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Review

Transforming growth factor-β superfamily and interferon-τ in ovarian function and embryo development in female cattle: review of biology and application

Michael J. D'Occhio[A], *Giuseppe Campanile*[B] *and Pietro S. Baruselli*[C,D]

[A]School of Life and Environmental Sciences, Faculty of Science, The University of Sydney, 410 Werombi Road, Camden, NSW 2006, Australia.
[B]Department of Veterinary Medicine and Animal Production, University of Naples Federico II, V. F. Delpino, 1 80137 Naples, Italy.
[C]Department of Animal Reproduction, Faculty of Veterinary Medicine and Zootecnia, University of Sao Paulo, Sao Paulo, CEP 05508-270 Brazil.
[D]Corresponding author. Email: barusell@usp.br

Abstract. Survival of the embryo and establishment of a pregnancy is a critical period in the reproductive function of female cattle. This review examines how the transforming growth factor-β (TGFB) superfamily (i.e. bone morphogenetic protein (BMP) 15, growth differentiation factor (GDF) 9, anti-Müllerian hormone (AMH)) and interferon-τ (IFNT) affect ovarian function and embryo development. The oocyte in a primary follicle secretes BMP15 and GDF9, which, together, organise the surrounding granulosa and theca cells into the oocyte–cumulus–follicle complex. At the same time, the granulosa secretes AMH, which affects the oocyte. This autocrine–paracrine dialogue between the oocyte and somatic cells continues throughout follicle development and is fundamental in establishing the fertilisation potential and embryo developmental competency of oocytes. The early bovine embryo secretes IFNT, which acts at the uterine endometrium, corpus luteum and blood leucocytes. IFNT is involved in the maternal recognition of pregnancy and immunomodulation to prevent rejection of the embryo, and supports progesterone secretion. Manipulation of BMP15, GDF9, AMH and IFNT in both *in vivo* and *in vitro* studies has confirmed their importance in reproductive function in female cattle. This review makes the case that a deeper understanding of the biology of BMP15, GDF9, AMH and IFNT will lead to new strategies to increase embryo survival and improve fertility in cattle. The enhancement of oocyte quality, early embryo development and implantation is considered necessary for the next step change in the efficiency of natural and assisted reproduction in cattle.

Additional keywords: anti-Müllerian hormone, bone morphogenetic protein 15, embryo survival, growth differentiation factor 9.

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Introduction

The important role of cattle in global food systems is projected to grow as a result of the increasing demand for livestock products driven by world population growth, global demographics and dietary preferences (Thornton 2010; Smith *et al.* 2018). More than 85% of cattle production globally does not compete for food resources that could be used directly by humans (Mottet *et al.* 2017). Nevertheless, there is considerable pressure for greater efficiency in cattle production because of both perceived and real impacts of livestock on the environment (Herrero *et al.* 2013; Eisler *et al.* 2014; Salter 2017). Further improvements in the efficiency of cattle production will be achieved through genetic or genomic technologies, combined with greater use of assisted reproduction to multiply and disseminate cattle of high genetic merit.

The dairy industry recognised the important enabling role of assisted reproduction in genetic improvement more than 60 years ago (Foote 1996). Indeed, some of the earliest applications of AI in production animals were in dairy cattle (Foote 1993, 1999*a*, 2002). Cattle have remained a target species as assisted reproduction has expanded to include embryo technologies and, more recently, cloning (Foote 1999*b*; Bo and Mapletoft 2014; Hasler 2014; Keefer 2015). An understanding of ovarian follicular dynamics in cattle (Adams *et al.* 2008) led to the development of oestrus synchronisation treatments and fixed-time AI. The latter facilitated greater uptake of assisted breeding in dairy (Wiltbank and Pursley 2014) and beef (Baruselli *et al.* 2018) breeds.

It could be argued that assisted reproduction in cattle has tended to focus on improving AI and the production of embryos, the latter both *in vivo* and *in vitro*. Less attention has been given

to embryo survival and the establishment of a pregnancy. Embryo mortality accounts for 20–50% of pregnancy failures in cattle, yet it has been largely overlooked (Diskin and Morris 2008; Diskin *et al.* 2012, 2016; Wiltbank *et al.* 2016). This is surprising because fertilisation rates in cattle are relatively high (80–95%), but much of this fertility is lost because of the large proportion of embryos that do not establish a pregnancy (Humblot 2001; Wolf *et al.* 2003). Most embryo loss in cattle occurs between Days 8 and 20 of gestation, and is the main source of reproductive wastage (Sreenan and Diskin 1986; Diskin and Morris 2008; Berg *et al.* 2010). This window in embryo development is discussed below because it coincides with the period when the embryo secretes factors that are critical for the maternal recognition of pregnancy. Some embryos are compromised from the time of fertilisation because of the improper maturation of oocytes (Hansen 2002), and this is also discussed below. This review makes the case that because embryo mortality is a major source of reproductive wastage it needs to be addressed in order for the potential of assisted reproduction to be fully realised in cattle. The review primarily looks at two phases of reproduction in female cattle: (1) early events of oocyte–follicle interaction; and (2) embryo development. The review assumes that greater knowledge of these phases of reproduction will lead to strategies that increase embryo survival and the establishment of pregnancy. The focus of this review is on the transforming growth factor-β (TGFB) superfamily and interferon-τ (IFNT). These have been the subject of previous reviews (Knight and Glister 2003, 2006; Jones *et al.* 2006; Imakawa *et al.* 2017), but this is the first time that members of the TGFB superfamily (i.e. bone morphogenetic protein (BMP) 15, growth differentiation factor (GDF) 9, anti-Müllerian hormone (AMH)) and INFT are considered together in some detail in cattle. Hence, the review seeks to provide a comprehensive record in one article of current literature in cattle for BMP15, GDF9, AMH and IFNT. The reason for choosing members of the TGFB superfamily and IFNT is because they have major roles in early reproductive events that shape oocyte and embryo quality, and also affect the capacity of an embryo to establish a pregnancy.

This review first provides a biological overview and then considers how basic knowledge can be applied to enhance assisted reproduction. The emphasis is clearly on cattle, but information for other species is included where it helps provide a broader contextual background. The growing importance of cattle in global food systems provides strong justification for ongoing research to improve the efficiency of assisted breeding in cattle. A concerted effort to improve embryo survival is considered fundamental to achieving the next step change in assisted reproduction.

TGFB superfamily

BMP15 and GDF9

Biology

The TGFB superfamily has over 40 members and is the largest group of growth factors in mammals (Wu and Hill 2009; Li *et al.* 2011; Morikawa *et al.* 2016). Receptors for TGFB ligands are found throughout the reproductive system and have multiple roles in supporting reproductive function in females (Ingman and Robertson 2002; Li *et al.* 2011; Heath *et al.* 2017). The TGFB superfamily includes GDF9 and BMP15 (also known as GDF9B). Both BMP15 and GDF9 have been shown to have a central role in female fertility in large animals, including ruminants (Elvin *et al.* 2000; McNatty *et al.* 2006; Otsuka *et al.* 2011; Crawford and McNatty 2012; Persani *et al.* 2014). In ovaries, BMP15 and GDF9 are secreted by oocytes and act on the surrounding cumulus, granulosa and theca through paracrine mechanisms (Fig. 1; Elvin *et al.* 2000; Pennetier *et al.* 2004; Knight and Glister 2006; McNatty *et al.* 2006; Heath *et al.* 2017; Chen *et al.* 2017; Alam *et al.* 2018; Belli and Shimasaki 2018).

Functions assigned to BMP15 and GDF9 include regulation of follicle development, functioning of the cumulus and oocyte meiotic arrest (Paulini and Melo 2011; Gasperin *et al.* 2014; Monniaux 2016; Rossi *et al.* 2016). The synthesis of BMP15 and GDF9 by oocytes starts during the primordial to primary follicle transition (Knight and Glister 2006; Sanfins *et al.* 2018). At this stage, BMP15 and GDF9 act synergistically to direct the proliferation and organisation of the granulosa cell layer of primary follicles (Knight and Glister 2006; Paulini and Melo 2011; Sanfins *et al.* 2018). BMP15 and GDF9 were also shown to act synergistically to induce bovine granulosa cell complexes in culture to form antrum-like structures (Alam *et al.* 2018). GDF9 alone induced the proliferation of cultured bovine thecal cells (Spicer *et al.* 2008). Hence, BMP15 and GDF9 are fundamental for early organisation of the follicle, and both continue to influence the function of the cumulus during follicle development through to ovulation (Otsuka *et al.* 2011; Paulini and Melo 2011). BMP15 and GDF9 can act separately in a monomeric form at TGFB Type I and Type II receptors (TβRI and TβRII respectively) or synergistically, possibly as BMP15:GDF9 heterodimers (Heath *et al.* 2017). Other members of the TGFB superfamily are involved in folliculogenesis, but are beyond the scope of this review (Lee *et al.* 2001; Glister *et al.* 2004; Buratini and Price 2011; Rossi *et al.* 2016; da Cunha *et al.* 2018).

Application in assisted reproduction

In sheep, it has been clearly shown that single point mutations in BMP15 and GDF9, and the BMP receptor type 1B (BMPR1B; also known as ALK6), are associated with increases in ovulation rate (McNatty *et al.* 2004, 2005, 2006; Garcia-Guerra *et al.* 2018). It was reported that Chinese Holstein cows with single nucleotide polymorphisms at A485T and A625T of *GDF9* showed an increase in the total number of ova (A625T) and transferable embryos (A485T and A625T) in response to superovulation (Tang *et al.* 2013*a*). Although male cattle are not the subject of this review, the same *GDF9* polymorphisms were reported to be associated with sperm concentration and acrosome integrity in Holstein bulls (Tang *et al.* 2013*b*). These reports in Chinese Holstein cattle should be regarded as preliminary and require substantial validation.

Active immunisation against BMP15 and GDF9 was used to study their role in ovarian function and ovulation in cattle (Juengel *et al.* 2007, 2009). Immunisation of postpubertal Holstein crossbred heifers against either BMP15 or GDF9 was associated with an increase in ovulation, and it was concluded that both can affect the ovulation rate in cattle (Juengel *et al.*

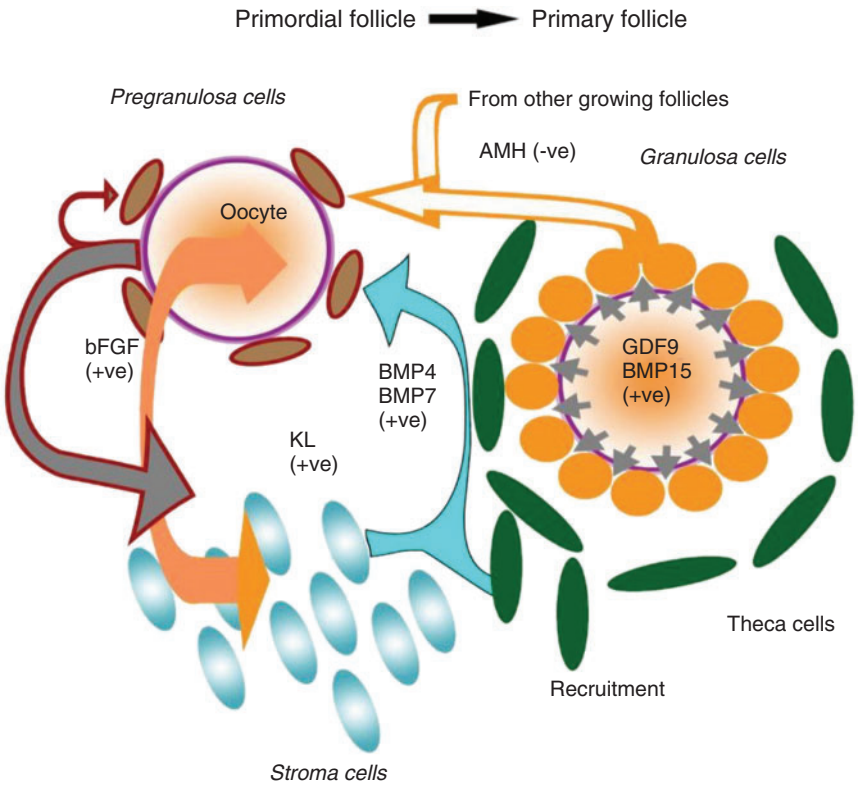

Fig. 1. The oocyte in a primary follicle secretes bone morphogenetic protein (BMP) 15 and growth differentiation factor (GDF) 9 (open arrow), as well as basic fibroblast growth factor (bFGF; left arrow) that act to influence the organisation of the granulosa cell layer. Pregranulosa cells secrete kit ligand (KL; centre-left arrow), which has a positive effect on both the oocyte and granulosa cells. Stromal and thecal cells secrete BMP4 and BMP7 (centre arrow), which facilitate follicle activation and survival. Anti-Müllerian hormone (AMH) from the growing pool of early antral follicles suppresses the transition of primordial follicles to primary follicles. +ve, positive action; −ve, negative action. Adapted from Knight and Glister (2006).

2007). However, the response to immunisation was variable and some heifers immunised against GDF9 did not show an increase in ovulation, whereas heifers immunised against BMP15, alone or in combination with GDF9, either had no ovulations or multiple ovulations (Juengel *et al.* 2009). Other features of heifers immunised against BMP15 or GDF9 were reduced numbers of antral follicles and generally smaller follicles (Juengel *et al.* 2009). These findings make it apparent that the potential use of immunisation against BMP15 and/or GDF9 in assisted reproduction in cattle (e.g. ovarian superstimulation) requires further research. Romney ewes immunised against BMP15 or GDF9 showed arrested follicle growth (Juengel *et al.* 2002; McNatty *et al.* 2004). The oocytes in immunised ewes were surrounded by a single layer of flatted or cuboidal granulosa cells, which is consistent with the important role of oocyte-derived BMP15 and GDF9 in the development of primary follicles (see above; Fig. 1). The findings in ewes suggested that immunisation against BMP15 and GDF9 may have potential for immunocontraception.

The addition of pro-mature BMP15 (the form secreted by oocytes; Persani *et al.* 2014; Mottershead *et al.* 2015) to bovine cumulus–oocyte complexes (COCs) *in vitro* increased the blastocyst development rate compared with control oocytes, as well as oocytes exposed to mature BMP15 and mature GDF9 (Sudiman 2014; Sudiman *et al.* 2014). In an earlier study, bovine COCs cultured together with denuded oocytes also showed an increase in blastocyst development rate, as did oocytes cultured with either BMP15 or GDF9 alone (Hussein *et al.* 2006, 2011). BMP15 was also beneficial in reducing oxidative stress in bovine oocytes during IVF culture (Sutton-McDowall *et al.* 2015). BMP15 also reduced the apoptosis of cumulus cells during IVF, whereas GDF9 did not have the same effect (Hussein *et al.* 2005). A preliminary conclusion from the above *in vitro* studies would be that BMP15 has a particularly important role in oocyte–cumulus communication in cattle.

Oocytes recovered from prepubertal heifers have a lower blastocyst development rate than oocytes from postpubertal heifers and adult cows (Revel *et al.* 1995; Khatir *et al.* 1998; Palma *et al.* 2001; Baruselli *et al.* 2016*b*; Seneda *et al.* 2019). Expression of BMP15 and GDF9 was lower in cumulus cells from calf ovaries than in cumulus cells of cows (Hosoe *et al.* 2011). Based on the improvement in blastocyst development observed

with BMP15 and GDF9 in IVF, it would be worth investigating whether the addition of BMP15 and/or GDF9 to prepubertal oocytes improves the blastocyst development rate. However, IVF blastocyst development needs to be accompanied by embryo transfer and the recording of pregnancy rates. This would need to be at scale to give confidence that any new IVF procedures are translating to substantially more pregnancies. It is possible that some oocytes are 'rescued' during IVF but may still lack full embryo developmental competency. Notwithstanding, given the importance of BMP15 and GDF9 in follicle development and the encouraging preliminary results with their application, particularly *in vitro*, there is strong justification for further research on whether these members of the TGFB superfamily can be used to improve the efficiency of assisted reproduction in cattle.

Anti-Müllerian hormone

Biology

AMH is also a member of the TGFB superfamily (Knight and Glister 2006; Hinck *et al.* 2016). AMH was initially described as a product of fetal Sertoli cells that induces regression of the Müllerian ducts in males during sexual differentiation (Jost 1947; Josso *et al.* 2001, 2005; Josso 2008). AMH is now known to have important roles in folliculogenesis and fertility in females (Durlinger *et al.* 2002; Gruijters *et al.* 2003; Knight and Glister 2003; Visser *et al.* 2006). Studies using mouse models established two fundamental roles for AMH: (1) suppression of the primordial to primary follicle transition (Durlinger *et al.* 1999; Fig. 1); and (2) attenuation of the response of granulosa cells to FSH (Durlinger *et al.* 2001; Gruijters *et al.* 2003). The suppression of follicle growth by AMH has since been demonstrated in cultured bovine ovarian tissue (Yang *et al.* 2017). With regard to the response to FSH, AMH is thought to suppress steroidogenesis in granulosa cells during the early period of multiplication and differentiation when the oocyte–somatic cell complex is being established (Gruijters *et al.* 2003). During this early period, development of the oocyte–somatic cell complex is driven by autocrine and paracrine mechanisms that are largely independent of gonadotrophins (Knight and Glister 2003, 2006). In this regard, AMH was shown to affect the differentiation and proliferation of bovine granulosa cells in culture (Poole *et al.* 2016). BMP15 also stimulated the production of AMH and AMH receptor Type 2 (AMHR2) in granulosa cells, and this could be interpreted as a paracrine loop that enhances the effect of AMH on granulosa cells (Pierre *et al.* 2016). However, granulosa cell responsiveness to FSH is required for follicles to progress beyond the small antral stage, and granulosa cell-derived activin is thought to increase sensitivity to FSH at this stage of follicle development (Knight and Glister 2003, 2006). AMH acts at AMHR2 on bovine granulosa cells (Poole *et al.* 2016), and in mouse granulosa cells AMH induces two micro-RNAs (miR-181a and miR-181b) that are involved in the action of FSH (Hayes *et al.* 2016).

In cycling beef cows, the abundance of *AMH* mRNA in granulosa cells was reported to be greater in the largest follicle in a follicular wave than in the second largest follicle at the time of deviation (Ilha *et al.* 2016). The abundance of *AMHR2* mRNA did not differ between the two largest follicles at the time of deviation, but *AMHR2* mRNA was more abundant in the largest follicle after deviation (Ilha *et al.* 2016). There was no difference in the abundance of either *AMH* or *AMHR2* mRNA between codominant follicles from cows that had been treated with FSH (Ilha *et al.* 2016). It was concluded that differences in AMH levels and *AMHR2* mRNA abundance between follicles are due to differences in sensitivity to FSH and that FSH treatment stimulates both AMH levels and *AMHR2* mRNA abundance in bovine follicles. Granulosa cell FSH receptor (*FSHR*) mRNA levels were not more abundant in the largest follicle at the time of deviation in cycling Holstein heifers (Evans and Fortune 1997). However, *FSHR* mRNA was more abundant in the dominant follicle after deviation (Fortune *et al.* 2001). The mechanism of follicle deviation in cattle is beyond the scope of this review, but there are also changes in granulosa LH receptors and the insulin-like growth factor (IGF) system (Beg *et al.* 2001; Beg and Ginther 2006; Glister *et al.* 2011; Garcia-Guerra *et al.* 2018).

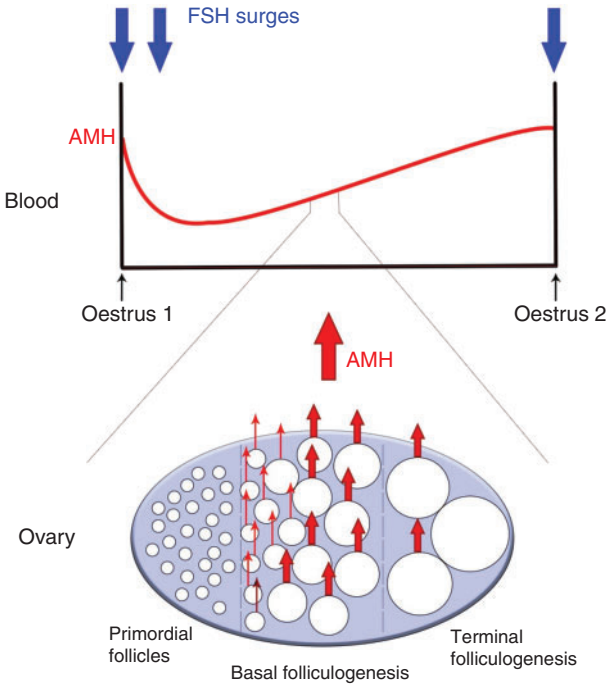

Fig. 2. The primary source of anti-Müllerian hormone (AMH) is from the pool of early antral follicles (1–5 mm) that comprise the largest cohort of follicles in ovarian follicular waves. Blood concentrations of AMH show repeatable fluctuations during oestrous cycles that are relatively consistent for individual animals. Adapted from Rico *et al.* (2012).

Application in assisted reproduction

The highest production of AMH is by granulosa cells of small antral follicles (1–5 mm), which are the largest pool of growing follicles in cyclic animals (Fig. 2; Rico *et al.* 2012). This section first examines the relationship between antral follicles and fertility, and then considers the relationship between the number of antral follicles and AMH concentrations. The size of the antral follicle pool was shown to be repeatable for individual cycling beef heifers, and this is now accepted as a biological phenomenon across cattle breeds (Ireland *et al.* 2007; Batista

Table 1. Relationship between blood concentrations of anti-Müllerian hormone (AMH) and measures of fertility in cattle
OPU, ovum pick-up

Fertility measure	Breed	Reference
AMH as a predictor of longevity in the breeder herd	Holstein	Jimenez-Krassel *et al.* (2015)
Positive relationship between AMH and fertility to AI	Holstein, Jersey, Holstein-Jersey	Ribeiro *et al.* (2014*a*)
Positive relationship between AMH, oocyte recovery with OPU and IVF embryos	Holstein, Nellore	Baruselli *et al.* (2016*a*)
Positive relationship between AMH and response to superovulation and embryo recovery	Beef	Ireland *et al.* (2007)
	Holstein	Rico *et al.* (2012)
	Normande × Holstein	Monniaux *et al.* (2010*a*, 2010*b*)
	Holstein, Nellore	Guerreiro *et al.* (2014)
	Holstein, Nellore (calves)	Batista *et al.* (2016)
	Holstein	Souza *et al.* (2015)
	Angus, Chianina, Hereford, Maine-Anjou, Shorthorn, Simmental, crossbred	Center *et al.* (2018)

et al. 2014). It was also shown that heifers with a greater number of antral follicles had an increased response to FSH stimulation and produced more embryos (Ireland *et al.* 2007; Monniaux *et al.* 2010*b*; Souza *et al*. 2015). However, the relative proportion of transferable embryos was lower for heifers with a high antral follicle count (AFC; Ireland *et al.* 2007). The initial finding of a relationship between AFC and 'fertility' was also observed in Hereford–Angus–Charolais beef cows (Ireland *et al.* 2008), Holstein dairy cows (Ireland *et al.* 2011) and Nellore (*Bos indicus*) beef cows and heifers (Baruselli *et al.* 2015; Monteiro *et al.* 2017; Seneda *et al.* 2019). One study suggested that the AFC at weaning could be used as a predictor of fertility in Brahman × Hereford heifers but not Hereford heifers (Santa Cruz *et al.* 2018). The AFC in Nellore × Hereford heifers was repeatable from weaning to yearling, which suggested it could be a reliable marker of reproductive function (Morotti *et al.* 2017*a*).

In contrast with the studies cited above, there was no apparent relationship between AFC and fertility to AI in Holstein cows in a pasture-based commercial dairy (Martinez *et al.* 2016) or in Nellore cows (Baruselli *et al.* 2015). In a recent study, conception rate to fixed-time AI was greater for Nellore cows with a low AFC compared with cows with intermediate and high AFCs (Morotti *et al.* 2018). The latter study highlighted the importance of undertaking applied research in a commercial environment. The standardisation of AFC has been noted as a requirement for broader integration of this technology in assisted reproduction in cattle (Morotti *et al.* 2017*b*). An important observation was that dairy heifers with a very high AFC had reduced lifetime fertility (Mossa and Ireland 2019).

Given that antral follicles are the predominant source of AMH, it would be predicted that AMH concentrations in the blood are also related to 'fertility' in cattle (Mossa *et al.* 2017). It was suggested that AMH concentrations could potentially be used as an endocrine marker and predictor of *in vitro* embryo production in cattle (Guerreiro *et al.* 2014). Table 1 summarises some of the relationships reported for AMH and fertility in female cattle. The studies in Table 1 provide evidence that AMH is a predictor of fertility, measured as responses to AI or embryo technologies. However, the favourable relationship between AMH and fertility traits has not been consistently observed, and further research is required (Baruselli *et al.* 2015). Plasma concentrations of AMH were positively related to AFC in cyclic Holstein (*Bos taurus*) and Nellore (*B. indicus*) heifers (Batista *et al.* 2014). In the latter study, Nellore heifers had a greater number of antral follicles and higher blood concentrations of AMH (Batista *et al.* 2014). In a companion study, cyclic Gyr heifers (*B. indicus*) had a greater number of antral follicles and greater AMH in blood than Holstein heifers (Baldrighi *et al.* 2014). The above findings in heifers were also observed in a comparison of cyclic Nellore and Red Angus (*B. taurus*) cows (Carter 2016; Stojsin-Carter *et al.* 2016). In the latter studies, follicular fluid AMH concentrations were greater in Nellore than Red Angus cows. AMH was positively associated with AFC in Tabapuã (*B. indicus*) heifers and cows (Maculan *et al.* 2018). AMH was also closely related to AFC in Girolanda (Gyr × Holstein) prepubertal heifers and cows (Cardoso *et al.* 2018). The comparisons between *B. indicus* (Zebu) and *B. taurus* cattle are consistent with earlier reports of a greater AFC in Zebu cattle (Sartori *et al.* 2010). There were no apparent relationships between AMH, ovulation rate and response to FSH in crossbred beef cattle that carried the Trio fecundity allele (Garcia-Guerra *et al.* 2017). It was proposed that the multiple ovulation trait in Trio allele carriers is not related to AFC or AMH (Garcia-Guerra *et al.* 2017). A recent review reported that AMH in dairy heifers is a reasonably heritable trait (36%) and is influenced by maternal nutrition during early pregnancy (Mossa and Ireland 2019). It was concluded that there are opportunities to manipulate AMH using genetic and environmental strategies (Mossa and Ireland 2019). In a recent study, genomic relationships were found between *AMH* and other genes associated with reproductive function (Grigoletto *et al.* 2018). The measurement of AMH at unknown stages of the oestrous cycle was highly repeatable compared with AFC, which had a lower repeatability (Gobikrushanth *et al.* 2017). Although AFC and AMH have shown promise as indicators of ovarian function, both require further validation before they can be widely, and confidently, used to select female cattle for fertility.

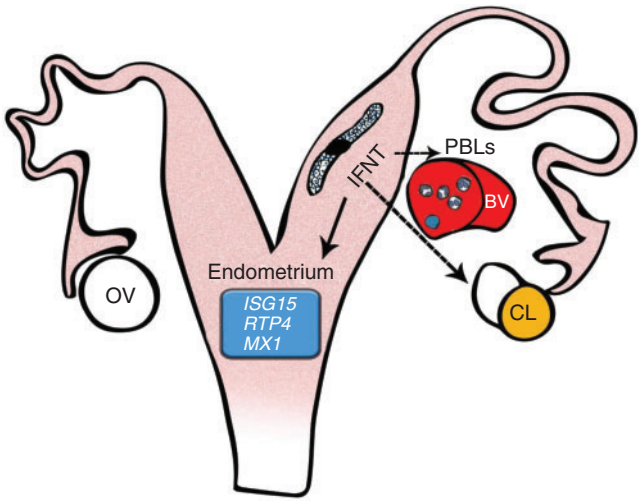

Fig. 3. Interferon-τ (IFNT) secreted by the conceptus acts at the endometrium of the uterus, corpus luteum (CL) and peripheral blood leucocytes (PBLs) in blood vessels (BV). In cattle, IFNT induces the expression of IFNT-stimulated genes, and their respective proteins, including ISG15 ubiquitin-like modifier (*ISG15*), IFN-induced MX dynamin like GTPase 1 (*MX1*) and receptor transporter protein 4 (*RTP4*) by the uterine endometrium. OV, ovary. Adapted from Kiyma *et al.* (2016).

Interferon-τ

Biology

IFNT is secreted by the early conceptus and is absolutely required for the maternal recognition of pregnancy around Day 14–18 of gestation in cattle (Fig. 3; Roberts 1989, 2007; Roberts *et al.* 1992; Bazer *et al.* 1996, 1997; Martal *et al.* 1998; Spencer *et al.* 2013; Forde and Lonergan 2017; Sandra *et al.* 2017; Sanchez *et al.* 2018; Lonergan *et al.* 2019). In order for IFNT to be successful in signalling the presence of a developing embryo, the uterus must first be primed by progesterone (Niswender *et al.* 2000; Spencer and Bazer 2002; Spencer *et al.* 2007, 2016; Forde and Lonergan 2012; Parr *et al.* 2017). The enabling role of progesterone in pregnancy recognition has received considerable attention and an exhaustive summary is beyond the scope of this review. Comprehensive reviews on the role of progesterone are available (Binelli *et al.* 2001; Bazer *et al.* 2008; Forde *et al.* 2011; Lonergan 2011; Lonergan and Forde 2014).

IFNT was first isolated and characterised in sheep as ovine trophoblast protein (TP)-1 (Bazer and Roberts 1983; Imakawa *et al.* 1987; Farin *et al.* 1989). It was subsequently identified in cattle as an analogous bovine TP-1 (Imakawa *et al.* 1989). To mark the 30th anniversary of the discovery of TP-1, a series of articles reviewed the history of IFNT (Bazer and Thatcher 2017; Roberts 2017), transcriptional control (Ezashi and Imakawa 2017), paracrine and endocrine actions (Hansen *et al.* 2017) and function in ruminants (Forde and Lonergan 2017).

IFNT is a Type 1 IFN and, similar to other IFNs, it has antiviral, antiproliferative and immunomodulatory activities (Pontzer *et al.* 1991; Emond *et al.* 2000). IFNT appears to be produced exclusively by the embryonic trophectoderm during Gestation days 8–17 and before the start of embryo attachment to the uterus in cattle around Day 18–20 (Forde and Lonergan 2017). There are at least two genes that code for IFNT subtypes, interferon tau-1 (*IFNT1/IFNT2*) and interferon tau-c1 (*IFNTc1*) (Sakurai *et al.* 2013; Kusama *et al.* 2017; Kim *et al.* 2018). IFNT blocks the upregulation of oestrogen and oxytocin receptors in the endometrial epithelium, which prevents the production of luteolytic prostaglandin (PG) $F_{2\alpha}$ (Spencer *et al.* 1995, 2004; Spencer and Bazer 1996, 2004; Sakurai *et al.* 2009; Forde and Lonergan 2017). Intrauterine administration of the IFNT cell-signalling blocker U0126 on Day 10 of the oestrous cycle induced luteolytic $PGF_{2\alpha}$ pulses in Romney ewes (Lee *et al.* 2014). IFNT also upregulates classical IFNT-stimulated genes (ISGs), and their respective proteins, in the uterine endometrium, which is thought to be important for elongation and attachment of the trophoblast (Brooks and Spencer 2015; Wilson *et al.* 2016; Kusama *et al.* 2017; Sponchiado *et al.* 2017; Kunii *et al.* 2018; Mathew *et al.* 2019). Angus × Polled Hereford beef cows classified as high fertile or subfertile based on the survival of transferred embryos showed differences in uterine ISGs, which, it was concluded, affected the ability of the conceptus to develop (Moraes *et al.* 2018). IFNT induces resistance to $PGF_{2\alpha}$ in the corpus luteum, further ensuring that luteolysis does not occur and progesterone continues to be secreted to support a pregnancy (Kerbler *et al.* 1997; Shirasuna *et al.* 2015; Basavaraja *et al.* 2017; Bazer and Thatcher 2017). It was proposed that IFNT promotes the synthesis of PGE_2, which could have a luteoprotective action in ruminants (Arosh *et al.* 2016). In addition to IFNT, the early conceptus secretes many other molecules that are assumed to be involved in both the development of the trophoblast and embryo–maternal interaction (Mamo *et al.* 2012; Imakawa *et al.* 2018). It was suggested that IFNT communication may include conceptus-derived exosomes (Nakamura *et al.* 2016).

ISGs include genes that code for cytokines that are involved in immunomodulation, which prevents maternal rejection of the conceptus (Emond *et al.* 2000; Ott and Gifford 2010; Shirasuna *et al.* 2012; Spencer and Hansen 2015; Hansen *et al.* 2017; Passaro *et al.* 2018; Yang *et al.* 2018). This includes cytokines produced by blood leucocytes (Hansen *et al.* 2010; Ott and Gifford 2010; Haq *et al.* 2016). Typical ISGs in reproductive tissues and granulocytes are ISG15 ubiquitin-like modifier (*ISG15*), IFN-induced MX dynamin like GTPase 1 (*MX1*) and MX dynamin like GTPase 2 (*MX2*; Ribeiro *et al.* 2014*b*; Haq *et al.* 2016; Kiyma *et al.* 2016; Toji *et al.* 2017; Zhao *et al.* 2017; Kunii *et al.* 2018; Yoshino *et al.* 2018). Leucocytes also produce interleukin (IL)-4 and IL-10 during early pregnancy in cattle (Shirasuna *et al.* 2012; Yang *et al.* 2018). It is abundantly clear from the above overview that IFNT produced by the early conceptus is fundamental to ensuring a conceptus–maternal dialogue that supports ongoing development of the embryo, attachment of the elongating embryo to the uterus and the establishment of a pregnancy.

Application in assisted reproduction

As noted above, ISGs are upregulated in leucocytes. This has led to studies on the potential use of a blood sample to measure ISGs as diagnostic markers of early pregnancy and embryo mortality in cattle (Lucy *et al.* 2011; Matsuyama *et al.*

2012; Sheikh *et al.* 2018). The expression of leucocyte ISGs was greater from Day 18 to Day 25 of gestation in Japanese Black × Holstein–Friesian cows that maintained a pregnancy after mating by AI and after embryo transfer (Matsuyama *et al.* 2012). The expression of blood leucocyte ISGs chemokine (C-C motif) ligand 18 gene (*CCl8*) and C-X-C motif chemokine 10 gene (*CXCL10*) on Day 18 of gestation was elevated in pregnant Japanese Black cows (Sakumoto *et al.* 2018). Karan Fries cows that maintained a pregnancy after AI had greater expression of leucocyte ISGs from Day 14 to Day 28 of gestation (Sheikh *et al.* 2018). Granulocyte ISGs were also expressed at a higher level from Day 20 to Day 22 of gestation in Holstein cows in four commercial herds and a research herd (Yoshino *et al.* 2018), as well as in a second Holstein research herd (Wijma *et al.* 2016). In one study, the expression of leucocyte ISGs on Day 18 of gestation was greater in primiparous Holstein heifers but not in multiparous cows (Green *et al.* 2010). A preliminary conclusion from the above studies is that leucocyte and granulocyte ISGs show good potential as diagnostic markers for early pregnancy in cattle. However, relationships between ISGs and embryo development have not been consistently observed, and further research is required in this area. In addition, the accuracy in identifying pregnancy in the above studies was around 80%, and a commercial diagnostic test would need to be more accurate and robust. An on-site diagnostic test would be particularly valuable to industry because pregnant and non-pregnant cattle could be managed appropriately soon after AI or embryo transfer. Non-pregnant cattle could be returned to the mating herd to reduce the period when cows are non-reproductive.

Cultured *in vivo*- and *in vitro*-derived bovine embryos classified as good quality secreted more IFNT than embryos classified as fair quality (Neira *et al.* 2007). This suggested that IFNT could be included in an index to select embryos with high potential to establish a pregnancy. The addition of IFNT to IVF bovine embryos increased the percentage of blastocyst development (Bao *et al.* 2014). In contrast with these findings, *in vitro* bovine embryos that produced more IFNT had a poorer developmental competence (Wrenzycki *et al.* 2001; Hue *et al.* 2019). In a recent study, *IFNT*-knockout bovine embryos produced by somatic cell nuclear transfer developed to blastocysts (Kim *et al.* 2019). It is apparent that this area requires further study to clarify relationships between embryo IFNT production and capacity to establish a pregnancy. The administration of IFNT increased the lifespan of the corpus luteum in cyclic cattle and sheep (Meyer *et al.* 1995; Martal *et al.* 1997; Binelli *et al.* 2001; Bott *et al.* 2010; Antoniazzi *et al.* 2013). This increase in life-span of the corpus luteum suggested the potential of targeted IFNT therapy early in gestation to support embryo development and attachment.

Summary

The case has been made that embryo survival must be addressed in order to achieve the next step change in assisted reproduction in cattle. A review of the role of TGFB superfamily members and IFNT in early development of the oocyte–somatic cell complex and in early gestation has identified areas for further investigation. Although there has been expansion of the literature on BMP15 and GDF9, there is likely to be considerably more that can be learned about communication within the oocyte–somatic cell unit during follicle growth, development and maturation. This communication is fundamental to preparing the oocyte for optimal fertilisation potential and embryo developmental competency. A proportion of oocytes is compromised at the time of fertilisation (Hansen 2002) and a greater understanding of the conditions that are supportive of oocyte maturation would be beneficial. The tight temporal coupling between exposure of the uterus to progesterone and IFNT is well recognised. The embryo has a limited capacity to advance a retarded uterine environment (Ashworth and Bazer 1989; Teh *et al.* 2016) and the potential of IFNT therapy to positively affect the uterus and systemic immune system during early gestation should be investigated. It is possible that IFNT therapy may help establish a pregnancy when there is a degree of asynchrony between the embryo and uterus (endometrium; Fig. 4). Any IFNT therapy would only be used if the embryo was not in other ways compromised because of abnormal development. Greater clarity is required on the biology of AMH in cattle. The highest production of AMH is by early antral follicles, and there is a direct relationship between the AFC and systemic AMH concentrations. The AFC is consistent within individual heifers and cows. AMH suppresses the primordial to primary follicle transition, and an explanation is required for continued greater AFC and elevated AMH in individual heifers and cows. The solution to a step change in assisted reproduction in cattle may require research that involves combinations of BMP15, GDF9, AMH and IFNT. This would apply to both *in vivo* and *in vitro* assisted reproduction in cattle.

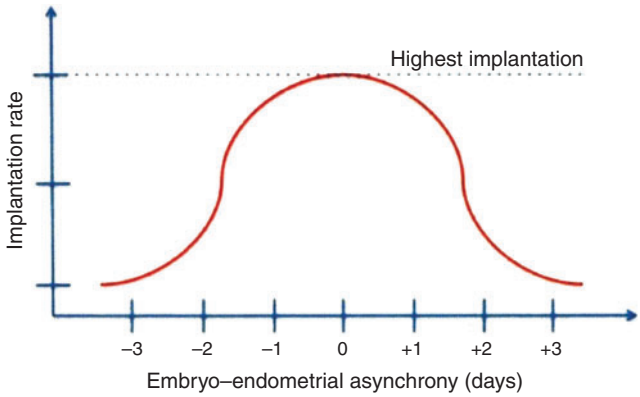

Fig. 4. Relationship between the degree of asynchrony between the embryo and endometrium and the likelihood of successful implantation. Adapted from Teh *et al.* (2016).

Conflicts of interest

The authors declare no conflicts of interest.

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