

Follicular determinants of pregnancy establishment and maintenance

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Abstract Synchronization of dominant follicle development and control of ovulation/oocyte retrieval are commonly used assisted reproductive technologies in both cattle and humans. The final maturation of the dominant follicle is intimately tied to the final maturation of the oocyte, preovulatory secretion of estradiol, preparation of follicular cells for luteinization, postovulatory secretion of progesterone and endocrine control of the oviductal and uterine environment for gamete and embryo development. The physiological maturity of a dominant/ovulatory follicle can affect the establishment and maintenance of pregnancy. Premature induction of the ovulatory process can reduce pregnancy rates and increase late embryonic/fetal mortality in cattle, which is likely mediated through inadequate oocyte competence and a compromised maternal environment. Oocyte competence increases with follicular maturity and is dependent upon acquisition of a complete complement of mRNA transcripts and establishment of the appropriate epigenetic marking of the oocyte genome before the preovulatory

gonadotropin surge. Preovulatory secretion of estradiol is a reflection of follicular maturity and affects the oocyte, follicular cells, oviduct and uterus. The corpus luteum is a continuation of follicular maturation and rate of progesterone secretion following ovulation is linked to fertility. Advancements in our understanding of how the follicular microenvironment affects pregnancy establishment and maintenance will improve the efficiency of assisted reproductive technologies in all species. The purpose of this review is to discuss how follicular microenvironment, oocyte competence, preovulatory secretion of estradiol and postovulatory secretion of progesterone can affect pregnancy establishment and embryo/fetal survival, with an emphasis on cattle.

Keywords Follicle · Oocyte · Estradiol · Progesterone · Cattle

Introduction

Reproductive loss is of critical importance in humans and domestic livestock species. In humans, clinical loss of pregnancies prior to the 20th week of gestation occurs approximately 15% of the time (Warburton and Fraser 1964; Alberman 1988) and over 20% of women of reproductive age are estimated to experience infertility (CDC Division of Reproductive Health 2009). In the U.S. beef industry, reproductive failure is estimated to cost approximately \$500 million annually (Bellows et al. 2002). Reproductive losses pose serious challenges in humans and livestock species and a focus on minimizing reproductive losses is required.

Over the past 3 decades, there has been a rapid increase in the development of reproductive technologies both for humans and domestic livestock. Currently, in the U.S. it is

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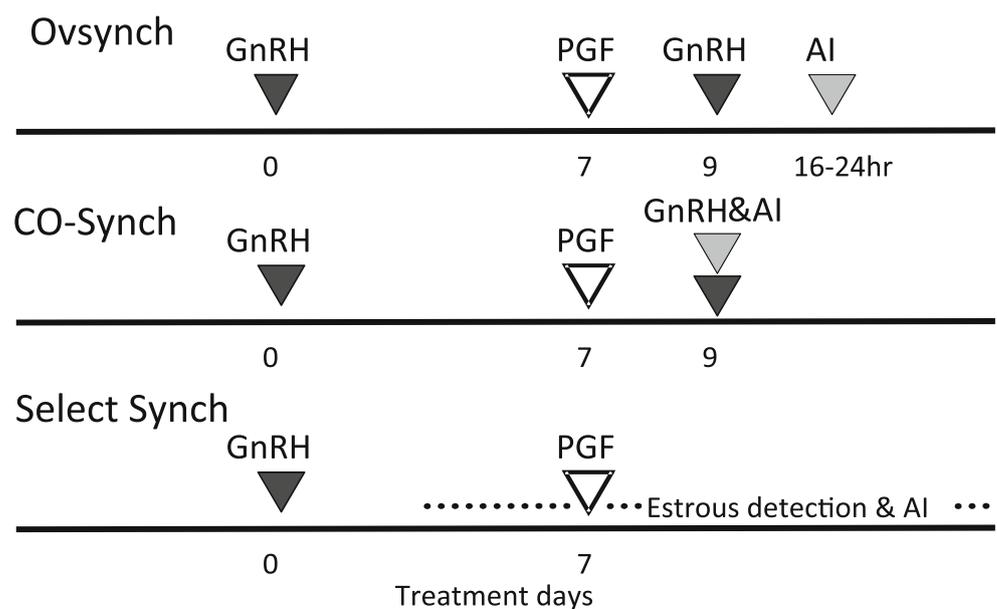
estimated that about 1% of all human infants born are conceived using assisted reproductive technologies (ART; CDC Division of Reproductive Health 2009) and about 4–6% (1.5 million calves) of the US beef calf crop result from artificial insemination (AI; NAHMS 2008). Unlike in humans, synchronization of ovulation and AI in cattle are administered on a whole herd basis rather than to individuals with fertility problems. Basic research on the physiology of the menstrual/estrous cycle, ovulation, corpus luteum function and pregnancy has contributed to the development and implementation of the preceding technologies. However, a major challenge has been to maximize the probability of pregnancy establishment and embryonic/fetal survival when implementing these technologies. Control of ovulation is an assisted reproductive technology that is commonly used in both humans and cattle and there is increasing evidence that the physiological maturity of an ovulatory follicle can affect fertility in both species. Many researchers have utilized cattle as a model to study numerous reproductive processes, including insight into human reproduction, specifically in the area of ovarian contributions to pregnancy (Campbell et al. 2003). The purpose of this review is to discuss how the follicular microenvironment, oocyte competence, preovulatory secretion of estradiol and postovulatory secretion of progesterone can affect pregnancy establishment and embryo/fetal survival, with an emphasis on cattle.

Ovulatory follicle size and the establishment and maintenance of pregnancy

Overview of synchronization of ovulation

Exogenous hormone regimes that precisely control timing of ovulation have been implemented in domestic livestock

Fig. 1 Methods that have been used to synchronize ovulation (*Ovsynch*, *CO-Synch*) or estrus (*Select Synch*) in cattle. Gonadotropin-releasing hormone (*GnRH*) injected on day 0 of treatment will induce ovulation of a dominant (≥ 10 mm) follicle and initiate a new follicular wave. Injection of prostaglandin $F_{2\alpha}$ (*PGF*) on day 7 will induce luteolysis (primary and accessory CL). *GnRH* injection on day 9 will induce ovulation in fixed-time *AI* protocols. An intravaginal progesterone-releasing device (*CIDR*) may be inserted at *GnRH* injection on day 0 and removed on day 7 to prevent expression of estrus before *PGF*-induced luteolysis



species and humans. In cattle, synchronization of estrus/ovulation and artificial insemination (AI) remain the most powerful technologies available to cattle producers for genetic improvement and reproductive management (Seidel 1995). However, adoption of these technologies by beef producers has been relatively low due to the time and labor associated with estrous detection. Therefore, fixed-time AI (FTAI) protocols that eliminate estrous detection and permit insemination of heifers and cows at a predetermined time were developed and resulted in pregnancy rates that are similar to insemination following detection of estrus.

Development of effective FTAI protocols in cattle requires control of the following 4 physiological processes: (1) synchronization of a follicular wave following an ovulatory stimulus [e.g., gonadotropin-releasing hormone (GnRH) injection] or induction of dominant follicle turnover (e.g., administration of estradiol and progesterone) culminating in development of a physiologically mature dominant follicle, (2) control of luteal lifespan via prostaglandin $F_{2\alpha}$ (PGF)-induced luteolysis, (3) GnRH-induced ovulation of a dominant follicle and (4) deposition of semen at the appropriate time relative to induction of ovulation. The preceding GnRH–PGF–GnRH injection sequence (Fig. 1) is based on the premise that the initial injection of GnRH will induce ovulation of a dominant follicle resulting in synchrony of a new follicular wave, followed by an injection of PGF 7 days later to induce luteolysis. Approximately 48–72 h following the PGF injection, a second injection of GnRH is administered to induce ovulation of a physiologically mature dominant follicle and insemination normally occurs at the second GnRH injection. Essentially, all FTAI protocols in the U.S. are variations of the GnRH–PGF–GnRH injection sequence with some differences in timing of injections and insemination.

In humans, a variety of protocols have been used for ovarian stimulation. In a conventional in vitro fertilization (IVF), ovarian stimulation protocol patients receive multiple injections of a GnRH agonist during the midluteal phase of the menstrual cycle to desensitize the pituitary gland, followed by exogenous hormonal stimulation to increase follicle growth and a single dose of a GnRH agonist or hCG about 36 h prior to oocyte retrieval (Murber et al. 2009; Bergh et al. 1998; Teissier et al. 2000). GnRH agonists have been used in human reproductive therapies to stimulate the release of luteinizing hormone (LH) from the pituitary, triggering final oocyte maturation (Gonen et al. 1990). However, GnRH agonist administration in women undergoing IVF resulted in lower pregnancy rates and increased early pregnancy loss (Kolibianakis et al. 2005), suggesting that perhaps optimal follicle development and maturation had not occurred before induced maturation.

Influence of ovulatory follicle size on fertility in cattle

In *Bos taurus* and *Bos indicus* cattle, ovulatory capacity of a follicle is obtained between 7 and 10 mm in diameter (Sartori et al. 2001; Gimenes et al. 2008) and is associated with acquisition of LH receptors in granulosa cells; however, a larger dose of LH was required to induce ovulation in a 10-mm follicle versus larger-sized follicles (Sartori et al. 2001). Ovulatory follicle size at GnRH-induced or spontaneous ovulation is variable (see Table 1). In postpartum beef cows, ovulatory follicle size was 15.0 ± 0.3 mm (mean \pm sSD with a range of ≤ 12 mm to ≥ 18 mm (Lamb et al. 2001). In

the preceding study, there was a significant decrease in pregnancy rate following GnRH-induced ovulation of follicles ≤ 12.0 mm regardless of treatment. Perry et al. (2005) also reported a decrease in pregnancy rates following GnRH-induced ovulation of small ovulatory-sized follicles; however, there was no effect on pregnancy rate when follicles within the same size range ovulated spontaneously. Furthermore, there was an increase in late embryonic/early fetal mortality in cows in which ovulatory follicles of < 11.3 mm were induced to ovulate; however, late embryonic/early fetal mortality was not related to ovulatory follicle size in cows that spontaneously ovulated (Perry et al. 2005). In dairy cows, GnRH-induced ovulation of dominant follicles resulted in a quadratic relationship between follicle size and pregnancy establishment in which pregnancy rate increased with dominant follicle size to a point (Bello et al. 2006). Other investigators have also reported that induced ovulation of small physiologically immature follicles reduced pregnancy rates in both beef and dairy cattle (Vasconcelos et al. 2001; Waldmann et al. 2006; Perry et al. 2007; Dias et al. 2009; Meneghetti et al. 2009; Peres et al. 2009; Sa Filho et al. 2009, 2010; see Table 1). The preceding observations suggest that the decrease in pregnancy establishment and maintenance following GnRH-induced ovulation was due to the physiological immaturity of the ovulatory follicle and not diameter alone.

There is accumulating evidence that length of proestrus can affect the establishment of pregnancy in cattle. Regardless of follicular diameter, luteal function and embryo development were reduced when bovine follicles

Table 1 Ovulatory follicle size and reproductive success (embryo development, conception and pregnancy)

Species	Follicle size at which embryo development/conception/pregnancy decreased ^a	Range in follicle size	Source
Beef cows	≤ 12.0 mm	< 12 mm to > 18 mm	Lamb et al. 2001
Beef cows	≤ 11.3 mm	10 mm to 17 mm	Perry et al. 2005
Beef heifers	< 10.7 mm > 15.7 mm	< 10 mm to > 16 mm	Perry et al. 2007
Beef cows and heifers	Linear	7.5 mm to 18.0 mm	Peres et al. 2009
Beef heifers	Linear	6 mm to 16 mm	Dias et al. 2009
Beef cows	Linear	< 9 mm to > 17 mm	Sa Filho et al. 2009
Beef cows	Linear	< 9 mm to > 16 mm	Meneghetti et al. 2009
Dairy cows	Quadratic	10 mm to 23 mm	Bello et al. 2006
Dairy cows	15 mm and 14.5 mm	8 mm to 17 mm	Lopes et al. 2007
Humans	< 14 mm	–	Teissier et al. 2000
Humans	< 16 mm	–	Bergh et al. 1998
Humans	Small, Avg=18.4 mm	12 mm to 26 mm	Yding Anderson 1993

^a Follicle size at which reproductive success was significantly decreased. Linear and quadratic refer to the significant line, which was fit to these data. *Linear* As ovulatory follicle size increased there was an increase in pregnancy rates. *Quadratic* As ovulatory follicle size increased there was an increase in pregnancy rates until a follicle diameter of ≈ 15.0 mm was reached in which time an increase in ovulatory follicle size decreased pregnancy rates

ovulated following a short versus a long proestrus period (Burke et al. 2001; Mussard et al. 2003, 2007; Bridges et al. 2006a, b). Furthermore, in the same study, pregnancy rates following embryo transfer were lower in cows with a shorter proestrus compared to cows with a longer proestrus (Mussard et al. 2003). The preceding data provide further support that it is the physiological maturity of the follicle and not simply size that contributes to establishment and maintenance of pregnancy.

To determine why pregnancy rates were decreased following GnRH-induced ovulation of small dominant follicles in beef cattle, a reciprocal embryo transfer experiment was conducted to differentiate between follicular effects on oocyte quality and uterine environment on the establishment and maintenance of pregnancy in cattle. Atkins et al. (2010) reported that both reduced oocyte competence and a compromised uterine environment contributed to decreased pregnancy rates of cows induced to ovulate small dominant follicles. More specifically, the probability of fertilization and recovering a transferable embryo were both positively associated with follicle size in donor cows. Consequently, the follicular microenvironment might affect oocyte competence and subsequent pregnancy establishment and maintenance. With regard to the uterine environment, serum estradiol concentration at the time of induced ovulation, along with serum progesterone concentration at the time of embryo transfer, were both positively associated with pregnancy establishment. Effects of the follicular microenvironment on oocyte competence and effects of preovulatory estradiol and postovulatory progesterone on the maternal environment are discussed in more detail below.

Influence of ovulatory follicle size in humans

Follicle size following an ovulatory stimulus has been linked to pregnancy success in humans as well as in cattle. Follicles from which oocytes were aspirated ranged from 12 to 26 mm (mean=18.4 mm) in women (Yding Anderson 1993). Nilsson and co-workers (1985) reported that sonographic measurements of follicular diameter provided a sole index of follicular maturity in an IVF program. In clinical trials, oocytes from IVF patients with follicles ≥ 14 mm had an increased probability of undergoing nuclear maturation prior to fertilization and developing into an embryo (Teissier et al. 2000). Yding Anderson (1993) reported that follicular diameter was greater in IVF patients that became pregnant compared to those that did not become pregnant. In a study that included over 200 conventional IVF patients, pregnancy rates (47%) following oocyte collection from follicles >16.0 mm were significantly higher than pregnancy rates (15%) from oocytes collected from follicles ≤ 16.0 mm (Bergh et al. 1998). However, in the preceding study, when intracytoplasmic sperm injection (ICSI) was performed,

there was no effect of follicle size on pregnancy rates. The reason for this difference is unknown. Collectively, these results suggest an effect of dominant follicle size on oocyte competence and that ICSI may be used to overcome barriers associated with oocytes recovered from small follicles.

Follicular determinants of oocyte competence

Folliculogenesis and oocyte growth/maturation depend upon bi-directional communication between the oocyte and surrounding follicular cells (Eppig 2001; Matzuk et al. 2002). In mammals, acquisition of oocyte competence is a prerequisite for embryo development and survival (Krisher 2004). Sirard et al. (2006) defined oocyte competence as the ability of an oocyte to resume meiosis following gonadotropin stimulation, undergo cleavage divisions after fertilization, develop to the blastocyst stage and result in birth of live offspring. Inadequate oocyte development could result in failure to complete meiosis, ability to fertilize and inadequate pre-implantation embryo development (Eppig 1991; Eppig et al. 2002; Gosden 2002; Matzuk et al. 2002). The ability to accurately assess oocyte competence could facilitate selection of competent oocytes resulting in improved pregnancy rates following in vitro fertilization.

Effect of diameter/physiological maturity of a dominant follicle on oocyte competence

Follicular diameter has been positively associated with acquisition of oocyte competence in several species. Oocytes recovered from large follicles had improved developmental competence in pigs (Ito et al. 2008) and horses (Goudet et al. 1997) compared to oocytes from smaller follicles. At the secondary stage of follicle growth in cattle, the zona pellucida begins to form adjacent to the vitelline membrane, cortical granules begin to form in the oocyte cytoplasm and RNA synthesis is initiated (Fair et al. 1997a, b). As follicular growth progresses to the tertiary stage, there is an increase in bovine oocyte growth and transcriptional activity that proceeds until the oocyte reaches about 110 μm in diameter (2–3 mm follicle diameter; Fair et al. 1995, 1996; Crozet et al. 1986), at which point bovine oocytes have been reported to become meiotically competent (Fair et al. 1995). In addition, a minimum follicle diameter of 2–3 mm is required for collection of an oocyte that is capable of fertilization; however, acquisition of oocyte competence in cattle continues up to 15 mm in diameter as the oocyte continues to acquire mRNA and proteins (Arlotto et al. 1996). With regard to oocyte diameter, there was no difference in fertilization rate between larger ($>115 \mu\text{m}$) versus smaller ($<114 \mu\text{m}$) bovine oocytes; however, there was an increased

rate of morula and blastocyst development following fertilization of the larger oocytes (Arlotto et al. 1996).

Bovine oocyte competence consistently improved when collected from more advanced stages of dominant follicles and oocytes from follicles exposed to an LH surge were more competent than oocytes from cows not exposed to an LH surge (reviewed in Sirard et al. 2006). In several species, the frequency of circulating pulses of LH increases following luteolysis and the pattern of LH pulses affected oocyte maturation in sheep. Oussaid et al. (1999) reported normal ovulation and fertilization rates in ewes with either a normal pre-ovulatory pattern of LH pulses or no LH pulses (treated with a GnRH antagonist) prior to the preovulatory LH surge. However, ewes with no LH pulses preceding the preovulatory LH surge had fewer embryos survive to the blastocyst stage (Oussaid et al. 1999). Therefore, circulating pulses of LH during the preovulatory period may be required for the final maturation of the oocyte.

Oocyte maturation

Coordination of nuclear and cytoplasmic maturation ensures the production of oocytes capable of supporting early stages of embryonic development (Albertini et al. 2003). Nuclear maturation pertains to meiotic progression of a primary oocyte at the late prophase/diplotene stage of meiosis I to a secondary oocyte at metaphase II following a preovulatory gonadotropin surge or removal of an oocyte from the follicular environment. The molecular mechanisms associated with nuclear maturation have been reviewed elsewhere (Eppig 1996).

Morphologically, resumption of meiosis is characterized by disappearance of the nuclear membrane, which is also called germinal vesicle breakdown (GVBD; Zhang et al. 2009). GVBD terminates the ability of an oocyte to produce mRNA by transcription until the maternal–zygotic transition (MZT). Consequently, from GVBD to MZT the oocyte and early embryo are dependent upon stored maternal mRNA and protein for embryonic development up to the 8–16 cell stage in cattle (Brevini-Gandolfi and Gandolfi 2001) and the 4–8 cell stage in humans (Braude et al. 1988).

Cytoplasmic maturation of an oocyte includes acquiring the capacity to complete nuclear maturation (reviewed by Eppig 1996), fertilization and early embryogenesis, thus providing a foundation for normal fetal development (Watson 2007). Bovine oocytes retrieved from follicles between 2.0 and 8.0 mm in diameter have the ability to progress to metaphase II with a success rate of about 47.8% (Fuhrer et al. 1989). Blondin and Sirard (1995) also demonstrated that bovine oocytes from follicles of >3.0 mm in diameter can progress to metaphase II, undergo fertilization and develop to the blastocyst stage. However, in the same study, oocytes from follicles <3.0 mm in diameter

were capable of undergoing maturation and fertilization but embryonic development was blocked between the 8–16 cell stage. Similarly, when oocytes were collected from random stages of antral follicle development, there was a difference in the proportion of oocytes that underwent maturation, fertilization and blastocyst formation (Mermillod et al. 1999). For example, 90% of oocytes reached metaphase II of meiosis after *in vitro* maturation, more than 70% were successfully fertilized and underwent cleavage division but only a third developed to the morula-blastocyst stage (Mermillod et al. 1999).

Molecular maturation: oocyte RNAs and proteins

Molecular maturation (epigenetic modification and final production and modification of mRNA and proteins) of the oocyte is not as well defined as nuclear and cytoplasmic maturation. During cytoplasmic maturation, there is accumulation of RNA, proteins, nutrients and substrates that are critical for completing oocyte maturation and subsequent embryo development (Watson 2007). Final mRNA and protein production along with epigenetic modifications seem to be necessary for acquisition of oocyte competence; however, the details have not been well characterized. Sirard and colleagues (2006) argued that, while many oocytes attain meiotic and cytoplasmic competence, the molecular milieu of an oocyte may determine the potential for embryonic/fetal development culminating in birth of viable offspring. Although molecular changes within the cytoplasm are difficult to investigate, Sirard and colleagues (2006) suggested that these final changes in the days preceding ovulation may be the “capacitators” that result in a normal pregnancy. Since the early cleavage stages of embryonic development are dependent upon maternal mRNAs transcribed prior to GVBD, premature induction of ovulation may produce oocytes/embryos in which transcription is not complete.

Abundance of maternal transcripts in oocytes following GVBD and early cleavage stage embryos decreases up to MZT (e.g., 8-cell stage in cattle). For example, Hwang et al. (2005) reported relatively high abundance of cytoplasmic dynein light chain 1 (DNCL1), fibronectin type3 and ankyrin repeat domain (FANK1), gene trap locus (GTL3) and zona pellucida 2 (ZP2) transcripts in germinal vesicle stage bovine oocytes, followed by a gradual decrease in abundance of transcripts to the 8-cell stage of embryonic development with no detection of transcripts in later stage embryos. Several other maternal effect genes including B cell translocation gene 4 (BTG4), cell cycle regulation gene 1 (cullin1), transforming sequence gene (MCF2), zygote arrest 1 (Zar1), growth differentiation factor-9 (GDF-9), bone morphogenetic protein-15 (BMP-15) and NACHT leucine-rich repeat and PYD containing 5 (Nalp5 or MATER) were expressed in bovine oocytes and abundance

of transcripts tended to decrease around the 8 to 16-cell stage (Pennetier et al. 2004, 2005). There are numerous maternal transcripts both in the oocyte and surrounding follicular cells that have been correlated with oocyte competence and are summarized in Table 2.

Epigenetic modifications

Genomic imprinting refers to an epigenetic phenomenon in mammals that results in differential expression of the parental alleles for a subset of genes (e.g., *H19*, *IGF2*). Parent-specific expression results from differential epigenetic markings (i.e., DNA methylation) of the paternal and maternal genomes during gamete formation. Imprinted genes are associated with a variety of physiological functions including embryonic and postnatal growth, placentation, behavior and metabolism (reviewed by Tycko and Morison 2002; Miyoshi et al. 2006).

A major enzyme involved in DNA methylation is DNA methyltransferase (DNMT1), which is required for normal development and X inactivation (Li et al. 1993). In fact, DNMT1 is one of the maternal effect genes described in mice (Minami et al. 2007) and *DNMT1* transcripts are detected in mature oocytes and early embryos (Howlett and Reick 1991). Mouse oocytes express a variant of DNMT1 called DNMT1o. Mice with homozygous mutations in *DNMT1o* were phenotypically normal except that the females were infertile due to fetal loss (Howell et al. 2001). Furthermore, the heterozygous fetuses from the homozygous knockout mice died between 14 and 21 days after mating (Howell et al. 2001). The pregnancy failure was likely due to oocyte incompetence and not the uterine environment since wild-type embryos transferred to the DNMT1o null mice had normal pregnancy rates (Howell et al. 2001). The heterozygote embryos had partial to complete biallelic expression of several imprinted genes (*H19*

Table 2 Genes associated with oocyte competence

Location	Abbreviation	Name	Relative expression in competent oocytes or follicular cells	Species	Reference
Oocyte	FST	Follistatin	High	Cattle	Patel et al. 2007
Oocyte	INHBA	Inhibin, beta A	High	Cattle	Patel et al. 2007
Oocyte	INHBB	Inhibin, beta B	High	Cattle	Patel et al. 2007
Cumulus cells	INHBA	Inhibin, beta A	High	Cattle	Patel et al. 2007; Assidi et al. 2008
Cumulus cells	TNFAIP6	Tumor necrosis factor, alpha-induced protein 6	High	Mouse, cattle, pig	Fulop et al. 2003; Assidi et al. 2008; Nagyova et al. 2009
Cumulus cells	CTSB	Cathepsins B	Low	Cattle	Bettegowda et al. 2008; Balboula et al. 2010
Cumulus cells	CTSZ	Cathepsins Z	Low	Cattle	Bettegowda et al. 2008
Cumulus cells	CTSS	Cathepsins S	Low	Cattle	Bettegowda et al. 2008
Cumulus cells	HAS2	Hyaluronic acid synthase 2	High	Humans, cattle	McKenzie et al. 2004; Cillo et al. 2007; Assidi et al. 2008
Cumulus cells	GREM1	Gremlin1	High	Humans, cattle	McKenzie et al. 2004; Cillo et al. 2007; Assidi et al. 2008
Cumulus cells	PTGS2	Prostaglandin-endoperoxide synthase 2	High	Humans, cattle	McKenzie et al. 2004; Assidi et al. 2008
Granulosa cells	HSD3B1	3-beta-hydroxysteroid dehydrogenase 1	High	Humans	Hamel et al. 2008
Granulosa cells	FDX1	Ferredoxin 1	High	Humans	Hamel et al. 2008
Granulosa cells	SERPINE2	Serine proteinase inhibitor clade E member 2	High	Humans	Hamel et al. 2008
Granulosa cells	CYP19A1	Cytochrome P450 aromatase	High	Humans	Hamel et al. 2008
Granulosa cells	CDC42	Cell division cycle 42	High	Humans	Hamel et al. 2008, 2010
Granulosa cells	SPRY 2	Sprouty homolog 2	High	Cattle, humans	Robert et al. 2001; Hamel et al. 2008
Granulosa cells	PGK1	Phosphoglycerate kinase I	High	Humans	Hamel et al. 2010
Granulosa cells	RGS2	Regulator of G-protein signaling	High	Humans	Hamel et al. 2010

snprn and *igf2*), suggesting that the DNMT1o was required for appropriate oocyte gene imprinting and fetal survival (Howell et al. 2001).

Imprinted genes are often clustered and their sex-specific expression is regulated by an imprinted control region (Verona et al. 2003). These regions can be up to several kilobases long and contain CpG islands (Hutter et al. 2006; Kobayashi et al. 2006). The epigenetic markings of imprinted loci are reversible and transferrable. The sex-specific methylation imprints are erased during primordial germ cell migration in the fetus (Barlow 2011). The erasing of the imprints appears similar in male and female primordial germ cells (Hajkova et al. 2002). However, reestablishment of the imprints during gametogenesis is sex-specific (reviewed by Miyoshi et al. 2006; Feil 2009). The methylation imprints are maintained in all somatic cells of the fetus and adult in which the imprints are required (John and Lefebvre 2011). In addition to DNA methylation, imprinting can be regulated by histone modifications (Grewel and Moazed 2003), by epigenetic modifiers such as Eed (a Polycomb group protein; Mager et al. 2003) and Lsh (Fan et al. 2005) and possibly by microRNAs (O'Neill 2005).

Nuclear transfer of nongrowing immature mouse oocytes (diplotene stage of first meiosis; 15–20 μm) into an ooplasm from a fully matured germinal vesicle stage de-nucleated oocyte resulted in normal fertilization and blastocyst development but a reduced number of pups born, suggesting that oocytes continue to undergo nuclear and/or molecular modifications that are important for embryo survival (Kono et al. 1996). A follow-up experiment from the same laboratory examined developmental competence of embryos that formed following nuclear transfer of progressively more mature oocytes from juvenile and adult mice (Bao et al. 2000). The authors reported a progressive increase in the number of live pups born when the more advanced oocytes were used for the nuclear transfer experiments (Bao et al. 2000).

The preceding data indicate that oocyte maturation is positively associated with an increase in the proportion of live births in mice. This can be in part due to the fact that establishment of the maternal imprint pattern is not complete in the oocyte until a follicle acquires the ability to ovulate. In mice, maternal methylation imprints are established during oocyte growth in an asynchronous manner during follicular growth (Lucifero et al. 2004; Hiura et al. 2006). For example, the imprinted genes *Snprn*, *Anf127* and *Ndn* acquire methylation imprints between the primordial and primary follicle stage, while *Peg3*, *Igf2r* and *Cdkn1c* become methylated at the secondary follicle stage (Obata and Kono 2002). *Peg1/Mest* become imprinted at the tertiary to early antral stage and *Impact* during the antral follicle stage (Obata and Kono 2002). Therefore, epigenetic marking of the oocyte genome is likely affected by the follicular

environment. Inadequate epigenetic markings of the oocyte could result in deleterious effects on pregnancy establishment and maintenance as well as altered embryonic, fetal and/or offspring development.

Preovulatory secretion of estradiol and the establishment and maintenance of pregnancy

Initiation of estrus occurs following a rise in serum concentrations of estradiol (see review by Allrich 1994). In cattle, serum concentrations of estradiol increase during a follicular wave around the time of follicular selection (Ginther et al. 2000; Kulick et al. 1999) and P450 aromatase (CYP19A1) is primarily expressed in the follicle that becomes dominant (≥ 8 mm in diameter; Evans and Fortune 1997). Preovulatory estradiol coordinates several physiological processes that contribute to the establishment and maintenance of pregnancy, including effects on follicular cells, the oocyte, gamete transport and preparation of the uterine environment. Furthermore, animals that exhibit estrus within 24 h of FTAI have greater fertility compared to cows that do not exhibit standing estrus (Perry et al. 2005, 2007).

Effects of estradiol on follicular cells

Estradiol increases granulosa cell mitosis (Goldenberg et al. 1972), promotes gap junction formation among granulosa cells (Merk et al. 1972), increases the stimulatory action of FSH on aromatase activity (Zhuang et al. 1982) and induces FSH/LH receptor expression in granulosa cells (Richards et al. 1976). There is a reciprocal relationship between theca and granulosa cells in which granulosa cells enhance the ability of theca interna cells to produce androgens by supplying them with pregnenolone and thecal androgen production provides granulosa cells with substrate to synthesize estradiol (Fortune 1986). High concentrations of estradiol within the follicular microenvironment regulate expression of several steroidogenic enzymes (reviewed in Gore-Langton and Armstrong 1994).

Effects on the oocyte

Bovine follicles containing oocytes that were more capable of being fertilized and developing to the blastocyst stage contained less progesterone (Hazeleger et al. 1995) and three- to eightfold greater CYP19A1 activity (Driancourt et al. 1998). In addition, the ability of human oocytes to develop into embryos increased when they were collected from follicles having increased follicular fluid concentrations of estradiol compared to oocytes collected from follicles that had lower concentrations of estradiol (Teissier et al. 2000). Exposure to high concentrations of estradiol

within preovulatory follicles may impact bovine oocyte maturation and competence directly through genomic estrogen receptors present in the oocyte and/or indirectly through receptors in cumulus cells surrounding the oocyte (Driancourt et al. 1998). Estrogen receptor β (ESR2) mRNA is expressed in bovine oocytes and both ESR1 and 2 are expressed in bovine cumulus cells (Beker-van Woudenberg et al. 2004). Thus, there is potential for estradiol to act through nuclear receptors present in the oocyte and (or) cumulus cells, which are in close association with the oocyte during development (reviewed in Su et al. 2009).

In beef cattle, oocytes from preovulatory follicles with greater concentrations of estradiol were more likely to develop into blastocysts after *in vitro* maturation and fertilization (Mermillod et al. 1999). Furthermore, competence of bovine oocytes to be fertilized increased as follicular diameter increased (Arlotto et al. 1996) and as follicular size increased so estradiol production increased (Martin et al. 1991); however, data examining the specific effects of estradiol on the maturing oocyte are lacking. Addition of estradiol to *in vitro* maturation media resulted in either a detrimental effect (Beker-van Woudenberg et al. 2004), or no effect (Beker-van Woudenberg et al. 2006) on nuclear maturation of bovine oocytes but a positive effect on canine oocytes (Kim et al. 2005).

Administration of an aromatase (CYP19A1) inhibitor had negative effects on nuclear maturation of oocytes and competence to undergo fertilization in the rhesus monkey and mouse (Zelinski-Wooten et al. 1993; Hu et al. 2002) along with decreased concentrations of estradiol and increased androgens in the follicular fluid. The number of oocytes capable of advancing to metaphase II and fertilization rates were also decreased in primates (Zelinski-Wooten et al. 1993). It is unclear whether the preceding effects were due to decreased estradiol and/or increased androgens within the follicular environment. Andriesz and Trounson (1995) reported that, as androgens within the culture media increased, there was a dose-dependent inhibition of oocyte nuclear maturation in mice.

Gamete transport

Increased circulating concentrations of estradiol may facilitate fertilization through more efficient transport of ova and sperm (Crisman et al. 1980; Hawk 1983; respectively). Sperm transport through the uterus is affected by estradiol and is optimized at estrus or when females are under the influence of estrogen (reviewed in Hawk 1983). Ovariectomized ewes required estradiol for appropriate sperm transport (Allison and Robinson 1972). Similarly, ovariectomized rabbits required estrogen for proper sperm transport but large quantities of estrogen were detrimental to sperm transport (Noyes et al. 1959).

A potential explanation for how estradiol affects sperm transport is by altering uterine pH around the time of estrus. Intracellular pH regulates motility and viability of sperm in a number of species (Schackmann et al. 1981; Christen et al. 1982; Johnson et al. 1983; Lee et al. 1983) and intracellular pH was directly correlated with extracellular pH. An acidic pH maintained mouse (Morton et al. 1978), rat (Wyker and Howards 1977; Morton et al. 1978), hamster (Morton et al. 1974, 1978; Morton et al. 1979) and bull (Cascieri et al. 1976) sperm in a quiescent state. An increase in pH, via a sodium/hydrogen exchange mechanism, initiated sperm motility in rats (Wong et al. (1981). Jones and Bavister (2000) demonstrated that decreasing the intracellular pH of bull sperm by at least 0.5 pH units completely suppressed motility and suppression of motility was reversible for up to 24 h. Recent work by Perry and Perry (2008a, b) focused on the effects of exogenous estradiol administration and standing estrus on uterine pH of cattle. Cows in estrus or supplemented with estradiol had increased concentrations of estradiol and decreased uterine pH compared to cows not displaying estrus (pH 6.7 vs. 7.0, respectively).

Changes in uterine pH appear to be mediated through the sodium–hydrogen exchangers (Wang et al. 2003; Grant and Perry 2010) and as uterine pH decreased pregnancy rate increased following FTAI in cattle (Lares et al. 2008). When bull sperm were cultured at a pH less than 7.02, the acrosome reaction was inhibited (Parrish et al. 1989). Therefore, the preceding increase in pregnancy rate may have been due to an estradiol-induced decrease in uterine pH around the time of insemination and a corresponding increase in sperm longevity. These data are relevant to FTAI protocols in which the semen is deposited at the time of GnRH administration (approximately 26–30 h before ovulation) instead of 8–12 h after estrous detection (<18–22 h before ovulation). With the interval from the initiation of estrus (or second GnRH injection) to ovulation being around 30 h (Pursley et al. 1995; Vasconcelos et al. 1999), a decrease in uterine pH at the initiation of standing estrus may transiently decrease sperm motility and thereby increase sperm longevity.

Importance of estradiol for preparation of the maternal environment for pregnancy

Serum concentrations of estradiol prior to the LH surge and ovulation appear to regulate changes in the uterine environment in several species. In humans, serum concentrations of estradiol peak approximately 48 h before ovulation (Groothuis et al. 2007) and increased concentrations before ovulation are necessary to establish uterine receptiveness (Ghosh et al. 1994; Groothuis et al. 2007). Among cattle, serum estradiol concentrations peak approximately 36 h before ovulation (Chenault et al. 1975) and increased

preovulatory concentrations of estradiol resulted in increased pregnancy success (Perry et al. 2005, 2007). A series of studies involving administration of estradiol and progesterone to ovariectomized ewes in combination with embryo transfer determined the sequence of ovarian steroid administration that is required to establish pregnancy. Moore (1985) reported that a period of progesterone priming followed by an increase in estradiol and a subsequent increase in progesterone was required for pregnancy. Ewes that did not receive estradiol to simulate preovulatory concentrations of estradiol had reduced total protein in the uterine lumen, reduced estrogen and progesterone receptor expression in the endometrium, decreased uterine weight at embryo transfer and lower pregnancy rate (Miller et al. 1977).

Administration of estradiol to ovariectomized ewes altered uterine protein secretion, weight and progesterone and estrogen receptors independent of either progesterone priming prior to estradiol or progesterone administration after estradiol (Miller et al. 1977). Specific temporal expression patterns of genes expressed in the uterus are steroid dependent. Among postpartum beef cows and heifers with elevated preovulatory concentrations of estradiol, there were gene-dependent changes in mRNA expression for steroid receptors [ESR1 and nuclear progesterone receptor (PGR), oxytocin receptor (OTR)] and uterine expressed proteins (cyclooxygenase-2, inhibin beta A subunit, SERPINA14 and Period 1) during the subsequent estrous cycle compared to cows with decreased concentrations of preovulatory estradiol (Bridges et al. 2005, 2006a, b; Schiefelbein et al. 2008; Perry et al. 2009). Furthermore, estrogen replacement prior to progesterone replacement in ovariectomized ewes resulted in the appearance of the NUDT16, a member of nudix domain family, which was upregulated in the epithelial tissue from day 5 to day 9 and subsequently down-regulated by day 13 of pregnancy in sheep (Ing et al. 2006). This expression pattern was similar to normal pregnant sheep (Ing et al. 2006). While the functional role of this gene product in pregnancy is unknown, this experiment and others suggest that preovulatory concentrations of estradiol can affect the uterine environment days later. Recent studies have also reported that microRNAs are expressed in human endometrium (Ohlsson Teague et al. 2009) and are differentially expressed during different physiological phases (Kuokkanen et al. 2010). More specifically, estrogen regulates specific microRNAs (Nothnick and Healy 2010) and microRNA biogenesis components (Nothnick et al. 2010).

Evidence for the importance of increased preovulatory secretion of estradiol for pregnancy has also been provided in cattle. Bridges et al. (2010) studied the effects of a long versus short proestrus period in beef cattle. Induction of ovulation of dominant follicles following a short proestrus period (1.2 days) had a shorter exposure to preovulatory

estradiol and reduced pregnancy rates compared with follicles having a longer proestrus period (2.2 days). The mechanism by which preovulatory estradiol exerts its effects on the uterus and facilitates the establishment of pregnancy is unknown; however, estradiol is known to induce endometrial receptors and to induce the expression of various uterine proteins (Bartol et al. 1981), which are likely important for uterine function and pregnancy success. More specifically, at estrus, there is up-regulation of several genes involved in remodeling of the extracellular matrix (Bauersachs et al. 2005) and estradiol played a direct role in regulating oviductal secreted glycoproteins (Buhi 2002) and in the regulation of the biological clock in the uterus (Nakamura et al. 2005).

Preovulatory estradiol may also have an indirect action on the maternal environment via luteal progesterone secretion. Follicular concentrations of estradiol have been associated with increased luteal progesterone synthesis following gonadotropin stimulation (McNatty 1979). Among cows that had a longer proestrus period, subsequent concentrations of progesterone were increased compared to cows with a short proestrus when follicle size did not differ between treatments (Bridges et al. 2010). However, there was no difference in luteal expression of LH receptor or steroidogenic enzymes between cows that did or did not exhibit estrus before GnRH-induced ovulation. Furthermore, for every 1 mm increase in ovulatory follicle size (range 13.5–16 mm), luteal weight on day 10 increased by 1.5 g and as day 10 luteal weight increased, circulating concentrations of progesterone increased (Fields et al. 2012). Preovulatory concentrations of estradiol have also been associated with induction of endometrial progesterone receptors (Stone et al. 1978; Zelinski et al. 1982; Ing and Tornesi 1997). Therefore, fewer endometrial progesterone receptors and/or decreased concentrations of progesterone could result in a uterine environment unable to support pregnancy.

Postovulatory concentrations of progesterone

The corpus luteum is the primary source of progestogen during the establishment of pregnancy in mammalian species, including cattle and humans. Subnormal luteal function has been associated with infertility in domestic ruminants (Garverick and Smith 1986) and in humans luteal phase defects account for about 3–4% of female infertility (Speroff et al. 1994). Subnormal luteal function has been characterized as corpora lutea having a short lifespan or corpora lutea having a normal lifespan but decreased secretion of progesterone (Garverick and Smith 1986).

The corpus luteum is a continuation of follicular maturation and preparation of follicular cells to synthesize and

secrete progesterone begins prior to ovulation. Therefore, inadequate gonadotropin secretion or decreased estradiol production during the preovulatory period may have an adverse effect on subsequent luteal lifespan or progesterone secretion. During the preovulatory period in humans and primates, decreased circulating concentrations of FSH or a decreased FSH:LH ratio was followed by suboptimal luteal function (Sherman and Korenman 1974; Wilks et al. 1976). Furthermore, transient suppression of preovulatory (Stouffer and Hodgen 1980; Sheehan et al. 1982) but not postovulatory (Stouffer et al. 1984) circulating FSH led to a decrease in circulating progesterone during the subsequent luteal phase. Conversely, a transient rise in FSH and LH during the follicular phase was followed by increased circulating concentrations of progesterone during the subsequent luteal phase (Goodman and Hodgen 1979). In addition to FSH, peripheral concentrations of estradiol were also reduced during the follicular phase preceding subnormal luteal function (Sherman and Korenman 1974). The role of estradiol in maturation and preparation of follicular cells for luteinization is discussed in the preceding section.

Progesterone stimulates the production of growth factors and uterine secretions (Geisert et al. 1992; Spencer and Bazer 2002) needed to nourish the early conceptus in ruminants. Decreased pregnancy rates following GnRH-induced ovulation in beef cows was associated with decreased preovulatory estradiol secretion, decreased rate of increase in progesterone post-insemination and reduced serum concentrations of progesterone (Perry et al. 2005). A delayed rise in progesterone is implicated in asynchrony between the embryo signal for maternal recognition of pregnancy and luteal regression. Interferon- τ (INF τ) is released by the trophoblast of the bovine and ovine embryo, which reduces uterine PGF release by blocking expression of oxytocin receptors (reviewed by Spencer et al. 2007). Embryos (16 days after breeding) collected from cows with a delayed rise in progesterone (6 days following estrus) had reduced INF τ production and were less developed compared to embryos recovered from cows with an advanced increase in concentrations of progesterone (Mann and Lamming 2001; Kerbler et al. 1997). Recently, Clemente et al. (2009) reported progesterone receptor mRNA in the bovine embryo. Culturing in vitro-produced embryos with progesterone had little effect (Fukui and Ono 1989) on embryo development, while others have reported improved embryo development after progesterone supplementation in culture (inconsistencies reviewed by Lonergan 2009).

Human patients undergoing ART to conceive frequently receive progesterone supplementation for luteal phase support. Supplementing progesterone during the luteal phase following an IVF cycle compared to a placebo significantly increased pregnancy rates in a number of randomized clinical trials (meta-analysis; Soliman et al. 1994; Pritts and

Atwood 2002). Since the rate of progesterone rise has been shown to be greater for cows that become pregnant (Perry et al. 2005), efforts have also been directed toward examining the effect of progesterone supplementation on pregnancy rate in cattle. Progesterone supplementation for 4 days (beginning 36 h after ovulation) increased protein secretion by the uterus 5 and 14 days after ovulation (Garret et al. 1988). Progesterone stimulated histotrophe secretion by the uterine glands (Geisert et al. 1992; Spencer et al. 2004) and uterine gland knock-out ewe models are unable to maintain pregnancy past day 12 to day 14 (Gray et al. 2002). Many reports of progesterone supplementation suggest an improvement in embryo development with an early rise in progesterone (e.g., Garret et al. 1988; Kerbler et al. 1997; Mann and Lamming 2001; Carter et al. 2008), while others report no consistent improvement in pregnancy following progesterone supplementation (Funston et al. 2005; Hanlon et al. 2005; Galvao et al. 2006; Stevenson et al. 2007, 2008). Mann and Lamming (1999) conducted a meta-analysis of 17 reports of progesterone supplementation post-insemination in cattle and concluded that progesterone supplementation resulted in a 5% improvement in pregnancy rates. The authors suggested that progesterone supplementation may result in conflicting results as day of treatment and relative fertility of cattle may alter the end results (Mann and Lamming 1999). Progesterone supplementation improved pregnancy rates when cows had low concentrations of progesterone on day 5 (1–2 ng/ml; day 0=AI) but did not improve pregnancy rates when cows had high progesterone on day 5 (Starbuck et al. 2001). While pregnant cows frequently have increased serum concentrations of progesterone following breeding compared to cows that failed to conceive (Perry et al. 2005; Lopes et al. 2007), there is a wide range in individual progesterone concentrations and progesterone cannot be used to predict pregnancy success (reviewed by Mann and Lamming 1999). Stronge and colleagues (2005) reported a linear and quadratic relationship between rate of change of concentrations of progesterone (in milk) from days 5, 6 and 7 (day 0=AI) and pregnancy rates. A similar relationship was reported by McNeill et al. (2006) and Starbuck et al. (2001). Collectively, these studies suggest that, while progesterone is certainly important, we do not know the minimum concentrations of progesterone needed to establish and maintain a pregnancy in cattle.

Summary

The physiological maturity of a dominant follicle at induction of ovulation can affect the establishment and maintenance of pregnancy. Mechanisms contributing to reduced pregnancy rates and late embryonic/fetal survival following induction of physiologically immature dominant follicles

have not been elucidated. The maturity of a preovulatory follicle affects the follicular microenvironment, which can impact oocyte competence, preovulatory estradiol secretion and postovulatory secretion of progesterone. Each of the preceding factors has been shown to affect pregnancy establishment and maintenance in cattle. Identifying physiological, cellular and molecular factors involved in ovulation of a fully competent oocyte and development of a maternal environment conducive to pregnancy establishment and maintenance, is important for maximizing reproductive success associated with assisted reproductive technologies in cattle and humans.

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