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Review: The ovarian follicular reserve – implications for fertility in ruminants

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ABSTRACT

Ruminants are born with a finite number of healthy ovarian follicles and oocytes (ovarian reserve) and germ cell proliferation in the developing foetal gonad predominantly occurs during early gestation. Two markers have been established to reliably estimate the size of the ovarian reserve in cattle: the number of antral follicles ≤3 mm in diameter recruited per follicular wave (Antral Follicle Count, **AFC**) and peripheral concentrations of the Anti-Müllerian hormone (**AMH**). Studies that used one or both indicators show that the size of ovarian reserve varies greatly among age-matched individuals, but is highly repeatable in the same animal. Conditions during prenatal life are likely among the causes of such variation in the ovarian reserve. In addition, the size of the ovarian reserve is a moderately heritable trait in cattle. The association between ovarian reserve and fertility is controversial. Several studies indicate that cattle with a low ovarian reserve have phenotypic characteristics that are associated with suboptimal fertility. On the contrary, the presence and absence of a positive association between AFC and/or AMH and fertility measures (i.e. no. on services/conception, pregnancy rates, pregnancy loss) have been equally reported in cattle. In conclusion, the size of the ovarian reserve in the progeny can be enhanced by improving management of the dam from preconception to early gestation and also through genetic selection. However, although the ovarian reserve may be among the determinants of reproductive success in ruminants, the use of AFC/AMH as reliable predictors of fertility is yet to be established. Furthermore, the possibility that there is a complex interaction of AFC, AMH and reproduction has yet to be fully characterised and exploited to improve fertility in cattle.

Implications

The total number of healthy ovarian follicles and oocytes (ovarian reserve) is established prenatally in female mammals. The size of the ovarian reserve may be enhanced by genetic selection in cattle, as well as by appropriate management of pregnant dams, including correct nutritional plans and avoiding exposure to high environmental temperatures from periconception to early gestation. Antral follicle count and Anti-Müllerian hormone circulating concentrations may be used to select the best responders to gonadotropin stimulation in cattle, but they are not yet validated predictors of fertility in ruminants.

Introduction

The term "ovarian follicular reserve" was originally introduced to describe the pool of primordial follicles within ovaries, but it is now commonly used to refer to the total number of healthy ovarian follicles and oocytes. Female mammals are born with a finite number of oocytes that progressively decreases with age, leading to the end of their ability to conceive (Grieve et al., 2015); in contrast, testicles support long-term and continuous spermatogenesis from spermatogonial stem cells throughout adult life. Thus, investigating the establishment of the ovarian reserve is important to understand menopause regulation and subfertility in women (Hansen et al., 2011). Even though ruminants are usually culled before reproductive senescence, the ovarian reserve warrants investigation in these species because it may be among the chief determinants of fertility. This review focuses on the establishment of the ovarian reserve and on its implications for fertility in ruminants, mainly in Bos taurus taurus cattle. Indeed, understanding what factors influence the creation of the ovarian reserve may

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lead to prenatal or other management approaches to enhance fertility in female offspring, with potential positive impacts on ruminant production systems.

The ovarian reserve is established before birth in ruminants

The ovary develops from the mesonephros and is first visible around day 22 of gestation in sheep and day 30 in cattle. Primordial germ cells migrate from the endoderm of the yolk sack from day 17 to day 21 in sheep and day 18 to day 31 in cattle; during their migration, germ cells proliferate by mitotic divisions. In the ovaries, germ cells are surrounded with somatic pregranulosa cells and continue to proliferate. The primordial germ cells, also called oogonia, give rise to primary meiotic oocytes as they enter prophase of the first meiotic division (day 52 in sheep, days 75–80 in cattle) (Smitz and Cortvrindt, 2002; Juengel et al., 2021). In male mammals, primordial germ cells generate germ cells which are able to self-renew after birth and throughout adult life, whereas in females, the presence of germ cells in the postnatal ovary is controversial. Albeit oogonial stem cells have been identified in postnatal mouse and human ovaries (Johnson et al., 2004; White et al, 2012), numerous studies support the absence of oogonial stem cells in adult female mammals (reviewed by Hainaut and Clarke, 2021). To our knowledge, ovarian stem cells have been identified in adult sheep (Patel et al., 2018), but not in cattle and goats, and evidence of their ability to undergo neo-oogenesis in ruminants is lacking (De Felici, 2010). Consequently, foetal life appears crucial for the establishment of the number of follicles/oocytes in ruminants.

In ruminants, the transition from primordial to primary follicles (primordial follicle activation) starts during foetal life (Fortune et al., 2000; Fair, 2003); primordial follicles consisting of a primary oocyte surrounded by flattened pregranulosa cells are visible around day 75 in sheep and days 74–90 in cattle. When they are activated, the oocytes grow as the granulosa cells become cuboidal, forming primary follicles, which are visible on days 100–110 in sheep and days 74–140 in cattle. Secondary follicles form when theca cells are visible, together with two or three layers of granulosa cells (day 120 in sheep, days 120–210 in cattle), and also, antral follicles have been detected in ovine foetal ovaries as early as day 135 (Russe, 1983; McNatty et al., 1995; Dupont et al., 2012). Interestingly, follicular development during foetal life is accompanied by ovarian germ cell death. Evidence indicates that the peak number of germ cells is reached by days 91–110 in cattle, with an estimated maximum number of 2.1 million (Smitz and Cortvrindt, 2002), but from this peak in numbers, 80–90% of germ cells die (reviewed by Juengel et al., 2021). At the same time, the germ cell proliferation rate decreases and the number of healthy follicles and oocytes at birth ranges from 10 000 to 350 000 in cattle, with a high variation among individuals (Erickson, 1966, Aerts and Bols, 2010). It has been suggested that germ cell death is caused by either failure of meiosis or poor follicle formation; indeed, understanding what factors control and influence the creation of the ovarian reserve may lead to innovative prenatal approaches to enhance the ovarian reserve and, potentially, fertility in female offspring.

Antral follicle count and anti-Müllerian hormone concentrations are indicative of the size of the ovarian reserve

It is estimated that follicular development from primordial to ovulatory stage takes 4–6 months in cattle (Fortune et al, 2000; Mihm et al., 2002; Fair, 2003). Antral follicles are characterised by a cavity (antrum) filled with serum-like follicular fluid, which can be detected by ultrasonography when follicles reach approximately 2–3 mm in diameter. Thanks to this technique, it has been firmly established that antral follicles grow in an organised pattern, called follicular waves, with two or three FSH-induced waves per bovine oestrous cycle (Sirois and Fortune, 1988). Evidence indicates that in cattle, the peak number of antral follicles $\leq$3 mm in diameter recruited per follicular wave (Antral Follicle Count, **AFC**) is highly variable among individuals (range 8–54), but highly repeatable (0.95, with 1.0 indicating perfect repeatability) in the same or consecutive oestrous cycles in the same animal (Burns et al., 2005). Subsequent studies confirmed AFC repeatability regardless of cattle age or breed, season or stage of lactation and span of time between AFC assessments in the same individual (Burns et al., 2005; Ireland et al., 2007; Ireland et al., 2008; Ireland et al., 2009; Jimenez-Krassel et al., 2009; Mossa et al., 2012; Succu et al., 2020). More recently, AFC repeatability was also reported: (i) between an unknown stage of follicular growth and the day of wave emergence in lactating dairy cows (0.37; Gobikrushanth et al., 2017); (ii) from puberty to yearling age in Bos taurus indicus beef cattle (0.89–0.92; Morotti et al., 2017) and (iii) from postweaning to preservice in Hereford and Braford heifers (0.72; Santa Cruz et al., 2018).

The high individual variability in AFC has also been confirmed in numerous studies; in Holstein heifers, AFC ranged from 18 to 110 (Baldrighi et al., 2014) and 3 to 36 (Succu et al. 2020), in lactating Holstein cows, it varied from 4 to 61 (Mossa et al., 2012), from 10 to 53 at an unknown stage of follicular growth, from 6 to 45 on the expected day of follicular wave emergence (Gobikrushanth et al., 2017). In cross-bred beef heifers, AFC ranged from 4 to 56 (Cushman et al., 2009) and 7 to 54 in Angus (McNeel et al., 2017). In multiparous Bos taurus indicus dairy Nelore cows, the AFC range was 21–51 (De Lima et al., 2020) and 2–50 (Santos et al., 2016), whereas in Bos taurus indicus beef cattle, AFC varied from 3 to 64 in (Morotti et al., 2017). Differences in the detection of the antral follicles can differ among operators and settings (i.e. experimental vs commercial farm) and may also be influenced by the frequency of AFC assessments.

Further, the total number of morphologically healthy follicles and oocytes was very highly positively correlated with AFC (r, correlation coefficient; $r = 0.89$, $P < 0.001$), indicating that the AFC can be used to estimate the size of the ovarian reserve in Bos taurus taurus cattle (Ireland et al., 2008). More recently, a positive correlation ($P < 0.05$) between the number of visible antral follicles assessed postmortem and the numbers of healthy primordial, secondary and total follicles has been reported in Bos taurus indicus cows (de Vasconcelos et al., 2020), thus confirming the validity of AFC as an indicator of the size of the ovarian reserve in cattle.

Peripheral concentrations of the Anti-Müllerian hormone (**AMH**) have also been identified as a marker of the size of the ovarian reserve in cattle, because AMH in females is predominantly produced by granulosa cells of healthy, growing ovarian follicles in women, cattle and sheep and goats (Vigier et al., 1984; Takahashi et al., 1986; Bézard et al., 1987; La Marca et al., 2006; Monniaux et al., 2012). Indeed, AMH is not produced by primordial or atretic follicles, but starts to be produced when follicles are recruited (McGee and Hsueh, 2000), and peaks when the follicles are in the preantral and small antral follicle stages, and then decreases as the selected follicle grows to the preovulatory stage under the FSH stimulus (Monniaux et al., 2008, Veiga-Lopez et al., 2012). Similar to AFC, serum concentrations of AMH vary greatly among individuals, but are highly repeatable in the same animal (Ireland et al., 2011). Moreover, evidence indicates a high positive association between AMH serum levels and the antral follicle population in cattle (Ireland et al., 2008; Rico et al., 2009; Baldrighi et al., 2014), sheep and goats (Monniaux et al., 2014), thus both indicators have been used to estimate the size of the total number of healthy oocytes in these species.

Conditions during prenatal life and genetics influence the establishment of the ovarian reserve

What determines the size of the ovarian reserve in ruminants? Several studies indicate that the number of follicles might be influenced by the conditions encountered during foetal life (reviewed by Sloboda et al., 2011; Mossa et al., 2015). Indeed, the concept of developmental programming states that a stimulus occurring during a specific window of prenatal life can permanently influence the anatomy and physiology of different systems (Barker, 1992). The potential to programme the number of ovarian follicles in the progeny by factors such as maternal nutrition, heat stress and lactation has been investigated in ruminants. Evidence supporting the heritability of the size of the ovarian reserve has also been presented in cattle (reviewed in Mossa and Ireland, 2019).

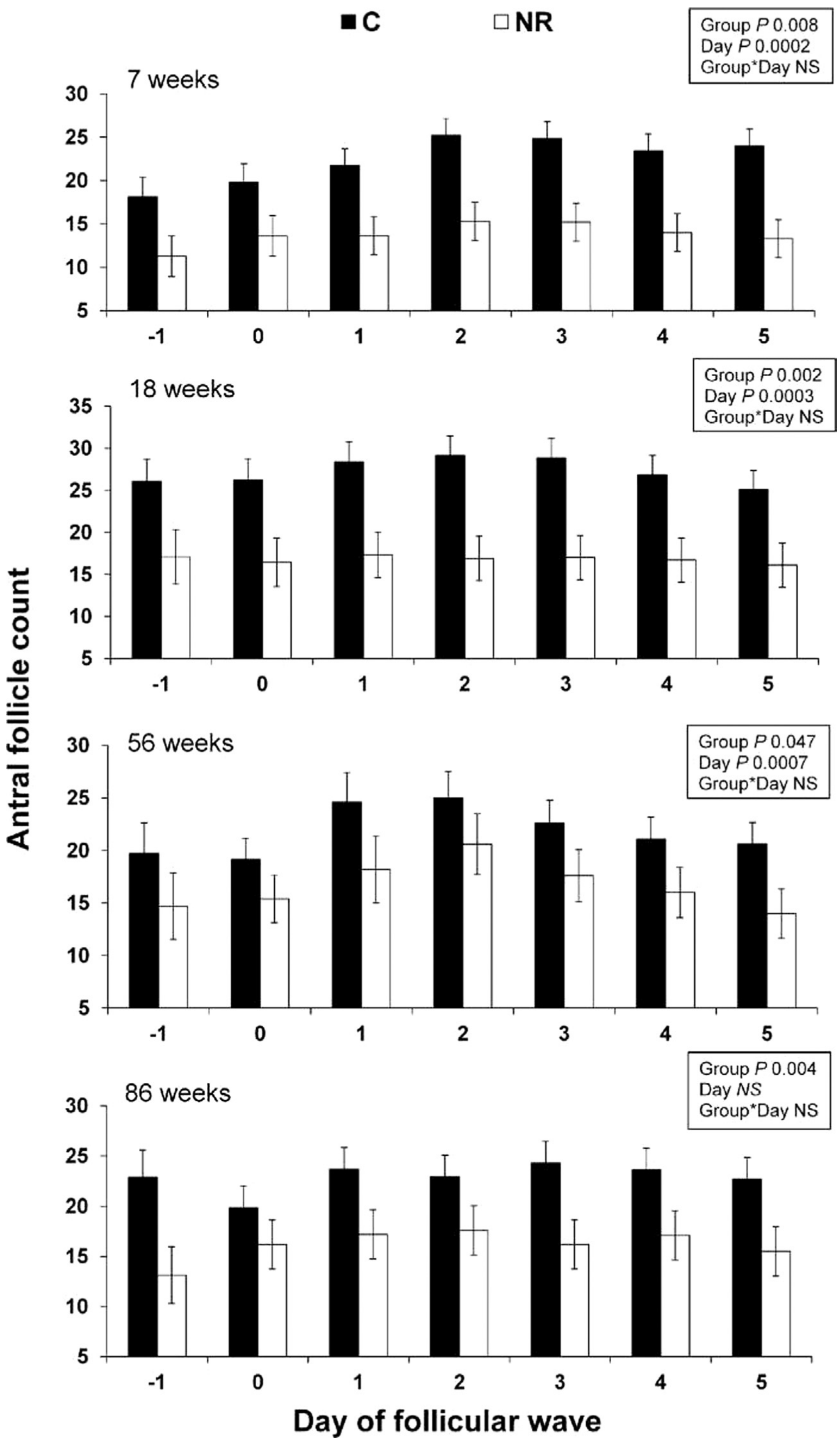

Fig. 1. AFC, assessed by daily ultrasonography, during waves of follicular development at different ages in offspring of cows in the NR (n.10, open symbols) and C (n.13, solid symbols) groups. NR mothers were individually fed 0.6 M, while C mothers were fed 1.2 M from Day 11 to Day 110 of gestation. At 7 and 18 wk, heifers were not sexually mature, while at 56 and 86 wk, data were collected during the first follicular wave of the oestrous cycle. Data were aligned relative to the day of wave emergence. Each symbol represents the daily mean (±SEM) AFC. Probabilities for the main effects of the repeated-measures ANOVA are given. NS, not significant (Mossa et al., 2013). AFC = antral follicle count; NR = nutrient restricted; M = maintenance energy requirements; C = control.

Maternal nutrition

We tested the hypothesis that maternal nutritional restriction during the first trimester of gestation impairs the establishment of the offspring ovarian reserve in cattle. This window of exposure was chosen because the peak number of germ cells in the foetus is reached within the first trimester of gestation (Erickson, 1966). Beef heifers were individually fed at either 1.2 or 0.6 of their maintenance energy requirements from 11 days before artificial insemination to day 110 of pregnancy (Mossa et al., 2013). Daughters of nutrient-restricted dams had consistently diminished peripheral AMH concentrations, lower AFC (Fig. 1), and increased FSH concentrations (Mossa et al., 2013). Peripheral blood pressure was also increased in offspring of energy-restricted mothers compared to herd mates born to control mothers. We concluded that the development of the bovine ovarian reserve can be negatively programmed by insufficient energy supply of the dam in early gestation.

Maternal exposure to high environmental temperatures

We recently tested the hypothesis that high environmental temperatures during the first trimester of foetal life (which coincides with the peak number of germ cells in foetal ovaries) are negatively associated with the establishment of the ovarian reserve in dairy cattle (Succu et al., 2020). We examined 310 sixteen-month-old dairy heifers born to mothers that conceived and spent the first trimester of pregnancy during May through August (summer group; mean monthly temperature-humidity index (THI) = 69.33 ± 2.6) or November through March 2016 (winter group; mean monthly temperature-humidity index = 54.91 ± 1.08). A THI $\geq$ 68 was considered an indicator of high environmental temperatures and potential heat stress (Zimbelman et al., 2009). Both AMH and AFC were lower in young adult heifers exposed to high environmental temperatures during the first trimester of their foetal life (419.27 ± 22.81 pg/mL and 9.32 ± 0.42 follicles, respectively) compared with heifers that were not exposed to lower temperatures in their early uterine life (634.91 ± 47.60 pg/mL and 11.84 ± 0.46 follicles, respectively (Fig. 2; (Succu et al., 2020)). Others have reported that cows exposed to heat stress during the second and third trimester of gestation produced female offspring with lower AMH concentrations (Akbarinejad et al., 2017). The biological pathways by which maternal heat stress may impair ovarian development in the conceptus are unknown, but exposure to high temperatures could reduce feed intake in the mothers during early gestation (Ominski et al., 2002), thus reducing the energy supply during foetal gonadal development.

Maternal lactation

For the most part, cows are milked during gestation to produce their next calves, and the potential impact of the concomitant maternal lactation and foetal ovarian development on the establishment of the ovarian reserve in the progeny has been investigated. In a study of Irish Holstein Friesian cattle in a pasture-based system, daughters of heifers had on average three follicles less than daughters of lactating dams (Walsh et al., 2014). Similarly, yet in a confined all-year calving system, lower AMH and AFC were assessed in Holstein heifers born to mothers that were not being milked while pregnant compared to daughters of cows in their first lactation, whereas the ovarian reserve was similar in the progeny of cows on their first and subsequent lactations (Succu et al., 2020). Other research groups have reported similar evidence with AMH concentrations being greater in Holstein heifers born to multiparous cows compared with nulliparous heifers (Akbarinejad et al., 2018), and beef heifers born to cows had more

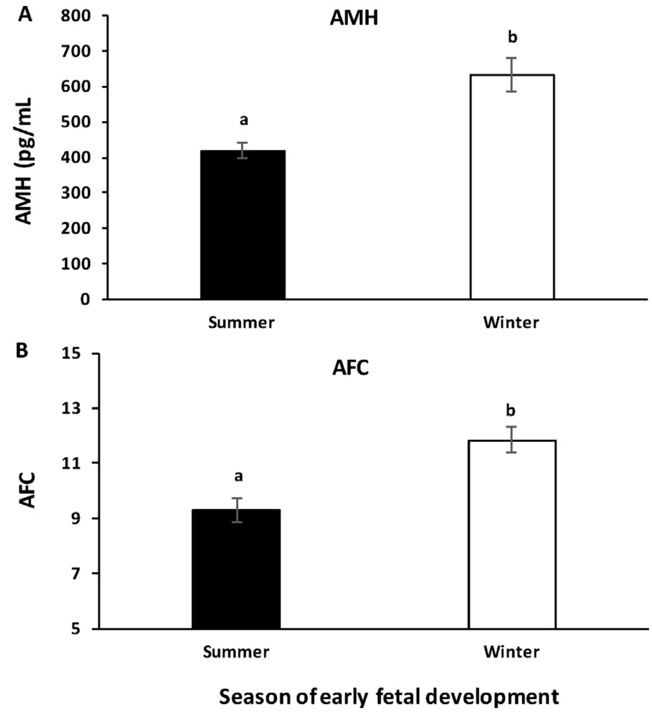

Fig. 2. Mean (±SEM) peripheral concentrations of anti-Müllerian hormone (AMH; panel A) and total number of follicles $\geq$ 3 mm in diameter (Antral follicle Count, AFC; panel B) on a random day of the oestrous cycle in 310 16-month-old Holstein Friesian dairy heifers that were conceived and spent the first trimester on their foetal life in May–August (Summer; n = 176) or November-March (Winter; n = 134). a vs b P < 0.0001 (Succu et al., 2020).

antral follicles than herd mates born to non-lactating dams (Tenley et al., 2019). Dairy heifers are usually inseminated for the first time when they are 15 month-old, having reached 55–60% of their mature BW. Thus, the first pregnancy takes place while the mother is still growing, leading to a potential competition in nutrient demands between the conceptus and the dam growth (Scholl et al., 1994). It is possible that such competition may result in the impairment of the ovarian follicular reserve in the progeny. This hypothesis is in accordance with the finding that heifers born to nutritionally restricted mothers in early gestation had a diminished ovarian reserve (Mossa et al., 2013).

Heritability

Most reproductive traits are lowly heritable in both dairy and beef cattle (Berry et al., 2014). We investigated the heritability of AFC and found it to be a moderately heritable genetic trait in dairy cows (0. 31 ± 0.14) and heifers (0.25 ± 0.13) (Walsh et al., 2014). In a subsequent study conducted in 2 905 Holstein heifers, AMH pedigree-based heritability was 0.43 ± 0.07 (heritability estimate) and AMH genomic heritability was 0.36 ± 0.03 (Nawaz et al., 2018). A similar genomic heritability estimation was reported on 198 Canadian Holstein cows in a separate study (0.46 ± 0.31; (Gobikrushanth et al., 2018). Since these estimates (Walsh et al., 2014; Gobikrushanth et al., 2018; Nawaz et al., 2018) are the highest for any trait associated with reproduction in female cattle (Berry et al., 2014), it can be concluded that genetic selection may be used to increase the size of the ovarian reserve in dairy cattle.

The ovarian reserve may be positively associated with fertility

Does size matter in females? In 2011, we published a review of the existing evidence supporting the hypothesis that the inherently high variation in the number of ovarian follicles and oocytes may be among the chief determinant of fertility in cattle (Ireland et al., 2011). After 10 years, such hypothesis has been further tested, but results still appear controversial. Further, several studies have been conducted to investigate the differences in fertility in Bos indicus females with high versus low ovarian follicular reserve but are beyond the scope of this review (de Lima et al., 2020; Santos et al., 2016).

Evidence supporting the association between ovarian reserve and fertility

In a pasture-based, seasonal calving system, dairy cows with a low AFC had lower pregnancy rates, longer calving to conception intervals and received more services during the breeding season compared with cows with a high AFC (Mossa et al., 2012). In another study, 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). Higher pregnancy rates have also been reported in beef heifers with a high vs a lower AFC (Cushman et al., 2009). Further, greater pregnancy rates and lower incidence of pregnancy loss between days 30 and 65 of gestation were reported in dairy cows with high vs low AMH in a separate study (Ribeiro et al., 2014).

In addition, several studies conducted under experimental conditions show that cattle with a low ovarian reserve have phenotypic characteristics that are associated with suboptimal fertility, such as increased FSH concentrations, reduced progesterone concentrations and endometrial growth. Chronically heightened FSH secretion is considered an indicator of age-related suboptimal fertility in single-ovulating species (reviewed in Ireland et al., 2011). Increased FSH secretion in age-matched individuals with reduced ovarian reserve was reported in young adult and lactating beef cattle (Singh et al., 2004; Burns et al., 2005), dairy heifers (Haughian et al., 2004), late lactation (Burns et al., 2005; Ireland et al., 2007) and culled non-lactating Holstein dairy cows (Mossa et al., 2010). Low serum progesterone concentrations are associated with embryo mortality in cattle (Diskin and Morris, 2008); young adult beef cattle and late lactation dairy cows with a low AFC had progesterone concentrations consistently 30–50% lower than cattle with a high AFC and poor endometrial development during the early luteal phase of oestrous cycles compared with cattle with a high AFC (Jimenez-Krassel et al., 2009). In addition, uterine luminal protein concentration was lower in beef heifers with low compared to high AFC (McNeel et al., 2017). Finally, the positive association between the size of the ovarian reserve and the response to gonadotropin stimulation has now been consistently reported by many independent studies that have used either AFC or AMH (reviewed in Mossa and Ireland, 2019).

Evidence indicating that the ovarian reserve is moderately or not associated with fertility

Several studies conducted in cattle using AMH concentrations as a proxy of the size of the ovarian reserve reported null or limited association between AMH and fertility. Serum AMH concentrations were assessed in young adult Holstein heifers when they were 11–15 months of age and heifers were partitioned into quartiles based on their AMH concentrations. Conception rates to the first artificial insemination and total percentage pregnant as heifers were similar among quartiles. Also, the number of inseminations per conception and days open until calving in the first, second and third lactation did not differ among AMH quartiles. On the other hand, the quartile of cows with the lowest AMH as heifers (Q1) had lower pregnancy rates in three consecutive lactations than in Q2 and Q3, whereas no differences were detected between Q1 and Q4. During their first lactation, Q1 cows had the highest culling rates for poor fertility (Jimenez-Krassel et al., 2015). More, Q1 dairy cows completed fewer lactations compared to Q3 herd mates and had a shorter productive herd life compared with Q2 and Q3 cows (Jimenez-Krassel et al., 2015). These findings imply that AMH concentrations in dairy heifers may be indicative of the length of their productive life.

More recently, no association was detected between pregnancy per service, pregnancy loss between 30 and 60 days after artificial insemination, pregnancy risk up to 250 days postpartum and AMH categories based on lowest 20%, intermediate 60% and highest 20% circulating AMH, in grazing dairy cows in a seasonal calving system (Gobikrushanth et al., 2018). In a subsequent study under the same farming conditions, pregnancy per artificial insemination and pregnancy rate within 21 and 42 days after the start of the mating season were similar among AMH categories. Nonetheless, cows with high and intermediate plasma AMH concentrations had 1.42- and 1.51-times-greater odds of becoming pregnant within 84 d after the beginning of the mating season than those with low plasma AMH (Gobikrushanth et al., 2019).

Further, we recently investigated the hypothesis that cattle with a high ovarian follicular population are more fertile than herd mates with smaller ovarian reserve in Holstein Friesian cattle in a confined system (Succu et al., 2020). Serum AMH concentrations and AFC were assessed on a random day of the oestrous cycle in 310 sixteen-month-old dairy heifers. Heifers were ranked into three groups (low = 20%, intermediate = 60%, high = 20%) based on AMH concentrations and AFC. Age at first service was greater in heifers with low compared with intermediate AMH concentrations, but age at first calving and the number of services per conception were similar among heifers with different AMH concentrations. No difference was detected in any of the fertility measures among AFC categories (Succu et al., 2020).

In summary, the size of the ovarian follicle reserve is closely associated with AFC in Bos taurus cattle. Also, AFC is a function of both environmental (conditions during in-utero development) and genetic factors (heritability of AFC is 0.25–0.31; Walsh et al., 2014). Similarly circulating concentrations of AMH are a function of the size of the ovarian follicular reserve and genetic factors (her-

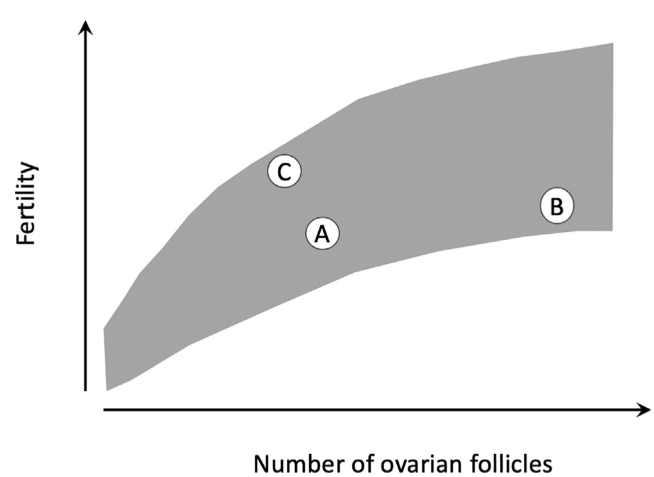

Fig. 3. Schematic presentation of a hypothesised relationship between the number of ovarian follicles and fertility in cattle (indicated by the shaded area). This is based on the observation that most, but not all, published studies suggest that there is a positive relationship. A, B, and C represent individual animals. Note that the fertility levels of animals A and B are similar, despite B having many more follicles than A, and that the fertility of animal C is higher than A despite having fewer follicles. The reasons for differences in fertility among these animals have yet to be fully established, but likely include several factors, such as differences in hormone concentrations (e.g. Anti-Müllerian hormone (AMH) and progesterone) and management factors (e.g. environmental and metabolic challenges).

itability of AMH is 0.36–0.46; Gobikrushanth et al., 2018; Nawaz et al., 2018). Considering the predictability of fertility in cattle, we conclude that the assessment of the size of the ovarian reserve, either by AMH or AFC, in heifers cannot be used as a truly reliable tool to predict fertility in cattle (Fig. 3). This could be caused by a weak lack of association between the ovarian reserve and fertility or by the presence of stronger factors that influence reproductive efficiency on farms (i.e. management practices) that overcome the impact of ovarian reserve on herd fertility. It is however possible that there is a complex interaction of AFC, AMH and reproduction that has yet to be fully characterised and exploited to improve fertility in cattle.

Ethics approval

Not applicable.

Data and model availability statement

Data or models were not deposited in an official repository. No new datasets were created.

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Authors contribution

Francesca Mossa: Writing - Original Draft.
Alex Evans: Writing - Review and Editing.

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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Transparency Declaration

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