

Interactions Between Nutrition and Reproduction to Increase Efficiency

W. R. Butler. Department of Animal Science, Cornell University, Ithaca, NY

INTRODUCTION

Over the last several decades, large increases in milk production capability among dairy cows have been associated with declining fertility. Conception rate now stands at 40% in dairy herds in the eastern USA (Butler, 2003; DHI Raleigh Center, 2012).

In high genetic merit cows, dry matter intake (**DMI**) and energy balance begin decreasing prepartum that results in mobilization of body fat as nonesterified fatty acids (**NEFA**) in blood (Butler et al., 2006). The onset of lactation after calving is associated with a prolonged period of negative energy balance (**NEBAL**) during which energy intake lags behind the energy requirements of rapidly increasing milk production and consequently delays ovarian cycles.

With regard to fertility to AI, there is a strong positive association between early commencement of postpartum ovulatory cycles and pregnancy during lactation (Butler, 2000; Galvao et al., 2010). This important relationship has focused research attention on the regulation and re-initiation of ovarian activity and ovulation in early lactation prior to the breeding period. Energy balance, re-initiation of ovarian activity, and metabolic health status are inter-connected in transition dairy cows.

ENERGY BALANCE RELATED FACTORS AFFECT RESUMPTION OF OVARIAN ACTIVITY IN TRANSITION COWS

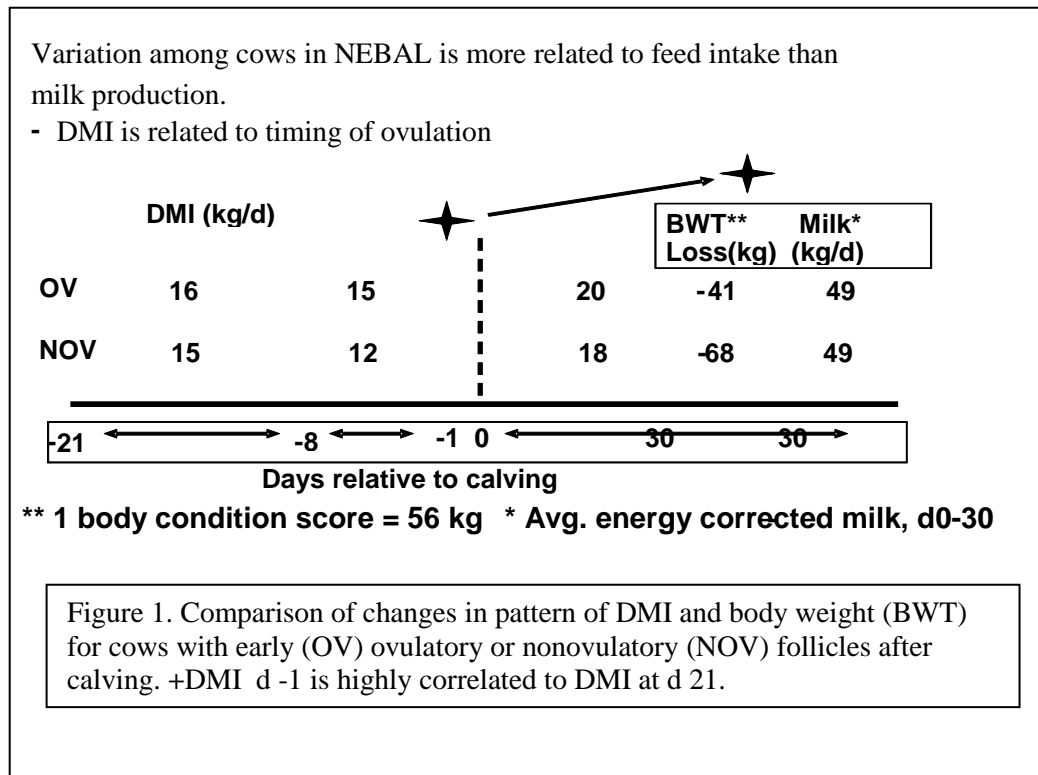
Relationships during the Transition Period

The transition period extends from 3 weeks before calving through the first 3 weeks of lactation. During late pregnancy elevated plasma levels of steroid hormones (estradiol and progesterone) suppress the release of pituitary gonadotropins (LH and FSH) and ovarian follicular activity. Following calving, steroids are reduced and increased secretion of FSH and LH pulses become re-established to stimulate development of large ovarian follicles and ovulatory ovarian cycles. With the onset of lactation, the liver must support a heavy and rapidly increasing metabolic load for glucose production and fatty acid oxidation and processing. The liver also plays an important role as the primary source of insulin-like growth factor-I (**IGF-I**) that stimulates development of ovarian follicles. The functional activity of the ovary and liver is negatively influenced by NEBAL (Butler, 2003; Overton, 2001).

Negative energy balance, acting through the combined metabolic signaling of low blood glucose, insulin and IGF-I concentrations along with elevated NEFA, β -hydroxybutyrate, and liver accumulation of triglycerides delays the increases in LH and FSH necessary for stimulation of ovarian follicles, estradiol production, and ovulation (Butler et al., 2006). Low blood insulin concentrations are responsible for low IGF-I production from the liver (Butler et al., 2003) which together reduce responsiveness of ovarian follicles to gonadotropins. Physiologically the metabolic and gonadotropin signals controlling early follicle development are interrelated: FSH stimulates granulosa cells in follicles to develop receptors for insulin, growth hormone and IGF-I; insulin and IGF-I then provide the hormonal stimulus for full development of preovulatory ovarian follicles (Beam and Butler, 1999; Kawashima et al., 2007; Kawashima et al., 2012; Shimizu et al., 2008; Sudo et al., 2007).

By way of various metabolic factors, interactions and responses, NEBAL shifts the course of postpartum ovarian activity and strongly influences the resumption of ovulatory cycles. At least one large follicle develops on the ovaries in all dairy cows by 6-8 d after calving. What is different among cows is that this first large follicle has 3 outcomes which relate to the variation among cows in days to first ovulation: a) Ovulation occurs successfully in about 45 % of cows by around d 20 of lactation; b) Atresia

(death) of the follicle occurs; or c) The follicle becomes cystic. In either case of b *or* c, first ovulation is delayed at least an additional 3-4 wk (Beam and Butler, 1999; Butler et al., 2006).



Prepartum Differences in DMI, Energy Balance and Metabolic Hormones Associated with Postpartum Ovarian Follicle Outcome

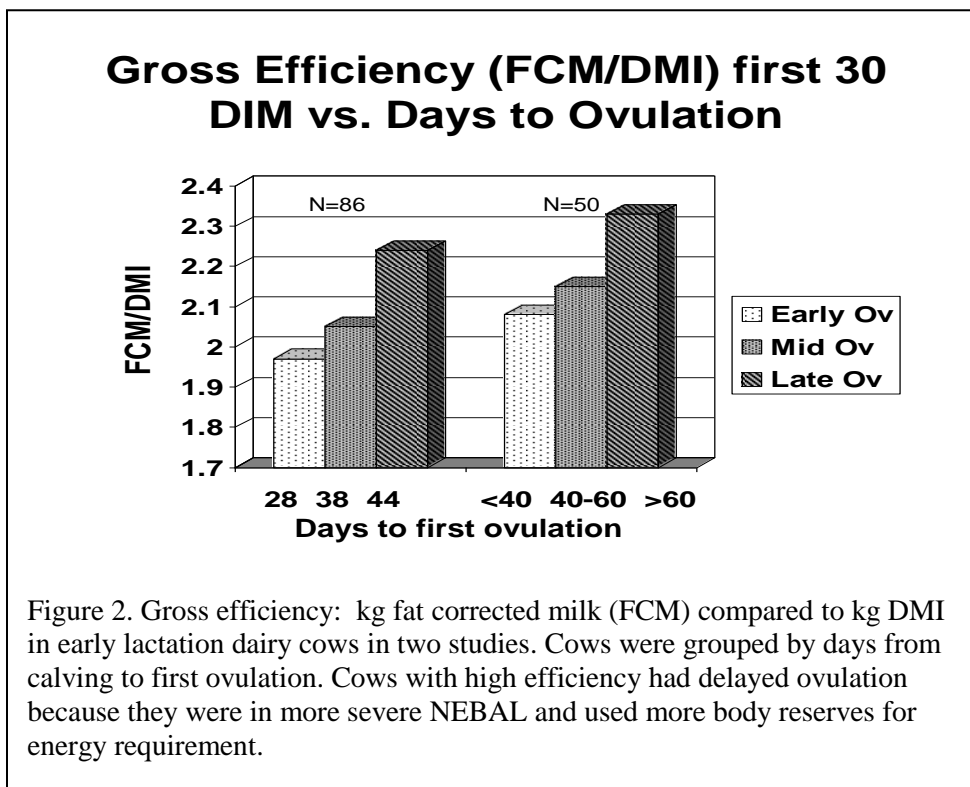
Following calving, ovarian follicle development in dairy cows was monitored for determination of ovulatory or nonovulatory outcome and for comparison, retrospectively, with differences in prepartum DMI, energy balance, and metabolic hormone profiles (Butler et al., 2006). The main difference between ovulatory or nonovulatory follicles is their capacity to produce large amounts of estradiol. As early as 3 weeks prepartum, the nonovulatory low estradiol cows would have lower DMI, energy balance, and plasma concentrations of insulin and IGF-I. The NEBAL was more severe for nonovulatory cows and NEFA concentrations were higher. Overall, NEBAL is minimized in cows that maintain high DMI until the day of calving and rapidly increase their intake, thereafter, over the first several weeks of lactation. As reported previously, DMI on d 21 of lactation is directly related to DMI on the day before calving (Grummer, 1995). Figure 1 summarizes changes throughout the transition period in DMI, milk production, and body weight loss i.e. NEBAL for cows ovulating (**OV**) early after calving or with nonovulatory follicles (**NOV**).

NEBAL, DMI AND METABOLIC EFFECTS ON FERTILITY DURING LACTATION

In early lactation dairy cows, the extent of NEBAL is apparent from degree of body condition score (**BCS**) loss. Cows with more severe NEBAL lose more BCS during the first 30 d of lactation and experience longer intervals to first ovulation (Butler, 2005; Patton et al., 2007). The variation in the degree of NEBAL among individual cows is explained largely by differences in energy intake rather than milk yield (Villa-Godoy et al., 1988) and DMI during the first 28 DIM is positively associated with earlier ovulation (Patton et al., 2007). Interestingly, milk protein % during the first 28 DIM is also related

to earlier first ovulation, presumably because it is recognized as an important indicator of energy balance (Patton et al., 2007). The importance of DMI is further demonstrated by grouping cows by days to first postpartum ovulation and calculating gross efficiency of milk production. Cows with the lowest efficiency ratio (milk production/DMI) have the shortest interval to first ovulation. Conversely, the most efficient cows (highest milk production compared to DMI) have extended delays to first ovulation (Figure 2). Since the metabolic energy efficiency of milk production is similar in all cows, the cows producing more milk per unit DMI experience more severe NEBAL as more of the energy requirement for milk is derived from body reserves rather than dietary intake. This is an unusual situation where *high efficiency is not beneficial* because delayed onset of ovulatory cycles results in lower fertility. The positive association of DMI during 28 DIM with daily energy balance, early ovulation and fewer days open lead Patton et al. (2007) to identify DMI as the principal component of energy balance influencing subsequent fertility in dairy cows.

The bottom line - high producing cows that increase DMI to better match requirements for milk production will have better energy status and likelihood of higher fertility during breeding.



CARRYOVER EFFECTS OF EARLY NEBAL ON FERTILITY

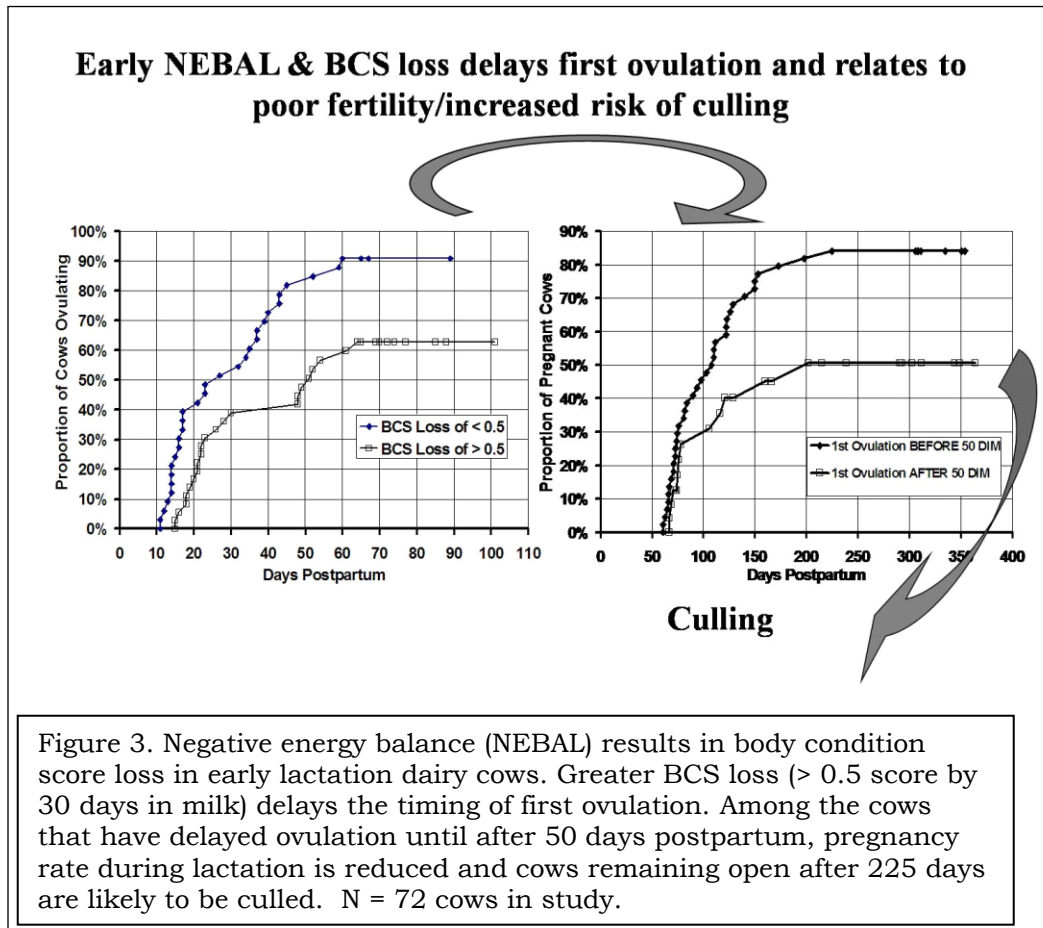
Prolonged Anovulatory Periods

Using cows that lose ≤ 0.5 BCS during the first 30 d of lactation as an example, more than 90 % will initiate ovulatory cycles by 60 d of lactation (see Figure 3, left panel). However, by comparison as many as 30-40 % of cows losing more than 0.5 BCS in early lactation may remain anovulatory. Cows remaining anovulatory beyond 50 DIM have increased risk of non-pregnancy by 225 DIM with the consequence of being culled at the end of lactation (Figure 3, Right Panel).

Coception Rate to AI

Delayed ovulation and insemination provides some explanation for the observed low pregnancy rate; however, as loss of BCS becomes more extensive, the reduction in conception rate to AI becomes

greater (Butler, 2003; Roche et al., 2009 for reviews). Cows losing one unit or more BCS (5 point scale) during early lactation are at greatest risk for low fertility (Santos et al., 2009). As a guideline, conception rate decreases about 10%/0.5 unit BCS loss (Butler, 2001). Extended calving to conception intervals were associated with low BCS by week +7 and greater peak milk yield (Patton et al., 2007; Wathes et al., 2007).



Oocyte and Embryo Quality

Another possible carryover effect of early NEBAL may be that oocytes are imprinted by deleterious conditions within the follicle during their development period of 60-80 d. Evidence has been reviewed on the metabolic environment during NEBAL that may impair oocyte development and embryo quality (Leroy et al., 2008a; Leroy et al., 2008b). One consequence of more severe NEBAL on fertility is through reduced plasma IGF-I levels. Cows which failed to become pregnant despite multiple AI had low IGF-I in the week after calving and continuing low plasma IGF-I values through the breeding period (Taylor et al., 2004). Another study found a high incidence of inferior embryo quality and viability in normal healthy high-producing cows in early lactation as compared to embryos from non-lactating cows (Sartori et al., 2010). Because of combined metabolic differences, the reproductive tract of lactating cows is less capable of supporting early embryonic development than that in heifers resulting in lower fertility (Rizos et al., 2010).

NUTRITIONAL AND MANAGEMENT STRATEGIES

Dietary Strategies During the Dry Period to Reduce NEBAL and Improve Fertility

Nutritional management of dairy cattle during the dry and transition period have important carryover effects on DMI, health and reproduction in early lactation. During late pregnancy, insulin resistance in adipose tissue contributes to increasing plasma NEFA concentrations and subsequent oxidation of NEFA by the liver is the cause of decreasing DMI as cows approach calving (Overton, 2011). Studies over the past few years suggest that energy nutrition during the dry period interacts with insulin resistance during the late prepartum period. Excess energy intake not only during the close-up period, but also during the far-off dry period exacerbates insulin resistance. Collectively, these reports indicate that overfeeding energy to dry cows results in changes in metabolism that, in turn, likely predispose cows to decreased DMI and higher NEFA in the periparturient period. Cows with high BCS scores are particularly at risk. Recommendations for energy nutrition of dairy cows during both the far-off and close-up periods have evolved over the past several years toward the goal of meeting, but not markedly exceeding energy requirements *ie.* no more than 110 to 120%. Controlling energy intake via high-bulk diets (containing straw) or moderately restricted feeding prepartum result in similar metabolic profiles (Janovick et al., 2011), but limit feeding is difficult to manage successfully, especially when cows and heifers are co-mingled in pens with the associated social and behavioral interactions.

Future Opportunities

Currently there is global interest and widespread research activity toward identifying mechanisms regulating feed intake, feed efficiency and early ovulation. Feed conversion ratio (**FCR**) is often used on-farm to benchmark efficiency and is calculated as the amount of DMI required to produce a pound of butterfat and protein combined. On commercial dairy farms, FCR will range from 13 (poor) to 8 (very good), with 9-10 being a good target. From the standpoint of genetic improvement, there are several definitions of feed efficiency: feed conversion efficiency, residual feed intake (**RFI**) and residual solids production (**RSP**). RFI is defined as the difference between an animal's actual feed intake and its expected feed intake from performance (Coleman et al., 2010; Williams et al., 2011). Substantial genetic variation in RFI exists in dairy heifers to be used as a selection tool (Williams et al., 2011), but RSP rather than RFI is more appropriate for evaluating lactating cows *ie.* animals that produce greater amounts of milk solids at similar DMI without excessive body tissue mobilization (Coleman et al., 2010). ***Cows exhibiting increased RSP had improved fertility performance!***

Other studies seek to relate feed efficiency characteristics to single nucleotide polymorphisms utilizing the tools of genomic analysis, data records on performance, and genetic selection. As an early example, Fert (+) cows express higher milk yield and higher conception rates to AI, but no difference in feed intake or energy balance (Cummins et al., 2012). Large chips for genotyping cattle show promise for identification of chromosomes carrying genes related to RFI and energy metabolism (Pryce et al., 2012). Future benefits and opportunities from this type of research will have major impacts for improving efficiency of DMI and reproduction.

SUMMARY

Negative energy balance (NEBAL) may begin prepartum in association with declining feed intake. Excess body condition is one factor related to decreased feed intake. During the first 3 weeks of lactation, NEBAL delays early ovulation and recovery of postpartum reproductive function and provides the major nutritional link to low fertility in lactating dairy cows. NEBAL may detrimentally impact the oocyte that is released after ovulation and exert other carryover effects on uterine conditions resulting in reduced conception rate to insemination. Reducing NEBAL is beneficial, but very difficult to achieve in cows being managed for high milk yield. Maintaining intakes through the prepartum period to calving and increasing intake rapidly thereafter reduce NEBAL and the detrimental effects on coordinated ovarian

and liver function. Management of feed intake, nutrition, and metabolism of lactating cows for improved reproductive performance must begin prepartum in the dry period and continue through early lactation.

CONCLUSIONS

Metabolic changes in periparturient cows associated with onset of NEBAL appear most responsible for the coordinated detrimental effects on reproductive performance.

Negative energy balance during lactation is related to decreasing feed intake prepartum and delaying early ovulation that reduces fertility during the breeding period.

High producing cows that increase DMI to better match requirements for milk production will have better energy status and higher fertility.

REFERENCES

- Beam, S. W. and W. R. Butler. 1999. Effects of energy balance on follicular development and first ovulation in postpartum dairy cows. *J. Reprod. Fertil. Supplement* 54:411-424.
- Butler, S. T., A. L. Marr, S. H. Pelton, R. P. Radcliff, M. C. Lucy, and W. R. Butler. 2003. Insulin restores GH responsiveness during lactation-induced negative energy balance in dairy cattle: effects on expression of IGF-I and GH receptor 1A. *Journal of Endocrinology* 176:205-217.
- Butler, S. T., S. H. Pelton, and W. R. Butler. 2006. Energy balance, metabolic status, and the first postpartum ovarian follicle wave in cows administered propylene glycol. *J. Dairy Sci.* 89:2938-2951.
- Butler, W. R. 2000. Nutritional interactions with reproductive performance in dairy cattle. *Anim. Reprod. Sci.* 60:449-457.
- Butler, W. R. 2001. Nutritional effects on resumption of ovarian cyclicity and conception rate in postpartum dairy cows. *Brit. Soc. Anim. Sci. Occasional Publication No. 26 (Vol.1):*133-145.
- Butler, W. R. 2003. Energy balance relationships with follicular development, ovulation and fertility in postpartum dairy cows. *Livest. Prod. Sci.* 83:211-218.
- Butler, W. R. 2005. Inhibition of ovulation in the postpartum cow and the lactating sow. *Livest. Prod. Sci.* 98:5-12.
- Coleman, J., D. P. Berry, K. M. Pierce, A. Brennan, and B. Horan. 2010. Dry matter intake and feed efficiency profiles of 3 genotypes of Holstein-Friesian within pasture-based systems of milk production. *J. Dairy Sci.* 93:4318-4331.
- Cummins, S. B., P. Lonergan, A. C. Evans, D. P. Berry, R. D. Evans, and S. T. Butler. 2012. Genetic merit for fertility traits in Holstein cows: I. Production characteristics and reproductive efficiency in a pasture-based system. *J. Dairy Sci.* 95:1310-1322.
- Galvao, K. N., M. Frajblat, W. R. Butler, S. B. Brittin, C. L. Guard, and R. O. Gilbert. 2010. Effect of early postpartum ovulation on fertility in dairy cows. *Reprod. Dom. Anim.* 45:e207-e211.
- Grummer, R. R. 1995. Impact of changes in organic nutrient metabolism on feeding the transition dairy cow. *J. Animal Science* 78:2820-2833.
- Janovick, N. A., Y. R. Boisclair, and J. K. Drackley. 2011. Prepartum dietary energy intake affects metabolism and health during the periparturient period in primiparous and multiparous Holstein cows. *J. Dairy Sci.* 94:1385-1400.
- Kawashima, C., S. Fukihara, M. Maeda, E. Kaneko, C. A. Montoya, M. Matsui, T. Shimizu, N. Matsunaga, K. Kida, Y. Miyake, D. Schams, and A. Miyamoto. 2007. Relationship between metabolic hormones and ovulation of dominant follicle during the first follicular wave post-partum in high-producing dairy cows. *Reproduction* 133:155-163.
- Kawashima, C., M. Matsui, T. Shimizu, K. Kida, and A. Miyamoto. 2012. Nutritional factors that regulate ovulation of the dominant follicle during the first follicular wave postpartum in high-producing dairy cows. *J. Reprod. Dev.* 58:10-16.
- Leroy, J. L. M. R., G. Opsomer, S. A. Van, I. G. Goovaerts, and P. E. Bols. 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, J. L. M. R., T. Vanholder, A. T. Van Knegsel, I. Garcia-Ispuerto, and P. E. Bols. 2008b. Nutrient prioritization in dairy cows early postpartum: mismatch between metabolism and fertility? *Reprod. Domest. Anim.* 43 Suppl 2:96-103.
- Overton, T. R. 2001. Healthy livers make healthy cows. *Advances in Dairy Technology* 13:169-180.
- Overton, T. R. 2011. Managing the dynamics of feed intake and body condition score during the transition period and early lactation. 73rd Meeting, 204-213. Proceedings of the Cornell Nutrition Conference for Feed Manufacturers.
- Patton, J., D. A. Kenny, S. McNamara, J. F. Mee, F. P. O'Mara, M. G. Diskin, and J. J. Murphy. 2007. Relationships among milk production, energy balance, plasma analytes, and reproduction in Holstein-Friesian cows. *J Dairy Sci.* 90:649-658.
- Pryce, J. E., J. Arias, P. J. Bowman, S. R. Davis, K. A. Macdonald, G. C. Waghorn, W. J. Wales, Y. J. Williams, R. J. Spelman, and B. J. Hayes. 2012. Accuracy of genomic predictions of residual feed intake and 250-day body weight in growing heifers using 625,000 single nucleotide polymorphism markers. *J. Dairy Sci.* 95:2108-2119.

- Rizos, D., F. Carter, U. Besenfelder, V. Havlicek, and P. Lonergan. 2010. Contribution of the female reproductive tract to low fertility in postpartum lactating dairy cows. *J. Dairy Sci.* 93:1022-1029.
- Roche, J. R., N. C. Friggens, J. K. Kay, M. W. Fisher, K. J. Stafford, and D. P. Berry. 2009. Invited review: Body condition score and its association with dairy cow productivity, health, and welfare. *J. Dairy Sci.* 92:5769-5801.
- Santos, J. E. P., H. M. Rutigliano, and M. F. Sa Filho. 2009. Risk factors for resumption of postpartum estrous cycles and embryonic survival in lactating dairy cows. *Anim Reprod. Sci.* 110:207-221.
- Sartori, R., M. R. Bastos, and M. C. Wiltbank. 2010. Factors affecting fertilisation and early embryo quality in single- and superovulated dairy cattle. *Reprod. Fertil. Dev.* 22:151-158.
- Shimizu, T., C. Murayama, N. Sudo, C. Kawashima, M. Tetsuka, and A. Miyamoto. 2008. Involvement of insulin and growth hormone (GH) during follicular development in the bovine ovary. *Anim. Reprod. Sci.* 106:143-152.
- Sudo, N., T. Shimizu, C. Kawashima, E. Kaneko, M. Tetsuka, and A. Miyamoto. 2007. Insulin-like growth factor-I (IGF-I) system during follicle development in the bovine ovary: Relationship among IGF-I, type 1 IGF receptor (IGFR-1) and pregnancy-associated plasma protein-A (PAPP-A). *Mol. Cell. Endocrinol.* 264:197-203.
- Taylor, V. J., Z. Cheng, P. G. A. Pushpakumara, D. E. Beever, and D. C. Wathes. 2004. Relationships between the plasma concentrations of insulin-like growth factor-I in dairy cows and their fertility and milk yield. *Veterinary Record* 155:583-588.
- Villa-Godoy, A., T. L. Hughes, R. S. Emery, L. T. Chapin, and R. L. Fogwell. 1988. Association between energy balance and luteal function in lactating dairy cows. *J. Dairy Sci.* 71:1063-1072.
- Wathes, D. C., M. Fenwick, Z. Cheng, N. Bourne, S. Llewellyn, D. G. Morris, D. Kenny, J. Murphy, and R. Fitzpatrick. 2007. Influence of negative energy balance on cyclicity and fertility in the high producing dairy cow. *Theriogenology* 68 Suppl 1:S232-S241.
- Williams, Y. J., J. E. Pryce, C. Grainger, W. J. Wales, N. Linden, M. Porker, and B. J. Hayes. 2011. Variation in residual feed intake in Holstein-Friesian dairy heifers in southern Australia. *J. Dairy Sci.* 94:4715-4725.