ABSTRACT: The objective was to review the effects of production stressors on reproductive performance of dairy cows. It has been well documented that genetic selection for milk yield over the last 50 yr has been associated with reduced fertility. In addition to negative associations between yield and conception rate, there is also an association between milk production and expression of behavioral estrus. Stress caused by production diseases in high-yielding dairy cows also contributes to the problems of poor fertility. Lameness results in reduced intensity of estrus and can contribute to ovulation failure, which is largely due to reduced pre-ovulatory estradiol secretion and failure of the LH surge. Mastitis has been associated with prolonged intervals to dominant follicle selection, and in animals with uterine infection the dominant follicle grows slower and produces less estradiol. In a recent study, we identified that milk yield was associated with an increased incidence of uterine infection, which is known to contribute to reduced fertility and prolonged calving-to-conception intervals. The incidence of uterine disease was 73% in high-yielding, compared with 45% in low-yielding cows. As well as effects at the ovary, various models of stress have also been shown to perturb endocrine secretion in the hypothalamus and anterior pituitary. In conclusion, the adverse effects on fertility associated with genetic selection for yield in dairy cows is, in part, associated with increased incidences of production disease-induced stress but is also associated with high milk yield.

Keywords: dairy cow, estrus, fertility, lameness, production disease, uterine infection

INTRODUCTION

Fertility in dairy cows has decreased over the time period from the 1960s to the present day. This had been associated with a period of intense selection for cows having increased production of milk (Figure 1; Butler, 1998). The causes of this decline in fertility are multifactorial but revolve around the issue of supplying sufficient resources for milk production at the expense of other physiological processes including reproduction (Walsh et al., 2011). Conception rates to a single service for postpartum dairy cows have decreased from about 65 to 38% over the last 40 yr (Figure 1; Butler, 1998). There is clear evidence that increased milk production is related to reduced fertility, which in part may be mediated by production effects on uterine health.

In addition to the documented effects of increased milk yield on pregnancy rates, there is evidence of reductions in the expression and duration of estrous behavior associated with increased milk yield (recently reviewed by Dobson et al., 2008). Based on a compilation of numerous publications since 1959 to the present day, the evidence indicates that the percentage of cows standing to be mounted and the duration of standing to be mounted have both declined as milk yield has increased (Figure 2; Dobson et al., 2008). Based on milk progesterone (albeit in a small number of studies), there is evidence of an increase in the incidence of abnormal cycles in cows after resumption of cyclicity in the postpartum period; specifically there has been an increase in the proportion of cows displaying atypical estrous cycles (based on progesterone profiles; Figure 3; Dobson et al., 2008).

Health status is also related to fertility, with many production diseases having clear negative effects on the reproductive system in dairy cows. Some of the problems of production and health status may be mediated by adverse effects on the stress and immune axes.
This review sets out to describe some of the production effects on uterine health and fertility, and health effects on fertility.

**PRODUCTION EFFECTS ON UTERINE HEALTH**

Postpartum uterine infection is a major contributor to reduced fertility in dairy cattle. After parturition the uterus becomes contaminated with bacteria, and although many animals can clear this contamination, infection persists in up to 20% of animals as endometritis (Sheldon et al., 2009). Notably, the establishment of uterine infection occurs around the same time as peak milk yield, and there is evidence to suggest that negative energy balance during the early postpartum period may be associated with an increased incidence of uterine disease (Hammon et al., 2006). In a recent study of 61 postpartum dairy cows, the relationship between milk production and uterine health was investigated. At wk 5 postpartum, around the time of the energy nadir, animals producing less than the median value of 35 kg milk/d (“low yielding”) had significantly less energy requirements and intake than animals producing more than 35 kg of milk/d (“high yielding”; Table 1). In addition, a greater proportion of energy requirements were met by intake in low-yielding animals, and these animals had reduced energy deficits compared with high-yielding animals. Interestingly, BCS were not different between the 2 groups.

Uterine health was assessed by vaginal mucus scores (Williams et al., 2005) and diagnosed based on the clinical definitions of uterine disease described by Sheldon et al. (2006). Of the animals in the high-yielding group, 73.3% suffered from uterine infection (metritis and endometritis), whereas only 45.2% of the low-yielding group suffered uterine disease (Figure 4).

The reason for increased incidence of uterine disease in animals producing more milk is unknown. However, the increased energy deficit in high-yielding animals may contribute to an increase in uterine disease because increased negative energy balance has been suggested to

### Table 1. Week 5 postpartum energy, intake, and BCS (scale 1 to 5) for dairy cows (n = 61) producing more or less than the median herd value of 35 kg of milk/d

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-yielding cows (&lt;35 kg of milk/d)</th>
<th>High-yielding cows (&gt;35 kg of milk/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy requirement, MJ</td>
<td>216 ± 6.0</td>
<td>298 ± 6.0*</td>
</tr>
<tr>
<td>Milk energy requirement, MJ</td>
<td>91 ± 3.0</td>
<td>134 ± 3.0*</td>
</tr>
<tr>
<td>Maintenance and milk energy requirement, MJ</td>
<td>215 ± 6.0</td>
<td>297 ± 6.0*</td>
</tr>
<tr>
<td>DMI, kg</td>
<td>15 ± 0.5</td>
<td>19 ± 0.4*</td>
</tr>
<tr>
<td>ME intake, MJ</td>
<td>194 ± 7.0</td>
<td>234 ± 5.0*</td>
</tr>
<tr>
<td>Proportion of energy requirements met by ME intake</td>
<td>0.8 ± 0.03</td>
<td>0.7 ± 0.02*</td>
</tr>
<tr>
<td>Average daily energy balance, MJ</td>
<td>−22 ± 7.0</td>
<td>−64 ± 6.0*</td>
</tr>
<tr>
<td>Cumulative energy balance, MJ</td>
<td>−354 ± 99.0</td>
<td>−885 ± 92.0*</td>
</tr>
<tr>
<td>BCS,</td>
<td>2.5 ± 0.1</td>
<td>2.5 ± 0.1</td>
</tr>
</tbody>
</table>

*Differs from low-yielding cows, P < 0.05.
influence uterine health. Indeed, cows with severe negative energy balance have been found to have impaired neutrophil function (Hammon et al., 2006) as well as increased expression of inflammatory response genes in the endometrium 2 wk after calving (Wathes et al., 2009). These observations suggest that negative energy balance results in impaired immune function, which may affect the ability of dairy cows to clear bacterial contamination from the uterus.

It is likely that the physiological resources required for high milk production and the resultant energy deficit common in high-yielding cows result in impaired uterine function, leading to a greater incidence of uterine infection and, as a consequence, reduced fertility.

HEALTH EFFECTS ON FERTILITY

Cows suffering from health and disease problems are prime candidates for reduced fertility (Dobson et al., 2008; Figure 5). Clearly, cows with a range of problems including cesarean parturition, lameness (Collick et al., 1989; Melendez et al., 2003; Hernandez et al., 2005), endometritis (Borsberry and Dobson, 1989), retained fetal membranes (Borsberry and Dobson, 1989), dys-tocia, mastitis (Borsberry and Dobson, 1989; Schrick et al., 2001), milk fever (Parker, 1992), and poor BCS (López-Gatius et al., 2003; Garnsworthy, 2006) have extended intervals from calving to subsequent pregnancy establishment or may fail to become pregnant. In many cases, these problems become compounded with one of these conditions increasing the risk of another condition also occurring. In many of these health problems, there are clear risk factors associated with cow management and nutrition (Mulligan et al., 2006). Specifically, lameness decreases the intensity of estrous behavior (Walker et al., 2008). This was mediated through interruption of the LH surge, decreased LH pulse frequency, decreased estradiol concentrations during the follicular phase, and failure of ovulation (Dobson et al., 2008; Morris et al., 2011). Mastitis also has a negative effect on reproductive function. Up to 30% of cows with clinical mastitis infection fail to ovulate while infected (Dobson et al., 2008; Wolfenson et al., 2008). These data provide evidence that the consequences of disease include suppression of reproductive performance.

One of the major health issues in postpartum cows is uterine infection (i.e., metritis and endometritis). There is evidence that uterine infections of various forms contribute to reduced fertility. As well as direct effects on the uterus, bacteria, bacterial products, or immune mediators produced in response to bacterial infection also suppress pituitary LH secretion and are associated with inhibition of folliculogenesis, decreased ovarian steroidogenesis, and abnormal luteal phases (Peter et al., 1989; Huszenicza et al., 1999, Opsomer et al., 2000; Mateus et al., 2002, 2003; Sheldon et al., 2002; Williams et al., 2007). In dairy cows, infections are associated with changes in luteal phase length and greater incidence of cystic ovarian disease (Peter et al., 1989; Opsomer et al., 2000), and the first postpartum ovarian follicle is smaller and produces less estradiol in animals with greater numbers of bacteria in the postpartum uterus (Sheldon et al., 2002). In a study of 82 clinically normal postpartum cattle with no risk factors for uterine disease, 75% of the animals had increased numbers of uterine pathogens on d 7 postpartum, the predominant isolate being *Escherichia coli*. These animals also had retarded ovarian follicle growth; the first postpartum dominant follicle grew slower and produced less estradiol (Figure 6; Williams et al., 2007, 2008a). Furthermore, in the animals that ovulated, the corpus luteum (CL) was smaller and produced less progesterone (Figure 7; Williams et al., 2007). Within the uterus, *E. coli* may disrupt the mechanisms of PG-induced luteolysis in cyclic cows and therefore contribute to prolonged luteal phases by...
switching PG synthesis away from PGF$_{2\alpha}$ toward PGE$_2$ (Williams et al., 2008b; Herath et al., 2009).

These observations show a direct correlation between the presence of uterine pathogens, particularly E. coli, on d 7 postpartum and suboptimal ovarian function for the following 3 wk. It is well known that a large estrogenic follicle is required to produce good expression of estrous behavior and a healthy oocyte, and that after ovulation a healthy CL producing greater concentrations of progesterone is required for embryo survival. However, the evidence shows that early postpartum uterine disease contributes to infertility in cows by disrupting ovarian function and that these effects are residual. The specific mechanisms by which uterine infection disrupts ovarian function are many and varied and are beyond the scope of the present review. However, it likely involves the tumor necrosis factor (TNF) α and IGF-I systems where it has been shown that TNFα suppressed ovarian steroid production and that IGF-I can interact to attenuate the negative effects of TNFα (Benyo and Pate, 1992; Spicer, 1998; Sakumoto et al., 2003).

**STRESS EFFECTS AND MODELS OF STRESS**

The stress axis (i.e., hypothalamic-pituitary-adrenal axis) shares endocrine glands with the reproductive axis (i.e., hypothalamic-pituitary-gonadal axis). It is often postulated that effects at the hypothalamic-pituitary level associated by 1 axis may influence the other. It makes sense biologically that if an animal is under stress it may not be in the best interests of the animal to reproduce at that time. Some of the effects of disease on ovarian function mentioned above may in part be associated with the disease stressor influencing secretion of gonadotropin hormones by the anterior pituitary gland. In a series of studies carried out by Dobson and coworkers (described...
below) at the University of Liverpool, several targets in the stress axis were manipulated and then the responses on the reproductive axis were measured.

Administration of cortisol (betamethasone 15 mg twice/d) on d 10 to 20 of the estrous cycle in dairy cows prolonged the associated luteal phases by 7 to 20 d (thereby inhibiting luteolysis) and was also associated with a reduced ability of the anterior pituitary gland to secrete LH in response to a GnRH challenge (20 μg of gonadorelin; 7 ± 1.0 vs. 16 ± 3.0 ng/mL; Dobson et al., 1987). Administration of dexamethasone (44 μg/kg of BW) to dairy cows during the growth of the first follicle wave of a cycle did not disrupt growth of the dominant follicle, but reduced IGF-I and IGF-II, and increased insulin and glucose, decreased progesterone from the developing CL, suggesting that cortisol or indeed a stressor could disrupt metabolic signals, thereby affecting reproductive responses (Maciel et al., 2001). It is clear from these and other observations that glucocorticoids can have direct effects at the level of the follicle (Spicer and Chamberlain, 1998) and pituitary gonadotropin secretion (Padmanabhan et al., 1983).

Exposure of dairy cows to a road transport stressor and challenge with either GnRH or estradiol to test feedback mechanisms in the reproductive axis resulted in a reduced LH response to GnRH (20 or 40 μg; 11 ± 2 vs. 17 ± 3 ng/mL; Dobson, 1987) and both delayed (18 vs. 26 h) and reduced the LH surge response (64 vs. 35 ng/mL) to an estradiol (1 mg of estradiol benzoate) challenge (Nanda et al., 1990).

Exposure of heifers to an adenocorticotropic hormone challenge (100 IU) every 12 h from d 15 to 22 of the cycle induced persistence of dominant follicles and delayed ovulation by approximately 9 d (Figure 8; Dobson et al., 2000). This was mediated by an almost complete block of pulsatile secretion of LH during the acute period of exposure to adenocorticotropic hormone. Collectively, these studies demonstrate mechanistically that exposure to stressors disrupts the reproductive axis and lends support to the observational studies that indicate that disease and production stressors contribute to reduced fertility in dairy cows.

SUMMARY AND CONCLUSIONS

In conclusion, fertility in dairy cows is a multifactorial problem and is dependent on genetics, nutrition, metabolic state, management, health status, and the interactions of these factors. Genetic selection for increased milk yield in dairy cows increases metabolic and nutritional stressors, and in turn, may affect uterine health, uterine immune status, or both, which has consequences for clearance of uterine disease. Studies on the effects of manipulation of the stress axis demonstrate that disruption of this axis will perturb the reproductive axis. Therefore, disease state and associated stress during the peri-parturient period affect reproductive function and fertility, likely due to its effects on the immune and stress responses of the animals. High-yielding dairy cows are highly tuned genetic beings, and management of these animals to minimize metabolic and nutritional stressors to optimize yield, health, and reproductive performance is an ongoing challenge.

LITERATURE CITED


Figure 8. Mean (±SEM) peripheral plasma concentrations of a) estradiol and b) follicle diameters for 6 control heifers (○) and 5 heifers that formed a prolonged follicle after treatment with 100 IU of ACTH every 12 h for 7 d from d 15 of the estrous cycle (♦). *Control estradiol values were significantly different from prolonged follicle estradiol values (P < 0.05). Modified from Dobson et al. (2000); H. Dobson, A. Y. Ribadu, K. M. Noble, J. E. Tebble, and W. R. Ward, 2000, Journal of Reproduction and Fertility, vol. 120, pages 405–410. Society for Reproduction and Fertility (2000).


