, girls have an average of 295,000 primordial follicles in their ovarian reserve with an extremely large predicted range of 34,800 - 2,508.000 primordial follicles. Using this number of primordial follicles at birth and the rate of subsequent decline, their model estimates an average age at menopause of 49.6 years with a predicted interval of 38.7 - 60.0 years, demonstrating that it is possible to predict the fertility potential of a female.

3. DIFFERENCES IN OVARIAN RESERVE BETWEEN CATTLE AND BUFFALOES

Cattle (*Bos taurus or Bos indicus*) and water buffalo (*Bubalus bubalis*) belong to the subfamily Bovinae. The former species was domesticated between 8,000 and 10,000 years ago, while domestication of the latter species occurred at least 7,000 years ago [23]. Although the species shared a common ancestor approximately 16.9 million years ago [24], their phenotypic divarication has continued to present time.

One of the main factors limiting the application of biotechnology technologies in buffalo is the high variability between animals and within the same animals in the number of ova/embryos produced [25]. Moreover, the intrinsic species-specific lower number of primordial [13] and antral follicles [26, 27] compared to cattle accentuates the problem of the high variability in follicular recruitment in this species.

In buffaloes, follicular quantification showed larger populations of primordial follicles in buffalo fetuses between 12 and 34 cm of crown rump length (CRL) it is approximately 3 months of gestation, There are no statistical differences in primary and secondary follicle populations between 12–34 and 35 60 cm CRL (4 months), Quantification revealed number of primordial, primary and secondary follicles of 48 857 ± 17 506, 26 000 ± 20 452, 18 428 ±10 875 and 18 375 ± 19 690, 225 ± 349, 326 ± 288 at 12–34 cm and 35–60 cm crown rump length (CRL) respectively [13].

It has been reported that buffalo has a smaller number of primordial follicles than bovine species do (10 000–19 000 vs 150 000, respectively), smaller antral follicles, and higher incidence of atresia (82–92%) [28, 29]. The number of healthy follicles and oocytes in ovaries of newborn calves ranges from 10 000 to 350 000 at birth and from 1. 920 to 40 960 in 12-month-old heifers [30]. Moreover, by 1 year of age, cows have lost 80% of their original stock of healthy oocytes, the neonatal bovine ovary has many primordial follicles; however, less than 0.1% of these follicles will grow to maturity and ovulate during the reproductive lifespan of a cow [7]. The ovaries in buffaloes are typically smaller than in cattle

4. ANTIMÜLLERIAN HORMONE (AMH)

The development of a prognostic method to determine the intrinsic capacity of a potential donor cow to produce an expected number of embryos might be based on the measurement of molecules related reproductive function. Recent results indicate that AMH (also known as Mullerian inhibiting substance MIS), specifically expressed by the granulosa cells of small growing follicles expression is detected in the granulosa cells of all growing follicles and is highest in healthy small antral follicles, which contribute most significantly to AMH endocrine levels [31].

AMH is a reliable endocrine marker of this population of gonadotropin-responsive follicles in ruminants and, over the longer term, plasma AMH concentrations are characteristic of individual animals is an endocrine marker for the size of the pool of ovarian gonadotropin responsive follicles in the cow and can help to predict the ovulatory responses of individuals [32] very few papers have been published in buffaloes.

These interesting findings suggest that AMH, which is secreted by ovarian follicles, is an intraovarian inhibitor of follicle activation. Fortune *et al*. [10], cultured cortical pieces from cattle fetuses between Day 91 and 120 of gestation, during 10 days with graded doses of recombinant human AMH (100, 500 or 1000 ng/mL). All doses decreased the percentage of follicles at the primary stage and increased the percentage at the primordial stage, compared to control cultures, whereas an inactive, mutant form of AMH had no effect, this results strongly suggest that AMH, produced by follicles at the secondary and later stages, inhibits activation and slows the growth of primary follicles

Nilson *et al*. studying the follicular development evaluate in rats, the effect of AMH over gene expression and found that AMH inhibited the stimulatory actions of KITL, βFGF, and KGF. Therefore, AMH can inhibit the basal and stimulated development of primordial follicles. To investigate the mechanism of AMH actions, the influence AMH has on the ovarian transcriptome was analyzed. AMH treatment when compared with controls was found to alter the expression of 707 genes [33].

At birth It has been reported in humans that AMH levels at 3 months of age were significantly higher (15 pmol/liter average; 4.5–29.5 pmol/liter range) and at 12 months of age (8 pmol/liter; 3.0–18.9 pmol/liter) (P > 0.001) in the longitudinal follow-up, all infant girls (37 of 37) demonstrated a marked postnatal rise of AMH levels. Being constant until puberty and declining at the menopause [34], same type of results by Batista *et al.* comparing *Bos taurus* and *Bos indicus* calves with prepuberal heifers [35]. Circulating AMH concentrations are positively associated with the total number of ovarian follicles in mice [11] and in women [36]. Antimullerian hormone expression is high in granulosa cells of small antral follicles and decreases during terminal follicular growth [37].

5. AMH GENE AND PROTEIN STRUCTURE

AMH is a member of the TGF-β superfamily of growth factors [38], it is a 140kD homodimeric glycoprotein [39]. Human AMH is synthetized as a 560 amino acid precursor with a 24-25 amino acid leader containing a 16- 18 amino acid signal sequence and a putative 7-8 residue pro-sequence [38]. The carboxyl-terminal region of AMH shares homology with that of members of the transforming growth factor-β (TGF-β superfamily). AMH is encoded by a 2.75kb gene divided into 5 exons, characterized by a high GC content [40].

In cattle AMH gene has been mapped in chromosome 7 [41], Bos_taurus_UMD 3 AC_000164.1 (22696978..) According with Bos_taurus_UMD_3.1.1 version, it has a length 3,7 kb, 5 exons and an mRNA for coding sequence of 1728 bp, protein are fully reviewed (UNIprot P03972) but not cristalized, it has not registered protein data bank, it has 551 aa, in the case of buffaloes and *Bos indicus* cattle the gene (Gene ID: 102405218are) are not assigned to an specific chromosome, BLAST alignment shows 100 % of homology with cattle (ALIGNMENTS>JQ326296)

6. GOING TO THE FARM

The genetic background of cattle significantly impacts their reproductive performance. It is believed that increased inbreeding to achieve maximal milk yield has negatively impacted reproductive efficiency in temperate, *Bos taurus taurus* (European type cattle) animals [42]. By comparison, the tropical and subtropical subspecies of cattle, *Bos taurus indicus* (Zebu), generally found in India and South America, are known for lower milk yields, but greater reproductive efficiency [43].

The development of genomic selection has recently induced dramatic changes in the management of genetic selection schemes, but the efficiency of multiple ovulation and embryo transfer (MOET) and ovum pick-up and in vitro production (OPU–IVP) appears even more critical to produce large numbers of animals to be genotyped [44]. High between-animal variability in the number of embryos produced by MOET and OPU–IVP methods remains a major limit to the development of embryo biotechnologies in cattle and buffaloes [45].

Gimenes *et al*. [48] found that buffalo heifers (13.1 ± 1.4) had lower number of follicles at the synchronized follicular wave emergence than Nelore *(Bos indicus)* heifers (29.7 ±3.1). A positive correlation was observed between the plasma AMH and number of *in vitro* embryos produced from Holstein (r = 0.36, P < 0.001) and Nelore (r = 0.50, P= 0.003) donors [35]. Other authors have been confirmed this results in prepuberal *Bos indicus* and *Bos taurus* calves [49]. Other authors have been reported in other *Bos taurus* breed, Japanese black [50].

The numbers of large follicles at OPU were significantly correlated with plasma AMH concentrations before hormonal treatment (r=0.56, P < 0.0001) and at the time of OPU (r=0.65, P=0.0001). Moreover, the average AMH concentrations per cow were significantly correlated with the average numbers of large follicles (LF) and oocytes recovered at OPU per cow (R= 0.75 and r=0.70, respectively, both P <0.01, n=13 cows) [51]. The follicular and ovulatory responses to the gonadotropin treatment administered to 51 cows were highly variable between animals. The AMH concentrations measured in heparinized plasma before treatment varied in the range 5 to 244 pg/mL; one cow had a very high AMH concentration of 413 pg/mL. The numbers of LF at oestrus were significantly correlated with plasma AMH concentrations before treatment (r=0.46, P < 0.001 n=51) and the correlation coefficient was higher when the cow with a very high AMH concentration was removed from the analysis (r=0.60, P < 0.0001, n=50) [51].

Baldrighi, *et al*. 2014. [52] performed the only report that compare buffaloes and different types of bovines. He and his coworkers valuate plasma concentrations of anti-Mullerian hormone (AMH) and the ovarian antral follicle population (AFP) in three different genetic groups, synchronized and maintained under same management. Cyclic buffalo heifers (13 *Bubalus bubalis*; 15 *Bos taurus* and 10 *Bos indicus*) After the second d-cloprostenol treatment, heifers had their ovaries scanned daily by ultrasound to define the day of ovulation. On the same day, a plasma sample was taken and AFP was determined. Murrah heifers had less AFP (25.6 ± 2.1 follicles; p = 0.01) and plasma AMH concentration (0.18 ± 0.03 ng/ml; p < 0.001) than Gyr (60.0 ±12.2 follicles and 0.60 ± 0.12 ng/ml of AMH); however, buffalo data were similar when compared to Holstein (35.9 ± 6.8 follicles and 0.24 ± 0.06 ng/ml of AMH) heifers.

Carter *et al*. [53] provide evidence that AMH, from different sources either plasma and follicular fluid, are significantly different between Zebu and European type cattle. Relationship between AMH and reproductive parameters was found to be significantly greater in Zebu compared to European cattle. Average Plasmatic AMH mean ± SE for Zebu and European cattle was 0.77 ± 0.09 and 0.33 ± 0.24 ng/ml respectively (p = 0.01), whereas average antral folicular fluid AMH mean ± SE for Zebu and European cattle was 4934.3 ± 568.5 and 2977.9 ± 214.1 ng/ml respectively (p < 0.05)

The plasma AMH concentration profiles followed similar pattern of the follicular population recorded by

each breed the animals classified with high-plasmatic AMH concentration within genetic group and confirm the observation that the greater AMH levels shows the bigger AFP count [52].

The intrafollicular AMH concentration was positively correlated with the antral follicular count (r= 0.31; P < 0.05). Interestingly, good donors (>12 follicles) had a higher (P < 0.05) concentration of AMH and AMHR2 levels in small follicles and higher (P < 0.05) LHR levels in large follicles than bad donors (<12 follicles) [54]. The physiological mechanisms of the AMH changes in concentration and their effect over development of follicles remain unclear.

Between-animal differences in AMH concentrations were found to be unchanged after a 3-mo delay (r = 0.87, P < 0.01), indicating that AMH endocrine levels were characteristic of each animal on a long term period [55].

Regardless of the genetic group, calves that received pFSH (3.6 ± 1.1 in Nelore and 4.6 ± 1.2 in Holstein) or did not receive pFSH (3.2 ± 1.0 in Nelore and 2.5 ± 0.8 in Holstein) had greater plasma AMH concentrations (*P* = 0.01 in Nelore and *P* = 0.003 in Holstein) than cycling heifers (1.1 ± 0.2 in Nelore and 0.6 ± 0.07 in Holstein). AMH concentrations in calves with or without pFSH were similar in both genetic groups (3.6 ± 1.1 vs 3.2 ± 1.0 in Nelore; 4.6 ± 1.2 vs 2.5 ± 0.8 in Holstein). However, the AMH class did not distinguish donors that produced COCs with greater *in vitro* ability to reach the blastocyst stage [49].

During years the are enough evidence that suggest that buffaloes has lower reproductive potential than cattle evidenced by the reduced response in buffaloes to ovarian follicular stimulation treatments, low recovery of embryos and oocytes, and low number of transferable embryos reported by others [43, 56, 57], today with the evidence showed, based on the study of closely related species it is possible to understand the origin of the biological differences observed and to have the opportunity to give answers to reproductive biology and to improve the reproductive biotechnology programs.

The expression of AMH within the follicle was dependent on the stage of follicular development. At the ovarian level, the size of the pool of small antral growing follicles determined ovarian AMH production. At the endocrine level, AMH followed a specific dynamic profile during the estrous cycle, which occurred independently of the follicular waves of terminal follicular development [58], it is very likely that AMH is the regulator of the number of follicles of each female to be used during their reproductive lifespan, but it is not clear that if this action are cause or consequence of their function.

It has been presented evidence regarding the use of AMH as marker for reproductive potential of two the species of interest, two closely related bovines with quite differences. Based on the differences in ovarian function between buffaloes and cattle it could hypothesized that the lower counts of primordial follicles are part of the problem, but if that follicles have different physiology that are responsible for the differences in the answer are still unknown.

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