EARLY EMBRYONIC MORTALITY IN MODERN DAIRY COWS: CAUSES, CONSEQUENCES AND REMEDIES

Vroege embryonale sterfte bij hoogproductief melkvee: oorzaak, gevolg en aanpak

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ABSTRACT

Lactating dairy cows experience a temporary infertility syndrome. There is a multiplicity of factors contributing to early and late embryonic losses. Some of these factors begin within the postpartum period in association with dynamic metabolic and condition changes of the cow. Other factors include uterine health, as the cow enters the breeding period. Programming the preovulatory period with optimal recruitment and growth of the follicle influences subsequent quality, viability and survival of the embryo via direct effects associated with quality of the oocyte and indirectly via endocrine regulation (i.e., follicle and corpus luteum function) of the oviduct and uterus. The maternal-embryo unit appears to be responsive to reproductive management as well as pharmaceutical and nutraceutical programs to enhance pregnancy rates.

SAMENVATTING

Hoogproductieve melkkoeien ervaren een tijdelijke periode van verminderde vruchtbaarheid tijdens de periode kort na het afkalven. Vroege en late embryonale sterfte spelen hierin een belangrijke rol en worden beïnvloed door een veelvoud van factoren. Heel wat van die oorzakelijke factoren vinden hun oorsprong in de periode vroeg na het afkalven, die gekenmerkt wordt door metabole en conditionele veranderingen bij de koe. Een andere belangrijke factor is de algemene gezondheidstoestand van de uterus op het moment van inseminatie. Het monitoren van de preovulatoire periode (de rekrutering en groei van de dominante follikel) beïnvloedt in belangrijke mate de kwaliteit en de levensvatbaarheid van het gevormde embryo. Dit kan gebeuren door het beïnvloeden van de eicelkwaliteit of via endocriene modulaties die een invloed hebben op de eileider en de baarmoeder. Een goed fertiliteitsmanagement in combinatie met een gepast farmaceutisch of nutritioneel ingrijpen kan de vruchtbaarheidsresultaten doen verbeteren.

INTRODUCTION

In high producing dairy cows, herd pregnancy rates are reduced due to poor estrus expression and/or detection, anestrus, low conception rates and increased embryo mortality. Furthermore, these impediments to optimal reproductive performance are exacerbated under stressful environmental conditions such as heat stress. Reasons for the decline are multi-factorial and not entirely associated with an increase in milk production (Lucy, 2001). The challenge, to characterize the factors compromising embryo development and developing strategies to improve embryo survival in the lactating dairy cow, is complex. It should involve several crucial steps in fertility such as steroidogenesis, follicle development, ovulation, fertilization, corpus luteum development and maintenance, oviductal and uterine functions, embryo development and function, implantation and subsequent fetal growth. Indeed our current day production and reproductive management systems impact on all of these coordinated events which need to be optimized if reproductive efficiency in lactating dairy cows is to be enhanced. Objectives of this review article are to characterize early embryonic mortality and describe the possible causes and potential remedies to improve pregnancy rate.

Embryo development and losses

During the early cleavage stages from 1-cell through to the early blastocyst stage, at day 8, the embryo stays

within the zona pellucida (Sreenan *et al.*, 2001). Between 3 and 4 days after fertilization, the embryo migrates from the oviduct to the uterus at the 8-16 cell stage. At 5 to 6 days (16-32 cell stage), the embryo undergoes compaction and begins to be designated as the morula. At 8 days of age, the blastocyst develops the blastocoel cavity and cells (~120 cells) associated with the inner cell mass (25%) and trophectoderm (75%). At approximately 9 to 10 days, the blastocyst hatches from the zona pellucida and undergoes expansion until it begins to elongate at approximately 13 days of age. Elongation represents a transition in appearance from spherical to ovoid to filamentous with embryo length increasing from 5.25 mm at day 13 to 52 mm on day 16. On day 17, it is not uncommon to see embryos plus extraembryonic membranes with lengths of 30-40 cm that occupy the major part of the uterine horn ipsilateral to the CL. However, there is considerable variation in size of embryos. Early attachment of the conceptus occurs at day 19 with visible caruncular-cotyledonary attachment points faintly visible on day 21. At day 42, the embryonic period ends with completion of differentiation. The embryo is now called a fetus in which the major tissues, systems and organs are formed.

Several recent reports have evaluated fertilization rates in modern day high producing dairy cows whose overall fertility is low. In studies involving the use of the 6-day old bovine embryo (i.e., morula) as a biomonitor, it was demonstrated in non-lactating dairy cows that fertilization rates were 66, 74 and 82% when inseminations were made at 0, 12 and 24 h after onset of estrus, respectively (Dalton *et al.*, 2001). The percentages of excellent to good embryos were 77, 52 and 47% for the 0, 12 and 24 h time periods. Consequently, AI 12 h after onset of estrus is the recommended time for insemination, which is a compromise between a potentially lower fertilization rate at 0 h AI and lowered embryo quality with AI at 24 h.

A recent summary indicates fertilization rates are similar between lactating and nonlactating dairy cows and averaged 76.2% and 78.1%, respectively (Santos *et al.*, 2004a). However, at days 5–6 post-insemination in lactating cows, only 65% of the fertilized eggs are considered viable. Thus at 5 to 6 days after insemination potential pregnancy rate is approximately 50% considering both fertilization failure and poor embryo development. With the use of ultrasound diagnosis at 27-31 days, pregnancy rates are 35-45% which reflects additional embryonic loss of ~10%. Consequently, between days 5 to 30 after insemination embryo losses are approximately 48%.

An alternative and more practical mean to estimate embryonic losses is to further divide embryonic losses (EL) into early (EEL) and late (LEL) embryonic losses

that are determined with such techniques as milk progesterone (P_4), pregnancy specific protein B (PSPB; a protein secreted by the binucleate cells of the trophoectoderm), ultrasound (US) and rectal palpation. Humblot (2001) proposed that luteolysis within 24 days after AI could be associated with either a lack of fertilization or EEL that did not allow the CL to be maintained. In contrast, extended CL maintenance and return to estrus after 24 days could be associated with LEL occurring at or more than 16 days after AI. With this rationale and utilizing a sequence of these techniques, cows were classified pregnant or experiencing either EEL or LEL. In a study involving 44 dairy herds (1395 Holstein cows) of low fertility in a temperate environment of France, pregnancy rate, EEL and LEL rates after first AI were 42.9, 31.6 and 14.7%, respectively (Humblot 2001). Numerous estimates of LEL approximate 12.8% (Santos *et al.,* 2004b), based upon a positive pregnancy diagnosis via ultrasound at ~27 days and no pregnancy at 45 days upon rectal palpation. These are in agreement with the above laboratory and rectal palpation estimates.

Physiological windows contributing to pregnancy losses

Cycle prior to insemination and periovulatory period

Several reports indicate that low plasma progesterone concentrations during the luteal phase of the estrous cycle preceding AI were associated with lower fertility than cows with high plasma progesterone concentrations. Progesterone concentrations can influence several physiological events such as ovarian follicular dynamics and subsequent uterine function. Sangsritavong *et al.,* (2002) demonstrated in classical experiments that liver blood flow was elevated following feeding in nonlactating and lactating dairy cows. Both progesterone and estradiol metabolism in the liver were elevated acutely with feed consumption. Higher rates of liver blood flow and steroid metabolism in lactating dairy cows may reflect the chronic effects of higher feed intakes leading to lower steroid concentrations. The lower concentrations of progesterone and estradiol in lactating dairy cows compared to nonlactating dairy cows (De La Sota *et al.,* 1993; Sartori *et al.,* 2002a) appear to influence ovarian follicular dynamics. Evidence support the concept that lactating dairy cows have a greater number of larger follicles, a larger ovulatory follicle, lower concentrations of estradiol, and a longer interval to ovulation. Of critical importance is the subsequent ability of the oocyte arising from such follicles to form normal embryos. Sartori *et al.,* (2002b) demonstrated that day 5 embryo quality was reduced in lactating dairy

cows. Possible greater clearance of estradiol in high producing lactating dairy cows may result in less inhibition of FSH secretion that would alter follicular deviation leading to a greater occurrence of double ovulations (Wiltbank *et al.,* 2000). Furthermore, lower concentrations of progesterone may influence LH pulsatility and lead to longer persistence of the dominant follicle.

Israeli investigators (Shaham-Albalancy *et al.,* 2001) established an experimental model to induce CL that secreted ascending concentrations of progesterone that were substantially lower than control cows. During the next cycle when progesterone concentrations were normal, both groups were challenged with oxytocin to evaluate PGF_2 secretion (i.e., 13, 14, dihydro-15keto PGF_2 [PGFM]) on day 15 of the cycle. The PGFM response in the low progesterone group was markedly higher. One interpretation of these findings is that low progesterone concentrations during an estrous cycle may have a delayed stimulatory effect on uterine responsiveness to oxytocin during the late luteal phase of the subsequent cycle that approaches the time when the embryo initiates maintenance of the CL. A series of experiments in beef cattle indicate that shortened CL lifespan associated with first ovulation is associated with premature uterine secretion of PGF_2 (Inskeep, 2002). Oxytocin secretion from the CL may be contributing to this phenomenon. However, treatment of these cows with a progestin during the synchronization period eliminates this problem. Whether such a phenomenon is contributing to early embryo death in lactating dairy cows that have anovulatory follicle turnover before induction of first ovulation warrants investigation. It is clear that the preovulatory/periovulatory changes in steroids regulate subsequent estradiol and progesterone receptor concentrations that influence subsequent functions of the oviduct, uterus and ovary.

An additional factor associated with the preovulatory period that reduces fertility is the development of persistent follicles. Again this is coupled with the lower concentrations of progesterone, which predisposes the cow to a higher LH pulse frequency and maintenance of the dominant follicle. When a persistent follicle ovulates, the oocyte is at a later stage of maturation (Mihm *et al.,* 1999). The oocyte undergoes fertilization but early embryonic death occurs. It is important to recognize this phenomenon when we deal with types of synchronization systems. We need to use synchronization and/or ovulatory control systems that do not entail long periods of low progesterone exposure. Secondly, it is necessary to promote induction of a new dominant follicle that is induced to ovulate before expressing dominance beyond a 5-day period. Period of follicular dominance longer than 8 days is associated with reduced fertility (Austin *et al.,* 1999). Nor-

mally cows have two or three wave cycles. Fertility was greater in lactating cows inseminated after ovulation of the third-wave follicle that had developed for fewer days of the estrous cycle (81% pregnancy rate) as compared with two-wave cows (63% pregnancy rate; Townson *et al.*, 2002). The longer developed ovulatory follicle of the second wave group should not be considered a persistent follicle, but it does emphasize the potential importance of recruiting a fresh follicle as part of a synchronization or timed-insemination program. Optimizing follicular dynamics, duration of follicular dominance, and length of the proestrus period appear to be critical in allowing for ovulation of oocytes that have a higher probability of producing viable embryos.

Post ovulatory cycle

Elevation of progesterone soon after ovulation may advance maturation of the uterine endometrium and accelerate growth of the developing embryo (Barnes, 2000). Indeed, size of the ovulatory follicle in dairy heifers was related positively to subsequent increases in plasma progesterone concentrations (Moreira *et al.,* 2000). A very interesting association was shown among lactational statuses between ovulatory follicle volume, subsequent CL volume on day 7 of the cycle, and plasma progesterone concentration on day 7 (Sartori *et al.*, 2002a). Basically a clear positive association existed between ovulatory follicle and CL volume that appeared to be similar between heifers, dry cows and lactating cows. However, due to lactation state the ng/ml increase in progesterone concentration per mm^3 volume of the CL was 2x greater at day 7 for dairy heifers and 1.38 times greater for dry cows compared to lactating dairy cows. It is clear that lactation is reducing luteal phase progesterone concentrations. The reduced postovulatory concentrations in progesterone of lactating dairy cows may reduce embryo development (Mann and Lamming, 2001) and thereby reduce interferon production by the subsequent filamentous embryo that would contribute to both EEL and LEL. Hernandez-Ceron and Morales (2001) reported that lactating dairy cows with a follicle < 15 mm between 12 to 14 days after insemination had a higher conception rate (49.7%) than cows with follicles ≥15 mm (37.1%). Perhaps this reflects differences in follicular dynamics of cows with 3 follicular waves versus 2 follicular waves. Cows with a smaller follicle at 12 to 14 days may be cows undergoing 3 follicular waves and would ultimately have a longer interval before the conceptus needs to ablate the luteolytic secretion of PGF_2.

With the advent of timed insemination programs, investigators have been able to show that anovulatory cows have a lower pregnancy rate than cyclic cows which is

not unexpected. However, LEL was also greater in ano-vulatory cows versus ovulatory cows (26% versus 15%). Body condition score at the time of breeding is related to pregnancy rates with low BCS being associated with lower pregnancy rates. A greater decline in BCS from calving to breeding was associated with greater rates of LEL (Rutigliano and Santos, 2005). Furthermore, pregnancy rates are lower for multiparous cows than primiparous cows (Rutigliano and Santos, 2005). This complex of responses is symptomatic that embryo development and survival are influenced markedly by the postpartum platform of lactating dairy cows.

Occurrence of mastitis influences both EEL and/or LEL. Cows that had clinical mastitis during the first 45 d of gestation were 2.7 times at higher risk of abortion within the next 90 d (Risco *et. al.,* 1999). Both days open and services per pregnancy were increased in cows with clinical mastitis that occurred between first service and establishment of pregnancy (Schrick *et al.,* 2001).

The status of the uterus in lactating dairy cows is likely contributing to the infertility syndrome of lactating dairy cows. A vivid example is the repeat breeder cow that appears to be clinically normal regarding the reproductive tract but has repeated normal cycles and fails to conceive. A proportion of the repeat breeder cows have distinct alterations in spatial endometrial architecture characterized by walled off and occluded uterine glands, degeneration of the glandular epithelium, thickening of the underlying stroma, and infiltration of either eosinophils or lymphocytes or both (Cupps, 1973). It was hypothesized that this localized condition was a carry over from prior inflammatory responses to metritis and endometritis in the early postpartum period. This is an interesting observation in that 41% of normal lactating dairy cows (i.e., did not experience either external discharges on the tail, perineum and vulva or internally by vaginoscopy between 20-33 days postpartum) were diagnosed with subclinical endometritis at 34-47 days postpartum and experienced a lower pregnancy rate to first insemination (Kasimanickam *et al.,* 2004). Is there a parallel between the repeat breeder and the high producing population of cows regarding similar uterine statuses that compromise embryo survival? Recent findings indicate that repeat breeder cows have an abnormal pattern of epidermal growth factor (EGF) concentrations in endometrial tissue during the estrous cycle and that treatment involving exposure to estradiol may restore a normal secretory pattern and fertility (Katagiri and Takahasi, 2005). Clearly, the repeat breeder problem is multifactorial in nature, but reciprocal embryo transfers between repeat breeder and virgin heifers indicated that the uterine environment in repeat breeder heifers is

suboptimal for the support of normal embryonic development (Gustafsson and Larsson, 1985). In lactating dairy cows managed in a temperate environment, embryo transfer failed to enhance conception or calving rates compared to cows artificially inseminated to a fixed timed insemination program (Sartori *et al.,* 2005). Thus the lactating dairy cow may have other limitations not overcome by transfer of an embryo such as a sub-optimal uterine environment associated with lactation. The role of growth factors and cytokines on regulation of the embryo and uterus warrant investigation. Granulocyte-macrophage colony stimulating factor, that is present in both the endometrium and embryo, will stimulate early embryo secretion of interferon- (Rooke *et al.,* 2005). Likewise, insulin-like growth factor (IGF-I), which is readily secreted by the maternal unit and expressed in the endometrium, will stimulate in vitro embryo development (Moreira *et al.,* 2002a) and improve pregnancy rates following transfer of in vitro produced embryos that were cultured with IGF-I (Block *et al.,* 2003).

Strategies to improve pregnancy rates

Development and Optimization of Timed Insemination Programs

The ability to control the time of ovulation precisely permits a timed insemination, following a period in which follicular development and CL regression have been programmed sequentially. With the implementation of fixed timed artificial inseminations (TAI), specific timed treatments to improve embryo survival can be implemented effectively. Such programs are essential in high producing dairy cows that experience a reduction in estrus intensity that contributes to undetected heats, re-occurring luteal phases without estrus expression, or re-occurring waves of follicles that fail to ovulate. Development of timed insemination programs has been based upon a thorough understanding of the factors controlling ovarian follicular growth.

The OvSynch timed insemination program permits a fixed time insemination for first service without the need for detection of estrus. The OvSynch program entails injection of GnRH 7 d before and 48 h after an injection of PGF$_2$ and cows are inseminated 12 to 16 h after the second injection of GnRH (Thatcher *et al.*, 2004). This system synchronizes follicle maturation with regression of the corpus luteum before the GnRH-induced ovulation and timed insemination. Numerous studies indicate that pregnancy rates (proportion of all treated cows that were pregnant) to the OvSynch program were comparable and in some studies greater than the appropriate control group (Thatcher *et al.,* 2004).

There are several stages of the estrous cycle when initiation of the OvSynch program causes reduced pregnancy rates. Initiation of the program between days 13 to 17 of the cycle or during the early stages of the cycle (e.g., days 2 to 4), results in lower pregnancy rates. Presynchronization of cows prior to implementation of the OvSynch program should improve pregnancy rates if cows enter the OvSynch program at the most favorable period of the estrous cycle (i.e., days 5 to 12 of the cycle). A program defined as Presynch-OvSynch was developed in which pre-synchronization is achieved with a standard estrous synchronization protocol (PGF$_2$ given twice at a 14-day interval) with the OvSynch program initiated 12 days after the second injection of PGF$_2$ (Thatcher *et al.*, 2004). A Presynch-OvSynch program increased pregnancy rates with 18 percentage units (i.e., 25% to 43%) in lactating cyclic cows. Future programs for further optimization of fertility likely will consider programs that manipulate ovarian function such that follicular turnover via ovulation or induced follicular atresia occurs in all cows, and luteal phase like progesterone concentrations are sustained until the time of induced CL regression.

An alternative strategy to control the time of ovulation is the ability of exogenous estradiol to induce a LH surge by stimulating hypothalamic secretion of GnRH when given in a low progesterone environment during late diestrus and proestrus. An estradiol induced LH surge lasts for approximately 10 h, which is comparable to a spontaneous LH surge and longer than the LH surge induced by GnRH. Furthermore, an exogenous injection of estradiol in the proestrus period will elevate concentrations of estradiol in lactating dairy cows that are deficient in estradiol (i.e., due to rapid clearance) and perhaps improve subsequent fertility. Estradiol cypionate (ECP) is used to replace the second GnRH injection of an OvSynch program and is called Heatsynch (Thatcher *et al.,* 2004). Cows are pre-synchronized with two injections of PGF$_2$ given 14 d apart with Heatsynch beginning 14 d after the second injection of PGF$_2$. Cows are then injected with GnRH followed by PGF$_2$ 7d later. The ECP (1 mg, i.m.) is injected 24 h after PGF$_2$, and cows are inseminated 48 h later. Any cow observed in estrus prior to the TAI should be inseminated at detected estrus. Cerri *et al.* (2004) demonstrated that pregnancy rates on d 45 after AI were higher for cows receiving a Heatsynch management program compared to a program involving injections of GnRH and PGF$_2$ given 7 days apart and AI following estrus detection (i.e., 43% >35%).

Bovine Somatotropin (bST) to Improve Embryo Development and Pregnancy rates

Exogenous bST increased pregnancy rates when administered as part of a TAI protocol in cyclic lactating dairy cows (Moreira *et al.,* 2001; Santos *et al.*, 2004a) or in protocols involving cows being inseminated at detected oestrus (Morales *et al.,* 2001; Santos *et al.,* 2004b). Furthermore, pregnancy losses were reduced in pregnant cows that had received bST at the time of the GnRH injection of either an OvSynch protocol or a GnRH-PGF$_2$ protocol (i.e., 7 days apart) with AI at detected estrus (Santos *et al.,* 2004).

Since bST was effective at insemination, it is likely that bST stimulated embryonic development and survival following insemination in lactating dairy cows. Several studies showed that bST stimulated bovine in vitro maturation of oocytes and embryonic development (Izadyar *et al.,* 2000; Moreira *et al.,* 2002a). Both bST and IGF-1 stimulated embryo development and blastocyst cell number at day 8 in vitro (Moreira *et al.*, 2002a). Administration of bST at AI to superovulated donor cows decreased the number of unfertilized ova, increased the percentage of transferable embryos, and stimulated embryonic development to the blastocyst stage. Furthermore, bST affected both early embryonic development and recipient components to increase pregnancy rates following embryo transfer (Moreira *et al.*, 2002b). In lactating dairy cows, bST treatment increased expression of oviductal insulin-like growth factor II (IGF-II) mRNA and endometrial IGFBP3 mRNA on days 3 and 7 of the estrous cycle, respectively (Pershing *et al.* 2002). The mRNA encoding for the growth hormone (GH) receptor was present in the endometrium and increased from day 3 to day 7. These findings indicate that the GH and IGF system appear to be a functional component potentially affecting embryo-maternal interactions.

We have extended our investigations involving bST to the period approaching pregnancy recognition associated with CL maintenance at day 17 in lactating dairy cows (Bilby *et al.,* 2004 a,b). Injections of bST (500 mg) on day 0 (i.e., at a timed insemination) and 11 days later increased pregnancy rate (83% [5/6] > 40% [4/10]), conceptus length (45 > 34 cm) and interferon-tau in the uterine luminal flushings (9.4 > 5.3 g) with no effect on interferon-tau mRNA concentration in the conceptus. Treatment with bST increased plasma GH and IGF-I. Endometrial IGF-II mRNA was increased in the endometrium of bST-treated cyclic cows. The insulin-like growth factor binding protein-2 (IGFBP-2) mRNA was increased in bST treated cows, whereas administration of bST decreased the IGFBP-2 mRNA in cyclic cows. Bo-

vine Somatotropin treatment and second generation regulatory factors appeared to modulate maternal and conceptus interactions that are beneficial to the developing conceptus and pregnancy rate.

HCG induction of accessory CL, three wave cycles and enhanced pregnancy rate

The opportunity to regulate ovarian function after insemination to improve pregnancy rates is an additional production management strategy. The ability to induce ovulation of the healthy first wave follicle on day 5 either of the cycle or after insemination results in two altered endocrine states. The hCG induces ovulation with the subsequent formation of a functional accessory CL and cows will experience three-follicular wave cycles due to the earlier emergence of the second wave follicle. Injection of 3300 IU of hCG in lactating cows at 5 days after AI increased pregnancy rates on days 28, 42, and 90, but late embryonic and fetal losses remained unaltered (Santos et al., 2001). Therefore, the positive effect of hCG was mediated by reducing EEL. The benefit of hCG to increase pregnancy rate was most apparent in lactating dairy cows losing BCS between AI and day 28 of pregnancy.

Effect of non-steroidal suppressors of prostaglandin secretion on reproductive performance

As described previously, 48% of the embryos are lost in lactating dairy cows between days 5 and 30 after insemination. A certain percentage of these losses would be associated with a failure to attenuate the luteolytic secretion of PGF_2 due to either inadequate conceptus secretion of interferon- or an inability of the endometrium to suppress PGF_2 secretion in response to interferon-. Dairy heifers are an excellent experimental model to examine the window of CL maintenance (i.e., days 16-17 days) because fertilization rates, early embryonic losses and ultimate pregnancy rates are higher than in lactating dairy cows. When dairy heifers received flunixin meglumine (FM; 1.1 mg/kg BW; i.m) twice daily, 12 h apart on the evening of day 15 and the morning of day 16 (Guzeloglu et al., 2006) pregnancy rates were higher at day 29 (76.9 %; 20 of 26 [FM] vs. 50 %; 13 of 26 [Control]; P < 0.05) and tended to be higher at day 65 (69.2 %; 18 of 26 [FM] vs 46.2 %; 12 of 26 [Control]; P < 0.10). It would appear that flunixin meglumine (i.e., a non-steroidal inhibitor of prostaglandin synthesis), administered two times at a critical stage when the corpus luteum is maintained, increased early embryo survival and pregnancy rate via an additive antiluteolytic effect with the conceptus. Thus strategies to attenuate PGF_2 secretion offer promise to reduce EEL in lactating dairy cows where such losses are even greater.

Several experiments performed in vivo and in vitro indicate that the omega-3 fatty acids are able to decrease secretion of PGF_2 (Mattos et al., 2000; Mattos et al., 2003). Feeding fish meal (8% of dry matter is oil which contains two polyunsaturated fatty acids of the n-3 family, eicosapentaenoic acid [EPA, C20:5] and docosahexaenoic acid [DHA, C22:6]) increased fertility of lactating dairy cows (Burke et al., 1997). Various fat feeding studies are encouraging in that selective nutrients (i.e., omega 3 fatty acids such as EPA, DHA, -linolenic acids and omega 6 fatty acids such as Linoleic and Monoenoic Trans Fatty Acids) appear to be candidates to improve pregnancy rates (Thatcher et al., 2006). Some of these fatty acids (i.e., EPA and DHA) are capable of decreasing the secretion of PGF_2 and would compliment the antiluteolytic action of interferon- (Mattos et al., 2003). Both EPA and DHA are known to have distinct anti-inflammatory and immunosuppressive effects that may actually compliment the normal immunosuppressive and anti-inflammatory effects of progesterone and interferon- in early pregnancy. It would be interesting to determine if cows fed anti-inflammatory lipid diets would reduce the incidence of early and late embryonic mortality associated with the occurrence of mastitis. The effects of nutraceuticals, such as specific fatty acids, on embryo development and survival warrant additional investigation.

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