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Manipulation of Follicle Development to Ensure Optimal Oocyte Quality and Conception Rates in Cattle

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Contents

Over the last several decades, a number of therapies have been developed that manipulate ovarian follicle growth to improve oocyte quality and conception rates in cattle. Various strategies have been proposed to improve the responses to reproductive biotechnologies following timed artificial insemination (TAI), superovulation (SOV) or ovum pickup (OPU) programmes. During TAI protocols, final follicular growth and size of the ovulatory follicle are key factors that may significantly influence oocyte quality, ovulation, the uterine environment and consequently pregnancy outcomes. Progesterone concentrations during SOV protocols influence follicular growth, oocyte quality and embryo quality; therefore, several adjustments to SOV protocols have been proposed depending on the animal category and breed. In addition, the success of *in vitro* embryo production is directly related to the number and quality of cumulus oocyte complexes harvested by OPU. Control of follicle development has a significant impact on the OPU outcome. This article discusses a number of key points related to the manipulation of ovarian follicular growth to maximize oocyte quality and improve conception rates following TAI and embryo transfer of *in vivo*- and *in vitro*-derived embryos in cattle.

Introduction

The success of several reproductive programmes is closely related to ovarian follicular development and oocyte quality. Over the past several decades, several therapies have been proposed for manipulating ovarian follicle growth in cattle. These hormonal manipulations have been successfully used to optimize the reproductive outcomes following the application of various biotechnologies.

Timed artificial insemination (TAI) programmes provide an organized approach to enhance the use of artificial insemination (AI) and the progress of genetic gain and to improve reproductive efficiency in dairy and beef herds (Pursley et al. 1995; Baruselli et al. 2004). The success of biotechnologies, such as TAI, is dependent on the evolution of ovarian follicular manipulation techniques. The final follicular growth and the diameter of the dominant follicle at TAI are key factors that may significantly affect oocyte quality, ovulation, the uterine environment and consequently pregnancy outcomes.

The use of superovulation (SOV) followed by AI is technique that generates greater numbers of embryos per donor. These techniques, which are associated with embryo transfer (ET) to recipients, are powerful tools that disseminate high genetic quality and improve reproductive performance mainly in heat-stressed dairy cattle and repeat breeders (Ambrose et al. 1999; Hansen et al. 2001; Baruselli et al. 2011).

Ovum pickup (OPU) associated with *in vitro* embryo production (IVP) is another interesting technology that produces embryos from selected donors. This technology has the potential to enhance genetic progression through the female lineage in cattle (Merton et al. 2003; Pontes et al. 2010). Currently, 36.5% (307 845/843 862) of embryos produced worldwide are *in vitro*-derived embryos (Embryo Transfer Newsletter 2010). The success of OPU–IVP is directly related to the oocyte quantity and quality.

This review discusses a number of key points relating to the manipulation of ovarian follicular growth to maximize oocyte quality and improve conception rates following TAI and ET of *in vivo*- and *in vitro*-derived embryos in cattle. The discussion focuses on (i) the effects of the final follicular growth and the diameter of the dominant follicle in protocols for the synchronization of ovulation for TAI, (ii) the importance of progesterone (P4) during the SOV treatment, and the timing of the induction of ovulation for TAI in SOV donors and (iii) factors related to donors that influence the competence of the oocyte to produce embryos *in vitro* following OPU programmes; these factors include breed, stage of ovarian follicular wave at OPU, nutrition and exposure to heat stress (HS).

Ovarian Follicular Manipulation in TAI Programmes

A variety of protocols for TAI have been developed to design specific treatments for various breeds, categories and types of management. The most common of these therapies uses GnRH or estradiol plus progesterone/progestin (P4)-releasing devices and prostaglandin $F_{2\alpha}$.

Beef cattle have a longer post-partum anoestrous period closely related to the presence of calves and poor nutrition (Montiel and Ahuja 2005). This condition limits the effectiveness of traditional TAI protocols (Baruselli et al. 2004). Post-partum anoestrous cows exhibit insufficient pulsatile release of LH to support the final stages of ovarian follicular development and ovulation. Treatment of cattle with equine chorionic gonadotrophin (eCG) has been suggested as an effective tool to increase follicular development and pregnancy rates in TAI programmes for suckled beef cows that exhibit a high prevalence of anoestrous or a low body condition score (Baruselli et al. 2004; Sá Filho et al. 2010a,b; Sales et al. 2011). The efficiency of this hormone is related to its FSH- and LH-like activities (Murphy and Martinuk 1991), which stimulate the

continuation of follicular growth in cows with compromised gonadotrophin secretion.

In contrast to beef cows, giving eCG to dairy cattle during TAI synchronization protocols has a limited overall positive effect (Veneranda et al. 2006; Souza et al. 2009). This difference may be explained by the observation that the incidence of anoestrous because of insufficient LH pulses is less of a problem in dairy cows compared with beef cows (Wiltbank et al. 2002). Although this is not a herd problem, the inclusion of eCG treatment in TAI synchronization protocols was shown to be advantageous only in cows with a low body condition score at the beginning of the protocol (Souza et al. 2009), in anoestrous (Garcia-Ispierto et al. 2011) or in those older than 5 years of age (Bryan et al. 2010). Thus, the necessity of using eCG may be dependent on the blood concentration of LH, which can differ among breeds or can change under different environmental conditions (even within the same breed).

Previous studies demonstrated that eCG-treated females exhibit improved final follicular growth, increased diameter of the dominant follicle at TAI and an increased ovulation rate (Sá Filho et al. 2010a,b; Sales et al. 2011). Furthermore, treatment with eCG increased the circulating P4 concentrations in the subsequent oestrous cycle (Baruselli et al. 2004; Sá Filho et al. 2010b). Increased P4 concentration in eCG-treated cows may be a result of the increased volume of CL, the alteration in the cell machinery involved in luteal P4 synthesis (Fátima et al. 2011) or a combination of these factors. It has been shown that treatment with eCG increases the expression of P450scc and 3b-HSD (Fátima et al. 2010). In addition, a significant increase in the expression of StAR in the CL, which is an important protein for steroid biosynthesis, was reported in eCG-treated cows (Fátima et al. 2011).

Optimization of follicle size and health has been an important objective in the current reproductive programmes, especially in TAI (Wiltbank et al. 2011). Larger ovulatory follicles exhibited a greater ovulation rate and resulted in a greater number of pregnancies per AI (P/AI) in beef cattle (Perry et al. 2007; Sá Filho et al. 2010c). Moreover, the presence of larger follicles on the day of the TAI in beef cows improved the ovulation rate, which may have mediated the increased P/AI. Furthermore, considering only those cows that ovulated following TAI, the P/AI increased as the ovarian follicle size increased (Fig. 1, Sá Filho et al. 2010c). Therefore, in addition to the increased ovulation rate, ovulation of larger follicles could be responsible for other events, such as the improvement of endogenous E2 production, oocyte competence, CL diameter and concentration of P4 in the subsequent oestrous cycle, which may benefit the fertility of beef cows following TAI.

Nevertheless, when lactating dairy cows or other females are synchronized with GnRH-based TAI protocols, there is frequently a point where follicle size reaches a maximum beyond which fertility declines (Bleach et al. 2004; Perry et al. 2007). Lactating dairy cows may present larger than normal follicles, not only when they are bred after a spontaneous oestrous cycle (Bleach et al. 2004), but also in particular situations following traditional GnRH-based TAI synchronization

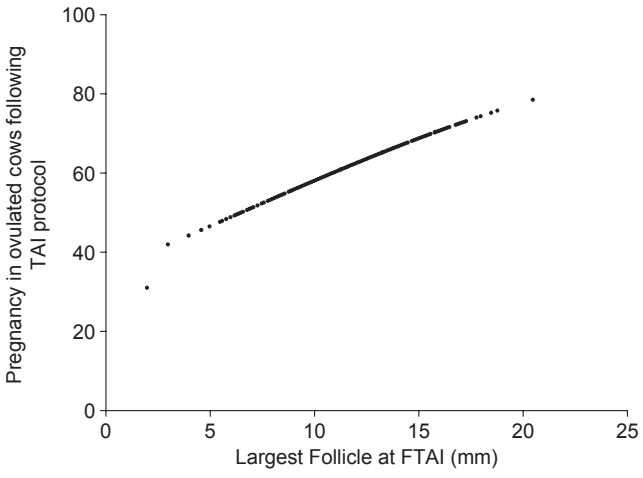

Fig. 1. Probability of pregnancy 30–42 days after timed artificial insemination (TAI) in suckled cows (n = 690) that ovulated following the TAI protocol, according to the diameter of their largest follicle (LF) at TAI. Adapted from Sá Filho et al. (2010c)

protocols (i.e. cows that fail to respond to the first GnRH of the Ovsynch protocol or cows that have their ovulatory follicle developed under low P4 concentrations) (Cerri et al. 2009, 2011). When the ovulatory follicle is developed in a low P4 environment, the diameter of the ovulatory follicle is larger; however, higher concentrations of PGFM and a tendency towards a shorter luteal phase during the subsequent oestrous cycle are observed (Cerri et al. 2011). Furthermore, a longer period of dominance can lead to an aged oocyte, resulting in reduced fertility (Revah and Butler 1996; Cerri et al. 2009; Lonergan 2011).

Ovarian Follicular Manipulation in SOV Programmes

Embryo transfer techniques are used worldwide; however, the variability in the response to the SOV treatments is an important limitation. An improved understanding of ovarian function has provided possibilities for a greater control of follicular development and ovulation in superovulated donor.

Controlling LH pulsatility and ovarian follicular development by P4 can influence oocyte quality (Lonergan 2011). During the SOV protocol, low circulating concentrations of P4 may interfere with follicular growth, oocyte and embryo quality (Chagas e Silva et al. 2002). In two recent studies, cyclic Holstein dairy cows (Rivera et al. 2011) and cyclic Nelore beef cows (Nasser et al. 2011) were superstimulated during the first follicular wave, and embryo quality was compromised when exogenous P4 was not provided during FSH treatments. In each experiment, embryo production and quality improved when P4 was provided by the insertion of one (Nasser et al. 2011) or two (Rivera et al. 2011) intravaginal P4 devices. In another study, a positive effect on the number of freezable embryos was observed when a second norgestomet implant was added to the TAI protocol in Holstein cows (Martins et al. 2012). Therefore, higher P4 concentrations during the SOV protocol may be necessary to regulate LH pulsatility,

which avoids the occurrence of premature nuclear maturation, and may be responsible for the improved ova/embryo quality observed following SOV protocols, especially in lactating Holstein cows.

Another important factor is the timing of ovulation induction after SOV in cattle (Baruselli et al. 2006; Bó et al. 2006). Interestingly, the SOV response and embryo production in lactating Holstein cows are higher when the ovulatory stimulus (GnRH or pLH) is administrated 24 h, as opposed to 12 h, after the last FSH treatment (Martins et al. 2012). In contrast, in Nelore (*Bos indicus*) donors, delaying the time of the pLH treatment to 24 h after the removal of P4 device adversely affected ova/embryo quality (Baruselli et al. 2006, 2011). Differences between *B. indicus* beef donors and *Bos taurus* dairy donors may be attributable to differences in the developmental stage of the follicle at the time that ovulation was induced (Baruselli et al. 2006; Bó et al. 2006). Therefore, delaying the LH to 24 h after the last FSH treatment is necessary to achieve more ovulatory-sized follicles in lactating Holstein cows, which should result in more synchronous ovulations and more transferable embryos.

Ovarian Follicular Manipulation in OPU-IVP Programmes

Influence of breed on the efficiency of OPU programmes

Breed can have a significant influence on the efficiency of commercial OPU/IVP programmes in cattle. However, the effect of different breeds on OPU/IVP programmes has not been elucidated fully. Lopes et al. (2006) reported that OPU in Holstein cows produces better-quality oocytes than Danish Red and White cows. Ratto et al. (2011), working with lactating cows under tropical pasture conditions, observed that Aberdeen Angus cows produced higher number of oocytes that exhibited greater in vitro competence than Holstein cows.

Improved IVP results have also been reported when *B. indicus* breeds are used instead of *B. taurus* breeds. The increased number of antral follicles found in *B. indicus* cattle (Carvalho et al. 2008) strongly correlates with an increased number of oocytes suitable for IVP (Pontes et al. 2010). Recent studies with *B. taurus* and *B. indicus* cattle maintained under controlled nutritional and environmental conditions were designed to more fully understand the particularities that may influence the outcomes of OPU-IVP programmes (Gimenes 2010; Sales 2011). Compared with *B. taurus* cattle, *B. indicus* cattle exhibit increased total numbers of oocytes, increased oocyte viability, increased blastocyst rate and a reduced rate of nuclear fragmentation in IVP blastocyst cells (Tables 1 and 2).

Table 1. Effect of donor (heifer) genetic group [*Bos indicus* (Nelore) and *Bos taurus* (Holstein)] on oocyte recovery rate and oocyte competence to develop into blastocysts *in vitro*. Adapted from Gimenes (2010)

	Genetic group	
	Nelore (n = 9)	Holstein (n = 9)
No. of replicates	6	6
Oocyte recovery and quality		
Visualized follicles	41.0 ± 2.1*	22.1 ± 1.3**
Total oocytes	37.1 ± 2.6*	15.4 ± 1.2**
Recovery rate (%)	90.5*	69.7**
Oocytes submitted to IVC	25.6 ± 1.8*	9.1 ± 0.9**
Developmental competence		
Cleaved structures	21.1 ± 1.6*	5.2 ± 0.5**
Cleavage rate (%)	82.4*	57.1**
Blastocysts 7 days after IVF	7.3 ± 0.9*	1.1 ± 0.2**
Blastocyst rate (%)	28.5*	12.1**

*, **$p < 0.05$.

Table 2. Effect of donor (non-lactating cows) genetic group [*Bos indicus* (Gir) and *Bos taurus* (Holstein)] on oocyte recovery rate and quality. Adapted from Sales (2011)

	Genetic group	
	Gir (n = 14)	Holstein (n = 14)
No. of replicates	8	8
Visualized follicles	25.5 ± 1.2	23.8 ± 1.1
Total oocytes	23.4 ± 1.6*	14.9 ± 0.9**
Recovery rate (%)	91.2 (2604/2856)*	61.1 (1633/2673)**
Oocyte quality		
Grade 1	5.3 ± 0.5*	1.6 ± 0.2**
Grade 2	9.8 ± 0.7*	5.2 ± 0.4**
Grade 3	4.8 ± 0.5	4.3 ± 0.4
Grade 4	0.9 ± 0.2	1.0 ± 0.2
Apoptosis by TUNEL (%)	16.6* (21/117)	40.6** (34/82)

*, **$p < 0.05$.

The influence of ovarian follicular manipulation on the efficiency of OPU-IVP programmes

The stage of the oestrous cycle at the time of the OPU session influences the recovery rate, oocyte quality and IVP (Merton et al. 2003; Vassena et al. 2003; Hendriksen et al. 2004). However, because of conflicting results, the ideal follicular phase to maximize performance of OPU remains unclear. Greater recovery rates when the OPU was performed close to the follicular wave emergence have been reported (Machatkova et al. 2004), and others described greater *in vitro* competence when the oocytes were obtained during the early dominance phase (Merton et al. 2003; Vassena et al. 2003; Hendriksen et al. 2004). Recently, a study was conducted comparing the day of aspiration relative to the time of the synchronized follicular wave emergence (1, 3 or 5 days after the expected wave emergence) in Holstein and Nelore heifers. The day of OPU relative to the follicular wave emergence did not have an effect on the number of follicles, viable oocytes recovered and blastocyst production, regardless of the breed (Gimenes 2010).

Reis et al. (2010) evaluated the effect of synchronizing follicular wave emergence in OPU programmes. Nelore and Brangus cows were assigned to be aspirated on a random day of the oestrous cycle or 5 days after the P4 + E2 treatment (i.e. 1 day after the expected follicular wave emergence). Only in Brangus donors, the synchronization of the ovarian follicular wave emergence improved the number of oocytes harvested (12.5 ± 0.6 vs 8.9 ± 1.3) and the blastocyst rate (56.2

vs 27.7%), indicating a possible beneficial effect of synchronization of wave emergence for OPU in this breed.

Another strategy to improve the efficiency of OPU is ovarian stimulation using gonadotrophins. Higher numbers of oocytes were retrieved by OPU in stimulated *B. taurus* cattle compared with non-stimulated cattle (Blondin et al. 2002). However, the beneficial effect of ovarian stimulation has not been confirmed in *B. indicus* females (Monteiro et al. 2009; Reis et al. 2010).

Recently, a series of experiments conducted in Argentina (Rodriguez et al. 2010) using Brangus and Angus donors evaluated the effect of different treatments for follicle wave synchronization and superstimulation on the number of oocytes and their competence to develop into blastocysts *in vitro*. Collectively, these experiments determined that IVP improved when the OPU was performed after synchronizing the follicular wave emergence (using either P4 + E2 treatment or follicular ablation). Additionally, increased IVP was achieved when FSH was used in four equal twice-daily doses beginning at the time of follicular wave emergence. In this case, OPU was performed 24 h after the last FSH treatment.

Influence of donor nutrition on the efficiency of OPU-IVP programmes

The nutritional and metabolic state can interfere with follicular growth patterns, secretion of reproductive hormones and oocyte quality in cattle (Adamiak et al. 2004, 2005; Leroy et al. 2008a,b; Santos et al. 2008; Sales 2011). The period of negative energy balance (NEB) is commonly associated with reduced fertility in cows (Lucy 2003; Santos et al. 2008). Studies have demonstrated that a potential cause of lower fertility is the adverse effect of NEB on the oocyte quality (Kendrick et al. 1999; Leroy et al. 2008a,b).

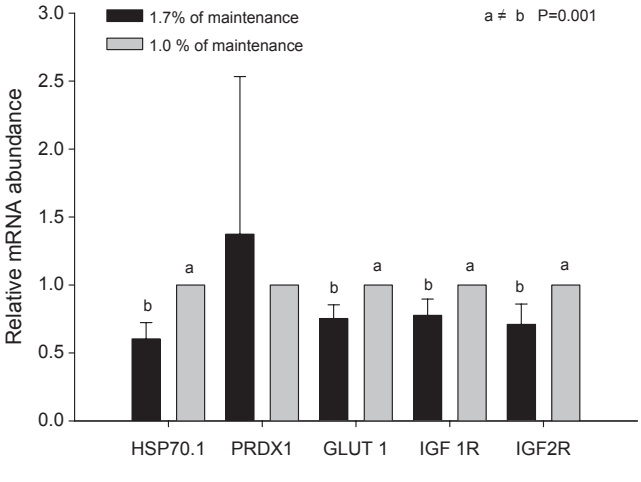

Fig. 3. Relative abundance of gene transcripts (real-time PCR) related to cellular stress (PRDX1, HSP70.1) and cellular metabolism (GLUT1, IGF1R and IGF2R) in oocytes of non-lactating cows fed diets to meet 100% (reference) or 170% of energy of maintenance (oocytes harvested 114 days after the beginning of diet). Adapted from Sales (2011)

In commercial OPU-IVP programmes, the use of non-lactating cows or cows late in lactation as donors is usually encouraged to avoid the negative effects of NEB on oocyte quality. However, when these animals are overfed (excessive energy intake), *in vitro* developmental competence of oocytes can be compromised, especially in overconditioned (high body condition score) females (Adamiak et al. 2005). The mechanisms that mediate these negative effects on oocyte competence could be due to endocrine and metabolic alterations, such as hyperinsulinaemia, peripheral resistance to insulin and increased glucose and IGF-I, which may interfere with glucose transport in the embryo cells and increase the

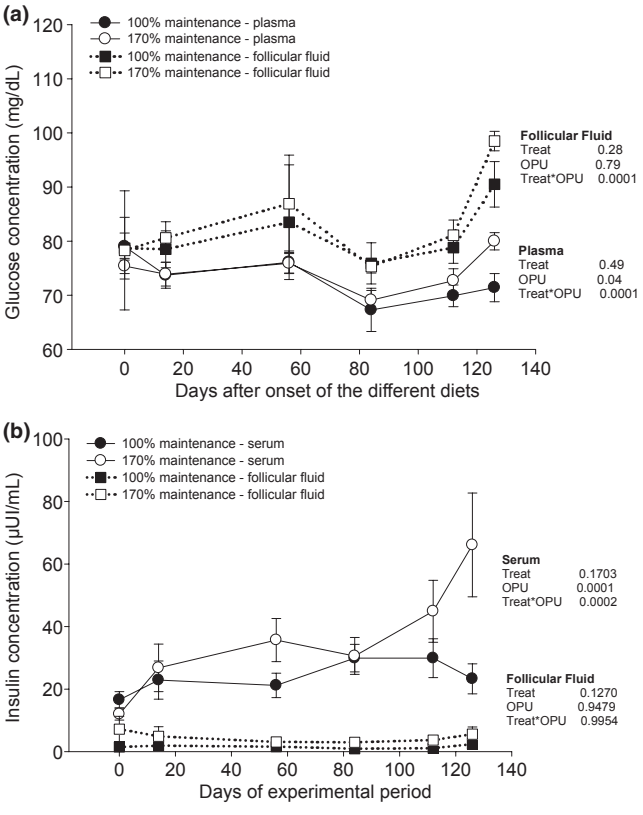

Fig. 2. Follicular fluid and circulating concentrations of glucose (a) and insulin (b) in non-lactating cows fed diets to meet 100 or 170% of energy of maintenance. Adapted from Sales (2011)

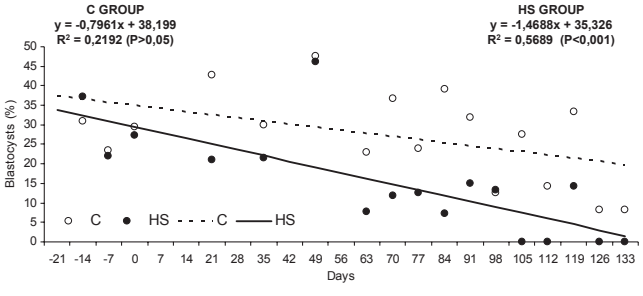

Fig. 4. Percentage of blastocyst and regression equation's adjusted lines of oocytes recovered from Gir (*Bos indicus*) cows exposed to thermoneutral (C) or heat-stress (HS) treatments. Adapted from Torres-Júnior et al. (2008)

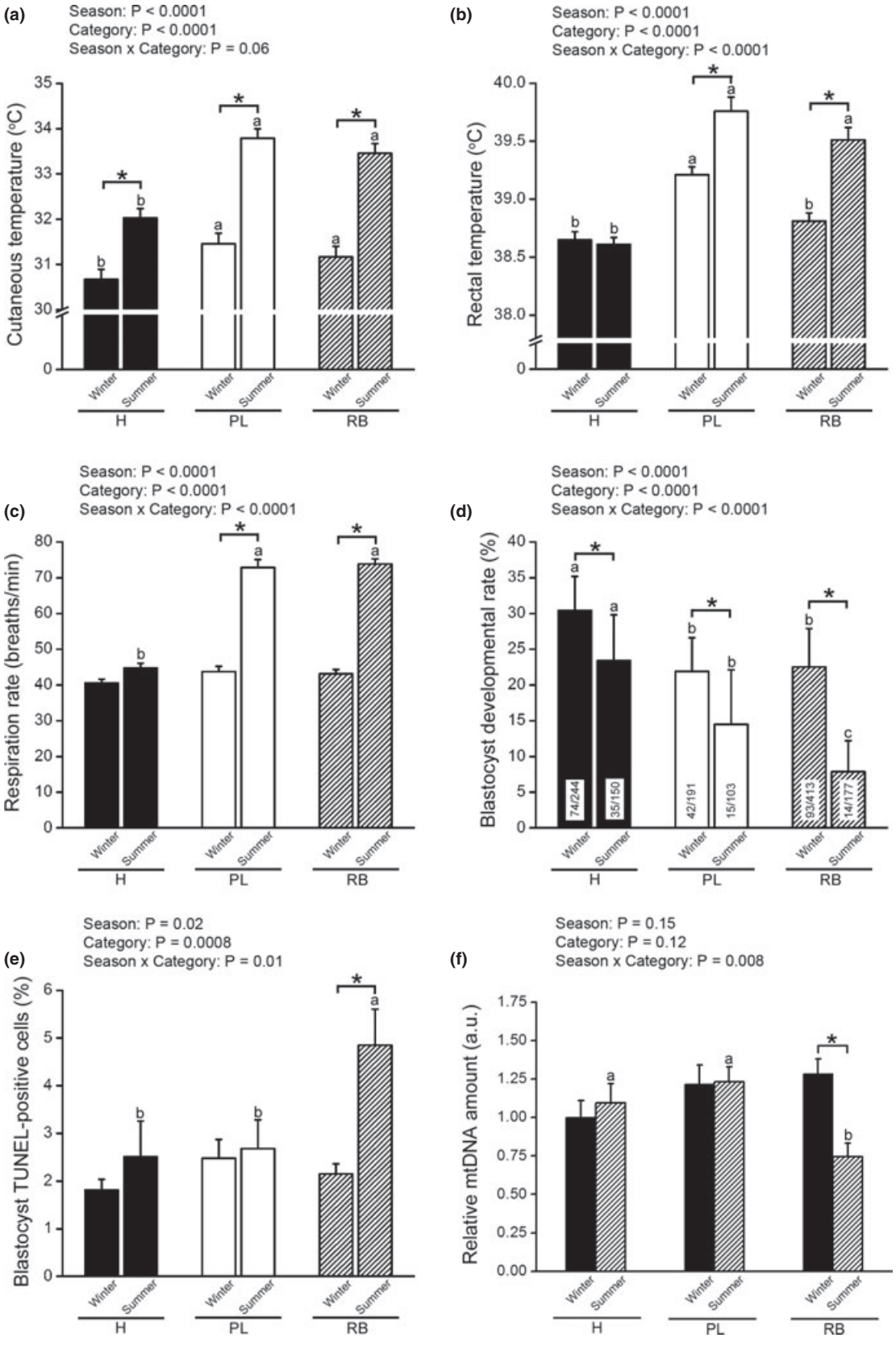

Fig. 5. (a) Cutaneous temperature, (b) rectal temperature, (c) respiration rate, (d)blastocyst rate, (e) blastocyst nuclei fragmentation rate and (f) relative content of mtDNA in the oocytes of Holstein heifers (H), cows in peak lactation (PL) and repeat breeders (RB) during summer and winter. Adapted from Ferreira et al. (2011a,b)

occurrence of apoptosis (Adamiak et al. 2005; Leroy et al. 2008a; Santos et al. 2008).

Recently, the potential adverse effects of high energy intake on metabolic profiles and oocyte quality in non-lactating Gir (*B. indicus*) cows submitted to successive OPU sessions were the subject of a PhD thesis (University of Sao Paulo; Sales 2011). The cows were subjected to nine successive OPU procedures 14 days apart (the cows were fed an adaptation maintenance (M) diet for the first 20 days, followed by 100 days on 100% M or 170% M diets). The negative effect of high levels of energy intake was cumulative, and the cows fed the 170% M diet exhibited a decreased blastocyst rate 60 days after the commencement of the high-energy diet. Glucose concentrations in the plasma and follicular fluid (Fig. 2a) as well as serum insulin concentrations (Fig. 2b) were higher in cows fed the 170% M diet. Furthermore, at the conclusion of the experimental period, the cows fed the high-energy diet exhibited a greater insulin peak with similar glucose clearance rates following glucose infusion (glucose tolerance test) than cows fed the control diet. This result suggests increased peripheral insulin resistance in the cows receiving the high-energy diet. Finally, oocytes harvested 114 days after the commencement of the high-energy diet intake demonstrated lower transcript levels for GLUT 1, IGF 1R, IGF 2R and HSP70.1 genes (Fig. 3).

Effects of HS on the efficiency of OPU-IVP programmes

The reproductive performance of bovine females can be severely compromised by HS (Hansen et al. 2001). Oocytes harvested from cows during the summer exhibit a decreased ability to develop into the blastocyst stage after in vitro fertilization when compared with oocytes harvested during the winter (Rocha et al. 1998; Al-Katanani et al. 2002; Ferreira et al. 2011a).

Torres-Júnior et al. (2008) designed an experiment using *B. indicus* dairy cows (Gir) to determine the immediate and delayed effects of HS on follicular dynamics, oocyte competence and hormonal profiles. In this study, HS cows were placed in an environmental chamber at 38.8°C and 80% relative humidity (RH) during the day and at 30.8°C and 80% RH during the night for 28 days. Compared with the thermoneutral control cows, HS increased the occurrence of ovarian follicular codominance and reduced P4 concentrations. Although HS had no significant effect on cleavage rate, blastocyst development was reduced.

Another seasonal study demonstrated that two or three oestrous cycles are required (after the end of HS) to restore the follicular pool and oocyte quality once the pool of ovarian oocytes is damaged by summer HS (Roth et al. 2001). However, the study described above (Torres-Júnior et al. 2008) demonstrated a carry-over effect of HS on blastocyst production that was maintained up to 105 days after the HS ended (Fig. 4).

The reproductive efficiency of repeat-breeder (RB) cows appears to also be affected by HS. Recently, an experiment was performed during the winter and summer to assess the physiological responses and the oocyte quality of RB Holstein cows (compared to Holstein heifers and high-producing cows in peak lactation (PL)) (Ferreira et al. 2011a). During OPU, heifers and cows provided similar numbers of recovered and viable oocytes during the winter. Nonetheless, during the summer, oocyte numbers decreased ($p < 0.0001$) in cows. However, when blastocyst rates were evaluated, an interaction between the groups and the season ($p < 0.0001$) was observed (Fig. 5), indicating that unlike the rate of cleavage, the effect of season was dependent on the group. Regardless of season, the blastocyst rates in RB cows were lower ($p < 0.0001$) than in the heifers. In the summer, the RB blastocyst rate dropped ($p < 0.002$) in comparison with the winter and was approximately twofold lower compared with the PL cows and threefold lower compared with the heifers ($p < 0.001$). In agreement with the blastocyst rate, the RB blastocyst quality was compromised in comparison with H and PL during the summer ($p = 0.01$) but not during the winter ($p = 0.3$), as indicated by the percentage of TUNEL-positive cells (Fig. 5).

The relative number of copies of mitochondrial DNA (mtDNA) was reduced for the RB cows during the summer (Fig. 5), suggesting a disruption of the oocyte quality (Ferreira et al. 2011b). In addition, the expression of nuclear genes (PPARG, NRF1, POLG, POLG2 and TFAM) related to mtDNA transcription and replication was greater in RB cows during the summer compared to non-RB cows and heifers, suggesting the activation of compensatory mechanisms in response to mitochondrial dysfunction (reduced number of copies of mtDNA) aiming to improve the generation of energy (ATP) required during early embryonic development.

Two retrospective studies using a large number of Holstein donors in Brazil confirmed that HS has deleterious effects on embryo production *in vivo* (Vieira et al. 2011) and *in vitro* (Pontes et al. 2012) (Fig. 6). During the period of follicular growth, HS may compromise the oocyte either because of a direct effect of the

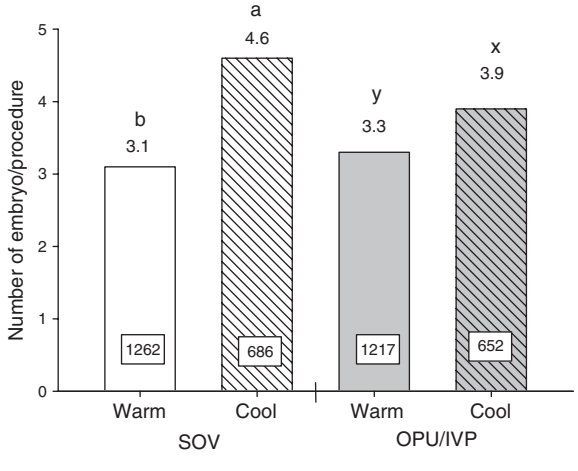

Fig. 6. Embryo production of Holstein cattle (cows and heifers) subjected to superovulation (*in vivo* production; n = 1948) or OPU/IVP (*in vitro* production; n = 1869; donors selected by high ovarian follicular population, > 20 follicles per donor) during the hot (spring/summer) or cool (autumn/winter) season, per procedure (SOV or OPU/IVP). [a,b/x,y]Within a procedure, bars without a common letter differed ($p < 0.001$). Numbers in boxes indicate the number of procedures (SOV or OPU/IVP). Adapted from Vieira et al. (2011) and Pontes et al. (2012)

elevated temperature on the gamete or because of changes in follicular function that damage the oocyte quality; however, the exact mechanisms by which the oocyte is compromised remain unknown.

The use of ET is considered a potential strategy for minimizing the negative effects of HS on bovine reproduction (reviewed by Baruselli et al. 2011). Indeed, several studies have shown that cows under HS exhibited more successful reproductive outcomes following ET compared with AI (Ambrose et al. 1999; Al-Katanani et al. 2002). Collectively, these results provide strong evidence that the major negative effect of HS on reproduction may be related to its deleterious effect on the oocyte quality, decreasing fertilization rates and first-week pregnancy losses.

Conclusion

Potential improvements in fertility after TAI in cattle caused by manipulation of follicle development have generally been associated with enhanced follicle development, increased diameter of the ovulatory follicle and improved oocyte quality. The progesterone concentration during the SOV protocol influences the follicular growth and the quality of the oocyte and embryo. In addition, the success of *in vitro* embryo production is directly related to the number and quality of the *cumulus* oocyte complex harvested by OPU. Ovarian follicular manipulation influences the efficiency of OPU-IVP programmes. However, factors related to breed, category, nutrition and HS should be considered.

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Conflicts of interest

None of the authors have any conflicts of interest to declare.

References

Adamiak SJ, Mackie K, Ewen M, Powell KA, Watt RG, Rooke JA, Webb R, Sinclair KD, 2004: Dietary carbohydrates and lipids affect in vitro embryo production following OPU in heifers. Reprod Fertil Dev **16,** 193–194.

Adamiak SJ, Mackie K, Watt RG, Webb R, Sinclair KD, 2005: Impact of nutrition on oocyte quality: cumulative effects of body composition and diet leading to hyperinsulinemia in cattle. Biol Reprod **73,** 918–926.

Al-Katanani YM, Paula-Lopes FF, Hansen PJ, 2002: Effect of season and exposure to heat stress on oocyte competence in Holstein cows. J Dairy Sci **85,** 390–396.

Ambrose JD, Drost M, Monson RL, Rutledge JJ, Leibfried-Rutledge ML, Thatcher MJ, Kassa T, Binelli M, Hansen PJ, Chenoweth PJ, Thatcher WW, 1999: Efficacy of timed embryo transfer with fresh and frozen in vitro produced embryos to increase pregnancy rates in heat-stressed dairy cattle. J Dairy Sci **82,** 2369–2376.

Baruselli PS, Reis EL, Marques MO, Nasser LF, Bó GA, 2004: The use of hormonal treatments to improve reproductive performance of anestrous beef cattle in tropical climates. Anim Reprod Sci **82–83,** 479–486.

Baruselli PS, Sá Filho MF, Martins CM, Nasser LF, Nogueira MFG, Barros CM, Bó GA, 2006: Superovulation and embryo transfer in *Bos indicus* cattle. Theriogenology **65,** 77–88.

Baruselli PS, Ferreira RM, Sales JNS, Gimenes LU, Sá Filho MF, Martins CM, Rodrigues CA, Bó GA, 2011: Timed embryo transfer programs for management of donor and recipient cattle. Theriogenology **76,** 1583–1593.

Bleach ECL, Glencross RG, Knight PG, 2004: Association between ovarian follicle development and pregnancy rates in dairy cows undergoing spontaneous oestrous cycles. Reproduction **127,** 621–629.

Blondin P, Bousquet D, Twagiramungu H, Barnes F, Sirard MA, 2002: Manipulation of follicular development to produce developmentally competent bovine oocytes. Biol Reprod **66,** 38–43.

Bó GA, Baruselli PS, Chesta P, Martins CM, 2006: The timing of ovulation and insemination schedules in superstimulated cattle. Theriogenology **65,** 89–101.

Bryan MA, Bó GA, Heuer C, Emslie FR, 2010: Use of equine chorionic gonadotrophin in synchronised AI of seasonal-breeding, pasture-based, anoestrous dairy cattle. Reprod Fertil Dev **22,** 126–131.

Carvalho JBP, Carvalho NAT, Reis EL, Nichi M, Souza AH, Baruselli PS, 2008: Effect of early luteolysis in progesterone-based timed AI protocols in *Bos indicus*, *Bos indicus* x *Bos taurus*, and *Bos taurus* heifers. Theriogenology **69,** 167–175.

Cerri RL, Rutigliano HM, Chebel RC, Santos JEP, 2009: Period of dominance of the ovulatory follicle influences embryo quality in lactating dairy cows. Reproduction **137,** 813–823.

Cerri RLA, Chebel RC, Rivera F, Narciso CD, Oliveira RA, Amstalden M, Baez-Sandoval GM, Thatcher WW, Santos JEP, 2011: Concentration of progesterone during the development of the ovulatory follicle: II. Ovarian and uterine responses. J Dairy Sci **94,** 3352–3365.

Chagas e Silva J, Da Costa LL, Silva JR, 2002: Plasma progesterone profiles and factors affecting embryo-fetal mortality following embryo transfer in dairy cattle. Theriogenology **58,** 51–59.

Fátima LA, Rigoglio NN, Souza LMMC, Gimenes LU, Rennó FP, Baruselli PS, Papa PC, 2010: Influence of eCG on sterioidogenic features in bovine corpus luteum. Anat Histol Embryol **39,** 285.

Fátima LA, Rigoglio NN, Bertolin K, Baruselli PS, Gimenes LU, Binelli M, Rennó FP, Murphy B, Papa PC, 2011: Regulation of gene expression in bovine corpus luteum by eCG treatment. World Congress on Reprod Biol **2,** 153.

Ferreira RM, Ayres H, Chiaratti MR, Ferraz ML, Araújo AB, Rodrigues CA, Watanabe YF, Vireque AA, Joaquim DC, Smith LC, Meirelles FV, Baruselli PS, 2011a: The low fertility of repeat breeder cows during summer heat stress is related to a low oocyte competence to develop into blastocysts. J Dairy Sci **94,** 2383–2392.

Ferreira RM, Chiaratti MR, Ayres H, Ferraz ML, Rodrigues CA, Watanabe YF, Yamazaki W, Netto AC, Meirelles FV, Baruselli PS, 2011b: Changes on oocyte quality of repeat breeder holstein cows may explain their reduced fertility. Acta Sci Vet **39,** 331 (abstract).

Garcia-Ispierto I, López-Helguera I, Martino A, López-Gatius F, 2011: Reproductive performance of anoestrous high-producing dairy cows improved by adding equine chorionic gonadotrophin to a progesterone-based oestrous synchronizing protocol. Reprod Domest Anim doi: 10.1111/j.1439-0531.2011.01954.x, [Epub, ahead of print].

Gimenes LU, 2010: Taxa de recuperação in vivo e competência in vitro de oócitos bubalinos, zebuínos e taurinos aspirados em diferentes fases da onda de crescimento folicular. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo.

Hansen PJ, Drost M, Rivera RM, Paula-Lopes FF, Al-Katanani YM, Krininger CE, Chase CC Jr, 2001: Adverse impact of heat stress on embryo production: causes and strategies for mitigation. Theriogenology **55,** 91–103.

Hendriksen PJM, Steenweg WNM, Harkema JC, Merton JS, Bevers MM, Vos PLAM, Dieleman SJ, 2004: Effect of different stages of the follicular wave on in vitro developmental competence of bovine oocytes. Theriogenology **61,** 909–920.

Kendrick KW, Bailey TL, Garst AS, Pryor AW, Ahmadzdeh A, Akers RM, 1999: Effects of energy balance on hormones, ovarian activity, and recovered oocytes in lactating Holstein cows using transvaginal follicular aspiration. J Dairy Sci **82,** 1731–1740.

Leroy JLMR, Opsomer G, Van Soom A, Goovaerts IGF, Bols PEJ, 2008a: Reduced fertility in high-yielding dairy cows:

are the oocyte and embryo in danger? Part I the importance of negative energy balance and altered corpus luteum function to the reduction of oocyte and embryo quality in high-yielding dairy cows Reprod Domest Anim **43,** 612–622.

Leroy JLMR, Van Soom G, Opsomer G, Goovaerts IGF, Bols PEJ, 2008b: Reduced fertility in high-yielding dairy cows: are the oocyte and embryo in danger? Part II mechanisms linking nutrition and reduced oocyte and embryo quality in high-yielding dairy cows Reprod Domest Anim **43,** 623–632.

Lonergan P, 2011: Influence of progesterone on oocyte quality and embryo development in cows. Theriogenology **76,** 1594–1601.

Lopes AS, Martinussen T, Greve T, Callesen H, 2006: Effect of days post-partum, breed and ovum pick-up scheme on bovine oocyte recovery and embryo development. Reprod Domest Anim **41,** 196–203.

Lucy MC, 2003: Mechanisms linking nutrition and reproduction in postpartum cows. Reprod Domest Rumant **61,** 415–417.

Machatkova M, Krausova K, Jokesova E, Tomanek M, 2004: Developmental competence of bovine oocytes: effects of follicle size and the phase of follicular wave on in vitro embryo production. Theriogenology **61,** 329–335.

Martins CM, Rodrigues CA, Vieira LM, Mapletoft RJ, Bó GA, Sá FM, Baruselli PS, 2012: The effect of timing of the induction of ovulation on embryo production in superstimulated lactating Holstein cows undergoing fixed-time artificial insemination. Theriogenology: doi: 10.1016/j.theriogenology.2012.05.007

Merton JS, De Roos APW, Mullaart E, De Ruigh L, Kaal L, Vos PLAM, Dieleman SJ, 2003: Factors affecting oocyte quality and quantity in commercial application of embryo technologies in the cattle breeding industry. Theriogenology **59,** 651–674.

Monteiro FM, Ferreira MMG, Potiens JR, Eberhardt BG, Trinca LA, Barros CM, 2009: Influence of superovulatory protocols on in vitro production of Nellore (*Bos indicus*) embryos. Reprod Domest Anim **4,** 1–5.

Montiel F, Ahuja C, 2005: Body condition and suckling as factors influencing the duration of postpartum anestrus in cattle: a review. Anim Reprod Sci **85,** 1–26.

Murphy BD, Martinuk SD, 1991: Equine chorionic gonadotropin. Endocr Rev **12,** 27–43.

Nasser LF, Sá Filho MF, Reis EL, Rezende CR, Mapletoft RJ, Bó GA, Baruselli PS, 2011: Exogenous progesterone enhances ova and embryo quality following superstimulation of the first follicular wave in Nelore (*Bos indicus*) donors. Theriogenology **76,** 320–327.

Perry GA, Smith MF, Roberts AJ, Macneil MD, Geary TW, 2007: Relationship between size of the ovulatory follicle and pregnancy success in beef heifers. J Anim Sci **85,** 684–689.

Pontes JHF, Silva KCF, Basso AC, Rigo AG, Ferreira CR, Santos GMG, Sanches BV, Porcionato JPF, Vieira PHS, Faifer FS, Sterza FAM, Schenkd JL, Seneda MM, 2010: Large-scale in vitro embryo production and pregnancy rates from *Bos taurus*, *Bos indicus*, and indicus-taurus dairy cows using sexed sperm. Theriogenology **74,** 1349–1355.

Pontes JHF, Basso AC, Mendanha MF, Baruselli PS, 2012: Effect of the season on the OPU/IVP efficiency in Holstein cow. Acta Sci Vet [unpublished data].

Pursley JR, Mee MO, Wiltbank MC, 1995: Synchronization of ovulation in dairy cows using PGF2 and GnRH. Theriogenology **44,** 915–923.

Ratto MH, Peralta OA, Mogollon G, Strobel P, Correa J, 2011: Transvaginal ultrasound-guided cumulus oocyte complexes aspiration and in vitro embryo production in suckled beef and lactating dairy cattle on pasture-based management conditions. Anim Reprod Sci **129,** 1–6.

Reis PO, Martins CM, Gimenes LU, Sales JNS, Baruselli PS, 2010: Effect of synchronization of the follicular wave emergence on OPU-IVP of Nelore (*Bos indicus*) and Brangus (*Bos taurus* x *Bos indicus*). Acta Sci Vet **38,** 385.

Revah I, Butler WR, 1996: Prolonged dominance of follicles and reduced viability of bovine oocytes. J Reprod Fertil **106,** 9–47.

Rivera FA, Mendonça LGD, Lopes G Jr, Santos JEP, Perez RV, Amstalden M, Correa-Calderon A, Chebel RC, 2011: Reduced progesterone concentration during growth of the first follicular wave affects embryo quality but has no effect on embryo survival post transfer in lactating dairy cows. Reproduction **141,** 333–342.

Rocha A, Randel RD, Broussard JR, Lim JM, Blair RM, Roussel JD, Godke RA, Hansel W, 1998: High environmental temperature and humidity decrease oocyte quality in *Bos taurus* but not in *Bos indicus* cows. Theriogenology **49,** 657–665.

Rodriguez P, Tribulo A, Ramos M, Ongaratto FL, Bó GA, 2010: Comparison of oocyte recovery rates and morphology obtained by OPU after different hormonal treatments in cattle. *XXVI World Buiatrics Congress*, Santiago, Chile.

Roth Z, Arav A, Bor A, Zeron Y, Braw-Tal R, Wolfenson D, 2001: Improvement of quality of oocytes collected in the autumn by enhanced removal of impaired follicles from previously heatstressed cows. Reproduction **122,** 737–744.

Sá Filho MF, Ayres H, Ferreira RM, Marques MO, Reis EL, Silva RC, Rodrigues CA, Madureira EH, Bó GA, Baruselli PS, 2010a: Equine chorionic gonadotropin and gonadotropin-releasing hormone enhance fertility in a norgestomet-based, timed artificial insemination protocol in suckled Nelore (*Bos indicus*) cows. Theriogenology **73,** 651–658.

Sá Filho MF, Torres-Júnior JRS, Penteado L, Gimenes LU, Ferreira RM, Ayres H, Castro e Paula LA, Sales JNS, Baruselli PS, 2010b: Equine chorionic gonadotropin improves the efficacy of a progestin-based fixed-time artificial insemination protocol in Nelore (*Bos indicus*) heifers. Anim Reprod Sci **118,** 182–187.

Sá Filho MF, Crespilho AM, Santos JE, Perry GA, Baruselli PS, 2010c: Ovarian follicle diameter at timed insemination and estrous response influence likelihood of ovulation and pregnancy after estrous synchronization with progesterone or progestin-based protocols in suckled *Bos indicus* cows. Anim Reprod Sci **120,** 23–30.

Sales JNS, 2011: Efeito da dieta com alta energia nos parâmetros metabólicos, endócrinos e reprodutivos de vacas Bos indicus e Bos taurus. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo.

Sales JNS, Crepaldi GA, Girotto RW, Souza AH, Baruselli PS, 2011: Fixed-time AI protocols replacing eCG with a single dose of FSH were less effective in stimulating follicular growth, ovulation and fertility in suckled-anestrus Nelore beef cows. Anim Reprod Sci **124,** 12–18.

Santos JEP, Cerri RL, Sartori R, 2008: Nutritional management of the donor cow. Theriogenology **69,** 88–97.

Souza AH, Viechnieski S, Lima FA, Silva FF, Araújo R, Bó GA, Wiltbank MC, Baruselli PS, 2009: Effects of equine chorionic gonadotropin and type of ovulatory stimulus in a timed-AI protocol on reproductive responses in dairy cows. Theriogenology **72,** 10–21.

Torres-Júnior JRS, Pires MFA, De Sá WF, Ferreira ADM, Viana JHM, Camargo LSA, Ramos AA, Folhadella IM, Polisseni J, De Freitas C, Clemente CAA, Sá Filho MF, Paula-Lopes FF, Baruselli PS, 2008: Effect of maternal heat-stress on follicular growth and oocyte competence in *Bos indicus* cattle. Theriogenology **69,** 155–166.

Vassena R, Mapletoft RJ, Allodi S, Singh J, Adams JP, 2003: Morphology and developmental competence of bovine oocytes relative to follicular status. Theriogenology **60,** 923–932.

Veneranda G, Filippi L, Racca D, Romero G, Balla E, Cutaia L, Bó GA, 2006: Pregnancy rates in dairy cows treated with intravaginal progesterone devices and different fixed-time AI protocols. Reprod Fertil Dev **18,** 118.

Vieira LM, Rodrigues CA, Silva PRL, Sales JNS, Sá Filho MF, Ranieri AL, Baruselli PS, 2011: Superovulatory response and pregnancy rates of Holstein cows in vivo embryo production within different categories during summer and winter. Acta Sci Vet **39,** 365.

Wiltbank MC, Gumen A, Sartori R, 2002: Physiological classification of anovulatory conditions in cattle. Theriogenology **57,** 21–52.

Wiltbank MC, Sartori R, Herlihy MM, Vasconcelos JLM, Nascimento AB, Souza AH, Ayres H, Cunha AP, Keskin A, Guenther JN, Gumen A, 2011: Managing the dominant follicle in lactating dairy cows. Theriogenology **76,** 1568–1582.

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