A 100-Year Review: Historical development of female reproductive physiology in dairy cattle¹

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ABSTRACT

The objective of this historical review in female reproductive physiology is to encapsulate major advancements since the founding of the American Dairy Science Association in 1906. The emphasis is on landmark publications in the *Journal of Dairy Science* since its first volume in 1917. A historical perspective and inferences are made in forecasting evolution of female reproduction and links between physiology of reproduction and the mammary gland. Subsequent sections are focused into main physiological categories and the temporal advancements within these physiological windows. Time points of understanding vary considerably within categories due to various advancements in technology, biological techniques, experimental design, data collection, statistical analyses, and computational forecasting. The physiological windows examined are hypothalamic and pituitary control of the ovary related to estrous behavior and cycle; differential control of the corpus luteum and uterus as influenced by cycling and pregnancy statuses; peripartum and postpartum programming of reproduction; and scientific foundation for the next century. The importance of interdisciplinary programs and integration of reproduction, nutrition/metabolism, genetics, health, and management are emphasized. The modern dairy cow of 2017 exemplifies excellence in both reproductive and lactational performance and is the foundation biological model for the next century.

Key words: reproductive physiology, pregnancy, estrous behavior, 100-year review

INTRODUCTION

It is quite appropriate to reflect on the landmark contributions over the last 100 years of the *Journal of*

Dairy Science related to female reproductive physiology in dairy cattle. The modern dairy cow has been selected and managed for high production and efficiency. Indeed, it is a particular challenge to optimize the fertility of the lactating dairy cow, but major advancements have been made that are operational and based on our understanding of the underlying processes of reproductive physiology. These advancements provide the basic technology that has been transferred to the modern day dairy producer (Appendix Table A1). This historical review of female reproduction sets the stage for current and future advancements in female reproduction.

Of course, not all original advancements were published in the *Journal of Dairy Science*, and the dairy cow animal model is not necessarily the all-encompassing original animal model for initial advancements in female reproductive physiology. However, there is indeed a legacy of advancements, based on the scientific method, that have been published in the *Journal of Dairy Science*. The foundation of knowledge in the bovine provides unique insights that benefit not only the health and well-being of cattle species but other species as well, including humans. It is indeed insightful as to how accurate early sequential descriptions of female reproduction (Willett, 1956) predicted our current in-depth understanding of reproductive function utilizing the temporal advancements in the array of scientific tools and methodology developed to date. The classical areas of reproductive physiology focused on disciplines of anatomy and physiology and expanded with advancements in development of knowledge and technology such as branches of microscopy (i.e., optical, electron, and scanning probe microscopy), chemistry, biochemistry, endocrinology, hormonal measurements, tissue/cell culture, quantitation of DNA/RNA, in vitro maturation, fertilization, and development of embryos, experimental models, ultrasonography, statistics combined with computer technology, sequencing of the bovine genome, functional quantitation of the transcriptome (i.e., RNA microarrays and deep RNA sequencing), genomic selection, and gene editing. These historical and temporal advancements are instrumental to understanding the fundamental makeup and complexity of reproductive processes subsequently described.

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HISTORICAL INSIGHTS FORECASTING STRATEGIES AND WINDOWS OF INVESTIGATION IN FEMALE REPRODUCTION

Gaines (1927) hypothesized that the service period (between date of calving and date of successful conception; comparable to days open) would be related to high milk production during the first calendar month of lactation. He pointed out that lactation is known to affect the reproductive cycle in humans and some of the lower animals such as the rabbit, whereby lactation proceeding at a high level inhibited pregnancy. Nevertheless, the coefficient of variation for service period was high and not associated with yield during the first calendar month of lactation. He noted that these 2 responses appeared to be independent of each other. The mean estimate for service period was 170 d in 1927 (Gaines, 1927). The mean estimate published in 2010 (2.1 million observations between 2001 and 2007) was 146.5 d and the 50th percentile was 119 d (Pinedo and De Vries, 2010). The processes of lactation, homeorhetic metabolic changes, postpartum diseases, and so on may contribute to timing of first estrus, ovulation, and pregnancy at first service. Indeed, the specific level of production early in lactation may not be the sole source associated with fertility.

At the time of these early scientific investigations, it is useful to reference the earlier publications of Halban (1905), an obstetrician/gynecologist in Vienna who linked and described in women the dynamics of mammary gland and uterine development throughout their lifespan (i.e., embryonic to postmenopausal senescence) and conducted early experimental investigations in animal models. This is a vivid example of the past that retrospectively provided the framework for reproduction and lactational physiology for dairy cattle during the subsequent 112 years captured in the publications of the *Journal of Dairy Science*. “Embryonal impulse” represented rapid growth of the fetal mammary gland and uterus in the 8th and 9th months of pregnancy. Neonatal swelling and regression of the mammary gland and uterus were due to active substances from the placenta and their withdrawal. There was a “puberty impulse” on the mammary gland and uterus due to activity of the ovaries, and this was further characterized by ovariectomy and re-transplantation experiments. After puberty, periodic swelling of the mammary gland and uterus occurs with re-occurring estrous cycles (i.e., in humans, the “menstrual impulse”). There is the “pregnancy impulse” of rapid proliferation, with hyperplasia of the glandular tissue but at a much greater rate than postpubertal changes, leading to the inference that the placenta produces more regulatory substances than does the ovary. Pregnancy changes were not due to the

fetus but to the placenta because mammary growth proceeded after death of the fetus and subsided with loss of placenta. Secretions produced by epithelium of the placenta (i.e., trophoblast and chorionic epithelium) and not stromal tissue were inferred. The corpus luteum (CL) persisted during pregnancy under influence of the placenta. Changes in the maternal and fetal uterus were correlated because both regress in the postpartum or puerperium period. Puerperal involution of the maternal uterus occurred only after delivery of the placenta and was considered a true atrophy. Emptying of the uterus was considered critical to onset of milk secretion (i.e., 3 to 4 d after birth). Secretion from the mammary gland before placental delivery was characterized as colostrum, not milk. Suckling did not induce milk secretion and only maintained secretion after the uterus was emptied, and suckling was associated with quiescence of the ovary. Distinct differences or uncoupling were observed between uterus and mammary gland following pregnancies in the nonsuckled and suckled states. Nonsuckled or nonlactating state resulted in a coupled decrease in both the uterus and mammary gland and an earlier recrudescence of ovarian cycles. In contrast, the suckled or lactating state resulted in a greater rate of uterine regression and a marked delay in recrudescence of ovarian cycles.

Willett (1956) noted, “A pygmy sitting on the shoulders of a giant can see farther than the giant.” Due to the background of fundamental research during the half-century preceding 1906, physiologists thereafter have been pygmies or giants able to see and understand phenomena that were beyond the view of the giants of yesteryear and were able to broaden ever further the horizons of our knowledge. When Asdell (1949a,b) reviewed the studies dealing with hormonal and nutritional treatments of sterility in dairy cattle, he emphasized the need to develop more sensitive tools of investigation and specified the need for adequate controls to account for spontaneous recovery of experimental animals and the need for the biochemist or nutritionist to work closely with the physiologist. These basic principles have been emphasized extensively within the *Journal of Dairy Science* with publication of strategies for design and statistical analyses of sensitive experiments across a wide array of experimental variables (discrete and continuous) with chosen confidence (α) and power (β) to detect treatment differences (Tempelman, 2009; Lean et al., 2016).

A classical experiment begun in 1947 and completed over a 7-yr period (Reid et al., 1957, 1964; Sorenson et al., 1959) examined the influence of 3 planes of nutrition fed to heifers from birth until first calving. The dietary treatments provided approximately 65% (low), 100% (medium), and 140% (high) of Morrison’s TDN

standards. After first calving, all cows were fed adequately. Age of puberty was greater in the low group (20.2 mo) compared with the medium (11.2 mo) and high (9.2 mo) groups. However, both wither height and BW at the time of puberty were comparable between dietary treatments. Consequently, cow BW at first calving was lower (440, 539, and 614 kg) and occurrence of calving difficulty was greater (48, 27, and 25%) for the low, medium, and high diet groups, respectively. Reproductive responses such as services per conception and percent conception on first service did not differ. However, postpartum intervals to first estrus or ovulation were not reported, which could influence service period. These findings, and others reviewed by Schultz (1969), set the stage for subsequent investigations of basic physiology and nutritional regulation of gestation and postpartum periods on reproductive performance. With the greater milk production of recent generations of dairy cows, Butler and Smith (1989) documented that both milk production per day and days to ovulation during the first 20 d postpartum were associated negatively with average energy balance (Mcal/d) and predicted potential physiological and endocrine control mechanisms.

HYPOTHALAMIC AND PITUITARY CONTROL OF THE OVARY RELATED TO ESTROUS BEHAVIOR AND CYCLE

Hypothalamic and pituitary control of reproductive and metabolic hormones are pivotal to the integration of the reproductive system and its function during key physiological periods such as the estrous cycle/pregnancy and the transition/postpartum phases leading to restoration of reproductive competence. The ability to quantify hormones using specific, sensitive, and accurate techniques coalesced many advancements in our understanding of the endocrine system. Trenkle (1972) described the overall basic principles allowing for the use of valid radioimmunoassays (RIA) to measure hormones in plasma precisely and accurately. Indeed, such principles are applicable and essential to current systems of biological measurements based on RIA, ELISA, mRNA expression via PCR, and protein abundance. It is well established that GnRH secreted from hypothalamic neurosecretory neurons terminating in the median eminence passes into the blood vessels of the hypophyseal portal system and is transported to the anterior pituitary. The ultimate action of GnRH is to induce secretion of FSH and LH from gonadotrophs that are important for follicular growth, maturation, and ultimately ovulation with subsequent formation of the CL. Several previous temporal reviews have characterized pituitary ovarian relationships (Hansel and

Snook, 1970) and further temporal advances in reproductive physiology including physiological responses to a synthetic GnRH (Britt et al., 1981).

Failure to express estrus, detect estrus, or both are major impediments to herd fertility. With use of either collar-mounted activity meters in a pasture-based production system (Kamphuis et al., 2012) or devices composed of a pressure-sensitive radiotelemetric transmitter on cows in a freestall barn (Lopez et al., 2005), approximately 28.6 and 28.5% of the cows failed to be detected in estrus, respectively. In all likelihood, anovulatory cows or cows with insufficient plasma estradiol fail to express sufficient estrus responses for detection. High-producing dairy cows have shorter durations of estrus, fewer standing events and lesser standing times, lower plasma estradiol concentrations, and greater occurrence of multiple ovulations (Lopez et al., 2005). The importance of estradiol to influence the acute release of LH in response to an injection of GnRH is demonstrated vividly in an experimental model with lactating dairy cows during a timed AI (TAI) program (Stevenson and Pulley, 2016). Cows with a low progesterone (P4) concentration at the time of a GnRH injection released more LH than cows classified as having medium to high P4 concentrations in plasma; within each progesterone classification (i.e., medium or high versus low), cows with high estradiol concentrations released more LH in response to GnRH compared with those with low estradiol concentrations in plasma. Thus, the ratio of estradiol to progesterone influences responsiveness of the pituitary to GnRH. This same phenomenon was evident in characterizing the responsiveness of the pituitary to GnRH given at different times after a luteolytic injection of PGF_{2α} to cows with a CL. The LH response to GnRH increased as the estradiol (pg/mL):progesterone (ng/mL) ratios increased in plasma at 0 (0.47), 12 (2.03), 24 (5.99), 48 (12.99), and 60 (14.04) h after injection of PGF_{2α} (Thatcher and Chenault, 1976). The preovulatory follicle increase of estradiol secretion increases sensitivity of the anterior pituitary to GnRH.

The actions of estradiol to enhance responsiveness of the pituitary to exogenous GnRH does not preclude effects at a higher level to enhance endogenous hypothalamic GnRH secretion or higher loci in the brain to regulate estrous behavior (EB). Kommadath et al. (2013) utilized a systems biology approach relating quantitative EB scores in cows to identified genes and biological processes shared among the anterior pituitary (AP) and 4 brain areas: dorsal hypothalamus (DH), ventral hypothalamus (VH), amygdala (AM), and hippocampus (HC) of lactating dairy cows. Quantitative values of EB expression in 14 cows were recorded during multiple consecutive cycles per cow beginning

at 30 DIM, and cows were euthanized on the day of estrus between 77 and 139 DIM. Tissues from the AP and the higher brain areas (i.e., DH, VH, AM and HC) were collected and underwent transcriptome analyses with a bovine oligonucleotide microarray system. For the respective tissue pairs, numbers of consensus modules of co-expressed genes and numbers of genes within the consensus modules were identified between the networks: AP–DH (23; 1,904), HC–DH (10; 846), AM–HC (8; 843), AM–DH (3; 225) and VH–DH (2 197), respectively.

The correlation between the module's eigengene (weighted average gene expression profile representative of the gene expression profiles in a module) and levels of EB exhibited by the experimental cows were tested (eigengene significance). One of the strengths of this method is that the problem of multiple testing corrections is eliminated because the correlation is between the EB trait of the cow and the module eigengene (i.e., not to individual gene expression values). Estrous behavior–correlated modules were found to be enriched for gene ontology terms such as glial cell development and regulation of neural projection development, as well as pathway terms related to brain degenerative diseases. Indicative of increased transcription and protein synthesis, cellular biosynthetic processes such as oxidative phosphorylation and ribosomal RNA synthesis were enriched in several correlated modules.

In rodent studies, stimulation of ribosomal RNA synthesis is a primary event in the activation of neuronal cells and pathways associated with female reproductive behavior. This activation precedes the estrogen-driven expansion of dendrites and synapses. Similar processes also appear to operate in cows to affect EB. Hub genes (i.e., genes in the network highly connected with other genes) within EB-correlated modules are strong candidate genes for regulating EB expression. The following hub candidate genes in the AP–DH tissue pair were notable: *NEFL* [neurofilament protein, intracellular transport to axons and dendrites, targeting and regulation of phosphatase(s) within neurons], *NDRG2*, *THY1*, and *GAP43* (involved in neural growth and plasticity), and *TCF7L2* (effector in the Wnt signaling pathway, which is active in development of blood brain barrier), *OXY* (oxytocin prepropeptide), and *AVP* (interacting to influence sexual behavior).

These findings enhance our understanding of the genomic regulation of EB in dairy cows, and provide insights into genes and biological processes shared among the bovine AP and brain areas functioning together to regulate EB. Such analytical approaches may lead to development of new biomarkers for strategic utilization to improve reproductive performance. Identification of genes associated with EB may be incorporated into de-

velopment of DNA and phenotypic databases utilizing genome-wide analyses to improve fertility.

In the early 1970s, only limited reports were available regarding blood concentrations of reproductive hormones (e.g., estradiol, progesterone, LH, and FSH) due to a lack of sensitive and accurate assays. Technical tools involved gas chromatography, gonadotrophin assays with high cross-reactivities with other hormones, and bioassays for hypothalamic peptides and pituitary hormones (Gomes and Erb, 1965; Hansel and Snook, 1970). However, very insightful relationships were documented or inferred such as (Hansel and Snook, 1970): increases in estimates of pituitary FSH and LH secretion and hypothalamic content of LH releasing factor during proestrus and estrus, respectively; preovulatory surge of plasma LH; identification of LH as the luteotrophin for CL growth and progesterone secretion; coordination of plasma LH and progesterone peaks during the luteal phase of the estrous cycle; precipitous decline in plasma progesterone associated with CL regression in late diestrus followed by a sharp increase in plasma LH; no detection of a preovulatory increase of progesterone to induce a LH surge; and inference for a role of estradiol for induction of EB and ovulation. Subsequent studies characterized extensively the temporal changes in progesterone, estradiol, and LH in plasma for the late diestrus through the periovulatory periods (Chenault et al., 1975, 1976).

Ireland et al. (2000) encapsulated historically the evolved experimental approaches to the turnover of dominant follicles during the bovine estrous cycle. Two salient experimental approaches emerged in the 1980s, which permitted investigators to access health status of individual follicles and dynamics of antral follicle development on a within-animal basis. Measurements of intrafollicular ratios of estradiol:progesterone within antral follicles allowed for the classification of follicles as estrogen-active (i.e., healthy; estradiol > progesterone or high estradiol:progesterone ratio) or estrogen-inactive (i.e., atretic; progesterone > estradiol or low estradiol:progesterone ratio (Badinga et al., 1992; Ireland et al., 2000). The 2-cell system (i.e., theca interna and granulosa cells) for estrogen biosynthesis of the follicle was modeled by J. E. Fortune (Hansel and Convey, 1983). Indeed, the follicular wall of dominant follicles at d 5 and 8 had high aromatase activities, but follicular fluid concentrations of estradiol were high at d 5 and markedly reduced by d 8 (Badinga et al., 1992). This was indicative that thecal cell androgen availability was likely limited at d 8, accounting for the decrease in the estradiol:progesterone ratio as an atresia marker of the dominant follicle.

Such markers of follicle quality, coupled with the use of ultrasonography to measure follicle diameter (Pier-

son and Ginther, 1984), facilitated the investigation of temporal follicle dynamics on a within-cow basis. Waves of follicular development comprise a dominant follicle (DF) and several subordinate or secondary follicles (Ireland et al., 2000). Follicular waves comprise periods of emergence, deviation (DF selected from the cohort), dominance (health DF sustains preferential bilateral growth over all follicles on the ovaries), and atresia of DF coupled with emergence of a new follicular wave. As cited by Ireland et al. (2000), transient peaks of FSH occur with each wave of follicular development at the time of follicular emergence. As FSH concentrations descend from peak (i.e., likely due to inhibin produced by follicles in the emerging wave), deviation occurs with continued sustained growth and dominance of the DF due to acquisition of LH responsiveness. Luteinizing hormone receptors develop on granulosa cells of the healthy DF on d 4, 6, and 8 (Xu et al., 1995). However, expression of LH receptor mRNA in granulosa cells was not detected in regressing dominant follicles collected on d 10. Pulsatile perfusion of LH in the first wave of postpartum lactating cows (7 to 12 d postpartum) caused ovulation to occur 14 d earlier than in control cows (Hampton et al., 2003). The ultimate fate of the DF (i.e., turnover during diestrus or continued development as a preovulatory follicle) depends on availability of LH receptors and basal LH (enhanced either following regression of CL or following infusion in anovulatory cows). Diestrus progesterone concentrations are associated with a lower LH pulse frequency.

Ultrasonographic analyses indicate that cattle usually have 2 and 3 waves of follicular development during the estrous cycle (Ireland et al., 2000). An understanding of ovarian follicular and CL functional dynamics is essential for the use of physiological pharmaceuticals such as GnRH, P4, and PGF_{2α} in development of reproductive management programs that achieve high fertility (see Stevenson and Britt, 2017).

Within the basic life cycle of female reproductive competence, the corpora lutea “cometh and goeth.” Secretions from the hypothalamus, pituitary gland, ovary, uterus, embryo, and fetal-placental unit control presence of the CL and its capability to secrete progesterone.

Corpus Luteum Development

The CL is a continuation of follicular development in which the preovulatory surge of LH induces luteinization of granulosa and theca cells. Smith (1986) reviewed a cross-section of physiological and molecular determinants that influence CL function, drawing on an extensive review of the literature among ruminant and nonruminant species. Following ovulation, subse-

quent growth and differentiation of small (theca interna) and large (granulosa) cells become the principal luteal cell components for synthesis of P4. Luteinizing hormone is the principal luteotrophin in the bovine CL (Donaldson and Hansel, 1965). Small luteal cells are responsive to LH, whereas large luteal cells have a high basal P4 secretion rate. Indeed, the majority of recurring pulses of P4 in the luteal phase are coupled with stimulatory peaks of LH, and additional pulses may be associated with peak occurrences of FSH and oxytocin. The potential functional capacity of the CL is programmed to some degree by prior preovulatory programming associated with a sequential exposure to diestrus P4 and proestrus secretions of gonadotrophins (i.e., FSH and LH) and estradiol. This programming influences size and estrogenic health status of the preovulatory follicle, subsequent size of the CL, and whether subsequent CL lifespan is shortened or normal due to potential programming of the uterus (Bisinotto et al., 2013). The secretory granules in large luteal cells contain P4 and oxytocin (Fields et al., 1992). The greatest percentage of large luteal cells with a cluster of large granules, containing oxytocin and neuropeptide Y, occurs mid-cycle on d 7 (84%) and 11 (64%) and decreases progressively on d 14 (26%), 17 (16%), and 19 (8%). From d 7 to 14, the 69% decline in large luteal cells containing oxytocin-laden secretory granules occurs before the reported increases in uterine oxytocin receptors and luteolytic pulses of PGF_{2α}. The early concurrent granule release of oxytocin and P4 into the inferior vena cava as pulses may account for spikes of P4 that are not necessarily associated with LH pulses (Walters et al., 1984).

With LH being the luteotrophic hormone in the dairy cow, cellular mechanisms associated with regulating progesterone secretion (+/–) are critical to understanding the transition of the mature steroidogenic CL to a regressing CL. The concentrations of receptors vary in the 2 cell types; LH receptors are primarily on small luteal cells, whereas prostaglandin and estradiol receptors are located primarily with large luteal cells. Basal progesterone production is greater in large luteal cells. Protein kinase A (PKA) and protein kinase C (PKC) are 2 intracellular effector systems that regulate luteal P4 production. Each of the enzymes are present in both luteal cell types. Binding of LH to the membrane receptor of small luteal cells activates adenylate cyclase to increase intracellular cAMP and activation of PKA. The 2 intracellular effector systems, PKA and PKC, have opposing effects on P4 production. Protein kinase A is responsive to LH in small luteal cells and is a potent stimulator of P4 production, whereas PKC in large luteal cells is responsive to PGF_{2α} as a potent inhibitor of P4 production.

In addition to large and small luteal cells, the CL also contains endothelial, immune, and fibroblast cells. Luteal steroidogenesis depends on steroidogenic acute regulatory protein (STAR) protein to transport cholesterol from the outer to the inner mitochondrial membrane. The cholesterol side-chain cleavage enzyme (P-450_{scc}), located on the inner membrane of mitochondria, converts cholesterol to pregnenolone. The 3 β -hydroxysteroid dehydrogenase (3 β -HSD) enzyme converts pregnenolone to P4 (Niswender, 2002).

Garverick et al. (1985) characterized changes and interrelationships in CL tissues of cows at 6 stages (d 4, 7, 10, 13, 16, and 19) for LH receptors, adenylate cyclase activity, and phosphodiesterase activity. Mean CL weight, luteal and plasma concentrations of P4, and unoccupied LH receptors increased from d 4 to d 10, plateaued (d 10 to 16), and then declined following luteal regression (d 19). Total number of occupied receptors/CL increased 4-fold from d 4 (47 fmol/CL) to d 10 (221 fmol/CL) and remained similar thereafter. Activities of basal adenylate cyclase, LH-activated adenylate cyclase, and guanylyl imidodiphosphate [Gpp(NH)p]-activated adenylate cyclase were greatest on d 7 to 16, compared with d 4 and 19. Luteinizing hormone stimulated ($P < 0.05$) adenylate cyclase activity relative to basal activity on d 7, 10, 13, and 16, whereas Gpp(NH)p stimulated ($P < 0.05$) adenylate cyclase activity at each period. Thus, adenylate cyclase activity is capable of being regulated in regressing CL at d 19. Phosphodiesterase was 46% greater on d 19 than on d 4. Furthermore, plasma P4 concentrations were correlated positively ($P < 0.01$) with unoccupied LH receptor concentrations ($r = 0.64$), and activities of basal adenylate cyclase ($r = 0.46$), LH-activated adenylate cyclase ($r = 0.52$), and Gpp(NH)p-activated adenylate cyclase ($r = 0.47$). A prior in vivo experiment monitoring plasma P4 concentrations following GnRH stimulation of plasma LH injected at 0, 12, 24, 48, and 60 h after injection of PGF_{2 α} indicated that functional CL regression was fully complete between 48 and 60 h (Thatcher and Chenault, 1976).

Uterine-Corpus Luteum Regression

Luteolysis is a uterine and neuroendocrine-mediated event. Functional luteolysis denotes the decline in P4 production by the CL. Structural luteolysis denotes the physical involution and regression of luteal tissues. The interrelationships between uterus and ovary have been well documented with experimentation and development of collateral models in sheep and cattle. The crossover of investigations in reproduction with these 2 species as models is reflected in *Journal of Dairy Science* and *Journal of Animal Science* publications,

symposia, and joint meetings for the last 100 years. This is further reflected through recent reviews of 2 interdisciplinary efforts in ruminant female reproduction related to control of the CL during the cycle and early pregnancy that entails multiple failsafe mechanisms to ensure success (Arosh et al., 2016; Spencer et al., 2016).

The phenomena in cattle controlling regression of the CL involve the effect of estradiol produced by a dominant follicle acting on a P4-primed uterus to induce endometrial secretion of PGF_{2 α} , which is the luteolytic hormone causing functional and structural luteolysis. Injection of estradiol in hysterectomized heifers failed to completely regress the CL compared with cows with a uterus, indicating that estradiol exerts its luteolytic effect by acting through the uterus (Brunner et al., 1969). Estradiol stimulates PGF_{2 α} at d 18 of the estrous cycle with maximal uterine production and metabolism at 6 h after injection (Knickerbocker et al., 1986a). The PGF_{2 α} travels to the ovary via a uterine venous transfer to the ovarian artery ipsilateral to the CL (Wolfenson et al., 1985). The estradiol acting in conjunction with oxytocin secreted by the posterior pituitary, by the ovary, or both (Fields et al., 1992) induces PGF_{2 α} availability for regression of the CL.

In intensive studies with sheep (see review by Arosh et al., 2016), at the time of luteolysis, PGF_{2 α} is released from the endometrium in a pulsatile pattern. Continuous exposure of endometrium to P4 for 8 to 10 d downregulates expression of nuclear progesterone receptor (PGR) in luminal epithelial (LE) cells between d 11 and 13, thereby allowing a rapid increase in expression of estrogen receptor α (**ESR1**) after d 13, followed by an increase in expression of oxytocin receptor (**OXTR**) after d 14 of the estrous cycle. Pulsatile release of oxytocin after d 13 to 14 of the estrous cycle acts on endometrial OXTR to induce the luminal endometrial epithelium to secrete 5 luteolytic pulses of PGF_{2 α} between d 14 and 16 of the estrous cycle. Luteal oxytocin acts as a supplemental source of oxytocin to boost the oxytocin pulse from the posterior pituitary during luteolysis. Binding of oxytocin to its receptor on LE cells activates phospholipase C (**PLC**), leading to increases in Ca²⁺ and PKC, which activates the PGF_{2 α} biosynthetic pathway (Figure 1A). Five PGF_{2 α} pulses of 1 h duration over a period of 48 h at 8-h intervals are required to consistently cause complete CL regression. Endometrial PGF_{2 α} pulses are transported from the uterine luminal cells through a prostaglandin transporter (**PGT**)-dependent mechanism, which increases local PGF_{2 α} availability in the utero-ovarian vein for countercurrent exchange in the uterine-ovarian plexus (**UOP**) via a simple diffusion to the ovarian artery. Local transport of PGF_{2 α} through the UOP is essential for regression of the CL, because 99% of PGF_{2 α} secreted by

the endometrium is catabolized into its inactive stable metabolite (PGFM) after a single systemic passage through the lungs. Endometrial luteolytic $\text{PGF}_{2\alpha}$ pulses act through the $\text{PGF}_{2\alpha}$ receptor (**FP**) of large luteal cells to activate Ca^{2+} and PKC pathways to stimulate $\text{PGF}_{2\alpha}$ biosynthetic machinery, as well as suppressing survival and activating apoptotic pathways to decrease P4 biosynthesis (see Figure 1B). Collectively, these coupled systems lead to regression of the CL.

Understanding the mechanisms of controlling follicle development, ovulation, CL development, and regression of the CL has resulted in development of the physiological pharmaceutical agents (i.e., GnRH, P4 intravaginal devices, and $\text{PGF}_{2\alpha}$) to control induction of estrus and ovulation for optimal fertility in dairy heifers and lactating dairy cows with the use of AI or embryo transfer (see Stevenson and Britt, 2017).

Uterine–Conceptus–Corpus Luteum Interactions to Sustain Pregnancy

Long-term cooperation between the laboratories of F. W. Bazer, R. M. Roberts, and W.W. Thatcher, as well as several distinct generations of academic descendants and cooperators, led to intensive mechanistic/molecular models and approaches to comprehend establishment of pregnancy in sheep and cows (reviews: Bazer et al., 2009; Arosh et al., 2016; Spencer et al., 2016).

Interferon- τ (**IFNT**), a type 1 interferon, is secreted by conceptus mononuclear cells of the trophectoderm and is the antiluteolytic factor to prevent regression of the CL in ruminants. Interferon- τ interacts locally within the conceptus–uterine–ovarian (**CUO**) complex such that the CL is maintained to sustain pregnancy due to differentials in uterine secretion and transport of $\text{PGF}_{2\alpha}$ and prostaglandin (PG) E_2 within the CUO complex. Differences in prostaglandin production are coupled with localized transport systems to the ovary bearing the CL that sustains secretion of P4.

Interferon- τ acts on uterine luminal epithelia (**LE**) and superficial glandular epithelia (**sGE**) to inhibit transcription of *ESR1* and *OXTR* genes and abrogate development of the endometrial luteolytic mechanism (Spencer and Bazer, 1996). The increases in expression of *ESR1* and *OXTR* mRNA in uterine luminal and superficial glandular epithelia between d 11 and 17 after estrus in cyclic sheep do not occur in pregnant ewes (Spencer and Bazer, 1995) or in cyclic ewes in which recombinant ovine IFNT is injected into the uterine lumen (Spencer et al., 1995). Thus, oxytocin is unable to induce secretion of luteolytic pulses of $\text{PGF}_{2\alpha}$. However, basal production of $\text{PGF}_{2\alpha}$ is greater in pregnant than in cyclic ewes, as IFNT does not inhibit expression of prostaglandin-endoperoxide synthase 2 (**PTGS2**) in

uterine LE or sGE (Charpigny et al., 1997). The molecular mechanisms involved in IFNT silencing expression of *ESR1* are likely due to IFNT inducing expression of IFN regulatory factor 2 (**IRF2**), a potent repressor of transcription, in uterine LE and sGE. In the absence of *ESR1*, ovine uterine epithelia do not express *OXTR* (Fleming et al., 2006).

In contrast to the ovine *OXTR* gene, the bovine *OXTR* gene lacks a classical palindromic estrogen response element (ERE). However, there are 3 ERE half-sites (Telgmann et al., 2003) such that estradiol activation of the *OXTR* may require either steroid receptor co-factors or the transcription factor SP-1. Nevertheless, IRF2 can regulate expression of the bovine *OXTR* gene (Telgmann et al., 2003). The IFNT induction of IRF-2 serves a common role in inhibiting presence of both *ESR1* and *OXTR*; IRF2 is the primary effector of IFNT antiluteolytic actions in bovine endometria.

A novel alternative and complementary noncanonical mechanism leading to suppression of $\text{PGF}_{2\alpha}$ in pregnancy is described by Arosh et al. (2016; Figure 1C). Interferon- τ activates the JAK-SRC-EGFR-RASRAF-ERK1/2-EGR-1 module signaling pathway in ovine endometrial LE cells in vitro. The IFNT treatment acts through extracellular signal-regulated protein kinases 1 and 2 (**ERK1/2**) and early growth response protein 1 (**EGR-1**) to phosphorylate PGT protein at tyrosine and threonine residues and concurrently dephosphorylate PGT protein at serine residues. Alterations in phosphorylation of PGT inhibits PGT function to suppress PGT-mediated transport of pulsatile release of $\text{PGF}_{2\alpha}$ from the endometrium. This proposed pathway (Figure 1C) to inhibit $\text{PGF}_{2\alpha}$ release occurs without necessarily being totally dependent on suppressing endometrial expression of either *ESR1* or *OXTR*. Concurrently, IFNT acts on both endometrial and stromal cells to increase net production of PGE_2 , and PGE_2 from the stroma cells acts in a paracrine manner through PGE_2 receptors (**EP**), EP2/EP4, to further enhance PGE_2 production by endometrial cells. As a consequence of these coordinated PG responses to IFNT, a greater amount of PGE_2 is transported through the UOP to the CL. Greater concentrations of PGE_2 , acting through the EP2/EP4 membrane receptors on large luteal cells (Figure 1D), activate the cAMP/PKA pathway: increasing PGE_2 secretion and autocrine uptake in large luteal cells, activation of antiapoptotic and survival pathways, and suppression of proapoptotic pathways. Collectively, these effects maintain survival of luteal cells and maintain P4 secretion.

A series of experiments published over the last 3 decades in cows paralleled investigations in sheep in examining the functional interrelationships of IFNT and prostaglandins. A variety of experimental models

documented in vivo and in vitro alterations in transport and attenuation of $\text{PGF}_{2\alpha}$ responses between cyclic and pregnant cows, at the time the CL regresses or is sustained, respectively (see reviews by Thatcher et al., 1984a,b). In pursuit of the antiluteolytic agent, temporal characterization (Bartol et al., 1985), and intrauterine administration (Knickerbocker et al., 1986b) of bovine conceptus proteins, bovine trophoblast protein-complex (Helmer et al., 1989) and recombinant bovine (b)IFNT (Meyer et al., 1995) clearly documented the antiluteolytic effects of bIFNT to maintain the CL. Both in vivo and in vitro experimental models documented that bIFNT attenuates uterine secretion of $\text{PGF}_{2\alpha}$. Mechanistic experimental approaches compared expression and abundance of candidate molecules in the endometrium, such as *ESR1* and *OXT* receptors, at d 17 post-insemination between pregnant and cyclic cows that were treated with or without bST and were nonlactating (Guzeloglu et al., 2004) or lactating (Bilby et al., 2006). Gene expression and protein abundance or quantities in the uterine lumen of luteolytic and antiluteolytic agents were evaluated. Quantities of *ESR1* mRNA, *ESR1* protein, *ESR1* immunostaining of LE, and *OXT* mRNA were decreased in endometrium of pregnant cows, whereas quantities of PGR immunostaining in endometrial glands, PGHS-2 protein, PGHS-2 immunostaining of LE, and total quantities of both $\text{PGF}_{2\alpha}$ and PGE_2 ($\text{PGF}_{2\alpha} > \text{PGE}_2$) in the uterine flush were greater in pregnant cows. These findings further document suppression of the endometrial luteolytic mechanism to maintain ovarian P4 production in cattle.

Uterine–Conceptus–Corpus Luteum Interactions to Enhance Growth and Development of the Conceptus

Beyond the mechanisms dealing with maintenance of the CL, an understanding of the factors controlling the coordinated growth and development of the conceptus is essential to improving fertility. An optimal level of luteal P4 during the cycle before ovulation, the rise in P4 following ovulation, and sustained luteal-phase concentrations of P4 are essential to program the endometrium to produce an enriched histotrophic environment within the uterine lumen to support the developing blastocyst and differentiation of the conceptus. The enriched pool of histotroph at the critical period of pregnancy recognition (i.e., maintenance of the CL) contains embryotrophic factors (e.g., amino acids, sugars, proteins, prostaglandins, lipids). Certain components alter gene expression of the endometrium and conceptus to support development of a conceptus–maternal unit approaching the transitional processes of implantation and placentation. Rapid elongation of the

conceptus and extraembryonic membranes is a dynamic and extensive process with major alterations of endometrial biosynthetic and metabolic pathways to support conceptus growth and development. Alterations in immune function within the endometrium appear to be driven in a manner to prevent rejection of the conceptus. These vital interrelationships have been reviewed extensively in sheep and cattle (Dorniak et al., 2011; Spencer et al., 2016).

Application of transcriptomics allows for the complete identification of RNA transcripts that are differentially expressed from the genome of a population of cells from different states that control conceptus–endometrial interactions. The major changes required to drive conceptus elongation and uterine receptivity for the gradual process of implantation occur between d 7 and 13 in response to P4 from the CL. This occurs regardless of whether an appropriate embryo or developing conceptus is present. Comparisons of the endometrial transcriptome between cyclic and pregnant heifers showed no difference before pregnancy recognition, indicating that P4 programming sets the stage for subsequent differential responses associated with or without presence of a conceptus (Forde et al., 2011).

An experiment was designed to determine effects of pregnancy and lactation on endometrial gene expression on d 17 of the estrous cycle and pregnancy in primiparous nonlactating and lactating cows (Cerri et al., 2012). Regulation of different immune functions is an extremely important event within the d 17 endometrium in the presence of a conceptus (pregnancy). Results from Gene Ontology (GO; <http://www.geneontology.org/>) analyses show an upregulation of many genes related to the immune system such as defense response (GO:0006952), interferon regulatory factor (IPR001346), and immune effector process (GO:0002252).

A great portion of these genes (the vast majority upregulated by pregnancy) were in fact IFN-stimulated genes (ISG) such as myxovirus resistance 1, interferon-inducible protein p78 (*MX1*), myxovirus resistance 2 (*MX2*), similar to putative ISG12(a) protein (*ISG12*), ISG15 ubiquitin-like modifier (*ISG15*), IFN-stimulated exonuclease gene (*ISG20*); IFN regulatory factors (*IRF1*, *IRF3*, *IRF5*, *IRF6*, *IRF7*, *IRF8*, *IRF9*), IFN induced with helicase C domain 1 (*IFIH1*); chemokines chemokine (C-C motif) ligand (*CCL2*, *CCL8*, *CCL11*), chemokine (C-X-C motif) ligand (*CXCL2*, *CXCL10*), chemokine (C-C motif) receptor 7 (*CCR7*); signal transducer and activator of transcription (*STAT1*, *STAT2*), with many of them previously described in sheep (Spencer et al., 2008).

The genes that encode for the Fc fragment of IgG (*FCGRT*), T-cell receptor delta chain (*TRD*), immu-

noglobulin heavy constant gamma 1 (*IGHG1*), and immunoglobulin light chain, lambda gene cluster (*IGLL1*) were all upregulated (approximately 2- to 8-fold

increases) by lactation but were not altered by pregnancy (Cerri et al., 2012). These differences in immune responses to the physiological states of lactation and

Figure 1. Working model on novel concepts on action of prostaglandins (PG) on luteal maintenance and maternal recognition of pregnancy (MRP) and establishment of pregnancy (ESP) in ruminants: (I) Luteolysis (panel A): (1) Oxytocin (OT) acts on its receptor OXTR, (2) activates Ca^{2+} and protein kinase C (PKC) pathways, (3) which in turn activates the endometrial $\text{PGF}_{2\alpha}$ biosynthetic machinery, and (4) induces endometrial $\text{PGF}_{2\alpha}$ production. Luteolytic $\text{PGF}_{2\alpha}$ pulses are transported through (5) prostaglandin transport (PGT)-dependent mechanisms and basal release of $\text{PGF}_{2\alpha}$ is mediated through (6) PGT-independent mechanism or simple diffusion from the endometrial epithelial cells to the corpus luteum (CL) through the utero-ovarian plexus (UOP). (Panel B) Endometrial luteolytic $\text{PGF}_{2\alpha}$ pulses (7) act on the $\text{PGF}_{2\alpha}$ receptor (FP) in large luteal cells, (8) activate Ca^{2+} and PKC pathways, (9) which in turn activates the luteal $\text{PGF}_{2\alpha}$ biosynthetic machinery, and (10) induces intraluteal $\text{PGF}_{2\alpha}$ production, and (11) further auto-amplifies luteal $\text{PGF}_{2\alpha}$ production by autocrine and paracrine mechanisms. In addition, $\text{PGF}_{2\alpha}$ -FP signaling (12) suppresses survival pathways and (13) activates apoptotic pathways. (14) Importantly, endometrial PGE_2 production is suppressed at the time of luteolysis, which leads to (15) repressed PGE_2 -EP2/EP4 (PGE_2 receptor) signaling in large luteal cells, thus expediting (16) suppression of survival and (17) activation of apoptotic pathways in large luteal cells. Together, activation of FP and suppression of EP2/EP4 signaling (18) decrease progesterone (P4) biosynthesis and secretion, (19) induce apoptosis of large luteal cells, which eventually culminates in (20) functional and structural luteolysis. II. MRP/ESP: (panel C) (21) Interferon-tau (IFNT) acts on its receptors IFNR1 and IFNR2 and (22) suppresses estrogen receptor α (ESR-1) and oxytocin receptor (OXTR) through (23) IFN regulatory factor-2 (IRF-2) or (24) specificity protein 1 (SP1) (sequential signaling cascades from IFNR to IRF2 or SP1 is yet to be confirmed). In parallel, IFNT activates (25) the IFNR-JAK-SRCEGFR-RAS-RAF-ERK1/2-EGR1 module. (26) Early growth response protein 1 (EGR1) and SP1 are competing for the same GC-rich elements, and EGR1 may compete or replace binding with SP1 and suppresses OXTR (this mechanism yet to be confirmed). (27) ERK1/2 and EGR1 inhibits PGT function and (28) suppresses PGT-mediated transport of pulsatile release of $\text{PGF}_{2\alpha}$ from the endometrium to the CL through the UOP. Interestingly, (29) IFNT does not inhibit basal endometrial production of $\text{PGF}_{2\alpha}$, which is transported by PGT-independent mechanism or simple diffusion from the endometrium to the UOP. It supports the increased basal concentration of $\text{PGF}_{2\alpha}$ (30) found in the UOP at the time of ESP. (31) $\text{PGF}_{2\alpha}$ acts on the FP in the large luteal cells but the CL of early pregnancy is resistant to both basal and luteolytic $\text{PGF}_{2\alpha}$ action. Concurrently, IFNT acts on (32) the endometrial epithelial cells and (33) stromal cells through multiple mechanisms, (34) increases net endometrial PGE_2 production, (35) which further auto-amplifies endometrial PGE_2 production through autocrine/paracrine EP2/EP4 signaling. (36) PGE_2 is transported from the endometrium to the CL through the UOP via PGT- or MRP4-mediated mechanisms. (Panel D) (37) Endometrial PGE_2 acts on the EP2/EP4 in the large luteal cells, activates cAMP/PKA and SRC pathways, and in turn auto-amplifies (38) intraluteal PGE_2 production via (39) autocrine and paracrine EP2/EP4 signaling. In parallel, EP2/EP4 signaling activates (40) antiapoptotic or survival pathways, (41) suppresses proapoptotic pathways, thus protecting the CL from structural luteolysis. PGE_2 through (42) cAMP/protein kinase A (PKA) and (43) SRC-ERK1/2 or SRC-AKT pathways may drive the (44) constitutive production of progesterone by the large luteal cells and thus protects the CL from functional luteolysis. Collectively, (45) IFNT or pregnancy-induced endometrial PGE_2 and luteal PGE_2 promote resistance of the CL against $\text{PGF}_{2\alpha}$ through multiple intracellular mechanisms and protect the CL from regression during MRP or ESP. Note: Considering the focus of this review, we are not able to include other important signaling pathways such as nitric oxide, endothelin, cytokines, and antioxidants in the large luteal cells. Given the complexity of the signaling network, we limited our model to large luteal cells for clarity and readability. Color version available online. Reproduced from Arosh et al. (2016) with permission.

pregnancy provide some new insight into how lactation could affect the normal mechanism of early embryonic development. Except for *TRD*, these genes are related to immunoglobulins and indicate a possible increase in B-lymphocyte and $\gamma\delta$ T-cell activity or an increase in the endometrial B-lymphocyte population in lactating dairy cows. None of these immunoglobulin genes were affected by pregnancy and no interaction with lactation was observed. Lactation could promote an imbalance in the immune system in the peri-implantation period, with potential negative effects on conceptus survivability. Several chemokines and cytokines are responsible for the stimulation of B-lymphocyte plasma cells to produce antibodies; however, conclusions on how lactation affects immunoglobulin production require further investigation. The gene *TRD* encodes for a cell receptor delta locus associated specifically with the $\gamma\delta$ T-cell, which is an important cell regulating the embryo-maternal relationship. The immune system is perhaps the most affected system in the endometrium when the conceptus is present. A vast number of genes with distinct immune functions (i.e., pro- and anti-inflammatory) may serve to create a uterine environment that is sufficiently protected against viral and bacterial infections but still tolerant enough to accept the implantation of the embryo. Lactation is likely to affect

this balanced immune environment in the endometrium with potential negative effects on embryo survivability.

Pregnancy increased expression of Dickkopf homolog 1 (*DKK1*) and decreased expression of the Wnt signaling pathway, indicative of an important feature of uterine regulation to accommodate the conceptus (Cerri et al., 2012). Furthermore, *DKK1* of endometrial origin may affect embryo development through its antagonism of the Wnt signaling pathway, which ultimately serves a key role in heart, head, and forelimb development during morphogenesis of the embryo. A downregulation of *DKK1* expression by lactation counters the positive effect of pregnancy on *DKK1* expression indicative of a powerful candidate gene mediating the effects of lactation on endometrium transcriptome. An important pregnancy-lactation process, involving differential effects on Wnt signaling pathway and *DKK1* expression in the endometrium, may regulate embryonic loss in lactating dairy cows. Such insight provides a platform of candidate genes for subsequent manipulation to improve fertility. In addition, the negative effect of lactation on *RELN* (i.e., involved in embryonic brain development) expression in pregnant lactating cows but not nonlactating cows reinforces the potential effect of lactational status on embryonic differentiation and development.

Cell adhesion (represented by cadherins, claudins, collagens, and L-galectins) is a function mostly down-regulated by pregnancy at d 17. This may reflect strong tissue remodeling, as well as a window of time that facilitates the flow of substrates to the uterine lumen to support the elongating embryo. Because of these activities within endometrial tissue on d 17 of gestation, genes related to carbohydrate, lipid, and AA metabolism and transport are upregulated by pregnancy. However, upregulation of pyruvate dehydrogenase kinase, isozyme 4 (*PDK4*) by lactation indicates that lactation exerts a negative effect on glucose homeostasis (see Cerri et al., 2012 for descriptive metabolism gene responses). Carbolic acid, cellular lipid, cellular amino acid and derivative, fatty acid, and glucose metabolic processes were upregulated by pregnancy (Cerri et al., 2012). These coordinated gene expression responses indicate that the uterus is in a high metabolic state to support anabolic and catabolic activities during the period of conceptus implantation. Several transcripts are responsive to pregnancy at d 17 in relation to lipid metabolism and transport: fatty acid binding protein 3 (*FABP3*), acetyl-CoA acyltransferase 1 (*ACAA1*), acetyl-CoA acetyltransferase 2 (*ACAT2*), carnitine/choline acetyltransferase family (*CPT1B*), carnitine palmitoyltransferase 1C (*CPT1C*), carnitine acetyltransferase (*CRAT*), and solute carrier family 27 (fatty acid transporter), member 2 (*SLC27A2*), which may reflect endometrium support in development of extra-embryonic membranes during elongation of the embryo.

The extensive and novel investigation of Ribeiro et al. (2016b) examined changes in the bovine transcriptome of preimplantation conceptuses at the onset of elongation on d 15 and associated changes in uterine histotroph composition and endometrial physiology. Transcriptome analyses revealed drastic changes in the transition from ovoid to tubular and from tubular to filamentous conceptuses. Differentially expressed genes were associated with cellular movement, cell-to-cell signaling, cellular assembly and organization, lipid metabolism, small molecule biochemistry, and molecular transport. Specific changes included reorganization of cytoskeleton and cell migration, arginine metabolism, growth factor signaling, and lipid metabolism. Functional analysis revealed fatty acids and peroxisome proliferator activated receptor gamma (**PPARG**), as upstream regulators of transcriptome changes. Expression of *PPARG* increased 17-fold during the onset of elongation and was highly correlated with expression of genes involved in lipid metabolism. Figure 2 depicts potential upstream regulators (i.e., fatty acid, *PPARG*, and *PTGS2*) and their target genes that were differentially expressed between ovoid and filamentous conceptuses. Expression of *PPARG* was positively and signifi-

cantly correlated with *PTGS2* ($r = 0.70$), *IFNT* ($r = 0.73$), and pregnancy-associated glycoprotein 2 (*PAG2*; $r = 0.88$). The histotroph is rich in amino acids, lipids, saccharides, and other intermediate metabolites, and important changes in composition occur in the presence of a conceptus. Pregnancy has a major impact on the concentrations of important lipids in the uterine fluid and expression of genes in the endometrium. Collectively, conceptus elongation involves remarkable changes in transcriptome, composition of the histotroph, and endometrial physiology, which help elucidate important events in uterine and conceptus biology at the onset of elongation.

PERIPARTUM AND POSTPARTUM PROGRAMMING OF REPRODUCTION

The phenotypic decline in daughter pregnancy rate (**DPR**) from the mid-1970s to a nadir in the late 1990s has been followed by an increase of DPR to a level in 2017 comparable to that of the late 1970s (https://www.uscdcb.com/eval/summary/trend.cfm?R_Menu=HO.d#StartBody). This dynamic trend of reproductive performance occurred concomitantly with a steady increase in milk production per cow. The restoration of improved reproductive performance reflects advances made in reproductive management (i.e., application of timed AI protocols, assisted technology for detection of estrus), effective use of computer technology to monitor reproductive performance on a cow and herd basis, and genetic selection (e.g., DPR). In a national survey to demonstrate excellence in reproductive performance, Ferguson and Skidmore (2013) indicated that excellent herd reproductive performance was associated with reproductive management that resulted in high insemination rates combined with average conception rate. The featured column of the Dairy Cattle Reproduction Council's 2016 award winners for reproduction excellence had herd 21-d pregnancy rates between 26 and 39%, with high levels of milk production (<http://www.dcrcouncil.org/newsletters/newsletter-2016-december/>). It has become clear that the next leaps in reproductive performance will come with improving the reproductive competence of the lactating dairy cow presented for insemination at the designated voluntary waiting period.

Postpartum Diseases Associated with Reproduction

Morrow (1968) described a coordinated herd health program to maximize profit, which included a program for reproductive health. A major issue facing dairy cows under intensive management systems is the high incidence of health problems, particularly those that

affect the reproductive tract and those of metabolic origin that affect subsequent reproductive performance. With the current use of sound reproductive programs for insemination, estimates of peripartum or postpartum incidence of diseases on subsequent fertility are documented clearly. Under large herd intensive management environments, data were compiled from 5,719

postpartum dairy cows evaluated daily for health disorders from 7 dairy farms (Santos et al., 2011). Cows were subjected to presynchronized timed AI programs. Only 55.8% were considered healthy and did not develop any disease in the first 60 d postpartum. The incidence of clinical diseases (calving-related problems, 14.6%; metritis, 16.1%; clinical endometritis, 20.8%;

Figure 2. Potential upstream regulators fatty acid, PPARG (peroxisome proliferator-activated receptor gamma), and PTGS2 (prostaglandin-endoperoxide synthase 2), and their target genes that were differentially expressed between OV (ovoid) and FIL (filamentous) conceptuses. Red denotes genes upregulated and green denotes genes downregulated in FIL. Orange and blue represent predicted increased and predicted decreased activation, respectively. Solid and dashed lines imply direct and indirect relationships, respectively. The pointed and blunted arrow-heads represent activating and inhibitory relationships, respectively. Color version available online. Reproduced from Ribeiro et al. (2016b) with permission.

fever, 21.0%; mastitis, 12.2%; ketosis, 10.4%; lameness, 6.8%; digestive problems, 2.8%; pneumonia, 2.0%) was high. Moreover, 27.0% of the cows were diagnosed with a single disease event, whereas 17.2% had at least 2 disease events in the first 2 mo of lactation. In spite of similar milk yield, cows diagnosed with health problems were less likely to be cyclic (i.e., anovulatory) at 65 d postpartum. Calving-related disorders and those that affect the reproductive tract were the major contributors for the depression in cyclicity (cyclic: healthy 84.1% vs. 70.7% > 1 disease). Diagnosis of health disorders markedly depressed the risk of cows to become pregnant at the first postpartum AI (pregnancy per TAI: healthy 51.4% vs. 34.7% > 1 disease), and increased the risk of pregnancy loss in the first 60 d of gestation (pregnancy loss %: healthy 8.9% vs. 15.8% > 1 disease). Comparable associations between clinical and subclinical postpartum diseases with reductions in reproductive performance were detected in large herd systems of extensive seasonal grazing that underwent an intensive seasonal insemination program (Ribeiro et al., 2013). Cows managed extensively are not immune from the subsequent infertility syndrome associated with peripartum or postpartum clinical and subclinical diseases. These responses indicate that reduction in morbidity by prevention of periparturient or postpartum diseases has the potential to enhance fertility of dairy cows by improving resumption of postpartum ovulation, increasing pregnancy per AI, and minimizing the risk of pregnancy loss. Epidemiological data analyses are a powerful tool to identify reproductive inefficiencies and potential causative associations but do not prove cause and effect. Conceptus development and transcriptome arrays at preimplantation stages differed between distinct genetic groups of lactating dairy cows (Ribeiro et al., 2016c). Furthermore, postpartum inflammatory diseases altered both subsequent developmental biology of the conceptus and fertility (Ribeiro et al., 2016a). Restoration of uterine or ovarian function and optimization of immune function are considered important researchable areas to sustain reproduction in lactating dairy cows.

Maternal–Conceptus Unit Programs Potential Calf Welfare and Cow Performance

The initial vulnerability of the cow immediately after calving to postpartum clinical and subclinical diseases is likely influenced by the functional dialog of the maternal–conceptus unit. The optimal unit leads to successful birth of the calf and programming of the maternal unit to support the needs of the calf and the production goals of the producer (i.e., milk production and re-establishment of a pregnancy).

Genetic and environmental differences among cows in the peripartum period are associated with various endocrine and biochemical systems regulating parturition, postpartum milk secretion, ovarian recrudescence, uterine regression, and health of the maternal unit as well as the newborn. The conceptus (i.e., fetus and placenta) and maternal dialog is central to regulation of these various processes (Thatcher et al., 1980). A series of experiments demonstrated quantitative hormonal and physiological differences (1) among cows in the peripartum/postpartum period attributable to Jersey cows selected for milk yield versus a nonselected control line (Eley et al., 1981a,b); (2) in first-calf Holstein cows bearing Holstein, Holstein × Angus, or Holstein × Brahman conceptuses (Guilbault et al., 1985a,b); and (3) in cows under a shade heat-abatement system versus a control no-shade environment (Collier et al., 1982; Lewis et al., 1984) or current systems of forced ventilation and intermittent sprinkling (Tao and Dahl, 2013). Distinct differences in free and sulfated estrogens, P4, prolactin, 13,14 dihydro-15 keto PGF_{2α}, thyroxine, and triiodothyronine, as well as physiological differences in conceptus birth weights, postpartum milk yield, and uterine regression were detected in response to these various conceptus–maternal experimental models in the peripartum and postpartum period.

Whether the mean transfer of 248 g of IgG or 7 kg of colostrum to the newborn (Morin et al., 2010) contributes to the period of postpartum immunosuppression of the mother and is related to peripartum reproductive disorders (e.g., puberal metritis, endometritis, subclinical endometritis) warrants investigation (Herr et al., 2011). Colostrum contains a plethora of growth factors defined as lactoclines (e.g., epidermal growth factor, IGF-1, IGF-2, and other unidentified factors) that target the neonate to affect differentiation of anterior pituitary mammotropes, gastrointestinal tract development, and maturation of the immune system (Chen et al., 2011). Lactocrine-acting factors, whether natural or synthetic, may affect developmental events associated with programming of female reproductive tract tissues and subsequent reproductive competence, and warrant extensive investigation in dairy cattle.

Postpartum Coordination of Reproductive Processes and Lactation

Bauman and Currie (1980) established the concept of homeorhesis (i.e., coordinated control of metabolism in body tissues necessary to support a physiological state) in which metabolism is altered drastically to support lactation. Furthermore, this metabolic change for lactation followed the homeorhetic processes of supporting the needs for growth and development of the calf in

utero. The control systems in lactation are appreciably different from the processes during pregnancy with the presence of a placenta programming both maternal and fetal function. The processes are linked with development of the mammary gland in unison with development of the calf to ensure postnatal nourishment of the calf. Transition from a nonlactating to a lactating state and sustaining a high level of milk production is a drastic challenge and occurs at the expense of reducing immune function and increasing incidence of clinical and subclinical production disorders, metabolic diseases, and temporal infertility. The coordinated biochemical and metabolic responses reflect changes in energy balance of the lactating dairy cow. Butler and Smith (1989) described the biological responses controlling energy balance during lactation and their impact on the neuroendocrine and endocrine systems that partially account for variability in recrudescence of reproductive cyclicity and fertility.

After the gradual withdrawal of progesterone due to metabolism and then its acute decline with regression of the CL, coupled with high placental secretion of estrogens and their abrupt decline with parturition, the dairy cow escapes from negative steroid feedback. Consequently, an early increase in plasma FSH concentrations occurs during d 1 to 5 postpartum (Beam and Butler, 1997). Most cows have a first follicle wave occurring within the first 14 d postpartum but only about 40% ovulate. Whether the first follicular wave is estrogenic and ovulates (ovulatory vs. nonovulatory) depends on greater LH pulse frequency, greater follicular fluid concentrations of estradiol and androstenedione, greater plasma estradiol and lower glucose concentrations, higher ME balance (Mcal/d; -12.0 vs -18.0), and decreased insulin resistance postpartum compared with nonovulatory cows (Cheong et al., 2016). Postpartum plasma concentrations of LH are low early postpartum with minimal release of LH in response to GnRH on d 3 and an attenuated response on d 10, and are not fully restored until d 20 postpartum (Fernandes et al., 1978). Collectively, these findings indicate that cows ovulating the first postpartum dominant follicle have a greater glucose utilization, supporting higher LH pulsatility and enhanced sensitivity to gonadotrophins accounting for greater steroidogenic activity. Cows that fail to ovulate may have recurring nonovulatory follicles or develop large persistent follicles that are not ovulatory. Hampton et al. (2003) demonstrated that pulsatile infusion of LH stimulated follicular growth and steroidogenesis and decreased time to first ovulation in anestrous postpartum cows.

Lucy et al. (2014) describes the vital mechanisms in place that center on the control of glucose availability and its role in increasing insulin and re-coupling the

somatotropic axis through effects on GH receptor 1A (GHR1A) to restore availability of IGF-1. The central role of glucose metabolism and the possible importance of a glucose set point at 3 d postpartum for subsequent recrudescence of both reproductive function and fertility is intriguing (Garverick et al., 2013).

A novel approach to examine ovum quality at different days postpartum within cows programmed to have distinct differences in energy balance was conducted with the use of transvaginal follicular aspiration twice weekly from 30 to 100 d postpartum (Kendrick et al., 1999). Oocytes were classified into 4 categories depending on ooplasm homogeneity and cumulus investment: 1 (good +), 2 (good), 3 (good -), and 4 (poor), and number of oocytes in each class for each aspiration was determined. Cows fed a high-energy (HE) diet had a slight increase in good quality (+) embryos per aspiration session compared with cows in the low-energy (LE) diet ($1.53 > 1.37$), but this difference was of questionable biological advantage. Cows on the HE diet had an increase of 1 good quality oocyte from 30 to 100 d postpartum (1.1 to 2.1), whereas those on the LE diet had an increase of 0.2 good quality (-) oocyte from 30 to 100 d postpartum (1.3 to 1.5). In contrast, cows on the HE diet had a much greater occurrence of poor quality embryos during the first 2 wk of aspiration and between 10 to 13 wk of lactation. The higher incidence of poor quality oocytes could be attributable to the HE diet increasing insulin secretion (Thatcher et al., 2011).

Beyond the issue of oocyte quality in lactating cows, the ability of the reproductive tract to support normal embryo development may be compromised. One of the earliest techniques of assisted reproductive technology was the successful surgical transplantation of single embryos (i.e., containing 8, 10, and 12 cells) to 3 un-bred recipients that resulted in 3 calves, normal at birth and in later development (Willett et al., 1953). Rizos et al. (2010) used an endoscopic embryo transfer technique to compare the ability of the reproductive tract of postpartum dairy cows to support development of early embryos to the blastocyst stage, compared with nulliparous heifers. Bovine embryos of 2 to 4 cells were produced by in vitro maturation and fertilization of oocytes derived from the ovaries of slaughtered cattle. On d 2 of a synchronized estrous cycle, 100 embryos were transferred endoscopically to the oviduct ipsilateral to the CL of Holstein heifers ($n = 10$) and postpartum Holstein cows ($n = 8$, approximately 60 d postpartum). On d 7, the oviduct and uterus were flushed nonsurgically to recover the embryos. The percent of recovered embryos was greater for heifers than cows (79.0 ± 7.0 vs. $57.2 \pm 11.4\%$). Of the embryos recovered, $33.9 \pm 3.6\%$ had developed to the blastocyst stage in the heifer compared with $18.3 \pm 7.9\%$ in the postpartum cow.

There was no difference in total cell number of blastocysts (71.2 ± 5.7 vs. 67.0 ± 5.3 , respectively). Rizos et al. (2010) concluded that the reproductive tract of the postpartum lactating dairy cow might be less capable of supporting early embryo development than that of the nonlactating heifer.

SCIENTIFIC FOUNDATION FOR THE NEXT CENTURY

Our deep and broad knowledge in many aspects of animal biology requires increasingly complex scientific hypotheses and experiments. With the evolution of extensive and intensive scientific tools that are now available for use across tissues, cells, and intracellular organelles, as well as the integration of groups and their management, scientific investigation has become much more interdisciplinary. This complexity requires computer programs for storage and analysis of data, and the use of biomathematical models to describe the processes. A full history of systems research and modeling in ruminant animals is available (Baldwin, 1995), and specific examples in nutrition and reproductive processes can be found here (McNamara and Shields, 2013; McNamara, 2015). The process of investigation comprises the traditional scientific method, whereby the experimenter gathers data to reveal whether a hypothesis is verified or not (i.e., hypothesis is rejected or not); with that data, a mathematical description is then built to describe the processes involved.

Using a systematic research approach, systems biology, and modeling constructs models based on verified experimental results, and in the case where the model adequately explains what we know, we can have increased confidence in our knowledge. When the model “fails” and cannot explain what we know, we have a clear focus for further experimentation. Advancements in computer technology allow for the integration of large databases within and across the areas described above. The systems biologist and biomathematician use computational and computer development to integrate large biological data sets from responses associated with genomics, transcriptomics, proteomics, metabolomics, and lipidomics to develop predictive biological response models. The multidisciplinary field of systems biology requires an understanding of both biological and mathematical concepts to predict outcomes. Results from such analyses and system simulation models are used to test and extend biological understandings and to suggest new hypotheses or experiments. Modeling with large libraries of data permits a scientist to form a hypothesis, utilize the available data and associations to test the hypothesis, and verify the new concept. Bioinformatics research involves pathway analyses that usually develop from high throughput

biology, and entail use of pathway collections and interaction networks related to structure and functionality of cells and tissues. Such analytics are powerful tools to determine the significance of “-omics” data and identify new targets or potential biomarkers within biological systems of interest. These scientific approaches further our understanding of the physiology of dairy cattle and can predict performance or, conversely, how the evolving dairy cow acquires new horizons for performance. It is exciting to see the marriage of scientific foundations and disciplines being applied in the various areas showcased in this special issue of the *Journal of Dairy Science* to celebrate its 100th year of publishing.

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APPENDIX

Table A1. Major advancements in female reproductive physiology in the past 100 years

Year	Milestone	Reference
1905	Integration of uterine and mammary gland development from embryo to senescence.	Halban, 1905
1927	Days open is not associated with rate of milk yield during first month.	Gaines, 1927
1949	Nutrition/reproduction needs include sensitive tools, adequate controls, and integration of physiologist, biochemist, and nutritionist.	Asdell, 1949a,b
1951	Plane of nutrition of heifers (birth to calving) influenced age of puberty, and calving difficulty. High level of feeding is uneconomical.	Reid et al., 1957 (1951), 1964
1953	Calves born after surgical transplantations of fertilized bovine eggs.	Willett et al., 1953
1963	Gas chromatographic estimates of cyclic progestins in blood, CL and ovaries.	Gomes et al., 1963
1965	LH is luteotrophin for the bovine CL.	Donaldson and Hansel, 1965
1968	Integration of Postpartum Herd Reproductive Management.	Morrow, 1968
1969	Luteolytic action of estradiol acts through uterus.	Brunner et al., 1969
1970	Integration of hypothalamic, pituitary control of FSH and LH with dynamics of progesterone secretion during estrous cycle.	Hansel and Snook, 1970
1972	Valid use of radioimmunoassay.	Trenkle, 1972
1976	Physiological effects and transitional progesterone, estradiol and LH responses to PGF _{2α} .	Thatcher and Chenault, 1976
1978	Restoration of LH responsiveness to GnRH during the postpartum period.	Fernandes et al., 1978
1981	Genetic (1981, 1985) and Environmental (1982, 1984, 2013) effects peripartum on endocrine and biochemical systems, milk secretion, ovarian-uterine restoration, and health of cow and calf.	Eley et al., 1981a,b; Guilbault et al., 1985a,b; Collier et al., 1982; Lewis et al., 1984; Tao and Dahl, 2013
1982	Assessment of antral follicle health and turnover based on intra-follicular concentrations of estradiol and progesterone.	Ireland and Roche, 1982

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Table A1 (Continued). Major advancements in female reproductive physiology in the past 100 years

Year	Milestone	Reference
1984	Identification of bovine Interferon Tau (IFNT) in early pregnancy (1984) and anti-luteolytic effect of recombinant IFNT (1995).	Thatcher et al., 1984a,b; Meyer et al., 1995
1984	Ultrasonography of ovary to monitor follicle and CL development.	Pierson and Ginther, 1984
1985	LH receptor and signal transduction of CL.	Garverick et al., 1985
1989	Interrelationships of energy balance (EB) on reproductive function.	Butler and Smith, 1989
1992	Evolution of first wave follicle (1992); follicular cell dynamics of LH and FSH receptor gene expression (1995).	Badinga et al., 1992; Xu et al., 1995
1992	Oxytocin localized in secretory granules of large steroidogenic luteal cells of cycle but not pregnancy.	Fields et al., 1992
1997	A first wave follicle developed following the early postpartum rise in FSH. Follicular competence was associated with higher plasma IGF-1 and shorter intervals to EB nadir.	Beam and Butler, 1997
1999	Oocyte quality following transvaginal follicular aspiration was related to EB.	Kendrick et al., 1999
2005	Multiple ovulations are associated with high milk production.	Lopez et al., 2005
2005	With activity monitors, approximately 28.5 % of cows failed to be detected in estrus likely due to anovulatory cows and insufficient plasma estradiol.	Lopez et al., 2005; Kamphuis et al., 2012
2010	Postpartum reproductive tract reduced embryo development compared to dairy heifers following transfer of 2-4 cell embryos (n=100).	Rizos et al., 2010
2012	Endometrial transcriptome analyses detected effects of pregnancy on immune, glucose and fatty acid regulatory pathways, which were antagonized by lactation.	Cerri et al., 2012
2013	Gene co-expression network analysis identified genes and biological processes shared among anterior pituitary and brain areas that affect estrous behavior.	Kommadath et al., 2013
2013	Prevalence of peri-parturient diseases alters fertility in grazing and intensely managed cows.	Ribeiro et al., 2013
2013	Targeted progesterone supplementation to anovulatory cows during follicular recruitment improves fertility.	Bisinotto et al., 2013
2013	Periparturient blood concentrations of NEFA and glucose are indicative of pregnancy at first service (2013), and glucose availability increases insulin and recoupling of GH axis (2014).	Garverick et al., 2013; Lucy et al., 2014
2013	Integrating nutritional aspects of reproductive control during lactation utilizing a systems research approach.	McNamara and Shields, 2013

Continued

Table A1 (Continued). Major advancements in female reproductive physiology in the past 100 years

Year	Milestone	Reference
2016	Distinct metabolic and endocrine differences between cows that ovulate or do not ovulate first postpartum dominant follicles.	Cheong et al., 2016
2016	Integration of molecular pathways associated with regression and maintenance of the CL (2016), and roles of progesterone and conceptus-derived factors in early pregnancy (2016).	Arosh et al., 2016; Spencer et al., 2016
2016	Recommendations for improving design, analysis, and interpretation of research on reproductive performance.	Lean et al., 2016