Milk Production and Fertility in Cattle

D.P. Berry,[1,*] N.C. Friggens,[2,3] M. Lucy,[4] and J.R. Roche[5]

[1]Animal & Grassland Research and Innovation Center, Teagasc, Moorepark, County Cork, Ireland; email: donagh.berry@teagasc.ie

[2]INRA and [3]AgroParisTech, UMR0791 Modélisation Systémique Appliqué aux Ruminants, 75231 Paris, France; email: nicolas.friggens@agroparistech.fr

[4]Division of Animal Science, University of Missouri, Columbia, Missouri 65211; email: LucyM@missouri.edu

[5]DairyNZ Ltd., Hamilton 3240, New Zealand; email: John.Roche@dairynz.co.nz

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*Corresponding author.

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Abstract

Evolutionary biology provides reasons for why the intensive selection for milk production reduces reproductive success rates. There is considerable exploitable genetic variation in reproductive performance in both dairy and beef cattle, and examination of national genetic trends demonstrates that genetic gain for both reproductive performance and milk production is possible in a well-structured breeding program. Reproductive failure is often postulated to be a consequence of the greater negative energy balance associated with the genetic selection for increased milk production. However, experimental results indicate that the majority of the decline in reproductive performance cannot be attributed to early lactation energy balance, per se; reproductive success will, therefore, not be greatly improved by nutritional interventions aimed at reducing the extent of negative energy balance. Modeling can aid in better pinpointing the key physiological components governing reproductive success and, also, the impact of individual improvements on overall fertility, helping to prioritize variables for inclusion in breeding programs.

INTRODUCTION

Compromised fertility in modern-day cattle-production systems is often considered a failure of reproductive physiology that must be fixed. However, from a broader evolutionary perspective, the antagonistic relationship between milk production and initiation of the next reproductive cycle is both logical and natural (1). The greater the number of viable offspring an animal produces in its lifetime, the fitter it is in evolutionary terms. To be successful, therefore, the animal must reproduce as intensively as possible without compromising offspring viability (i.e., number of viable young per unit time) or its own ability to survive for as long as possible (i.e., number of units of time). This hypothesis fits with the concept of trade-offs between life functions (2). In this case, the trade-off is between two aspects of reproduction: investment in the viability of the current calf versus investment in future offspring (3). Clearly, losing the offspring or neither cow nor calf surviving beyond the current reproductive effort is an unfavorable evolutionary outcome, but because both processes require resources (e.g., energy and time), there is a trade-off between them, especially when resources are limited.

Under certain conditions, however, selection need not favor one particular feature of the trade-off pairing (4). In general, if the increased resource requirements of selection are matched by a simultaneous increase in resources available, then trade-offs need not occur, but if selection surpasses the increase in resource availability, then trade-offs will likely emerge. Thus, trade-offs offer a framework for explaining why increased production impacts reproductive performance. This also suggests that, if they are to be sustainable, future breeding strategies must consider the trade-offs theory as well as the future environments in which the selected animals and their descendants will produce (5, 6). This review summarizes the physiological mechanisms underpinning the relationship between milk production and fertility in cattle, the contribution of the underlying animal genome and nutrition to this relationship, and the possible strategies that exist to increase milk production without compromising reproductive performance.

PHYSIOLOGICAL RATIONALE FOR AN ASSOCIATION BETWEEN MILK PRODUCTION AND FERTILITY

Pregnancy begins with the fertilization of an oocyte with a sperm cell. In many dairy systems, the first insemination is undertaken using artificial insemination. Although differences in male fertility of artificial insemination (AI) bulls exist (7), the use of AI programs often places considerable focus on the female and the events leading up to first ovulation, subsequent cyclicity, and the capacity for fertilization and pregnancy establishment in the female. The fact that cows are undergoing homeorhetic mechanisms to support an increase in milk production early postpartum and are typically at peak lactation during the breeding period has led to a large volume of research linking the physiological events controlling milk production with those that control the interval to first ovulation, cyclicity, and overall fertility.

The traditional view is that the postpartum interval to first ovulation is an important metric for reproduction (8). This is certainly true, because a cow cannot become pregnant before she ovulates. It is appropriate, therefore, to be concerned about noncycling cows. Noncycling cows that ovulate for the first time during the breeding period (either in response to synchronization or spontaneously) have compromised fertility (9). During the early postpartum period, the ovary is primarily dependent on luteinizing hormone (LH). LH is released from the pituitary in pulses, and the frequency of these pulses is a major determinant of ovarian function postpartum (10); greater frequency, on average, results in ovulation. Follicle-stimulating hormone (FSH), also released from the pituitary, is generally viewed as nonlimiting for early postpartum ovarian follicular growth and ovulation (11, 12). Cows that are not cycling generally have elevated FSH concentrations because the primary hormonal negative-feedback mechanism involving the dominant follicle is suppressed in noncycling cows (12).

Extended intervals to first postpartum ovulation are normal even in healthy, well-fed beef cattle because of the suckling effect (13). Approximately one-half of postpartum dairy cows will ovulate the first follicle that is growing on the ovary postpartum (14). Cows that do not ovulate are termed anovular (15). The term anovular was introduced to differentiate between a cow that has not been observed in estrus (i.e., anestrus) and a cow that has not ovulated (i.e., anovular). In some cases, an anestrus cow has ovulated (is ovular) but did not express or was not observed in estrus.

In dairy cows, a prolonged anovulatory period is not a normal event; rather, it indicates a block (perhaps metabolic) to restoration of the hypothalamic-pituitary-ovarian axis. In the past, negative energy balance (NEBAL) was considered a key risk factor of the anovulatory syndrome (16). Although the role of NEBAL is well accepted, recently the extent to which NEBAL explains the variation in interval to first ovulation has been questioned (discussed later). Hence, the extent to which the normal processes of nutrient partitioning control the interval to first ovulation in healthy, well-fed cattle may be overstated. There are situations where nutrition is clearly important. For example, in cattle with postpartum disease (e.g., acute metritis, mastitis, or pneumonia) or displaced abomasum the impact of these perturbations and the associated reduced feed intake, NEBAL, and weight loss on interval to first ovulation can be severe (17). Also, in herds with very poor nutrition (either confinement or grass-based systems), interval to first ovulation may be longer than desired (18). In general, however, the idea that interval to first ovulation is extended in high-production cows is probably incorrect. High-production cows are typically healthy and well fed. These two attributes would promote, not antagonize, the interval to first ovulation. Understanding the interactions between nutrition and reproduction in the postpartum beef cow on pasture is also challenging. When cows are undernourished, the combination of NEBAL and the suckling effect can severely delay the return to cyclicity (19).

There are central nervous system mechanisms regulating LH secretion that are affected by the nutrition and health of the cow. These involve metabolic signals acting on GnRH neurons themselves or on neurons that impinge upon GnRH neurons in the hypothalamus. There are also systemic mechanisms that involve circulating growth factors (insulin and IGF1) that affect the capacity of the ovary to respond to LH and FSH (20). Insulin responds to circulating blood glucose concentrations (21). Blood glucose is suppressed in the postpartum cow because supply fails to meet demand during lactation (22). Insulin controls hepatic IGF1 synthesis and secretion (23). Therefore, glucose, insulin, and IGF1 concentrations are correlated (21). Strong in vitro evidence indicates that insulin and IGF1 control the activity of LH and FSH receptors in the ovary (24). Additional hormones (e.g., growth hormone and leptin) and metabolites (e.g., nonesterified fatty acids and beta-hydroxy butyrate) are associated with changes in insulin and IGF1. Their concentrations are confounded with glucose, insulin, and IGF1 and also with one another (25). Thus, it is extremely difficult to perform hypothesis testing for an individual hormone or metabolite in vivo. The central and systemic mechanisms affecting the ovary are largely the same for beef and dairy cattle (26). The pulsatile release of LH is clearly the best end point to assess when attempting to understand central (hypothalamus and pituitary) effects of metabolism on the ovary. Unfortunately, measuring the pulsatile release of LH is labor intensive and expensive. This has severely reduced the volume of meaningful information on endocrine mechanisms controlling ovarian function postpartum.

The function of the ovary after first ovulation is the next important attribute in assessing the impact of milk production on fertility in cattle. Each of the two ovaries receives (LH and FSH) and returns (estradiol and inhibin) information from/to the hypothalamus and pituitary.

The mechanisms that control interval to first ovulation are closely related to those that control the normal function of the cycling ovary. In modern confinement dairy production systems, the cows' ovaries fail to communicate with one another and also fail to communicate with the hypothalamus and pituitary (27). Ovaries of cows in confinement production systems will very often contain multiple corpora lutea, luteinized unovulated follicles, and multiple dominant follicles (15). Intraovarian communication is mediated by the hypothalamus and pituitary via feedback mechanisms controlling FSH secretion. Likewise, the capacity of the preovulatory follicle to signal the hypothalamus and pituitary to trigger estrous behavior and the LH surge is compromised in the high-production cow (28). The communication failure may perhaps be explained by the long-term practice of selecting cows for milk production alone. The end result is a large and highly metabolically active cow. The reproductive system in all likelihood could have counterbalanced this selection with an ovary capable of maintaining a signal within this environment, perhaps via ovarian cells that are greater in number or more active in terms of hormone synthesis and secretion. In the absence of such "natural" selection, however, the ovarian signal was lost in the large, metabolically active cow.

The culmination of the estrous cycle is estrus that is followed by ovulation. There is good evidence to support the hypothesis that cows in modern-day confinement systems have low preovulatory estradiol concentrations (15, 28), which may explain their poor estrus expression. In the recent past, estradiol cypionate was used effectively to increase estrus expression in cows in the United States (29). The results of the estradiol cypionate research (29) indicated that the cow was capable of expressing estrus but that the ovarian signal was reduced, perhaps because of the metabolic activity of the cow. A second mitigating factor is confinement housing, which does not favor estrus expression (30). The improved estrus expression in pasture cows may perhaps be explained by a smaller cow that produces less milk and has improved ovarian estradiol signal.

Timed AI systems (31) have been widely adopted in the United States as a means to combat poor estrus expression in confinement systems. However, this practice may mask the underlying deficiencies in the reproductive biology of the cow (32) and, by extension, the effects of high milk production on reproduction. A further concern with this approach is that cows on timed AI must be coded appropriately in fertility genetic evaluations (or considered in the data editing/analysis); if they are not, genetic evaluations may be biased toward cows that respond well to timed AI.

There is good evidence that an early rise in progesterone after breeding favors a rapidly developing conceptus (33). The rapidly developing conceptus will theoretically send a strong signal to the dam and establish the maternal recognition of pregnancy (34, 35). Higher-producing cows have been reported to have greater progesterone metabolism (36), although this has not always been observed (e.g., 37). Whether or not the greater metabolism can lead to progesterone concentrations that are low enough to cause failure in embryonic development or maternal recognition of pregnancy is not known. Regardless, few would argue that progesterone is not important and is not related to milk production.

The link between embryonic loss between the fourth and eight week of gestation and milk production is open to question. Santos et al. (38) documented greater embryonic loss in US cows compared to Irish cows. Their data implied a relationship between confinement/high milk production and embryonic mortality. They also reviewed the data for possible causative factors, including body condition score (BCS) and milk production, and found little evidence that milk production affected the loss of the conceptus. Postpartum uterine disease, including acute metritis and purulent vaginal discharge, is clearly a risk factor for early embryonic loss later postpartum (38). Poor uterine health and its carryover effects may be the most important causes of embryonic loss. A commonly held theory is that high milk production and the metabolic environment supporting high milk production lead to dysfunction of the innate immune system postpartum (22). Suppressed immune cells fail to successfully combat the normal process of contamination and infection of the early postpartum uterus, predisposing the cow to embryonic loss.

GENETICS OF THE ASSOCIATION BETWEEN MILK PRODUCTION AND FERTILITY

Heritable genetic variation exists in reproductive performance in dairy and beef cows (39). Heritable genetic variation also exists in milk production measured either directly as milk weight or volume in dairy cows (40) or as maternal weaning weight (i.e., weaning weight after adjustment for direct genetic effects, thereby representing beef cow milk yield) in beef cows (41). The success of most developed dairy cow breeding programs in increasing milk production per cow is well accepted (39, 42). Genetic trends in milk yield in beef cows, based on maternal weaning weight, are less well documented; there is, however, anecdotal evidence that genetic merit for milk production in beef cattle is deteriorating in some populations. The Irish national genetic trends for maternal weaning weight in commercial beef cattle are illustrated in **Figure 1**. The deterioration in milk yield in beef cows is likely an artifact of aggressive selection for terminal traits, such as growth rate, size, and muscularity; genetic trends for a selection of size-related traits in the Irish beef herd are also presented in **Figure 1**. **Figure 1** also illustrates the deterioration in genetic merit

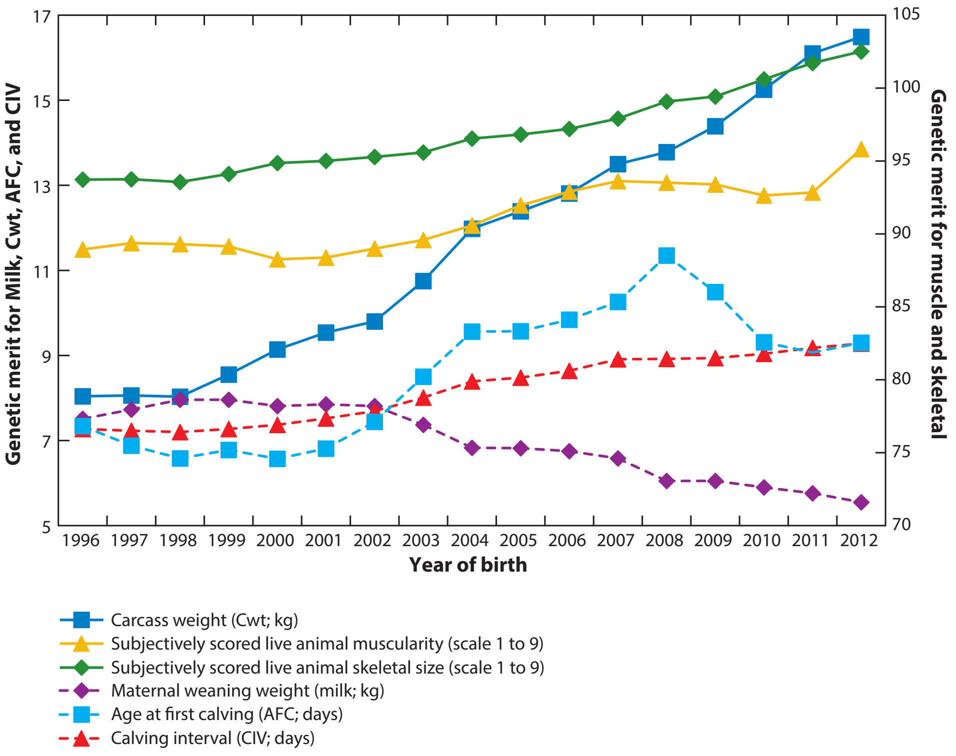

Figure 1

Genetic trends in terminal traits: carcass weight (Cwt; kg), subjectively scored live animal muscularity (scale 1 to 9), and subjectively scored live animal skeletal size (scale 1 to 9), as well as the maternal traits of maternal weaning weight (milk; kg), age at first calving (AFC; days), and calving interval (CIV; days) in commercial Irish beef cows with recorded parentage ($n = 5{,}261{,}789$).

for reproductive performance concurrent with selection for terminal traits; antagonistic genetic correlations exist between terminal traits and reproductive performance (43). Thus, beef breeding programs that aggressively select for improvements in terminal traits must take cognizance of maternal traits in accordance with the trade-off theory and resource use efficiency (2). Some breeding programs, for example, Angus in North America, are citing gains in milk yield in beef cows simultaneous with selection for improved terminal characteristics, signifying that gains in both sets of antagonistically correlated traits are indeed possible. More widely publicized is the simultaneous improvement in genetic merit for both milk production per lactation and reproductive performance in dairy cows (39); both traits are known to be antagonistically correlated (39). Inclusion of reproductive performance in the dairy cow breeding goals does not necessarily imply a reduction in genetic merit for the antagonistically correlated milk production, but instead a reduction in the rate of genetic gain in milk production owing to a reduction in selection intensity of the latter (39).

The generally accepted low heritability of reproductive performance in cattle (39) is often cited as a justification for not embarking on a breeding strategy to improve reproductive performance. Low heritability is often construed to suggest that genetic gain is not possible or, at best, will be slow; neither argument is necessarily correct. Heritability can be defined as the proportion of the phenotypic variation within a similarly managed population of animals that is due to genetic differences. The heritability of a range of reproductive traits in dairy and beef cattle is presented in **Figure 2** (39). Mean heritability of traditional reproductive traits varies from 0.02 to 0.05.

Variation associated with error contributes to phenotypic variance, the denominator of the heritability statistic. Therefore, all else being equal, inflated error variance will bias the heritability

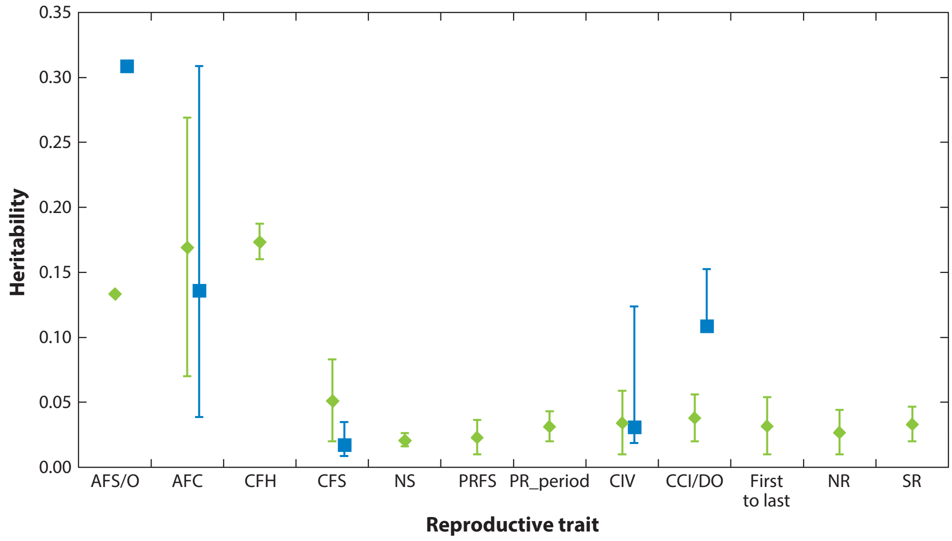

Figure 2

Mean heritability estimates as well as minimum and maximum heritability estimates per study from a meta-analysis (39) of Holstein-Friesian (*green diamonds*) and beef (*blue squares*) cattle for the fertility traits age at first service or ovulation (AFS/O), age at first calving (AFC), interval from calving to first heat (CFH), interval from calving to first service (CFS), number of services (NS), pregnant to first service (PRFS), pregnant in a given period of time relative to the start of a breeding season (PR_period), calving interval (CIV), calving to conception interval of days open (CCI/DO), interval from first to last insemination (first to last), nonreturn rate (NR), and submission rate (SR).

downward. Errors here could include, for example, parentage errors, data-recording errors (including failure to record some events for some animals), failure to detect estrus, mismanagement (e.g., inseminating animals at an inappropriate time of the estrous cycle during which, irrespective of genetic merit, the animal has negligible chance to conceive), unrecorded management decisions (e.g., unrecorded synchronization treatments of some animals), inappropriate statistical models, and random variation associated with the subjectivity of assessment of some traits (e.g., body condition score, lameness). For example, pedigree errors in dairy cattle in the United Kingdom are as high as 10% (44). Using milk progesterone data from a research herd, Royal et al. (45) concluded that 5% of inseminations were undertaken at an inappropriate point of the estrus cycle. Minimizing the effect of producer management decisions on reproductive phenotypes increases the estimated heritability; for example, the estimated heritability of commencement of luteal activity based on milk progesterone profiles is generally greater (0.13 to 0.17) than producer-recorded traits in the same populations (0.03 to 0.16) (45, 46).

Genetic Gain

It is potential genetic gain and not heritability per se that is of interest to breeders and producers. The expected rate of genetic gain in any trait may be described as (47)

$$\Delta G = \frac{i \cdot r \cdot \sigma}{L},$$

where ΔG is annual genetic gain, i is the intensity of selection, r is the accuracy of selection, σ is the genetic standard deviation, and L is the generation interval. Heritability influences only the accuracy of selection. In a well-structured breeding program (i.e., large progeny group sizes), high accuracy of selection for reproductive traits is achievable. Genomic selection (48, 49) also attempts to achieve high accuracy of selection by exploiting genomic information in genetic evaluations.

The coefficient of genetic variation for reproductive traits is similar to that for many other performance traits (**Figure 3**); heritable genetic variation also exists for binary reproductive traits (39). Thus, only selection intensity (i.e., the desire to make genetic gain) and generation interval affect genetic gain in well-structured breeding programs. Genetic gain for reproductive performance is therefore achievable in a well-structured breeding program. The past success of genetic selection for improved reproductive performance in dairy cows has been documented elsewhere (39).

Genetic Correlations

Genetic correlations are a result of either pleiotrophy or linkage. In pleiotrophy, a genomic polymorphism affects the performance of more than one animal characteristic. In linkage, polymorphisms, each affecting a single animal characteristic, tend to be coinherited. Selection affects the manifestation of genetic correlations; if (artificial or natural) selection has been for improvements in both traits (e.g., milk production to feed the newborn and reproduction success to generate the next generation), the correlation is expected to become unfavorable over time (50). This is because the pleiotropic alleles acting favorably on both characteristics will quickly become fixed under selection; these alleles will, therefore, contribute little to the variation or the covariation between the two characteristics. Alleles that affect both animal characteristics in opposing directions will remain in intermediate frequencies and, therefore, contribute more to the covariance between the traits; this also, however, implies little response to selection (50). Antagonistic pleiotropic effects cannot be resolved, but the portion of antagonistic genetic correlations owing to linkage can be resolved through animal breeding, because recombination at the genomic level during meiosis

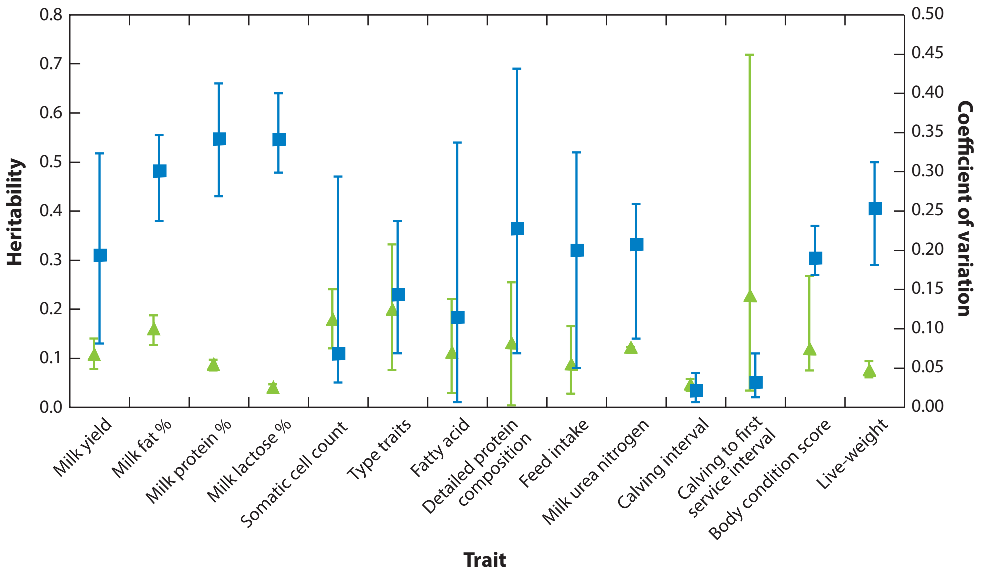

Figure 3

Mean heritability (*blue squares*) and coefficient of genetic variation (*green triangles*) as well as range in values (error bars) for milk yield, milk fat, protein and lactose composition, somatic cell count, linear type traits, milk fatty acid composition, milk protein composition, feed intake, milk urea nitrogen, calving interval, calving to first service interval, body condition score, and live-weight in dairy cows.

in gametogenesis can break the linkage disequilibrium between alleles. Antagonistic genetic correlations between traits like milk production and reproduction are, however, expected to persist because of the aforementioned trade-off hypothesis.

There is general consensus that unfavorable genetic correlations exist between milk yield and reproductive performance, at least in dairy cows (39); the associations between milk yield and reproductive performance in beef cattle are less well known. A genetic correlation of −0.50 between protein yield and calving interval (39) implies that a unit genetic standard deviation improvement in protein yield through single-trait selection is expected to result in a deterioriation of 0.5 genetic standard deviation units (i.e., longer) in calving interval. Thus, assuming a genetic standard deviation of protein yield of 11.9 kg (40) and a genetic standard deviation of calving interval of 12.9 days (51), this equates to an expected deterioration in calving interval of 5.4 days per 10-kg increase in genetic merit for protein yield. However, the genetic correlation between milk production and reproductive performance is not one, implying that the trade-off theory is not the only contributing factor to the antagonistic relationship, otherwise the correlation would be strong. Correlation of less than unity implies that simultaneous selection for improvement in both milk production and reproductive performance is possible, although genetic gain in both traits will be reduced compared with selection for either trait on its own. Berry et al. (39) reported that it is necessary to place a relative emphasis of 33% on calving interval to halt its deterioration in a breeding goal that also included milk production.

NUTRITIONAL EFFECTS ON REPRODUCTIVE PERFORMANCE

The trade-off theory revolves around a scarcity of nutrients for multiple important functions. There is, therefore, general acceptance that at least some of the poor fertility associated with milk production can be corrected through improved nutrition. Although logical, this is not simple. As per Liebig's principle of the minimum (52), any improvement in reproduction through changes in nutrition will be determined by the most limiting resource; a limiting resource may reflect either a deficiency of a nutritional factor or an oversupply that leads to an imbalance and undermines reproductive function.

On the whole, the role of nutrition in reproductive failure is probably overstated. Although early lactation NEBAL, carbohydrate type, and supply of protein, fat, vitamins, and minerals have all been implicated in reproductive function, and an imbalance in any would be expected to reduce pregnancy rate, it is the scale of the effect that is largely exaggerated.

The chain of reproduction events between when a cow calves and recalves can be split in two when considering the interaction with nutrition (53): preovulatory reproductive failure and postovulatory reproductive failure. The effects and appropriate timing of a nutritional intervention could be different for both components. The decline in reproduction associated with increased milk production is primarily manifested as a lower pregnancy rate and more days from calving to conception (days open; 54), although negative effects on the duration of postpartum anestrum have also been reported (3, 18, 55).

Negative Energy Balance

Reproductive failure is often postulated to be a result of the greater NEBAL associated with cows intensively selected for milk production (56). This hypothesis has merit, with association analyses implying relationships between measures of energy balance in early lactation and reproduction outcomes (57, 58). Care must be taken, however, not to confuse inductive reasoning from observed associations (hypothesis generation) with experimental evidence of cause and effect; the fact that something is associated with a particular reproductive outcome does not necessarily mean the outcome will be different if steps are taken to alter the associated factor. In addition, it is important to quantify the effect; the fact that something is causative does not mean it explains the majority of the reproductive failure associated with the increase in milk production.

Intensive selection for milk production has increased the mobilization of body reserves beyond that required for the sustenance of a calf (40, 59). This is a critical component of the trade-off between milk production and reproduction, with the increased prioritization of nutrients and energy for milk production being associated with a deterioration in fertility (55); the inference is that reproduction will be improved through the provision of nutrients that reduce NEBAL. This hypothesis is predicated on the beliefs that (*a*) all of the effect of cow genetics on reproductive failure is a result of increased levels of NEBAL associated with selection for increased milk production and (*b*) the provision of certain feeds or ration ingredients will reduce the extent of NEBAL.

There is logic in this line of postulation, as both in vivo and in vitro evidence indicates negative associations of BCS loss and positive associations of live weight gain on the likelihood of attaining a successful pregnancy outcome (60, 61). Early lactation energy balance is negatively associated with the duration of the postpartum anestrous interval, with shorter durations to first ovulation associated with a more positive energy balance (58, 61–63). In addition, postpartum energy balance is positively associated with pregnancy rate to first and subsequent inseminations (58, 60, 61).

The proposed hypothesis also has merit physiologically. NEBAL delays postpartum ovarian activity by impinging on the pulsatile secretion of LH, by reducing follicular responsiveness to LH and FSH, and ultimately by suppressing follicular estradiol production (64). Beam & Butler (65) reported that follicles emerging after the NEBAL nadir, rather than before, exhibited greater growth and diameter and enhanced estradiol production and were more likely to ovulate. Consistent with the effect of NEBAL on follicle development and oocyte quality, embryo competency is compromised shortly after fertilization in cows in NEBAL (38, 66, 67). There is, therefore, a plausible basis for the hypothesis that the greater NEBAL resulting from genetic selection for milk production has resulted (i.e., causation) in the lower pregnancy rates recorded in these cows. However, NEBAL in early lactation is an evolutionary adaptation to support the reproductive effort; thus, a certain level of genetically determined NEBAL is not expected to adversely affect reproduction (3).

There are, however, several factors that appear, at first sight, to be inconsistent with this hypothesis. Firstly, de Vries & Veerkamp (68) reported that only 3% to 4% of the variation in interval to first ovulation in dairy cows could be explained by total energy deficit or energy balance in early lactation. Secondly, genetic strain comparison studies in dairy cows (69, 70) indicated a 15% difference in six-week in-calf rate between North American Holstein-Friesian cows and Holstein-Friesian cows originating in New Zealand. However, the extent of the NEBAL between these strains accounted for only a 5% difference in this metric (61), indicating that two-thirds of the difference in six-week pregnancy rate in these strains was not accounted for by the difference in early lactation energy balance.

Although the effect of genetics on reproduction may not be primarily a result of energy balance differences, an argument could be made that improving energy balance within a herd (i.e., within a genotype) will improve reproduction. Consistent with this premise, both Buckley et al. (60) and Roche et al. (61) reported a favorable association between change in live-weight during the breeding period and three-week and six-week pregnancy rates. In support of these associations, three-week submission rate and the three- and six-week pregnancy rates were 6%, 8%, and 7% less, respectively, in cows subjected to a 45% feed restriction during the first two weeks of the seasonal breeding period in a large experiment (71). Although these are sizeable effects on reproduction, the scale of the reproductive failure must be viewed in the context of the size of the nutritional imposition; cows at peak lactation and at the onset of breeding in a seasonal reproductive program were subjected to a 45% reduction in dry matter intake. Energy balance was not measured in this experiment, but one would assume that such a restriction in dry matter intake would have resulted in a significant NEBAL at a crucial time, despite a significant drop in milk production. The size of this effect is consistent with the findings of Roche et al. (61), who predicted a 1% increase in six-week pregnancy rate for every 0.2 kg/day increase in live-weight gain. Contextualizing this, small changes in live-weight gain or energy balance elicited through nutrition (56, 58, 72) are unlikely to greatly affect reproduction.

An additional factor that must be considered in alleviating the NEBAL to improve reproduction is that nutrition during the period of greatest NEBAL (i.e., days in milk of 1 to 30) has only small effects on the homeorhetically directed lipolysis during this time, as cows "genetically" partition nutrients consumed toward milk production (73, 74). Consistent with this failure of nutritional strategies to greatly influence early lactation energy balance, experimental treatments in which grazing dairy cows have been either restricted (71, 75) or provided with additional feed (69, 76–79) have failed to positively affect pregnancy rates, although in some instances submission rates have been improved (70, 76).

Diet Composition

Different dietary ingredients result in different rumen fermentation patterns and, therefore, differences in postruminal products of digestion. On entering the blood, these products can have marked effects on blood ammonia, urea, and glucose concentrations, which, in turn, can affect hormone concentrations and the balance of hormone axes and, possibly, the composition of follicular and uterine fluids. The primary components of the diet that are considered most relevant for reproduction are carbohydrate composition, crude protein (CP) and the associated products of digestion/metabolism, and fat.

Carbohydrate composition. There is evidence for an anestrus-reducing effect of altering the nonstructural-to-structural carbohydrate ratio in early lactation (63, 80). Although there is a sound physiological basis for improved reproduction through the provision of nonstructural carbohydrates and increasing the concentration of both IGF1 and insulin to enhance follicular sensitivity to gonatotropins, experimental results are not consistent. It may be that there is a threshold level of these hormones, below which the provision of dietary nonstructural carbohydrates will benefit preovulatory reproductive function, but experimental designs, to date, have not identified such a tolerance level. Further research is required to better understand the effect of carbohydrate type on pre- and postovulatory reproductive function, as, if influential, there is a potential role for individualized feeding of different feed ingredients to dairy cows at different stages of lactation and/or relative to their reproduction stage.

Dietary protein. The effect of CP, soluble CP, and rumen degradable protein (RDP) in reproductive function is also not clear. For example, Garcia-Bojalil et al. (81) offered diets differing greatly in their CP content (12% and 27% of dry matter), resulting in different blood urea nitrogen (BUN) concentrations (9.8 mg/dl and 21.3 mg/dl, respectively). They reported no differences in the number or percentages of preovulatory, anovulatory, and ovulatory follicles induced during superovulation. In comparison, Jordan & Swanson (82) reported fewer days to first observed estrus (14 days postpartum) in cows receiving a high-CP (19% DM) ration, and Ordóñez et al. (83) reported a shorter postpartum anestrus interval (6 days) in cows grazing nitrogen-fertilized pastures. In direct contrast, Barton et al. (84) reported a delay of 4 days in the time to first estrus in cows receiving a diet containing 20% CP compared with one containing 13% CP, and Westwood et al. (85) noted a delayed resumption of estrus activity in cows consuming more RDP. The reason for the inconsistency in the effect of dietary CP on ovulatory function is not known, but the collated data indicate that dietary CP content in early lactation has little effect on follicle development and time to first postpartum estrus. Nutritional strategies to increase or reduce BUN are, therefore, unlikely to result in a greater submission rate.

At first glance, the effect of dietary CP on pregnancy rate is much more consistent, with the majority of studies suggesting a negative effect of excess RDP on the probability of conception (86–91). The physiological mechanisms whereby excess protein can affect reproductive function are hypothesized to be through elevated plasma urea and ammonia and the consequential exposure of the ovulating oocyte, embryo, and uterine environment to their toxic effects (85). In vitro embryo development is affected by elevated urea or ammonia when added to the culture medium. De Wit et al. (92) noted a reduced fertilization rate but not oocyte cleavage rate when urea was added to culture medium, suggesting that the primary effect of urea, in vitro at least, is associated with a lower fertilization rate. In vitro studies also confirmed a detrimental effect of ammonia on pregnancy rate, with both oocyte quality and blastocyst development compromised in a high-ammonia environment. However, most of these studies reporting a negative effect of CP on fertility have been undertaken in cows being fed a total mixed ration containing low to moderate dietary CP concentrations relative, for example, to the CP content of temperate pastures. Pregnancy rates, however, tend to be high in grazing systems (69) and do not appear to be influenced by dietary CP content or BUN concentration. Kenny et al. (93, 94) investigated the effect of dietary CP and fermentable energy supplementation on pregnancy outcomes in beef heifers. They concluded that although blood urea concentrations were 77% greater in their high-CP treatments (29.9 mg/dl versus 16.9 mg/dl), embryo survival was not affected, and in fact, embryo weight was greater in heifers receiving the high-CP diet (92). Ordóñez et al. (83) also reported no difference in embryo survival in dairy cows grazing 25% or 22% CP pastures, despite the very large differences in BUN (55 mg/dl versus 36 mg/dl).

It is unclear why there is an apparent difference in the effect of dietary protein on reproduction in grazing dairy cows compared with those fed total mixed ration. It is possible that genetic selection within a grazing system has resulted in a cow that is either more tolerant of urea and ammonia in circulation or more effective in the removal of potentially deleterious nitrogen compounds from circulation. A further factor may be in the adaptation of a cow's natural mechanisms for detoxifying ammonia, such as the ornithine cycle, due to extended exposure to such environments. Irrespective of the reason, there appears to be a clear system-level effect on the relationship between dietary crude protein and reproductive function.

Dietary fat. The rationale behind altering dietary fat to improve reproduction outcomes is twofold: to increase metabolizable energy intake (95) and maximize any positive physiological effects of fatty acids in reproductive tissues (96, 97). However, the influence of dietary fat on reproductive performance is poorly understood because much of the published data come from studies having nutritional rather than reproductive objectives (98).

Lucy et al. (98) validated the potential benefit of fat supplementation on ovarian function in early postpartum cows, reporting enhanced growth and function of the dominant ovarian follicle in cows supplemented with 2.2% DM of calcium salts of long-chain unsaturated fatty acids. Further research indicated that the positive effect of fat supplementation in early lactation was not due to improved energy balance, per se, but rather occurred through a more direct effect on follicular function (99). There is considerable evidence that dietary long-chain polyunsaturated fatty acids act as specific regulators of postovulatory reproductive processes, but the effects are inconsistent in vitro and in vivo. Dietary fatty acids can affect postovulatory reproductive function through (*a*) affecting oocyte and embryo quality and (*b*) altering the maternal physiological processes involved in luteal regression, thereby preventing the prostaglandin-induced termination of progesterone synthesis.

The effect of dietary fatty acid composition has been variable, with some reports of enhanced effects on early embryo development in response to changes in fatty acid content and ratios, whereas other reports observed no, and even negative, effects (for a complete review, see Reference 53). The reasons for the inconsistent effects of dietary fat content and fatty acid composition on oocyte and embryo quality are not known, making recommendations to improve fertility through this pathway impossible.

MODELING APPROACHES TO UNDERSTAND AND MODULATE THE RELATIONSHIP BETWEEN MILK PRODUCTION AND FERTILITY

Reproductive success depends on a chain of well-synchronized events that involve many interacting physiological entities (e.g., hypothalamus, pituitary, ovary, oocyte, follicle, uterus, and fetus). Given this, it is not surprising that examples exist of similar overall reproductive success levels being achieved through alternative combinations of the underlying reproductive functions (100). Such complexity makes it difficult to pinpoint the key physiological components governing reproductive success, but also to quantify what impact their improvement individually would have on overall fertility. Modeling can aid in generating a quantitative understanding of the functioning of a biological system as complex as the female reproductive system. A range of reproductive models exist, from herd-level economic models (101) to on-farm management tools (102) and even research models exploring the more detailed mechanisms involved in reproductive processes (103, 104).

Modeling Approaches to Facilitate Genetic Improvement of Fertility

Improved phenotyping strategies coupled with state-of-the-art breeding programs offer the opportunity to select directly on physiological mechanisms. However, given that these are intimately linked within the reproductive process, it is crucial to quantify the consequences of altering any given component on other aspects of reproductive performance. Several reproductive physiology models have facilitated the quantitative description of different aspects of reproduction, such as the hypothalomo-pituitary control of LH pulse patterns (105) or dynamics of follicule selection (106). A recent, highly promising development is the emergence of reproductive physiology models that create the link between underlying reproductive mechanisms and whole-animal reproductive performance (107, 108). Boer et al.'s (107) model represents the main components of female reproduction (i.e., the hypothalamus, pituitary, ovary, and uterus) with their associated hormone-producing capacities. The temporal patterns of reproductive hormones are simulated via differences in synthesis and clearance rates through time-dependent differential equations. The model was successfully calibrated to simulate normal hormonal dynamics through the estrous cycle for cycles with two or three follicular waves. Models of this type are of interest because they offer the possibility of identifying key mechanisms that are impacted when reproductive performance is compromised. The major environmental effecters of reproductive performance (i.e., yield, energy balance, body condition) are relatively clear, but it is much less clear precisely where in the underlying reproductive physiology these factors have their impact. If the most sensitive mechanisms could be identified, then better-targeted interventions, including genome-enabled selection, would be possible. Starting from the "normal cycling" reproductive model, Boer et al. (107) used sensitivity analyses to identify the parameters of the model that, when changed, generated abnormal profiles similar to those observed in very high-yielding cows. This revealed a key role of corpus luteum regression in the development of these abnormalities. Ongoing development of this type of model to connect with nutritional inputs will allow the effects of energy balance and body fatness to be similarly explored. Such models also could help quantify the relative importance of the different component mechanisms in genetically reduced fertility. The models should also be useful tools for predicting the consequences of selection for these different components on overall fertility.

Reproductive phenotypes in cattle are largely limited to a few simple measures, such as days open, calving interval, and conception rate. These reveal relatively little of the underlying physiology and are usually associated with a high degree of error owing to their reliance on visual observation; this is therefore a large contributor to their low heritability. In this context, a welcome development has been the advent of on-farm, real-time progesterone monitoring (e.g., **http://www.HerdNavigator.com**). Such systems that directly measure an aspect of reproductive physiology (as opposed to behavior measurements) have been shown to provide not only very reliable estrus detection (109) but also information on a range of other components of the reproductive process (110). Thus, it is now possible to phenotype sufficiently large numbers of cows for novel phenotypes, such as length of the postpartum anestrus; estrus cycle length, including luteal and follicular phases; and progesterone concentration in the different phases of the estrus cycle.

Modeling has two roles in adding value to such time-series data. The first is in the conversion of raw data into progesterone profile features, and the second is in accounting for environmental effects on the features. The conversion of progesterone profiles into physiologically usable features involves first identifying positions in the profile that represent the onset of estrus. This then allows the profile to be divided into estrous cycles, as well as identifying the end of the postpartum anestrous period. The following step is typically to characterize the estrous cycle into various types. Traditionally, both the identification of onset of estrus and the characterization of cycle types rely on a fixed set of rules; e.g., a decline in progesterone below 3 ng/ml equals onset of estrus, or luteal phases where progesterone levels are >12 ng/ml for longer than 19 days are classified as prolonged (111). Although the use of a fixed set of rules provides some standardization, it does have its limitations. Firstly, there is usually a need for visual verification and sometimes adjustment of the rules to accommodate noisy or irregular profiles, which can result in implausible estrous intervals. Secondly, classification into types of estrous cycle represents a considerable loss of information about the variability in cycle shapes. Accordingly, several statistical models now aim to capture more of the shape features and to reduce as far as possible the number of fixed assumptions needed to derive these features (112). These approaches have, for example, made it possible to define estrous cycles without using a fixed threshold, which allows for cow-to-cow variation in progesterone level at estrus (113). These approaches have also facilitated a substantially more nuanced analysis of the variation in estrus cycle shapes and the factors affecting them (112–114).

Under benign conditions, when the influence of perturbing factors is minimized, the profiles of reproductive hormones show relatively little individual variability (113, 115, 116). However, these profiles are dramatically modified by perturbing factors primarily associated with the nutritional environment, such as high milk production, excessive NEBAL, and levels of body reserves. This in turn modifies the values of fertility traits such as length of postpartum anestrus (117). The appropriate adjustment of phenotypes for the environmental component of the variation is crucial in obtaining higher heritability estimates of reproductive phenotypes. Unfortunately, because of the dynamic interplay between the reproductive hormones and the associated reproductive structures, these environmentally driven perturbing factors cause nonlinear changes that are not amenable to simple statistical adjustment (118). Thus, reproductive models that successfully describe the impact of perturbing factors on reproductive physiology, and hence on estrous cycle features, may be useful tools for providing genetic analyses with environmentally adjusted, and biologically meaningful, fertility traits.

STRATEGIES TO IMPROVE BOTH MILK PRODUCTION AND FERTILITY AND AREAS OF FUTURE RESEARCH

Supervised Genomic Predictions and Genome Editing

Genomic selection, as originally proposed by Meuwissen et al. (48), was based on a largely unsupervised statistical approach to the generation of more accurate estimates of genetic merit for individuals by directly exploiting genomic information. The promises of genome-wide association studies to detect causal mutations in cattle have to date been largely unsuccessful (119). However, access to full genome sequences on large populations of animals, coupled with more sophisticated statistical approaches that exploit data from multiple sources (e.g., genetical genomics approaches; 120), could aid in the detection of causal mutations. Such advances could therefore help resolve genetic antagonisms between traits owing to linkage. Solutions, however, will not always be straightforward. Some mutations, for example, may be advantageous for milk production in the heterozygote state but deleterious for reproductive performance in the homozygous state (121).

Once the mutations underlying phenotypic variance are known, approaches such as genome editing (122) can be used to ensure animals carry the favorable alleles. This approach can be particularly useful for altering alleles at loci in close proximity and contributing to antagonistic effects, but in tight linkage disequilibrium. However, to ensure no deleterious repercussions, the impact of both alleles on other animal characteristics must first be determined. Reducing genetic diversity across the genome may impact the ability of individuals to cope with futuristic perturbations (e.g., novel pathogen strains). Nonetheless, semen stores can be useful to regenerate lost genetic diversity, if needed.

Personalized Management Using Genetics

Personalized management based on individual genotype is receiving ever-growing attention in human medicinal and nutritional sciences (123, 124). For example, mutations in the BRCA1 and BRCA2 genes are known to confer greater risk to several cancers (125); a priori predictions of the likelihood of succumbing to a disease may invoke lifestyle changes, such as enhanced screening, prophylactic measures (e.g., surgery to remove at-risk tissue), or chemoprevention. Such approaches may also be beneficial in cattle.

Personalized management based on genotype has, in the broadest sense, been operational in cattle for decades. Animals with greater genetic merit for milk production (dairy) or growth rate (beef) were more favored in higher-production systems, whereas animals of more moderate genetic merit were favored in lower-input systems. This was successfully achieved with very limited knowledge of the underlying genome. Prediction of performance in young animals from pedigree indexes was not particularly accurate, however, because parents contribute to only half the genetic variance in progeny; the remaining half is due to Mendelian sampling, and the Mendelian sampling effect cannot be determined (for polygenic traits) without insight into the actual DNA inherited. Genomic information can, however, be used to better capture the total genetic variance; for low-heritability traits, such as exist for traditional fertility measures, the predictive ability of the eventual phenotype will still, however, be low (126). **Figure 4** illustrates the area under the curve (AUC) for a receiver operating curve (ROC) analysis for detecting a positive outcome for a binary trait of differing incidence and heritability (127). Assuming a heritability of 0.07 for cows detected as not cycling at ultrasound examination postcalving (128) and an incidence of 0.13 (128), the AUC of the ROC to detect such cows is expected to be 0.64 if all the genetic variance could be explained or 0.60 if half the genetic variance could be explained. Although the AUC provides an accuracy estimate for the population as a whole, different sensitivities and specificity thresholds can be used to more accurately detect the outcome for a specific group of animals (126). Cows that are predicted to not return to estrus rapidly postcalving can be appropriately treated, or in the case of beef cows, the suckling effect can be broken.

Personalized Management Using Phenotypes

The increasing deployment of automated technology on commercial farms will facilitate a huge increase in the precision of phenotyping that can be used not only in conjunction with genomics but also for personalized management. One example of changes in management approach that will become possible is to move from reproductive management in which the general rule is "inseminate to the first estrus you see" to a scenario of "inseminate to the best estrus." The farmer can afford to ignore a given estrus in the situation where (almost) perfect estrus detection can be achieved on-farm (using in-line progesterone or high-performance accelerometer-based systems). If the farmer has information to predict the insemination worth of any given estrus, then insemination strategy can be adjusted according to performance levels, length of postpartum anestrus, and estrus number (129). It can also be adjusted according to features of the preceding estrus cycle (110, 130). Other factors, such as prior energy balance or prior metritis, also impact on conception rates (131) and, thus, can be incorporated in predicting the insemination worth of a given estrus. There is emerging evidence that the optimum time interval (h) from onset of estrus to insemination is increased for higher-yielding cows (132). It is even conceivable that an insemination worth predictor combined with perfect estrus detection would provide a viable alternative to estrus-synchronization protocols. Clearly, there are important management opportunities associated with precision phenotyping to aid the farmer in choosing when in lactation to inseminate a cow

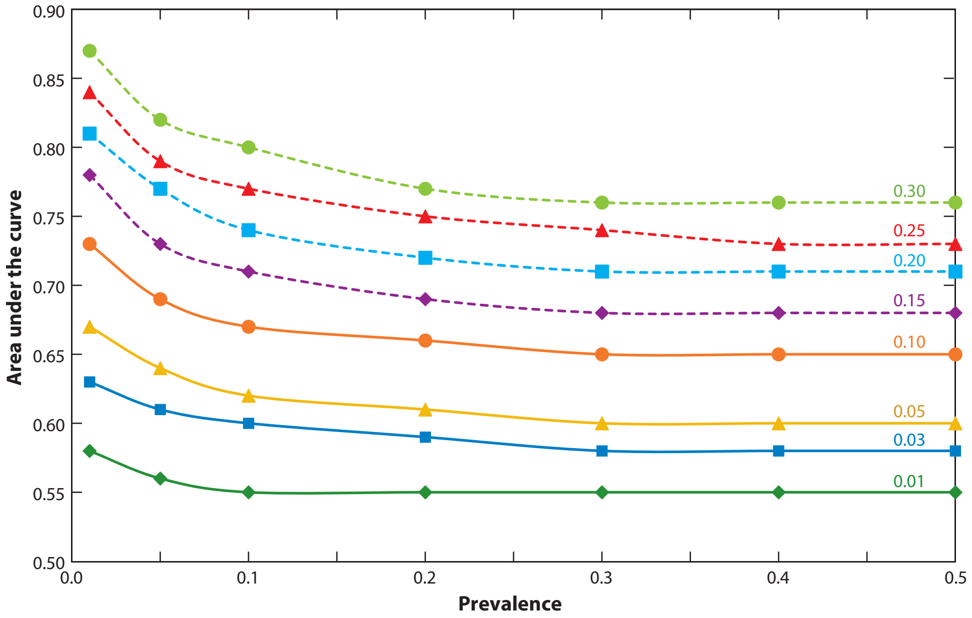

Figure 4

The area under the receiver operating curve to predict the likelihood of a positive result for binary traits across different prevalence levels for a trait with a heritability of 0.01, 0.03, 0.05, 0.10, 0.15, 0.20, 0.25, and 0.30.

according to their milk-yield potential. This not only will improve the chances of successful insemination but also is an important economic factor for the overall performance of the herd (101).

The advent of frequent measures of milk yield and live-weight (potentially at each milking) also provides the opportunity for phenotyping of reproduction in the context of production characteristics, such as rate of increase in milk production, peak milk, and persistency. Individual energy balance estimates also can be made directly from high-frequency measures of live-weight (ideally in association with BCS) without the need to measure intake (133, 134).

CONCLUSIONS

The antagonistic relationship between milk production and fertility (in dairy cattle at least) fits the evolutionary biology trade-off hypothesis. Much of this association is genetically determined, but, because the genetic correlation between both traits is not unity, simultaneous genetic improvement in both traits is possible. Advances in genomics and the associated knowledge it will generate, plus the feasibility of personalized management, imply that the concerns of the antagonistic relationship between milk production and fertility in cattle may be subdued.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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LITERATURE CITED

1. Knight CH. 2001. Lactation and gestation in dairy cows: Flexibility avoids nutritional extremes. *Proc. Nutr. Soc.* 60:527–37
2. Stearns SC. 1992. *The Evolution of Life Histories*. Oxford: Oxford Univ. Press
3. Friggens NC, Disenhaus C, Petit HV. 2010. Nutritional sub-fertility in the dairy cow: towards improved reproductive management through a better biological understanding. *Animal* 4:1197–213
4. Reznick D, Nunney L, Tessier A. 2000. Big houses, big cars, superfleas and the costs of reproduction. *Trends Ecol. Evol.* 15:421–25
5. Douhard F, Friggens NC, Amer PR, Tichit M. 2014. Synergy between selection for production and longevity and the use of extended lactation: insights from a resource allocation model in a dairy goat herd. *J. Anim. Sci.* 92:5251–66
6. Strandberg E. 2009. The role of environmental sensitivity and plasticity in breeding for robustness: lessons from evolutionary genetics. In *Breeding for Robustness*, ed. M Klopèiè, R Reents, J Philipsson, A Kuipers, 126:17–34. Wageningen, Neth.: Wagening. Acad. Publ.
7. Berry DP, Evans RD, McParland S. 2011. Evaluation of bull fertility in dairy and beef cattle using cow field data. *Theriogenology* 75:172–81
8. Petersson KJ, Berglund B, Strandberg E, Gustafsson H, Flint APF, et al. 2007. Genetic analysis of postpartum measures of luteal activity in dairy cows. *J. Dairy Sci.* 90:427–34
9. Thatcher WW, Wilcox CJ. 1973. Postpartum estrus as an indicator of reproductive status in the dairy cow. *J. Dairy Sci.* 56:608–10
10. Butler WR. 2000. Nutritional interactions with reproductive performance in dairy cattle. *Anim. Reprod. Sci.* 60–61:449–57
11. Lamming GE, Wathes DC, Peters AR. 1981. Endocrine patterns of the post-partum cow. *J. Reprod. Fertil. Suppl.* 30:155–70
12. Crowe MA, Diskin MG, Williams EJ. 2014. Parturition to resumption of ovarian cyclicity: comparative aspects of beef and dairy cows. *Animal* 8:40–53
13. Wright IA, Rhind SM, Whyte TK, Smith AJ, McMillen SR, Prado R. 1990. Circulating concentrations of LH and FSH and pituitary responsiveness to GnRH in intact and ovariectomized suckled beef cows in two levels of body condition. *Anim. Prod.* 51:93–101
14. Beam SW, Butler WR. 1998. Energy balance, metabolic hormones, and early postpartum follicular development in dairy cows fed prilled lipid. *J. Dairy Sci.* 81:121–31
15. Wiltbank MC, Sartori R, Herlihy MM, Vasconcelos JL, Nascimento AB, et al. 2011. Managing the dominant follicle in lactating dairy cows. *Theriogenology* 76:1568–82
16. Butler WR, Everett RW, Coppock CE. 1981. The relationships between energy balance, milk production and ovulation in postpartum Holstein cows. *J. Anim. Sci.* 53:742–48
17. Rukkwamsuk T, Kruip TA, Wensing T. 1999. Relationship between overfeeding and overconditioning in the dry period and the problems of high producing dairy cows during the postparturient period. *Vet. Q.* 21:71–77
18. Rhodes FM, McDougall S, Burke CR, Verkerk GA, Macmillan KL. 2003. Invited review: treatment of cows with an extended postpartum anestrous interval. *J. Dairy Sci.* 86:1876–94
19. Day ML. 2004. Hormonal induction of estrous cycles in anestrous *Bos taurus* beef cows. *Anim. Reprod. Sci.* 82–83:487–94
20. Lucy MC. 2011. Growth hormone regulation of follicular growth. *Reprod. Fertil. Dev.* 24:19–28
21. Lucy MC, Escalante RC, Keisler DH, Lamberson WR, Mathew DJ. 2013. Short communication: Glucose infusion into early postpartum cows defines an upper physiological set point for blood glucose and causes rapid and reversible changes in blood hormones and metabolites. *J. Dairy Sci.* 96:5762–68

22. Lucy MC, Butler ST, Garverick HA. 2014. Endocrine and metabolic mechanisms linking postpartum glucose with early embryonic and foetal development in dairy cows. *Animal* 8(Suppl. 1):82–90
23. Butler ST, Marr AL, Pelton SH, Radcliff RP, Lucy MC, Butler WR. 2003. Insulin restores GH responsiveness during lactation-induced negative energy balance in dairy cattle: effects on expression of IGF-I and GH receptor 1A. *J. Endocrinol.* 176:205–17
24. Dumesic DA, Richards JS. 2013. Ontogeny of the ovary in polycystic ovary syndrome. *Fertil. Steril.* 100:23–38
25. Chagas LM, Bass JJ, Blache D, Burke CR, Kay JK, et al. 2007. Invited review: new perspectives on the roles of nutrition and metabolic priorities in the subfertility of high-producing dairy cows. *J. Dairy Sci.* 90:4022–32
26. Diskin MG, Mackey DR, Roche JF, Sreenan JM. 2003. Effects of nutrition and metabolic status on circulating hormones and ovarian follicle development in cattle. *Anim. Reprod. Sci.* 78:345–70
27. Lopez H, Sartori R, Wiltbank MC. 2005. Reproductive hormones and follicular growth during development of one or multiple dominant follicles in cattle. *Biol. Reprod.* 72:788–95
28. Evans AC, Walsh SW. 2011. The physiology of multifactorial problems limiting the establishment of pregnancy in dairy cattle. *Reprod. Fertil. Dev.* 24:233–37
29. Thatcher WW, Moreira F, Pancarci SM, Bartolome JA, Santos JE. 2002. Strategies to optimize reproductive efficiency by regulation of ovarian function. *Domest. Anim. Endocrinol.* 23:243–54
30. Vailes LD, Britt JH. 1990. Influence of footing surface on mounting and other sexual behaviors of estrual Holstein cows. *J. Anim. Sci.* 68:2333–39
31. Wiltbank MC, Pursley JR. 2014. The cow as an induced ovulator: timed AI after synchronization of ovulation. *Theriogenology* 81:170–85
32. Lucy MC. 2007. Fertility in high-producing dairy cows: reasons for decline and corrective strategies for sustainable improvement. *Soc. Reprod. Fertil. Suppl.* 64:237–54
33. McNeill RE, Diskin MG, Sreenan JM, Morris DG. 2006. Associations between milk progesterone concentration on different days and with embryo survival during the early luteal phase in dairy cows. *Theriogenology* 65:1435–41
34. Bridges GA, Day ML, Geary TW, Cruppe LH. 2013. Triennial Reproduction Symposium: deficiencies in the uterine environment and failure to support embryonic development. *J. Anim. Sci.* 91:3002–13
35. Dorniak P, Bazer FW, Spencer TE. 2013. Physiology and Endocrinology Symposium: biological role of interferon tau in endometrial function and conceptus elongation. *J. Anim. Sci.* 91:1627–38
36. Wiltbank MC, Lopez H, Sartori R, Sangsritavong S, Gumen A. 2006. Changes in reproductive physiology of lactating dairy cows due to elevated steroid metabolism. *Theriogenology* 65:17–29
37. Green JC, Meyer JP, Williams AM, Newsom EM, Keisler DH, Lucy MC. 2012. Pregnancy development from day 28 to 42 of gestation in postpartum Holstein cows that were either milked (lactating) or not milked (not lactating) after calving. *Reproduction* 143:699–711
38. Santos JE, Thatcher WW, Chebel RC, Cerri RL, Galvão KN. 2004. The effect of embryonic death rates in cattle on the efficacy of estrus synchronization programs. *Anim. Reprod. Sci.* 82–83:513–35
39. Berry DP, Wall E, Pryce JE. 2014. Genetics and genomics of reproductive performances in dairy and beef cattle. *Animal* 8:105–21
40. Berry DP, Buckley F, Dillon PG, Evans RD, Rath M, Veerkamp RF. 2003. Genetic relationships among body condition score, body weight, milk yield and fertility in dairy cows. *J. Dairy Sci.* 86:2193–204
41. McHugh N, Evans RD, Amer PR, Fahey AG, Berry DP. 2011. Genetic parameters for cattle price and body weight from routinely collected data at livestock auctions and commercial farms. *J. Anim. Sci.* 89:29–39
42. Berry DP. 2008. Genetics—a tool to improve productivity and profitability. *Int. J. Dairy Technol.* 61:30–35
43. Berry DP, Evans RD. 2014. Genetics of reproductive performance in seasonal calving beef cows and its association with performance traits. *J. Anim. Sci.* 92:1412–22
44. Visscher PM, Woolliams JA, Smith D, Williams JL. 2002. Estimation of pedigree errors in the UK dairy population using microsatellite markers and the impact on selection. *J. Dairy Sci.* 85:2368–75
45. Royal MD, Flint APF, Woolliams JA. 2002. Genetic and phenotypic relationships among endocrine and traditional fertility traits and production traits in Holstein-Friesian dairy cows. *J. Dairy Sci.* 85:958–67

46. Berry DP, Bastiaansen JWM, Veerkamp RF, Wijga S, Wall E, et al. 2012. Genome-wide associations for fertility traits in Holstein-Friesian dairy cows using data from experimental research herds in four European countries. *Animal* 6:1206–15
47. Rendel J, Robertson A. 1950. Estimation of genetic gain in milk yield by selection in a closed herd of dairy cattle. *J. Genet.* 50:1–8
48. Meuwissen THE, Hayes BJ, Goddard ME. 2001. Prediction of total genetic value using genome-wide dense marker maps. *Genetics* 157:1819–29
49. Meuwissen THE, Hayes BJ, Goddard ME. 2013. Accelerating improvement of livestock with genomic selection. *Annu. Rev. Anim. Biosci.* 1:221–37
50. Falconer DS, Mackay TFC. 1996. *Introduction to Quantitative Genetics*. Harlow, UK: Pearson Educ. Ltd. 4th ed.
51. Berry DP, Kearney JF, Twomey K, Evans RD 2013. Genetics of reproductive performance in seasonal calving dairy cattle production systems. *Ir. J. Agric. Food Res.* 52:1–16
52. Liebig V. 1840. *Die Organische Chemie in Ihrer Anwen-Agrikultur und Physiologie*. Braunschweig, Ger.: Verlag von Friedrich Vieweg und Sohn. 353 pp.
53. Roche JR, Burke CR, Meier S, Walker CG. 2011. Nutrition × reproduction interaction in pasture-based systems: Is nutrition a factor in reproductive failure? *Anim. Prod. Sci.* 51:1045–66
54. Diskin MG. 2008. Reproductive management of dairy cows: a review (part I). *Ir. Vet. J.* 61:326–32
55. Lucy MC. 2001. Reproductive loss in high-producing dairy cattle: Where will it end? *J. Dairy Sci.* 84:1277–93
56. Roche JR, Berry DP, Kolver ES. 2006. Holstein-Friesian strain and feed effects on milk production, body weight, and body condition score profiles in grazing dairy cows. *J. Dairy Sci.* 89:3532–43
57. Beam SW, Butler WR. 1999. Effects of energy balance on follicular development and first ovulation in postpartum dairy cows. *J. Reprod. Fertil.* 54:411–24
58. Roche JR, Friggens NC, Kay JK, Fisher MW, Stafford KJ, Berry DP. 2009. Invited review: body condition score and its association with dairy cow productivity, health, and welfare. *J. Dairy Sci.* 92:5769–801
59. Pryce JE, Coffey MP, Brotherstone SH, Woolliams JA. 2002. Genetic relationships between calving interval and body condition score conditional on milk yield. *J. Dairy Sci.* 85:1590–95
60. Buckley F, O'Sullivan K, Mee JF, Evans RD, Dillon P. 2003. Relationships among milk yield, body condition, cow weight, and reproduction in spring-calved Holstein-Friesians. *J. Dairy Sci.* 86:2308–19
61. Roche JR, Macdonald KA, Burke CR, Lee JM, Berry DP. 2007. Associations among body condition score, body weight, and reproductive performance in seasonal-calving dairy cattle. *J. Dairy Sci.* 90:376–91
62. Patton J, Kenny DA, McNamara S, Mee JF, O'Mara FP, et al. 2007. Relationships among milk production, energy balance, plasma analytes, and reproduction in Holstein-Friesian cows. *J. Dairy Sci.* 90:649–58
63. Garnsworthy PC, Lock A, Mann GE, Sinclair KD, Webb R. 2008. Nutrition, metabolism, and fertility in dairy cows: 1. Dietary energy source and ovarian function. *J. Dairy Sci.* 91:3814–23
64. Diskin MG, Mackey DR, Roche JF, Sreenan JM. 2003. Effects of nutrition and metabolic status on circulating hormones and ovarian follicle development in cattle. *Anim. Reprod. Sci.* 78:345–70
65. Beam SW, Butler WR. 1997. Energy balance and ovarian follicle development prior to the first ovulation postpartum in dairy cows receiving three levels of dietary fat. *Biol. Reprod.* 56:133–42
66. Sartori R, Sartor-Bergfelt R, Mertens SA, Guenther JN, Parrish JJ, Wiltbank MC. 2002. Fertilization and early embryonic development in heifers and lactating cows in summer and lactating and dry cows in winter. *J. Dairy Sci.* 85:2803–12
67. Leroy J, Opsomer G, De Vliegher S, Vanholder T, Goossens L, et al. 2005. Comparison of embryo quality in high-yielding dairy cows, in dairy heifers and in beef cows. *Theriogenology* 64:2022–36
68. de Vries MJ, Veerkamp RF. 2000. Energy balance of dairy cattle in relation to milk production variables and fertility. *J. Dairy Sci.* 83:62–69
69. Horan B, Mee JF, Rath M, O'Connor P, Dillon P. 2004. The effect of strain of Holstein-Friesian cow and feeding system on reproductive performance in seasonal-calving milk production systems. *Anim. Sci.* 79:453–67

70. Macdonald KA, Verkerk GA, Thorrold BS, Pryce JE, Penno JW, et al. 2008. A comparison of three strains of Holstein-Friesian grazed on pasture and managed under different feed allowances. *J. Dairy Sci.* 91:1693–707
71. Burke CR, Williams YJ, Hofmann L, Kay JK, Phyn CV, Meier S. 2010. Effects of an acute feed restriction at the onset of the seasonal breeding period on reproductive performance and milk production in pasture-grazed dairy cows. *J. Dairy Sci.* 93:1116–25
72. McCarthy S, Berry DP, Dillon P, Rath M, Horan B. 2007. Influence of Holstein-Friesian strain and feed system on body weight and body condition score lactation profiles. *J. Dairy Sci.* 90:1859–69
73. McNamara JP, Hillers JK. 1986. Regulation of bovine adipose tissue metabolism during lactation. 1. Lipid synthesis in response to increased milk production and decreased energy intake. *J. Dairy Sci.* 69:3032–41
74. McNamara JP, Hillers JK. 1986. Regulation of bovine adipose tissue metabolism during lactation. 2. Lipolysis response to milk production and energy intake. *J. Dairy Sci.* 69:3042–50
75. Burke CR, Roche JR. 2007. Effects of pasture feeding during the periparturient period on postpartum anovulation in grazed dairy cows. *J. Dairy Sci.* 90:4304–12
76. Fulkerson WJ, Wilkins J, Dobos RC, Hough GM, Goddard ME, Davison T. 2001. Reproductive performance in Holstein-Friesian cows in relation to genetic merit and level of feeding when grazing pasture. *Anim. Sci.* 73:397–406
77. Kennedy J, Dillon P, Delaby L, Faverdin P, Stakelum G, Rath M. 2003. Effect of genetic merit and concentrate supplementation on grass intake and milk production with Holstein Friesian dairy cows. *J. Dairy Sci.* 86:610–21
78. Kolver ES, Burke CR, Roche JR. 2005. Genotype and feed effects on annual milk production and reproduction of grazing dairy cows. *J. Dairy Sci.* 88:93–94
79. Pedernera M, Garcia SC, Horagadoga A, Barchia I, Fulkerson WJ. 2008. Energy balance and reproduction on dairy cows fed to achieve low or high milk production on a pasture-based system. *J. Dairy Sci.* 91:3896–907
80. Gong JG, Lee WJ, Garnsworthy PC, Webb R. 2002. Effect of dietary-induced increases in circulating insulin concentrations during the early postpartum period on reproductive function in dairy cows. *Reproduction* 123:419–27
81. Garcia-Bojalil CM, Staples CR, Thatcher WW, Drost M. 1994. Protein-intake and development of ovarian follicles and embryos of superovulated nonlactating dairy-cows. *J. Dairy Sci.* 77:2537–48
82. Jordan ER, Swanson LV. 1979. Serum progesterone and luteinizing-hormone in dairy-cattle fed varying levels of crude protein. *J. Anim. Sci.* 48:1154–58
83. Ordóñez A, Parkinson TJ, Matthew C, Holmes CW, Miller RD, et al. 2007. Effects of application in spring of urea fertiliser on aspects of reproductive performance of pasture-fed dairy cows. *N.Z. Vet. J.* 55:69–76
84. Barton BA, Rosario HA, Anderson GW, Grindle BP, Carroll DJ. 1996. Effects of dietary crude protein, breed, parity, and health status on the fertility of dairy cows. *J. Dairy Sci.* 79:2225–36
85. Westwood CT, Lean IJ, Kellaway RC. 1998. Indications and implications for testing of milk urea in dairy cattle: a quantitative review. Part 2. Effect of dietary protein on reproductive performance. *N.Z. Vet. J.* 46:123–30
86. Ferguson JD, Blanchard T, Galligan DT, Hoshall DC, Chalupa W. 1988. Infertility in dairy-cattle fed a high percentage of protein degradable in the rumen. *J. Am. Vet. Med. Assoc.* 192:659–62
87. Ferguson JD, Chalupa W. 1989. Impact of protein nutrition on reproduction in dairy-cows. *J. Dairy Sci.* 72:746–66
88. Ferguson JD, Galligan DT, Blanchard T, Reeves M. 1993. Serum urea nitrogen and conception rate—the usefulness of test information. *J. Dairy Sci.* 76:3742–46
89. Westwood CT, Lean IJ, Garvin JK, Wynn PC. 2000. Effects of genetic merit and varying dietary protein degradability on lactating dairy cows. *J. Dairy Sci.* 83:2926–40
90. Arunvipas P, Leger ER, VanLeeuwen JE, Dohoo IR, Keefe GP. 2003. The effect of nutrition and management factors and milk urea nitrogen levels on reproductive performance in Canadian dairy herds. *Proc. 10th Symp. Int. Soc. Vet. Epidemiol. Econ., Vina del Mar, Chile, Nov.*, pp. 258–61

91. Rajala-Schutz PJ, Saville WJA, Frazer GS, Wittum TE. 2001. Association between milk urea nitrogen and fertility in Ohio dairy cows. *J. Dairy Sci.* 84:482–89
92. De Wit AA, Cesar ML, Kruip TA. 2001. Effect of urea during in vitro maturation on nuclear maturation and embryo development of bovine cumulus-oocyte-complexes. *J. Dairy Sci.* 84:1800–4
93. Kenny DA, Boland MP, Diskin MG, Sreenan JM. 2001. Effect of pasture crude protein and fermentable energy supplementation on blood metabolite and progesterone concentrations and on embryo survival in heifers. *Anim. Sci.* 73:501–11
94. Kenny DA, Boland MP, Diskin MG, Sreenan JM. 2002. Effect of rumen degradable protein with or without fermentable carbohydrate supplementation on blood metabolites and embryo survival in cattle. *Anim. Sci.* 74:529–37
95. Lucy MC, Savio JD, Badinga L, Delasota RL, Thatcher WW. 1992. Factors that affect ovarian follicular dynamics in cattle. *J. Anim. Sci.* 70:3615–26
96. Mattos R, Staples CR, Thatcher WW. 2000. Effects of dietary fatty acids on reproduction in ruminants. *Rev. Reprod.* 5:38–45
97. Wathes DC, Abayasekara DRE, Aitken RJ. 2007. Polyunsaturated fatty acids in male and female reproduction. *Biol. Reprod.* 77:190–201
98. Lucy MC, Staples CR, Michel FM, Thatcher WW, Bolt DJ. 1991. Effect of feeding calcium soaps to early postpartum dairy cows on plasma prostaglandin $F_{2\alpha}$, luteinizing hormone, and follicular growth. *J. Dairy Sci.* 74:483–89
99. Lucy MC, Delasota RL, Staples CR, Thatcher WW. 1993. Ovarian follicular populations in lactating dairy cows treated with recombinant bovine somatotropin (sometribove) or saline and fed diets differing in fat-content and energy. *J. Dairy Sci.* 76:1014–27
100. Cutullic E, Delaby L, Michel G, Disenhaus C. 2009. Consequence on reproduction of two feeding levels with opposite effects on milk yield and body condition loss in Holstein and Normande cows. *J. Dairy Sci.* 92(E-suppl. 1):355
101. Giordano JO, Fricke PM, Wiltbank MC, Cabrera VE. 2011. An economic decision-making support system for selection of reproductive management programs on dairy farms. *J. Dairy Sci.* 94:6216–32
102. McDougall S, Heuer C, Morton J, Brownlie T. 2014. Use of herd management programmes to improve the reproductive performance of dairy cattle. *Animal* 8:199–210
103. Blanc F, Martin GB, Bocquier F. 2001. Modelling reproduction in farm animals: a review. *Reprod. Fertil. Dev.* 13:337–53
104. Vetharaniam I, Peterson AJ, McNatty KP, Soboleva TK. 2011. Modelling female reproductive function in farmed animals. *Anim. Reprod. Sci.* 122:164–73
105. Zeeman ML, Weckesser W, Gokhman D. 2003. Resonance in the menstrual cycle: a new model of the LH surge. *Reprod. Biomed. Online* 7:295–300
106. Echenim N, Monniaux D, Sorine M, Clement F. 2005. Multi-scale modeling of the follicle selection process in the ovary. *Math. Biosci.* 198:57–79
107. Boer HMT, Apri M, Molenaar J, Stötzel C, Veerkamp RF, Woelders H. 2012. Candidate mechanisms underlying atypical progesterone profiles as deduced from parameter perturbations in a mathematical model of the bovine estrous cycle. *J. Dairy Sci.* 95:3837–51
108. Stötzel C, Plöntzke J, Heuwieser W, Röblitz S. 2012. Advances in modelling the bovine oestrus cycle: synchronization with PGF2α. *Theriogenology* 78:1415–28
109. Friggens NC, Bjerring M, Ridder C, Højsgaard S, Larsen T. 2008. Improved detection of reproductive status in dairy cows using milk progesterone profiles. *Reprod. Domest. Anim.* 43:113–21
110. Friggens NC, Chagunda MGG. 2005. Prediction of the reproductive status of cattle on the basis of milk progesterone measures: model description. *Theriogenology* 64:155–90
111. Lamming GE, Darwash AO. 1998. The use of milk progesterone profiles to characterise components of subfertility in milked dairy cows. *Anim. Reprod. Sci.* 52:175–90
112. Meier S, Roche JR, Kolver ES, Boston RC. 2009. A compartmental model describing changes in progesterone concentrations during the oestrous cycle. *J. Dairy Res.* 76:249–56
113. Gorzecka J, Codrea MC, Friggens NC, Callesen H. 2011. Progesterone profiles around the time of insemination do not show clear differences between pregnant and not pregnant cows. *Anim. Reprod. Sci.* 123:14–22

114. O'Connell J, Tøgersen FA, Friggens NC, Løvendahl P, Højsgaard S. 2011. Combining cattle activity and progesterone measurements using hidden semi-Markov models. *J. Agric. Biol. Environ. Stat.* 16:1–16
115. Gorzecka J, Callesen H, Pedersen KM, Friggens NC. 2011. The relationship between postpartum vaginal discharge symptoms and progesterone profile characteristics in lactating dairy cows in Denmark. *Theriogenology* 75:1016–28
116. Martin O, Friggens NC, Dupont J, Salvetti P, Freret S, et al. 2013. Data-derived reference profiles with corepresentation of progesterone, estradiol, LH, and FSH dynamics during the bovine oestrus cycle. *Theriogenology* 79:331–43
117. Royal MD, Darwash AO, Flint APF, Webb R, Woolliams JA, Lamming GE. 2000. Declining fertility in dairy cattle: changes in traditional and endocrine parameters of fertility. *Anim. Sci.* 70:487–501
118. Blanc F, Agabriel J. 2008. Modelling the reproductive efficiency in a beef cow herd: effect of calving date, bull exposure and body condition at calving on the calving-conception interval and calving distribution. *J. Agric. Sci.* 146:143–61
119. Visscher PM, Brown MA, McCarthy MI, Yang J. 2012. Five years of GWAS discovery. *Am. J. Hum. Genet.* 13:7–24
120. Jansen RC, Nap JP. 2001. Genetical genomics: the added value from segregation. *Trends Genet*. 17:388–91
121. Kadri NK, Sahana G, Charlier C, Iso-Touru T, Guldbrandtsen B, et al. 2014. A 660-Kb deletion with antagonistic effects on fertility and milk production segregates at high frequency in Nordic red cattle: additional evidence for the common occurrence of balancing selection in livestock. *PLOS Genet*. 10:e1004049
122. Joung JK, Sander JD. 2013. TALENs: a widely applicable technology for targeted genome editing. *Nat. Rev. Mol. Cell Biol.* 14:49–55
123. Hamburg MA, Collins FS. 2010. The path to personalized medicine. *N. Engl. J. Med.* 363:301–4
124. Philips CM. 2013. Nutrigenetics and metabolic disease: current status and implications for personalised nutrition. *Nutrients* 5:32–57
125. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, et al. 2003. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am. J. Hum. Genet.* 72:1117–30
126. Hempstalk K, McParland S, Berry DP. 2015. Machine learning algorithms for the prediction of conception success to a given insemination in lactating dairy cows. *J. Dairy Sci.* 98:5262–73
127. Wray NR, Yang J, Goddard ME, Visscher PM. 2010. The genetic interpretation of area under the ROC curve in genomic profiling. *PLOS Genet.* 6:e1000864
128. Carthy TR, Ryan DP, Fitzgerald AM, Evans RD, Berry DP. 2015. Genetic parameters of ovarian and uterine reproductive traits in dairy cows. *J. Dairy Sci.* 98:4095–106
129. Friggens NC, Labouriau R. 2010. Probability of pregnancy as affected by oestrus number and days to first oestrus in dairy cows of three different breeds and parities. *Anim. Reprod. Sci*. 118:155–62
130. Friggens NC, Løvendahl P. 2008. The potential of on-farm fertility profiles: in-line progesterone and activity measurements. In *Fertility in Dairy Cows: Bridging the Gaps*, ed. MD Royal, NC Friggens, RF Smith, pp. 72–78. Cambridge, UK: Cambridge Univ. Press
131. Cutullic E, Delaby L, Gallard Y, Disenhaus C. 2012. Towards a better understanding of the respective effects of milk yield and body reserve dynamics on reproduction in Holstein dairy cows. *Animal* 6:476–87
132. Aungier SFM, Roche JF, Duffy P, Scully S, Crowe MA. 2015. The relationship between activity clusters detected by an automatic monitor and endocrine changes during the periestrous period in lactating dairy cows. *J. Dairy Sci.* 98:1666–84
133. Thorup VM, Edwards D, Friggens NC. 2012. On-farm estimation of energy balance in dairy cows using only frequent body weight measurements and body condition score. *J. Dairy Sci.* 95:1784–93
134. Thorup VM, Højsgaard S, Weisberg MR, Friggens NC. 2013. Energy balance of individual cows can be estimated in real-time on-farm using frequent liveweight measures even in the absence of body condition score. *Animal* 7:1631–39