The role of IGF1 in the *in vivo* production of bovine embryos from superovulated donors

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Abstract

IGF1 plays an important role in bovine follicular growth, acquisition of oocyte competence and embryo viability. Current data also indicate a critical role for IGF1 in both the ovarian response and the embryo yield following the superovulatory treatments. IGF1 can have either positive or negative effects on embryo viability which is related to the concentration of IGF1 induced by superovulation treatment. These effects impact either on oocyte competence or directly on the embryo. Concentrations in the physiological range appear to result in the production of higher quality embryos, mainly due to the mitogenic and the anti-apoptotic activities of IGF1. However, high superovulatory responses are associated with decreased embryo viability and a concomitant increase in apoptosis. Studies in mice suggest that this increase in apoptosis is related to the downregulation of the IGF1 receptor in the embryo associated with high IGF1 concentrations. Strategies capable of controlling the IGF1 concentrations could be one approach to improve superovulation responses. A range of possible approaches for research within the IGF system in gonadotrophin-stimulated cattle is discussed in this review, including the possible use of superovulated female cattle as an alternative animal experimental model for research on reproductive disorders in humans associated with abnormal IGF1 concentrations.

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Introduction

Superovulatory treatments are being used worldwide for the production of bovine embryos in multiple ovulation and embryo transfer (MOET) programmes. The goal of superovulatory treatments in the cattle industry is the production of a large number of viable embryos capable of establishing and maintaining pregnancy after transfer and delivering healthy offspring. During superovulation, the quality of the embryo might be affected either through effects on the oocyte during follicular growth (Sirard *et al.* 2006) or directly during embryo development while in the oviduct and/or uterus (Barnes 2000, Greve & Callesen 2001, Killian 2004). Several growth factors have been shown to regulate follicular growth and embryo development, including insulin-like growth factor 1 (IGF1; Díaz-Cueto & Gerton 2001, Hardy & Spanos 2002, Diskin *et al.* 2003, Fortune 2003, Wolf *et al.* 2003, Webb *et al.* 2004). IGF1 plays an essential role in mammalian reproduction, as shown by

the impaired ovarian activity and embryo development in gene knockout mouse models (Liu *et al.* 1993, Baker *et al.* 1996, Zhou *et al.* 1997, Kadakia *et al.* 2001).

The effects of IGF1 on ovarian follicular growth and preimplantation embryo development of non-superovulated domestic ruminants have been the subject of a number of reviews (Kaye *et al.* 1992, Simmen *et al.* 1993, Spicer & Echternkamp 1995, Wathes *et al.* 1998, 2003, Watson *et al.* 1999, Lucy 2000, Kaiser *et al.* 2001, Khamsi *et al.* 2001a, Gong 2002, Mihm & Austin 2002, Zulu *et al.* 2002, Mazerbourg *et al.* 2003, Sinclair *et al.* 2003, Webb *et al.* 2003, Beg & Ginther 2006, Webb & Campbell 2007). Growing evidence has demonstrated the importance of IGF1 for the success of superovulatory treatments (Herrler *et al.* 1994, O'Callaghan *et al.* 2000, Cushman *et al.* 2001, Velazquez *et al.* 2005). For instance, oocyte quality and embryo viability have been associated with IGF1 concentrations in domestic ruminants undergoing superovulation (O'Callaghan *et al.* 2000, Velazquez *et al.* 2005). Moreover, treatments capable of increasing

IGF1 concentrations in ovarian follicular fluid of superstimulated donors were related to increased numbers of viable embryos *in vivo* (Herrler *et al.* 1994, Cushman *et al.* 2001).

In this review, we emphasize the link between both local and peripheral IGF1 concentrations and bovine embryo production *in vivo* by superovulation, and propose new directions for future research, including the possible use of superovulated cattle as an alternative model to investigate reproductive disorders in humans associated with IGF1 concentrations outside the physiological range.

The IGF superfamily

IGF1 and IGF2 were first identified by Salmon & Daughaday (1956, 1957), and designated 'sulphation factor' due to their ability to incorporate sulphate into rat cartilage *in vitro*. They were also known as non-suppressible insulin-like activity (NSILA) I and II (Froesch *et al.* 1963). A decade later, the terms sulphation factor and NSILA were replaced by the term 'somatomedin' (Daughaday *et al.* 1972) and subsequently they were renamed 'IGFs 1 and 2' due to their structural similarity with insulin and their growth-promoting activities (Rinderknecht & Humbel 1976a, 1976b).

IGF1 is one of two ligands of the IGF family (Hwa *et al.* 1999, Spicer 2004) and is a small peptide consisting of 70 amino acids with a molecular mass of 7649 kDa (Laron 2001). The established components of the IGF system also include two receptors, six high-affinity IGF-binding proteins (IGFBPs) and IGFBP proteases (Giudice 1995, Hwa *et al.* 1999, Spicer 2004). Furthermore, another group of low-affinity binding proteins, known as IGFBP-related proteins (IGFBP-rPs), belongs to the IGF family. However, no final nomenclature has been agreed for these proteins, as several research groups have identified the same protein and each group has used a different nomenclature (Hwa *et al.* 1999, Rosenfeld *et al.*

2001). Potential receptors for IGFBP(s) and IGFBP-rP(s) have also been reported to be part of the IGF family (Hwa *et al.* 1999; Table 1). Due to similarities in structure and sharing intracellular signalling cascades with other members of the IGF system, insulin, its receptor and a hybrid insulin/IGF receptor are also considered to be part of the IGF superfamily (Jones & Clemmons 1995, Monget & Martin 1997, McCusker 1998, Poretsky *et al.* 1999, Butler & Le Roith 2001, Juul 2003).

Brief overview on the role of IGF1 in non-superovulated cattle

Effects of IGF1 in bovine ovarian follicular growth and oocyte quality

The IGF1 receptor has been localized in bovine oocytes, cumulus cells and in both granulosa and theca cells (Yoshida *et al.* 1998, Perks *et al.* 1999, Armstrong *et al.* 2001, Schams *et al.* 2002, Nuttinck *et al.* 2004, Sudo *et al.* 2007). *In vitro* studies have shown that IGF1 synergizes with FSH to regulate the aromatase activity of granulosa cells (Spicer *et al.* 2002). Accordingly, a positive association was found between supplementation *in vitro* of the media with human recombinant IGF1 (100–400 ng/ml) and oestradiol production by bovine ovarian cells (Spicer *et al.* 1993, 2002, Yang & Rajamahendran 1998). Other *in vitro* effects of IGF1 include enhanced secretion of follistatin, inhibin-A, activin-A in granulosa cells (Glister *et al.* 2001, 2003, 2006), increased androstenedione production from theca cells (Stewart *et al.* 1995) and protection from apoptosis in oocytes and granulosa cells (Quirk *et al.* 2000, Yang & Rajamahendran 2000, Wasielak & Bogacki 2007). Several studies also observed that cumulus–oocyte complexes treated with IGF1, alone or in combination with either epidermal growth factor or angiotensin II, showed increased cumulus expansion,

Table 1 The insulin-like growth factor superfamily.

Ligands		Receptors
IGF1		Type 1 IGF receptor
IGF2		Type 2 IGF or IGF 2/mannose-6-phosphate (IGF2/M6P) receptor
Binding proteins	Binding protein proteases	Binding protein-related proteins
IGFBP1	IGFBP2 proteases	IGFBP-rP1 ^a (IGFBP7/MAC25/TAF/PSF)
IGFBP2	IGFBP3 proteases	IGFBP-rP2 ^a (CTGF)
IGFBP3	IGFBP4 proteases	IGFBP-rP3 ^a (NovH)
IGFBP4	IGFBP5 proteases	IGFBP-rP4 ^a (CYR61)
IGFBP5		IGFBP-rP5 ^a (L56/HTRA1)
IGFBP6		IGFBP-rP6 ^a (ESM1)
	Potential receptors	
	IGFBP(s)	IGFBP-rP7 ^a (rCOP-1/WISP2/CTGF-L)
	IGFBP-rP(s)	IGFBP-rP8 ^a (ELM1/WISP1)
		IGFBP-rP9 ^a (WISP3)

In italics are the components of the established IGF system. Based on Giudice (1995), Hwa *et al.* (1999), Monget & Bondy (2000) and Spicer (2004). ^aOther designations.

improved nuclear maturation rate and enhanced pyruvate metabolism (Lorenzo *et al.* 1994, 1995, Idris Anas *et al.* 1998, Iga *et al.* 1998, Rieger *et al.* 1998, Sakaguchi *et al.* 2000, 2002, Stefanello *et al.* 2006). The effect of IGF1 on bovine ovarian follicle growth also depends on various factors, such as follicular stage, cell cycle and treatment dose. For instance, 20 ng/ml human recombinant IGF1 and 1 ng/ml Long R3 IGF1, which have a 1000-fold reduced affinity for IGFBPs (Francis *et al.* 1992), promote antrum formation and increase oocyte diameter in preantral follicles (Gutierrez *et al.* 2000, Itoh *et al.* 2002). By contrast, 5–50 ng/ml Long R3 IGF1 and 1000 ng/ml human recombinant IGF1 induced detrimental effects on oocyte morphology, size and number of granulosa cell layers in the same category of follicles (McCaffery *et al.* 2000, Thomas *et al.* 2007). In small antral follicles, 1000 ng/ml human recombinant IGF1 can increase follicle diameter (165–215 µm), but not in medium-sized (216–280 µm) and large antral follicles (281–380 µm; Walters *et al.* 2006). In addition, the protective effects of IGF1 against apoptosis in granulosa cells are exerted only with unperturbed progression from the G₁- to S-phase of the cell cycle (Hu *et al.* 2004). Collectively, these data indicate that keeping IGF1 concentrations within a normal physiological range is required for proper ovarian follicular function.

The biological significance of IGF1 in ovarian physiology was further demonstrated in an autotransplanted ovarian sheep model in which the ovary is relocated to a site under the skin of the neck. Direct

infusion of an IGF1 analogue for 12 h (80–90 µg/h) into the ovarian artery of the conscious animal significantly enhanced the secretion of oestradiol (Scaramuzzi *et al.* 1999). Spicer *et al.* (2000) infused IGF1 concentrations closer to the physiological range with osmotic minipumps at a rate of 150 ng/ml per hour for 7 days directly into the ovary. This treatment increased the concentrations of oestradiol and IGF1 in the follicular fluid of small follicles (2–5 mm). Surprisingly, the follicle diameter was increased by IGF1 infusion only in the largest follicle, even though follicular fluid IGF1 concentrations were not altered. This discrepancy was attributed to an increased clearance of IGF1 in large follicles due to lower levels of IGFBPs when compared with small follicles (Spicer *et al.* 2000). IGFBPs play a pivotal role in the control of IGF1 bioavailability. IGFBPs inhibit the effects of IGF1 possibly by sequestering extracellular IGF1 and thereby limiting access to cell surface receptors. IGFBPs also potentiate IGF1 actions by prolonging its half-life (via protection against degradation), acting as a reservoir to sustain controlled delivery to target cells and facilitating transport from the peripheral circulation to target tissues (Clemmons 1998, Baxter 2000, Firth & Baxter 2002). As evidenced in several studies, high levels of IGFBP2, 4 and 5 were found in bovine follicular fluid from atretic subordinate follicles compared with dominant healthy follicles (Table 2). These three IGFBPs correlate negatively with follicular diameter during antral follicle development (Austin *et al.* 2001). IGFBP3 is the major circulatory

Table 2 Changes of insulin-like growth factor binding protein 2, 3, 4 and 5 (IGFBPs) and their proteolytic activity in bovine follicular fluid during ovarian follicular antrum development and atresia.

Follicular status				FF changes of IGFBP				Proteolytic activity in FF of IGFBP				References
Category	Diameter (mm)	Sampling frequency	Contrasting follicle ^a (mm)	2	3	4	5	2	3	4	5	
S-DF	(~13.5)	Single	SubF (~5–12)	↓	↑	–	–	–	–	–	–	Echternkamp <i>et al.</i> (1994)
	(?)	Multiple	SubF (?)	↓	↑	↓	↓	–	–	–	–	de la Sota <i>et al.</i> (1996)
	(~11–17)	Multiple	SubF (<9)	↓	↑	–	–	–	–	–	–	Stewart <i>et al.</i> (1996)
	(?)	Multiple	SubF (≤5)	–	↑	–	–	–	–	–	–	Funston <i>et al.</i> (1996)
	(≥8.5)	Multiple	SubF (~4–8.5)	↓	↑	↓	↓	–	–	–	–	Austin <i>et al.</i> (2001)
	(~11–16.5)	Multiple	SubF (~7 to 8.5)	–	–	↑	↑	–	–	–	–	Rhodes <i>et al.</i> (2001)
	(~12)	Single	SubF (~9)	↓	↑	↓	↓	–	–	↑	–	Rivera & Fortune (2001)
	(~19.5)	Single	SubF (~1–8.5)	↓	↑	↓	↓	↑	↑	↑	–	Spicer <i>et al.</i> (2001)
	(~16)	Single	SubF (~9–17)	↓	↓	↑	↑	–	–	–	–	Kojima <i>et al.</i> (2003)
	(~16)	Single	Atretic (~9–12.5)	↓	↓	↓	↓	–	–	–	–	Kojima <i>et al.</i> (2003)
	(≥8.5)	Multiple	SubF (~7–8)	↓	↓	↓	↓	–	–	↑	–	Rivera & Fortune (2003)
	(~11–14)	Single	SubF (~4–8)	↓	↑	↓	↓	–	–	–	–	Nicholas <i>et al.</i> (2005)
	(~17–19)	Multiple	SubF (~7–8.5)	↓	↑	↓	↓	–	–	–	–	Santiago <i>et al.</i> (2005)
	(~12)	Multiple	SubF (~6–8)	↓	↑	↓	↓	–	–	–	–	Canty <i>et al.</i> (2006)
Co-DF ^b	(~17)	Multiple	SubF (~<13.5)	↓	↑	–	–	–	–	–	–	Echternkamp <i>et al.</i> (1994)
	(~10.5–12)	Single	SubF (~9)	↓	↑	↓	↓	–	–	↑	–	Rivera & Fortune (2001)
	(~9)	Single	SubF (~7–8)	↓	↑	↓	↓	–	–	↑	↑	Rivera & Fortune (2003)
Healthy ^c	(3–5)	Single	Atretic(4–5)	↓	↑	↓	↓	–	–	–	–	Irving-Rodgers <i>et al.</i> (2003)

FF, follicular fluid; ?, not reported; S-DF, single dominant follicle; Co-DF, co-dominant follicle; SubF, subordinate follicle; ↑, levels increase; ↓, levels decrease; ↑, levels remain relatively constant; –, not analyzed or not clearly identified.

^aMakes reference to the category of ovarian follicle(s) used for comparison in the experiment. ^bCo-dominant follicles were induced with FSH treatment. ^cFollicles with an intact membrana granulosa with a few pyknotic nuclei.

carrier of IGF1 and is predominantly present in dominant follicles (Gradela *et al.* 1998, Nicholas *et al.* 2002). The complexity of the IGF system is further illustrated by specific IGFBP proteases described in several species including cattle (Spicer *et al.* 2004), which enhance the amount of free IGF1 within a follicle despite synthesis of IGFBPs (Mihm & Austin 2002).

The enhanced oestradiol production following exogenous treatment of IGF1 illustrates the importance of endocrine IGF1 for ovarian function in domestic ruminants. The endocrine function of IGF1 is supported by experiments where immunization against GH releasing factor significantly reduced serum and intrafollicular concentrations of IGF1 in both cows (Kirby *et al.* 1993) and heifers (Cohick *et al.* 1996). However, the major IGF ligand produced in bovine ovaries is IGF2. It is expressed mainly in theca cells from the time of antrum development up to ovulatory-sized follicles (Armstrong *et al.* 2000). Expression in granulosa cells is either low (Schams *et al.* 2002) or absent (Armstrong *et al.* 2000), and its effects on bovine theca and granulosa cell steroidogenesis are mediated via the IGF1 receptor (Spicer *et al.* 2004, Spicer & Aad 2007). Bovine IGF1 of extra-ovarian origin also has an important role in the transition from 2 to 5 mm diameter follicles to the FSH-dependent development (>5 mm; Monget & Bondy 2000). Indeed, treatment with recombinant bovine somatotrophin (bST) increased the number of follicles 2–5 mm in diameter, with a parallel increment in systemic IGF1 (Gong *et al.* 1991, 1993a, 1997, De la Sota *et al.* 1993). A possible mechanism underlying these observations might be the important function of IGF1 in increasing the sensitivity of small antral follicles to FSH action (Mazerbourg *et al.* 2003). The activity of IGF1 in follicular growth and steroidogenesis is critical in the selection of the dominant follicle in non-superovulated cattle (Beg & Ginther 2006). Accordingly, the enhanced follicular development observed in cows selected for twin ovulations has been associated with greater IGF1 concentrations in blood and follicular fluid when compared with non-selected control cattle (Echternkamp *et al.* 1990, 2004). However, IGF1 concentrations together with other key metabolic hormones such as insulin are crucial for oestrous cyclicity in both lactating and non-lactating cattle (Garnsworthy *et al.* 2008, Velazquez *et al.* 2008a).

Effects of IGF1 in bovine preimplantation embryo development

The effects of IGF1 on early bovine embryos are mediated by its own receptor (Matsui *et al.* 1997). Several studies have found *IGF1* mRNA in the bovine uterus (Geisert *et al.* 1991, Robinson *et al.* 2000, Meikle *et al.* 2001, Pershing *et al.* 2002), but not in the oviducts (Viuff *et al.* 1995, Xia *et al.* 1996, Pershing *et al.* 2002). However, other studies have reported that bovine

oviductal cells produce IGF1 (Schmidt *et al.* 1994, Makarevich & Sirotkin 1997, Winger *et al.* 1997, Pushpakumara *et al.* 2002). Hence, during the pre-implantation period, endocrine and/or paracrine IGF1 may act directly on the embryo or indirectly via modulation of the oviductal and uterine secretions (Wathes *et al.* 1998, 2003, Velazquez *et al.* 2008a).

Direct effects of IGF1 on *in vivo* embryo viability in non-superovulated cattle have not yet been demonstrated. A positive effect of IGF1 on embryogenesis has been proposed by the studies in which improved bovine embryo production *in vitro* was found after IGF1 supplementation in the concentrations ranging from 10 to 200 ng/ml (Herrler *et al.* 1992, Matsui *et al.* 1997, Palma *et al.* 1997, Prelle *et al.* 2001, Byrne *et al.* 2002a, Makarevich & Markkula 2002, Moreira *et al.* 2002a, Sirisathien & Brackett 2003, Sirisathien *et al.* 2003, Lima *et al.* 2006, Stefanello *et al.* 2006, Velazquez *et al.* 2008b). The beneficial effects of IGF1 were visible as decreased apoptosis and increased total cell number in preimplantation embryos (Byrne *et al.* 2002b, Makarevich & Markkula 2002). In bovine preimplantation embryos IGF1 stimulates cell proliferation through the mitogen-activated protein kinase signalling cascade, while the anti-apoptotic actions are mediated via the phosphatidylinositol 3-kinase (PI3K)/AKT1 (also known as protein kinase B) pathway (Jousan & Hansen 2007, Jousan *et al.* 2008). IGF1 blocked the induction of apoptosis in bovine embryos exposed to heat shock *in vitro*, suggesting a protective role against embryonic stressors (Jousan & Hansen 2004, 2007, Jousan *et al.* 2008). Similarly, IGF1 improved embryo development, cell proliferation and embryo diameter in rabbit embryos exposed to uv radiation (Herrler *et al.* 1998). In mouse embryos, the detrimental effects of oxidative stress induced by hydrogen peroxide could be alleviated by the addition of IGF1 to the culture medium (Kurzawa *et al.* 2002, 2004). Rodent embryos were protected against specific apoptosis inducing factors such as tumour necrosis factor- α , camptothecin or actinomycin D by supplementation of the culture media with IGF1 (Byrne *et al.* 2002b, Fabian *et al.* 2004, Glabowski *et al.* 2005). Pregnancy rates were increased after transfer of *in vitro*-produced cattle embryos treated with IGF1, showing a substantial improvement of the embryonic developmental capacity (Block *et al.* 2003, Block 2007, Block & Hansen 2007). However, IGF1 cannot overcome the negative effects following cryopreservation (Willemsen *et al.* 1995, Hernandez-Fonseca *et al.* 2002). It should also be noted that some authors did not find the beneficial effects of IGF1 treatment during *in vitro* production of bovine embryos (Flood *et al.* 1993, Lee & Fukui 1995, Quetglas *et al.* 2001, Hernandez-Fonseca *et al.* 2002, Block *et al.* 2008). Differences in culture media, protein supplementation and the concentrations of IGF1 utilised might explain these contrasting results.

Recent data indicate that IGF1 affects the physiology of the bovine embryo by altering the relative abundance of developmentally important mRNA transcripts, including desmocollin II, Na/K-ATPase, BAX, IGF1 receptor, IGFBP3 and heat shock protein 70. Furthermore, these gene expression changes may occur without detectable changes in cell number, apoptosis and the ratio between inner cell mass and trophectoderm cells (Block *et al.* 2008).

Effects of IGF1 in bovine superovulatory treatments

IGF1 concentrations during superovulation

Endocrine IGF1 production

Most of the IGF1 detected in bovine antral follicles is derived from the peripheral circulation (Wathes *et al.* 2003, Sudo *et al.* 2007), but granulosa cells from superovulated cattle can produce IGF1 (Spicer *et al.* 1993). A positive correlation between IGF1 concentrations in blood and follicular fluid has been found in superovulated cattle (Herrler *et al.* 1994). Some investigations have observed that circulating IGF1 concentrations remained relatively constant during superovulatory treatments (Herrler *et al.* 1994, Cushman *et al.* 2001), suggesting that peripheral IGF1 levels of superovulated cows may be more related to nutritional intake rather than to the gonadotrophin treatment *per se*. However, other studies have indicated that both plasma (Kuehner *et al.* 1993) and follicular (O'Callaghan *et al.* 2000) concentrations of IGF1 increase during superovulatory treatments. During a 5-day superovulatory treatment regime, increased concentrations of IGF1 in the plasma were observed in days 4 and 5 in comparison with days 1 and 2, and a positive correlation between IGF1 in the plasma and follicular fluid was found only on day 4 (Simpson *et al.* 1994). Increased follicular IGF1 concentrations were also found in gilts and goats treated with equine chorionic gonadotrophin (eCG) and FSH respectively, while the plasma levels were not altered (Khamisi *et al.* 2001a, Yu *et al.* 2003), indicating that intrafollicular IGF1 concentrations are affected more by the superovulatory treatment regime than peripheral concentrations. Whether this holds true for the oviducts and uterine horns of superovulated cows is unknown at present. In non-superovulated cattle, IGF1 concentrations in uterine luminal fluid and plasma were not correlated (Bilby *et al.* 2004, 2006). Therefore, circulating IGF1 might not always reflect the IGF1 milieu to which oocytes and embryos are exposed to during superovulation. Accordingly, IGF1 plasma concentrations cannot be used to predict the number of viable embryos in superovulated cattle, even though a positive correlation exists between these two variables (Velazquez *et al.* 2004). A similar situation has been reported in humans, where the serum concentrations of IGF1 did not allow the prediction of the ovarian response with regard

to the numbers of oocytes retrieved after superovulation (Keay *et al.* 2003).

During superovulation, IGF1 changes in plasma are also mediated primarily through oestradiol (Kuehner *et al.* 1993). Oestradiol stimulates IGF1 secretion in the liver (Richards *et al.* 1991), via an increase in the number of GH receptors (Enright *et al.* 1994). Changes in IGF1 concentrations might depend on the magnitude of the increment in oestradiol, which in turn will depend on the superovulatory response, i.e. the number of gonadotrophin-active follicles responding to the superstimulatory treatment. Indeed, a higher number of corpora lutea was observed when peripheral IGF1 concentrations were affected by superovulation (Kuehner *et al.* 1993) compared with unchanged IGF1 concentrations (Herrler *et al.* 1994, Cushman *et al.* 2001).

Paracrine IGF1 production

Studies on IGF1 production in bovine oviducts and uterus during superovulation have not been reported. Analysis of gene expression and determination of concentrations in oviductal and uterine fluids would be critical for understanding embryo–hormonal milieu interactions. This information will be valuable for the development of improved culture conditions during *in vitro* embryo production, especially for humans undergoing superovulation during *in vitro* fertilization–embryo transfer (IVF-ET) cycles, where the same individual acts as donor and recipient.

Effect of IGF1 during superovulation on follicular development and oocyte quality

The variability within and between animals in both the number of follicles that are stimulated and the number that ovulate is the limiting factor for the success of ET programmes (Adams 1994, Kanitz *et al.* 2002, Mapletoft *et al.* 2002, 2006). The number of gonadotrophin-responsive follicles present in both ovaries at the start of a superovulatory treatment is important to achieve a satisfactory superstimulatory response (González-Bulnes *et al.* 2003). In superstimulated animals the preovulatory LH surge occurs earlier, which is associated with a lack of time for the follicles to acquire adequate maturation and thus to ovulate (D'Occhio *et al.* 1999). This indicates that oocytes with a proper maturational period during superovulation could yield more viable embryos. IGF1 accelerates the meiotic progress of bovine oocytes in small (≤ 3 mm) follicles (Sakaguchi *et al.* 2000, 2002) and more viable embryos can be obtained in sheep (Veiga-Lopez *et al.* 2005) and cattle (Ireland *et al.* 2007) when a greater population of follicles around 3 mm in size is present at the time of stimulation. Accordingly, increments in blood IGF1 concentrations induced by bST treatment have been associated with increased numbers of follicles between 2 and 5 mm in diameter

(Gong *et al.* 1991, 1993a, 1997, De la Sota *et al.* 1993). This treatment was also effective in increasing the superovulatory response in cattle (Gong *et al.* 1993b, 1996, Herrler *et al.* 1994). Statistically significant increases in ovulation rate in terms of numbers of corpora lutea and embryo viability due to bST treatment have been found in some, but not all studies (Table 3). Variability between experiments could be related to several factors including the dose of bST, method of ovarian examination, type and dose of gonadotrophin, and both number and body condition of animals used in such studies. The effect of bST has been suggested to be mediated through GH, IGF1 and insulin acting either separately or in synergy (Gong *et al.* 1993b).

The effect of exogenous IGF1 on ovulation rate in cattle undergoing superovulatory treatments has not yet been tested. Studies in rats found that superovulated animals treated subcutaneously with Long R3 IGF1, which has negligible affinity for IGFBPs, had more ovulations than control animals (Khamisi *et al.* 2001b). In peripubertal cattle, intraovarian injections of IGF1 (6 µg) improved oocyte developmental competence *in vitro* in such a way that oocytes from superstimulated calves yielded a blastocyst rate similar to adult cattle (Oropeza *et al.* 2004). Oocytes from prepubertal calves showed a deficient mRNA expression pattern of facilitative glucose

transporters and insufficient protein translation as compared to their adult counterparts (Oropeza *et al.* 2004). Hence, intraovarian IGF1 treatment may correct this 'deficient oocyte machinery' resulting in improved blastocyst formation. However, the developmental potential of blastocysts produced using this treatment needs to be analysed after transfer to recipients.

It has been hypothesized that elevated intraovarian IGF1 levels are associated with enhanced follicular growth, but that these could be detrimental to oocyte maturation in growing follicles (Armstrong *et al.* 2003). Indeed, higher levels of follicular IGF1 in superovulated ruminants have been associated with abnormal oocyte morphology (O'Callaghan *et al.* 2000). Likewise, *in vitro* treatment with high IGF1 concentrations did increase follicular size (Walters *et al.* 2006), but higher IGF1 exposure induced smaller oocytes in treated follicles (McCaffery *et al.* 2000). Development to the morula and blastocyst stages is positively associated with oocyte diameter (Arlotto *et al.* 1996). Failure of the oocyte to reach a proper size coincides with the inability to undergo meiotic maturation and increased frequency of polyspermic fertilization (Fair *et al.* 1995, Otoi *et al.* 1997). The potentially deleterious action of high IGF1 levels on oocyte competence has been demonstrated in women, where low concentrations of IGF1 in the

Table 3 Effect of bovine somatotrophin (bST) on the superovulatory response in cattle.

Type of animal ^a	Period of treatment ^b	Amount of bST (mg)	ORE	Effect of treatment*				References
				Number of CL	Number of O/E	Number of VP	Percentage of TE	
Dairy heifers (n=31)	During SOV (4 days)	160	PPR	↑	↑	↑	↓	Rieger <i>et al.</i> (1991)
Beef×dairy heifers (n=24)	Day 7, before SOV	320	LAP	↑	↑	↑	↓	Gong <i>et al.</i> (1993b)
Beef×dairy heifers (n=24)	Day 7, before SOV	320	LAP	↑	↑	↑/↑ ^c	↓	Gong <i>et al.</i> (1993b)
Lactating beef cows (n=10)	For 41 days before SOV	25	?	?	↑	↑	?	Gray <i>et al.</i> (1993)
Non-lactating beef cows (n=10)	For 37 days before SOV	25	?	?	↑	↑	?	Gray <i>et al.</i> (1993)
Dairy heifers (n=17)	Day 4, before SOV	500	ULT	↓	↓	↓	↑	Kuehner <i>et al.</i> (1993)
Dairy heifers (n=18)	Day 11, first day of SOV	500	ULT	↑	↓	↓	↓	Kuehner <i>et al.</i> (1993)
Dairy heifers (n=17)	Day 15, after SOV	500	ULT	↓	↓	↓	↓	Kuehner <i>et al.</i> (1993)
Dairy cows (n=22)	Day 4, before SOV	640	SLA	↑	?	?	?	Herrler <i>et al.</i> (1994)
Dairy cows (n=38)	Day 4, before SOV	640	SLA	↓	↓	↑	↑	Herrler <i>et al.</i> (1994)
Dairy cows (n=21)	Day 13, after SOV	640	SLA	↓	↓	↓	?	Herrler <i>et al.</i> (1994)
Beef×dairy heifers (n=16)	Day 7, before SOV	320	LAP	↑	↑	↑	↓	Gong <i>et al.</i> (1996)
Beef×dairy heifers (n=16)	Day 7, before SOV	320	LAP	↑	↓	↑	↑	Gong <i>et al.</i> (1996)
Beef×dairy heifers (n=12)	Day 7, before SOV	320	?	?	↓	↑	↑	Gong <i>et al.</i> (1996)
Dairy cows (n=27)	4 to 5 doses, every 14 days, before SOV	500	SLA	↑/↑ ^d	?	?	?	Cushman <i>et al.</i> (2001)
Beef cattle (n=35)	5 to 6 doses, every 14 days, before SOV	500	?	↓	↑	↑	?	Cushman <i>et al.</i> (2001)
Dairy cows (n=12)	At the time of first AI	500	?	?	↓	↓	↑	Moreira <i>et al.</i> (2002b)
Beef cows (n=57)	One dose every 14 days for up to 4 SOV ^e	500	?	↓	?	↓	?	Hasler <i>et al.</i> (2003)
Beef cows (n=37)	One dose every 14 days for 1 SOV ^e	500	?	↓	?	↓	?	Hasler <i>et al.</i> (2003)

*Statistically significant ($P \leq 0.05$); ORE, ovulation rate examination; CL, corpora lutea; O/E, ova + embryos; VE, viable embryos; TE, transferable embryos; SOV, superovulation; PPR, palpation per rectum; LAP, laparoscopy; ULT, ultrasonography; SLA, slaughter; ?, not reported; ↑, increase; ↓, decrease; ↑/↑, no difference.

^aTotal number of animals in each experiment or study. ^bDay 0, day of oestrus. ^cDepending on the dose of gonadotrophin. ^dDepending on treatment with oestradiol. ^eStarting at oestrus before SOV.

follicular fluid of patients undergoing superovulation were correlated with successful early embryo development (Wang *et al.* 2006). Albeit speculative, this inverse relationship between oocyte competence and high intrafollicular IGF1 concentrations might be related to the fact that when more ovulations occur during superovulation less viable embryos are produced (Driancourt 2001, Ireland *et al.* 2007). In this regard, it is worthy to mention that higher levels of intrafollicular IGF1 were observed after the use of FSH when compared with human menopausal gonadotrophin (hMG; Fried *et al.* 1998, Hammadeh *et al.* 2000), indicating that the intrafollicular concentrations of IGF1 can be affected by the type of hormone used for superstimulation. Bovine superovulation has been induced with FSH extracted from either porcine, ovine or equine pituitaries (Staigmiller *et al.* 1992, Kanuya *et al.* 1997), eCG (Gonzalez *et al.* 1994), hMG (Lauria *et al.* 1982), recombinant bovine FSH (Wilson *et al.* 1993) or recombinant human FSH (Takagi *et al.* 2001). Notwithstanding, the effect of different gonadotrophin preparations upon intrafollicular IGF1 concentrations has not yet been studied in cattle.

The other ligand of the IGF system, IGF2, is also increased in the follicular fluid by superovulation, and has been associated with decreased oocyte quality (O'Callaghan *et al.* 2000). In superstimulated women, high follicular concentrations of IGF2 were positively related to oocyte maturation and early embryo development (Wang *et al.* 2006). By contrast, the intrafollicular microenvironment of IGF2 was not associated with clinical outcome in the patients subjected to IVF-ET cycles (Choi *et al.* 2006). However, studies on the role of IGF2 during bovine superovulation are lacking.

Oocyte maturation has been positively associated with follicular fluid levels of IGF1 in women undergoing ovarian superstimulation (Nardo *et al.* 2001). IGF1 levels in follicular fluid compatible with bovine oocyte competence are modulated to a great extent by IGFBPs (Nicholas *et al.* 2005). It has been observed that the amount of IGFBP2, 4 and 5 in the follicular fluid of follicles >8 mm from cows superstimulated with eCG was less compared with that of medium-sized follicles, and that IGFBP3 was present in all follicles (van de Leemput *et al.* 1997). FSH-stimulated cows had less IGFBP2 and relatively constant levels of IGFBP3 in large oestrogen-active follicles (~17 mm or greater) compared with large oestrogen-inactive (~12–14 mm), medium (5–7 mm) and small follicles (≤4 mm; Echternkamp *et al.* 1994). Superovulated ewes had lower concentrations of IGFBP2, 4 and 5 than non-superovulated controls in follicular fluid from follicles ≥3 mm (O'Callaghan *et al.* 2000). In a model of follicular co-dominance induction, treatment with 2–6 mg recombinant bovine FSH for 36–48 h decreased the amounts of IGFBP2, 4 and 5, and increased levels of IGFBP3 and IGFBP proteases 4 and 5 in the follicular fluid of co-dominant follicles (~9–12 mm) compared with

subordinate follicles (~7–9 mm; Rivera & Fortune 2001, 2003). Although these findings partially suggest that the action of the IGFBP system during superovulation operates in a manner similar to non-superovulated conditions, more work is required to further elucidate the role of IGFBPs in follicular development during bovine superovulatory treatments.

Effects of IGF1 during superovulation on preimplantation embryo development

The main objective of a superstimulatory treatment is to obtain the maximum number of viable embryos with a high probability of producing pregnancies. Although the best indicator of the success of an ET programme is the number of live calves born per donor over a given period of time (Armstrong 1993), the number of viable embryos produced per donor is frequently used as an indicator of MOET success (Peixoto *et al.* 2002). Embryo viability in the MOET programmes is not only affected by the ovulation rate but also depends critically on whether normal fertilization occurs (Armstrong 1993) and the oviductal and uterine milieu in which the embryo develops prior to embryo recovery (Barnes 2000).

The IGF1 receptor mediates the effects of IGF1 during the preimplantation period (Matsui *et al.* 1997). Day 7 bovine embryos collected from superovulated animals express the IGF1 receptor (Bertolini *et al.* 2002, Moore *et al.* 2007). Receptors for IGF1 are also observed in embryos produced either partially (Lazzari *et al.* 2002, Lonergan *et al.* 2003) or totally by standard *in vitro* procedures (Watson *et al.* 1992, Yoshida *et al.* 1998, Yaseen *et al.* 2001, Lazzari *et al.* 2002, Moore *et al.* 2007) or by somatic cell nuclear transfer (Sawai *et al.* 2005, 2007, Moore *et al.* 2007). *In vitro* procedures can alter the relative abundance of IGF1 receptor transcripts in bovine embryos (Bertolini *et al.* 2002, Lazzari *et al.* 2002, Sawai *et al.* 2005, 2007, Warzych *et al.* 2007). Preimplantation embryos collected from superovulated cows have shown either high (Bertolini *et al.* 2002), low (Lazzari *et al.* 2002, Sawai *et al.* 2007) or similar (Moore *et al.* 2007) transcript abundance when compared with *in vitro*-produced embryos. It is unknown whether or not differences exist between embryos derived from single spontaneous ovulations and stimulated multiple ovulations, with regard to the expression of the IGF1 receptor.

Convincing evidence has demonstrated that IGF1 can affect positively embryos from superovulated cattle. Improvements in embryo production have been achieved by treating superovulated donors with bST (Gong *et al.* 1993b, 1996, Herrler *et al.* 1994, Cushman *et al.* 2001, Moreira *et al.* 2002b, Neves *et al.* 2005), which was associated with increments in IGF1 concentrations in follicular fluid and peripheral plasma (Herrler *et al.* 1994, Cushman *et al.* 2001). Since bST also exerts direct effects on several reproductive events, including

embryogenesis (Kaiser *et al.* 2001, Sirotkin 2005), a complementary effect of bST and IGF1 cannot be ruled out. Support for a beneficial action of IGF1 on embryonic development during superovulation can be derived from the positive correlation found between the plasma concentrations of IGF1 and the number of viable embryos produced by superovulated mature cows (Velazquez *et al.* 2005). Insulin is closely linked with IGF1 during superovulation as shown by the greater diameter of large follicles and increased levels of IGF1 in the follicular fluid induced with exogenous application of insulin during the period of gonadotrophin treatment (Simpson *et al.* 1994). Both hormones were found to be closely related with body condition score (BCS) and embryo production in superovulated cows (Velazquez *et al.* 2005; Table 4).

Diet-induced increases in circulating insulin were associated with the recruitment of small ovarian follicles that resulted in an enhanced superovulatory response in terms of both the number of preovulatory follicles and ovulations (Gong *et al.* 2002). However, it remains to be determined whether such an approach will also improve oocyte competence *in vivo*. Ovum pick-up/IVF models found that increased dietary intake over maintenance requirements in superovulated donors increased circulating concentrations of insulin and IGF1. However, this treatment started to have a negative impact on *in vitro* embryo production after 6 weeks of overfeeding (Freret *et al.* 2006). Reduced blastocyst yields were reported in cattle with moderately high BCS fed twice maintenance requirements. The increased dietary intake in heifers with moderately high BCS resulted in hyperinsulinaemia (Adamiak *et al.* 2005), similar to the values reported in women with the polycystic ovary syndrome (PCOS; Dunaif 1997). By contrast, higher dietary intake positively affected blastocyst production in animals with low BCS (Adamiak *et al.* 2005). The inverse relationship between overfeeding and embryo production has also been observed during *in vivo* embryo production (Yaakub *et al.* 1999, Siddiqui *et al.* 2002, Stroud & Hasler 2006, Garcia Guerra *et al.* 2007, Kadokawa *et al.* 2008). These findings are in agreement with the hypothesis that a 'quiet' metabolism during

early mammalian embryo development is positively associated with embryo viability (Leese 2002, 2003, Bauman *et al.* 2007, Leese *et al.* 2007). Although plasma IGF1 was not associated with impaired oocyte competence during over-nutrition (Adamiak *et al.* 2005), it cannot be completely ruled out, as a direct effect of liver-produced IGF1 on ovarian activity will depend on how much circulating bioactive IGF1 impacts on the ovaries. IGF1 in follicular fluid has been found to be either lower (Echternkamp *et al.* 1990, Spicer *et al.* 1991), equal (Spicer *et al.* 1992) or greater than peripheral IGF1 (Spicer *et al.* 1992, Ortega *et al.* 2008). This emphasizes the importance of measuring both IGF1 and IGF1 concentrations in reproductive tracts in experimental trials.

Experiments in rodents found that locally enhanced IGF1 production in the uterus during a superovulatory treatment can be detrimental to early embryo development. This increase in IGF1 production is thought to be due to the hyperoestrogenaemia caused by superovulation, as uterine IGF1 production is primarily regulated by oestrogens (Murphy *et al.* 1987, Simmen *et al.* 1990, Sahlin *et al.* 1994, van Lier *et al.* 2006, Suzuki *et al.* 2007). Katagiri *et al.* (1996) reported a decrease in both the rate of blastocyst formation and blastocyst cell number, and an increased proportion of degenerated blastocysts after culturing eight-cell embryos with uterine luminal fluids isolated from rat uteri infused with IGF1, thus mimicking IGF1 concentrations caused during superovulation. The same results were obtained with uterine luminal fluid from superovulated animals, and even more interesting, a reversed trend was observed in both models (superovulation and IGF1 infusion) when the uterine fluids were treated with anti-IGF1 antibody (Katagiri *et al.* 1996). The same rat model was applied in a study in which an altered uterine electrolyte environment, especially cations, was suggested to be partially responsible for the detrimental effects of IGF1 on embryonic development after superovulatory treatment (Katagiri *et al.* 1997a). Recent studies have reported that exposure of mice embryos at the two- or four-cell stage to high IGF1 concentrations (950 ng/ml) triggered apoptosis in blastocysts via

Table 4 *In vivo* embryo production and insulin and insulin-like growth factor1 (IGF1) concentrations (mean $\pm$ S.E.M.) in superovulated dairy cows associated with body condition score (BCS).

	BCS (5 points scale)		P value ^a
	<2.5	>2.5	
Ova + embryos (n)	7.0 $\pm$ 1.4	14.1 $\pm$ 2.3	0.042
Viable embryos (n)	3.7 $\pm$ 1.1	8.9 $\pm$ 1.8	0.047
Quality 1 embryos (n)	2.2 $\pm$ 1.0	5.8 $\pm$ 1.5	0.062 ^b
Insulin (μ U/ml)	10.0 $\pm$ 2.4	20.3 $\pm$ 4.2	0.031
IGF1 (ng/ml)	128.6 $\pm$ 16.8	207.5 $\pm$ 28.0	0.035

n, total number. Based on data from Velazquez *et al.* (2005).

^aMann-Whitney test. ^bConsidered as a value towards significance.

downregulation of the IGF1 receptor (Chi *et al.* 2000), which in turn increased embryo resorption rates (Pinto *et al.* 2002, Eng *et al.* 2007). It has been suggested that this high IGF1 induced apoptosis in embryos associated with reduced IGF1 receptor signalling requires activation of the TP53 pathway (Moley *et al.* 2005). However, extrapolation of the results from rodents to cattle needs to be done with caution. The downregulation of the IGF1 receptor found in bovine embryos treated with IGF1 concentrations considered beneficial for embryogenesis (100 ng/ml; Prelle *et al.* 2001) highlights the importance of species-specific differences on the detrimental effects of IGF1 upon embryonic development.

Partial evidence for an adverse effect of IGF1 *in vivo* was found in superovulated maiden heifers in which a negative correlation between embryonic viability and plasma concentrations of IGF1 was observed (Velazquez *et al.* 2005). The concentrations of IGF1 in blood are higher in heifers than in cows (Wathes *et al.* 2001, Velazquez *et al.* 2004). Therefore, both high endogenous concentrations and the superovulatory gonadotrophins might elevate IGF1 concentrations in both oviduct and uterus to a level that is suboptimal for embryonic development (Figs 1 and 2). The potential deleterious effects of high concentrations of IGF1 on embryo viability are also partially supported by studies in non-superovulated cows in which a decrease in pregnancy rates was attributed to the hyperstimulation of IGF1 production induced by bST treatment (Bilby *et al.* 2004).

Modulation of the IGF system to improve results of superovulation in cattle

IGF1 is able to cross the blood–brain barrier (Reinhardt & Bondy 1994) and may act in either the hypothalamus and/or pituitary gland to modulate gonadotrophin secretion (Monget & Martin 1997). Studies in rodents have found that IGF1 is produced in several regions of the nervous system, including the arcuate nucleus and median eminence of the brain, where GnRH regulates the ovarian production of gonadotrophins (Daftary & Gore 2005). Accordingly, bovine IGF1 has been found to be involved in the regulation of LH release (Hashizume *et al.* 2002). No information is available regarding brain production of IGF1 in superovulated cattle. This may be especially relevant since it is known that nuclear and cytoplasmic maturation of bovine oocytes is critically dependent on precise patterns of LH secretion (Lindsey *et al.* 2002). Alteration in LH production associated with impaired oocyte maturation is one of the main problems caused by superovulation (D'Occhio *et al.* 1999).

The use of exogenous IGF1 to enhance *in vivo* embryo production in superovulated cows has not yet been tested. This approach could be useful to improve embryo yields in animals with reduced superovulatory response. Reliable methods for the prediction of embryo production in donor animals would be helpful in improving the outcome in the MOET programmes. Total plasma IGF1 concentrations have been found to be of limited value for the prediction of the number of viable embryos (Velazquez *et al.* 2005). Measuring the concentrations of

Figure 1 Possible effects of IGF1 on oocyte and preimplantation embryo development during superovulation in cattle. IGF1 milieu during gonadotrophic stimulation in follicles, oviduct and uterus will depend primarily on the dose and type of superstimulatory hormone (SH) used, the number of FSH-responding follicles at the time of treatment and the endocrine and paracrine production of IGF1 in the individual (inherent and nutritional induced). The stimulatory treatment will induce high oestradiol (E_2) production, which in turn will increase IGF1 production in reproductive tissues (paracrine) and possibly peripheral plasma (endocrine effect). The IGF1 increase in plasma could contribute even more to the paracrine effect of IGF1 during superovulation. This hyperstimulation of IGF1 is associated with the enhanced follicle growth occurring during superovulation. In the follicles destined to reach preovulatory size, the amount of IGFBP2, 4 and 5 will be decreased, allowing the increment of intrafollicular IGF1 concentrations. Positive effects on oocyte competence and embryo development are exerted by IGF1 when the concentrations remain within the normal physiological range (green arrows). If the superstimulatory response is too high, IGF1 concentrations are increased to supraphysiological levels, which could result in the ovulation of low-quality oocytes. The decrease in oocyte quality and the altered IGF1 environment present in the oviduct and uterus could interfere with the fertilization process and/or preimplantation embryo development (red arrows).

circulating IGF1 and IGFBPs in combination could improve the prediction of the number of viable embryos. This is supported by the fact that mouse embryos cultured in medium supplemented with dephosphorylated IGFBP1 in the form of an IGF1/IGFBP1 complex showed a higher increase in the rate of blastocyst formation compared with supplementation with IGF1 alone (Lin *et al.* 2003). The ratio of IGF1 and IGFBP1 in serum and follicular fluid has been suggested to reflect oocyte quality, which in turn influences embryo viability (Fried *et al.* 2003).

Stimulatory gonadotrophin treatments can also affect gamete transport in the oviductal–uterine tract and the fertilization process (Greve & Callesen 2001). IGF1 has been found in bovine seminal plasma and its receptor was present in ejaculated bovine sperm, indicating that it might play an important role during fertilization (Henricks *et al.* 1998, Hoefflich *et al.* 1999). *In vitro* studies have shown that treatment with IGF1 increased important characteristics of bovine spermatozoa, including the percentage of motile sperm and straight-line velocity (Henricks *et al.* 1998, Lackey *et al.* 1998). Significant fluctuations in the oviductal IGF1 concentrations have been found in superovulated ruminants (Kakar *et al.* 2005). However, the effects of different IGF1

concentrations in oviducts during superovulatory treatments on sperm viability and fertilization success have not yet been studied.

Although IGF1 ligand expression in the preimplantation stage has been proposed as a potential marker for embryo quality in humans and mice (Liu *et al.* 1997, Kowalik *et al.* 1999), the autocrine role of IGF1 in bovine embryogenesis has not been fully elucidated. Some studies have reported expression of the IGF1 ligand in bovine embryos during the preimplantation period (Schultz *et al.* 1992, Yoshida *et al.* 1998, Lonergan *et al.* 2000), while others did not find the molecule (Yaseen *et al.* 2001, Bertolini *et al.* 2002, Moore *et al.* 2007, Warzych *et al.* 2007). Nevertheless, it would be useful to determine whether oestradiol concentrations, associated with the superovulatory response, do induce expression of the IGF1 ligand in embryos, as has been observed in some types of brain cells (Shingo & Kito 2003).

It has been speculated that the high rates of embryonic mortality observed in dairy cows with severe negative energy balance could be due to impaired embryo development caused by increased signalling of IGF2 in the oviduct (Fenwick *et al.* 2008). Since IGF2 is produced in oviducts and uterus and both the ligand and the receptor are expressed from the zygote to the blastocyst stage (Yaseen *et al.* 2001), the interaction between IGF2 and preimplantation embryo development in superovulated cattle warrant future research.

Figure 2 The oviductal–uterus milieu can exert negative and positive effects on preimplantation embryos during superovulation. The embryos will be affected mainly by the endocrine and/or paracrine production of IGF1 as autocrine production has still to be elucidated. When IGF1 production within the normal physiological range is maintained in the oviducts and uterus, it is suggested that there will be an increase in the number of cells and a decrease in the level of apoptosis in the preimplantation embryo (+, positive effect, green arrows). However, when this positive threshold is altered (higher IGF1 concentrations) due mainly to an over-response during gonadotrophin stimulatory treatment, the level of apoptosis increases. This negative effect would be associated with the downregulation of the IGF1 receptor (–, negative effect, red arrows).

The superovulated bovine female as an alternative model to investigate reproductive endocrinological disorders associated with IGF1 in humans

Female cattle and women share significant similarities regarding the final stages of oocyte maturation and the biochemical and intrinsic paternal and maternal regulatory processes in preimplantation embryos (Ménézo & Héribel 2002). Thus, domestic cattle could be a suitable experimental model to study the mechanisms controlling folliculogenesis (Campbell *et al.* 2003) and preimplantation embryo development in humans (Niemann & Wrenzycki 2000, Wrenzycki *et al.* 2005, 2007, Bauman *et al.* 2007, Velazquez 2008). This approach could be extended to study reproductive endocrinological disorders associated with alterations of the IGF axis, such as the PCOS in humans. PCOS is a complex multifactorial disorder that accounts for more than 75% of the cases of anovulatory infertility (Gorry *et al.* 2006), and is responsible for up to 40% of human female sterility (Krysiak *et al.* 2006). The IGF system plays an important role in the pathogenesis of PCOS (Giudice 1992, Homburg *et al.* 1992, Druckman & Rohr 2002). Patients with this disorder have significantly higher IGF1 concentrations in blood (Berker *et al.* 2004, Abd El Aal *et al.* 2005, Hahn *et al.* 2006) and ovarian

follicular fluid (Eden *et al.* 1990) compared with women without PCOS. Recent data suggested that oocyte quality critically depends on the bioavailability of IGF1 in PCOS patients undergoing IVF-ET cycles (Schoyer *et al.* 2007).

As discussed above, high IGF1 concentrations associated with high superovulatory response may exert detrimental effects on oocyte and early embryo development in stimulated cattle. This raises the interesting possibility of producing high superovulatory profiles in domestic cattle, aiming at mimicking a polycystic-like ovarian milieu. This could be useful to develop strategies to enhance oocyte competence in order to improve the outcome of IVF-ET cycles in women with PCOS. Alternatively, this bovine model could be used to test the efficacy and/or to determine the method of action of drugs used for the treatment of PCOS, both *in vivo* and *in vitro*. Support for this hypothesis comes from *in vitro* studies recently carried out to investigate the effect of metformin on bovine ovarian steroidogenesis in response to IGF1 and FSH (Tosca *et al.* 2007). This drug is used for fertility treatment in women with PCOS (Palomba *et al.* 2008). Moreover, the use of artificial insemination in this bovine PCOS model could also be a valuable approach to study the fertilization success and preimplantation embryo development *in vivo*, with the goal of designing therapies to increase the chance of pregnancy in PCOS women.

Patients with PCOS that are stimulated in assisted reproduction cycles have an increased risk of developing the ovarian hyperstimulation syndrome (OHSS; Mikkelsen 2005, Tummon *et al.* 2005). Treatments leading to reduced IGF1 levels in blood of PCOS patients are associated with a decrease in ovarian stromal blood flow, which in turn is related to a lower likelihood of developing the OHSS (Amin *et al.* 2003). OHSS could also be investigated in the superovulated bovine model. For instance, after inducing a PCOS-like status by superovulation, animals developing multiple ovarian cysts (Todoroki *et al.* 2004) could be retreated with gonadotrophins in an attempt to mimic the conditions observed in humans. Another condition possibly associated with IGF1 is the low ovarian response after stimulation with gonadotrophins. Women with a poor response to ovarian stimulation have shown either similar (Hammadeh *et al.* 2003) or reduced levels of IGF1 in the follicular fluid (Bahceci *et al.* 2007) compared with good responders. Superovulated cattle could prove to be a superior approach to unravelling the underlying cause of this condition, as shown recently by Ireland *et al.* (2007). The feasibility of inducing these two contrasting superovulatory responses observed in women (OHSS and low ovarian response) is further supported by the fact that similar superovulatory profiles have been found in cattle, ranging from low to high responders (De Roover *et al.* 2005, Durocher *et al.* 2006).

Human polycystic ovaries have been shown to have a significantly reduced proportion of primordial follicles and an increased proportion of primary follicles compared with normal ovaries (Webber *et al.* 2003). It has been proposed that abnormal preantral folliculogenesis observed in polycystic ovaries is at least partially due to an excessive androgen exposure during the prenatal period (Forsdike *et al.* 2007). In primates, this androgen-induced ovarian follicular growth is thought to be mediated by an enhanced local IGF1 effect (Vendola *et al.* 1999). The accelerated progression of primordial follicles into the primary stages of development found in a prenatally androgenized sheep model is strikingly similar to the situation observed in women with PCOS (Forsdike *et al.* 2007). This model could be easily applied to cattle as both species have similar reproductive patterns (Campbell *et al.* 2003) and androgenization of cows is a well-established procedure in the cattle industry (Nix *et al.* 1998). Moreover, prenatally androgenized heifers used in a model to increase beef production showed higher body fat accumulation, higher serum IGF1 concentrations and a tendency for increased insulin levels compared with controls (Aldrich *et al.* 1995, 1996, Reiling *et al.* 1997). These features are largely similar to some characteristics of PCOS such as obesity and altered components of the IGF system (Chang 2007, Cocksedge 2008, Franks *et al.* 2008). Refinement of the bovine prenatal PCOS-like model will primarily relate androgen doses and timing of application during pregnancy. The assessment of the developmental competence of oocytes, both *in vivo* and *in vitro*, from adult superovulated cattle exposed to high androgens during foetal development may be relevant to the study of *in utero* programming of PCOS aetiology. The preantral stage last approximately 3 months in cattle (Webb & Campbell 2007), and the environment to which preantral oocytes are exposed during this period could potentially affect future oocyte competence. This has been shown by Adamiak *et al.* (2005) in a non-superovulated cattle model, in which nutritional-induced hyperinsulinaemia, similar to the high insulin concentrations present in PCOS, during three consecutive oestrous cycles induced a detrimental effect on oocyte developmental competence *in vitro*. It would be interesting to analyse the IGF system in the reproductive tract using this hyperinsulinaemic model, in conjunction with superovulation, to further explore embryo-maternal interactions under PCOS-like conditions.

Creation of a 'universal' PCOS animal model is unlikely, as the induction of all pathological conditions observed in PCOS women is not possible (Szukiewicz & Uilenbroek 1998, Singh 2005). Common clinical features of PCOS include polycystic ovaries, anovulation, hyperinsulinaemia, hyperandrogenism and hypersecretion of LH (Chang 2007, Cocksedge 2008, Franks *et al.* 2008). Still, the ultimate diagnostic criterion for PCOS is controversial and several phenotypes have been

proposed. For instance, a patient with anovulation and polycystic ovaries but with no clinical or biochemical evidence of androgen excess can be diagnosed as having PCOS (Norman *et al.* 2007). Development of a suitable animal model critically depends on the PCOS-related disorder to be investigated (Szukiewicz & Uilenbroek 1998). Although the model for prenatal exposure of androgens is hypothetical in cattle, some clinical conditions present in PCOS have been observed in cows, including polycystic ovaries, anovulation (Todoroki & Kaneko 2006) and hyperinsulinaemia (Adamiak *et al.* 2005).

Since the increase in uterine IGF1 concentrations following superovulation is related to hyperoestrogenaemia (Katagiri *et al.* 1997b), and high uterine maternal levels of oestrogen and IGF1 are linked to endometrial cancer (Schernhammer 2002, Moyano & Rotwein 2004), models to study uterine cancer development could also be created in superovulated cattle. This might be accomplished by the combined use of oestrogen implants and gonadotrophin stimulation, which could be applied as a chronic intermittent treatment monitored over the years. The suitability of this model, with regard to long-term monitoring and induction of neoplastic tumours, is supported partially by the current use of domestic cattle for the study of reproductive aging in women (Malhi *et al.* 2005, 2006) and the documentation of tumours in the bovine reproductive tract (García-Iglesias *et al.* 1991, 1995, Pérez-Martínez *et al.* 2001).

Cattle models are especially relevant as procedures that are rarely applied in women can be carried out more frequently in cattle, including intrafollicular drug treatments (Oropeza *et al.* 2004, 2006), interfollicular oocyte transfer (Bergfelt *et al.* 1998), intrafallopian transfer of gametes (Wetscher *et al.* 2005) and oviductal recovery and transfer of early embryos (Besenfelder & Brem 1998, Besenfelder *et al.* 2001). Valuable data could also be obtained with this experimental approach, especially when using *in vivo* collection and monitoring techniques presently used in women and already validated in cattle, such as cytology (Kasimanickam *et al.* 2004) and biopsy (Katagiri & Takahashi 2004) of endometrial tissue and reproductive ultrasound techniques (Rajamahendran *et al.* 1994, Ribadu & Nakao 1999, Miyamoto *et al.* 2006, Oropeza *et al.* 2006). Moreover, several variables such as nutrition, age, health and parity can be precisely controlled in cattle populations.

Conclusions

IGF1 is only one member of the complex IGF family. The important role of IGF1 in follicular development, oocyte quality and embryo development is well documented in non-superovulated cattle. Similarly, IGF1 has been found to be directly correlated with the production of viable embryos during superovulatory treatments.

The IGF1 milieu during superovulation in follicles, oviducts and uteri will depend on the inherent endocrine and paracrine secretion and on the nutritional- and gonadotrophin-induced production of IGF1. IGF2 acting via the IGF1 receptor could also affect the oocyte quality during superstimulatory protocols. There is an undetermined threshold in which IGF1 concentrations are detrimental for embryogenesis during superovulation. This negative effect is associated with high superovulatory responses that cause increments in oestrogen production and consequently increased IGF1 concentrations in the reproductive tract. These high IGF1 concentrations can affect embryo viability indirectly via oocyte quality during follicular development, and/or directly during the preimplantation period. Alterations in oocyte morphology and oocyte size are among the observed changes caused by high IGF1 concentrations in ruminants. Detrimental effects of high IGF1 levels on embryos have been suggested to be via induction of apoptosis, associated with a downregulation of the IGF1 receptor. The latter, however, still needs to be investigated in bovine embryos. There are still a number of unexplored aspects of the IGF system that needs to be elucidated to improve further responses following superovulatory treatments. As well as improvements in animal production, human-assisted reproduction could also benefit. Furthermore, superovulated cattle could serve as an excellent alternative animal model for investigating reproductive endocrinological disorders associated with variable IGF1 concentrations in women.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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