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BOARD INVITED REVIEW: The importance of the gestation period for welfare of calves: Maternal stressors and difficult births[1]

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ABSTRACT: The prenatal period is of critical importance in defining how individuals respond to their environment throughout life. Stress experienced by pregnant females has been shown to have detrimental effects on offspring biology in humans and a variety of other species. It also is becoming increasingly apparent that prenatal events can have important consequences for the behavior, health, and productivity of offspring in farmed species. Pregnant cattle may experience many potentially important stressors, for instance, relating to their social environment, housing system and physical environment, interactions with humans and husbandry procedures, and their state of health. We examined the available literature to provide a review of the implications of prenatal stress for offspring welfare in cattle. The long-term effects of dystocia on cattle offspring also are reviewed. To ensure a transparent and repeatable selection process, a systematic review approach was adopted. The research literature clearly demonstrates that prenatal stress and difficult births in beef and dairy cattle both have implications for offspring welfare and performance. Common husbandry practices, such as transport, were shown to influence offspring biology and the importance of environmental variables, including thermal stress and drought, also were highlighted. Maternal disease during pregnancy was shown to negatively impact offspring welfare. Moreover, dystocia-affected calves suffer increased mortality and morbidity, decreased transfer of passive immunity, and important physiological and behavioral changes. This review also identified considerable gaps in our knowledge and understanding of the effects of prenatal stress in cattle.

Key words: cattle, dystocia, gestation, offspring welfare, prenatal stress

INTRODUCTION

The prenatal period is of critical importance in defining how individuals respond to their environment throughout life. Fetal development is a complex biological process influenced by genetic, epigenetic, maternal, and environmental factors (Wu et al., 2006). In particular, stress experienced by pregnant females has been shown to have detrimental effects on offspring behavior (Braastad, 1998), health (Bell, 2006; Wu et al., 2006; McMillen et al., 2008), and productivity (Funston et al., 2010). This work has received considerable impetus by the publication of human epidemiological findings of correlations between a suite of adult-onset diseases, described as the metabolic syndrome, and birth weight (Barker, 2004). This "developmental origins of health and disease" hypothesis has led to numerous controlled experiments using animal models, mostly rodents (reviewed by Glover et al., 2010). Studies examining the implications for offspring of prenatal stress in farm animals, however, have only come to prominence more recently (Braastad, 1998; Rutherford et al., 2012). It is now becoming increasingly apparent that prenatal events can have important consequences for the offspring of farmed species (e.g., Bell, 2006; Wu et al., 2006; Funston et al., 2010; Greenwood et al., 2010a).

The effects of stress in general on the performance of farm animals have previously been reviewed (von Borell et al., 2007); however, to date, there have

been no reviews examining the implications of prenatal stress, defined as stress experienced by the pregnant mother that affects the development of the offspring (Braastad, 1998), for calf welfare. Nonetheless, pregnant cattle experience many potentially stressful management practices. For example, animals might be subjected to social stress by being kept in groups of inappropriate size or composition, being subjected to regular or intermittent mixing with unfamiliar individuals, or experiencing competition for limited resources (e.g., a dry lying area or access to feed). The housing system also could directly affect maternal welfare with consequences for their offspring (e.g., Sorrells et al., 2006). Moreover, the nutrition of gestating cattle is potentially a very important source of stress, especially as it is common for beef cows to experience a degree of food restriction as part of the production cycle. In addition, some routine husbandry practices could be acutely stressful to pregnant dams, examples of which include handling (Lay et al., 1992) and transportation (Mitchell et al., 1988), which cause activation of the hypothalamic–pituitary–adrenal (**HPA**) axis. Environmental variables such as temperature, humidity, and photoperiod experienced during pregnancy also could have important consequences for offspring biology. Out-wintered pregnant beef cows, for example, can routinely experience ambient temperatures below their lower critical temperature (**LCT**), resulting in physiological cold stress (Morgan et al., 2009). Furthermore, maternal health status and pain experienced by the mother could act as potent stressors affecting offspring development. Finally, the parturition process itself could have important consequences for offspring well-being, particularly when it is prolonged and difficult. Therefore, the purpose of our review is to investigate how prenatal stressors and difficult births affect offspring welfare. As a result of the wide-ranging nature of the literature relating to this topic, and to ensure a transparent and repeatable selection process, a systematic review (**SR**) approach was adopted.

Our SR was aimed at overcoming the limitations of a more traditional narrative review (e.g., Sargeant et al., 2006), the latter often being highly subjective as a consequence of being written by experts who might have preconceived opinions and biases concerning the topic. This can lead to selection bias whereby authors select studies for inclusion that support their own views. The goal of a SR is to use scientific review methods to minimize systematic and random errors (Cook et al., 1997), and there has recently been a call for animal science reviews to be conducted in a more transparent and systematic fashion (Sargeant et al., 2006). A SR uses a comprehensive and explicit search strategy, eliminating the selection bias that can be associated with narrative reviews. Selection of literature for inclusion in the SR

is based on specific criteria that are applied to all studies identified by the search. Subsequently, all the studies included in a SR are subject to critical appraisal.

Typically, SR use a quantitative approach (e.g., meta-analysis) to appraise studies; however, because of the broad nature of the present topic, this approach was deemed unsuitable. As such, we adopted a systematic, transparent search strategy that could be repeated by others. We also developed a suitable protocol to identify relevant studies for inclusion; however, once these studies were identified, as a result of our broad review question examining multiple outcomes, together with the relatively small number of relevant studies, a narrative approach was used to examine the findings of individual studies and draw suitable conclusions.

MATERIALS AND METHODS

Searches

The online database ISI Web of Knowledge (http://wok.mimas.ac.uk) was used to search the literature. Within the ISI Web of Knowledge, the following databases were searched simultaneously: ISI Web of Science (1970 to present), MEDLINE (1950 to present), and BIOSIS Previews (1969 to present).

The search terms used were designed to combine words relating to cattle and to prenatal stress. Several pilot searches were run with the aim of producing a search string that yielded a comprehensive but manageable number of initial results. The final search string is given below, an asterisk indicating where the electronic reference database looked for words beginning with the stated letters; for example, cow* was used to find references relating to the words "cow" and "cows": (prenatal OR perinatal OR maternal OR fetal OR foetal OR gestation*) AND (stress OR programm* OR nutrition*) AND (cattle OR bovine OR cow*).

No limits were set in any of the electronic database searches, and each database was searched from the earliest year available to the present by using the Topic/Title setting. To recover any relevant articles not identified by the above search, a detailed search of several relevant journals also was conducted. This was achieved by visiting the online journal homepage and entering the search term "prenatal OR pre-natal." The following journals were searched in this manner, over their full history: *Journal of Animal Science*, *Animal*, *Livestock Science*, *Journal of Dairy Science*, *Animal Welfare*, and *Applied Animal Behavior Science*. Furthermore, as a final measure to ensure adequate literature coverage, experts in the field of bovine early life research were consulted and any articles deemed relevant but missed by the literature searches were included under the term "expert ad-

ditions." After these initial searches, the reference lists of relevant studies were hand searched to identify any further articles.

Search Results

The initial search was conducted in ISI Web of Knowledge on November 17, 2009, with updates added after a repeated search using the same terms on January 18, 2011. After removal of duplicates, the search yielded 3,545 references. English and non-English language references were identified. The references, and abstracts when available, were imported into a bibliographic database (Reference Manager, Thomson Reuters, New York, NY) for manipulation. The relevant journal search yielded an additional 20 references for inclusion whereas "expert additions" yielded 16 references. Furthermore, hand searching the reference lists of relevant papers (see below as to how relevant papers were identified) yielded 9 more references. Therefore, a total of 3,590 references provided the raw material for this SR. These references then proceeded to the classification stage outlined below.

Classification of Results

Within the reference manager database, the references were initially screened for relevance. This involved reading the title and removing any obviously irrelevant references (3,230 in total), which were transferred to a separate database. The remaining references were examined in more detail using a combination of the title and abstract to classify them into one of the following 4 mutually exclusive categories (and transferred to a separate database with that title):

1) Maternal treatments: studies focusing on dam treatments and outcomes rather than offspring outcomes.

2) Review articles: Empirical studies are the raw material for a SR. It is therefore important to identify and remove review articles.

3) Offspring nutrition: studies that manipulated dam nutrition and then examined offspring outcomes; these studies were removed (for use in a separate study).

4) Offspring stress: studies that applied a stressor to the dam during pregnancy and then investigated offspring outcomes; for the purposes of this review the term "stressor" was used in its broadest possible sense as a form of nonnutritional challenge with effects on maternal biology (i.e., it was not limited to aspects of stress physiology or factors that were detrimental to maternal homeostasis).

Subsequently, it was necessary to further classify studies in the "offspring stress" category. Using the title and abstract, these studies were classified into 1 of the following mutually exclusive categories (a study may have crossed more than 1 category but for clarity it was placed into a single outcome category that best described it). The categories were 1) Welfare outcomes: included any studies that investigated welfare relevant offspring outcomes; these outcomes typically came under the headings of stress, health, behavior, mortality, and immunity. 2) Birth weight and growth: included studies investigating prenatal effects on offspring birth weight and growth. 3) Reproduction: included studies focusing on reproductive variables of offspring affected by stress or nutritional manipulations performed on their dams. 4) Physical defects: comprised any studies documenting physical defects in offspring as a result of stress or nutritional manipulation occurring in the dam during gestation. 5) Other production: considered offspring production variables not encompassed by the above groups; an example of studies falling into this category included those investigating aspects related to offspring meat quality. 6) Other: included any studies not applicable to the above groups.

To verify the repeatability and transparency of our classification procedure, 2 of the authors (G. Arnott and K. M. D. Rutherford) independently identified the welfare outcome studies from the offspring stress group. This led to complete agreement in the categorized welfare studies. Based on the welfare related aims of this review and the relatively large number of classified references, a decision was taken that the first 2 categories (welfare outcomes and birth weight and growth) would form the raw material for the review.

Because the primary goal of this review was to identify prenatal hazards that affect offspring welfare, the next step in our SR process was to classify references in the welfare outcome categories according to the early life treatment applied. Subsequently, 9 hazard categories were identified (see below for definition of hazards). Note that in this case, a study might have applied more than 1 type of stressor or treatment, meaning that a single study could have a number of hazard categories assigned to it. The hazard definitions were drawn up after meetings among the authors, with these definitions sent to external collaborators for critical appraisal.

Classification of Hazards

Early life hazards were considered under the following main headings: social environment, housing system, nutrition and feeding method, husbandry practices, environmental variables, infectious environment and maternal health, artificial challenges [involving exogenous manipulation of hypothalamic axis (**HPA**) function], and birthing difficulties. Studies falling within an "other" hazard category were subsequently eliminated from the review (2 references; Monserrat and Sanchez, 1991; Berry et al., 2008).

Studies remaining at this point formed the raw ma-

terial for detailed review. All English language publications were secured. As a result of time and language difficulties, 2 non-English language publications (Broucek et al., 2002; Gilles et al., 2009) were not obtained for subsequent classification.

Quality Assessment

As recommended by Sargeant et al. (2006), a quality assessment of studies was made using the following protocol (largely adapted from the REFLECT statement; O'Connor et al., 2010). Any studies not meeting the standards set out in our quality assessment protocol were subsequently discarded from the review. Factors taken into account were

1) Randomization: individuals allocated randomly to treatment groups; although this is often not specified in methods sections, papers were excluded when experimental allocation was clearly biased.

2) Treatment intervention: experimental treatment intervention clearly described including details of treatment, timing, and duration of application.

3) Control: use of a suitable control group.

4) Sample size: use of a sufficiently large sample size; studies with a sample size of less than 5 experimental units (animals) per treatment group were discarded. This decision was based on the recommendations of Festing and Altman (2002). These authors state that the degrees of freedom for the error term used to test the effect of the variable should not be less than 10 df.

5) Statistical methods: clear account of the statistical methods used to compare groups for all outcome(s), use of appropriate statistical methods, and, where applicable, use of methods to account for nonindependence of study subjects.

6) Avoidance of data repetition: cases were avoided of multiple publications reporting on the same study and data.

7) Exclusion of conference abstracts and proceedings: insufficient detail and information content for critical appraisal.

After the quality assessment, 1 reference within the welfare offspring stress group was identified as a conference abstract and therefore excluded from the review. Furthermore, 6 references failed to pass the quality assessment for reasons including lack of statistical use, small sample size, and lack of randomization. As such, a total of 20 welfare and 6 birth weight and growth offspring stress articles were included in the final detailed data extraction process of the SR (Table 1). Information relating to the maternal nutrition studies will be published separately.

DISCUSSION

No papers were found that examined aspects of the maternal social environment or housing system in relation to prenatal development.

Husbandry Practices

Common livestock production practices such as handling, restraint, and transportation are stressful, causing activation of the HPA axis (Mitchell et al., 1988; Clark et al., 1993; Roussel et al., 2006; Roussel-Huchette et al., 2008). Subjecting pregnant cattle to such stressors might have implications for the offspring. For example, Lay et al. (1997b) found that exposing pregnant Brahman cows to repeated transport on d 60, 80, 100, 120, and 140 of gestation increased the stress reactivity of their offspring, in terms of their cortisol response to restraint at 10 and 150 d of age, which could affect their ability to cope with challenges throughout life. Furthermore, when exposed to a stressful challenge, the offspring of transported dams had plasma cortisol concentrations that remained increased for longer (Lay et al., 1997b), which might result in harmful effects because of the long-term deleterious influence of cortisol on metabolism and the immune system (Chrousos, 2009). It should be noted, however, that the severity of the prenatal stressor applied might not translate well to commercial reality, where it is unlikely that pregnant cows would be exposed to the repeated transport used experimentally. Therefore, one should be cautious about extrapolating from such results to provide commercially relevant information.

Another study by Lay et al. (1997a) attempted to investigate the mechanisms responsible for an altered HPA response resulting from prenatal stress. The researchers investigated whether physiological or morphological differences or both existed in offspring from dams subjected to repeated transportation (as per Lay et al., 1997b). Calves were delivered by caesarean section on d 266 of gestation. There was a trend for calves from transported dams to weigh more than controls, which also was observed by Lay et al. (1997b). Moreover, the relative pituitary gland and heart weights of calves from transported dams were significantly greater than those of control calves; however, there were no significant differences in the relative weights of adrenals, kidneys, and liver or in the concentrations of plasma cortisol and ACTH at birth. These findings might reflect the small size of the study (6 control and transported cows), and results should be viewed with caution. Nonetheless, the fact that transportation resulted in larger pituitary glands in the calves is interesting and suggestive of an endocrine alteration.

Another potentially stressful and directly traumatic

Table 1. Summary of references proceeding to the final review stage

Reference	Dairy or beef	Breed	Hazard category	Hazard details
Adams et al. (1995)	Beef	Various beef	Birth	Parturitions given a calving difficulty score (CDS): no dystocia = unassisted delivery, CDS 1 (controls); dystocia group = CDS ≥ 2 (CDS 2 = mild traction, 3 = moderate traction, 4 = caesarean, and 5 = malpresentation).
Andreoli et al. (1988)	Beef	Simmental or Hereford	Environment	Dams exposed to ambient winter weather during final third of gestation (experimental group) or maintained in a thermoneutral environment (12°C) during final third of gestation (control group).
Beam et al. (2009)	Dairy	Not given	Birth	Observational study examining farms at risk of dystocia. Defined as farms that would not call a veterinarian for assistance when they were not able to correctly position a calf for delivery.
Bellows et al. (1988)	Beef	Various crossbred	Birth	Two experiments: Exp. 1, dams subjected to induced parturition or allowed a natural parturition; Exp. 2, dams subjected to forced early assistance at parturition or late (emergency only) obstetrical assistance.
Bellows and Lammoglia (2000)	Beef	Various crossbred	Birth	Parturitions given a CDS: no dystocia = unassisted delivery, CDS 1 (controls); dystocia group = CDS 2 (minor dystocia requiring manual assistance, CDS 3 (severe dystocia requiring use of mechanical calf puller), and CDS 4 (major dystocia requiring caesarean section).
Civelek et al. (2008)	Dairy	Holstein	Birth	Dams calved without assistance (controls), or dams experience dystocia, requiring assistance using a mechanical calving aid.
Collier et al. (1982)	Dairy	Holstein	Environment	Dams given access to shade (controls) or no shade (experimental group) during last third of gestation.
Field et al. (1989)	Beef	Various crossbred	Birth	Controls allowed natural parturition whereas in experimental groups, parturition was induced on d 270 of gestation.
Franco et al. (1987)	Dairy	Holstein–Friesian	Husbandry	Control dams not palpated per rectum for pregnancy diagnosis whereas the experimental group was palpated per rectum (twice) between d 42 and 46 after insemination.
Gianola and Tyler (1974)	Dairy	Holstein–Friesian	Husbandry	Breeding of dams at first heat postpartum or first estrus after 74 d postpartum.
Henderson et al. (2011)	Dairy	Holstein	Birth	Parturition given a calving ease score: 1 = unassisted delivery, 2 = easy pull, 3 = hard pull, and 4 = excessive force or surgery needed.
Hickson et al. (2008)	Beef	Angus	Birth	Nonassisted vs. assisted delivery (dystocia).
Laster and Gregory (1973)	Beef	Various	Birth	Parturition classified into 1 of 4 groups: no dystocia, calf puller, surgical removal, and posterior presentation.
Lay et al. (1997a)	Beef	Brahman	Husbandry, artificial	Dams subjected to either transportation or ACTH injection or walked through the handling facilities on d 60, 80, 100, 120, and 140 of gestation.
Lay et al. (1997b)	Beef	Brahman	Husbandry	Dams subjected to either transportation or walked through the handling facilities on d 60, 80, 100, 120, and 140 of gestation.
Lents et al. (2008)	Beef	Angus or Angus × Hereford	Infection or health	Controls did not receive intramammary antibiotic therapy whereas dams in the treatment group received intramammary antibiotic at drying off.
Lombard et al. (2007)	Dairy	Holstein	Birth	Parturition given a dystocia score: 1 = no assistance, delivery; 2 = mild dystocia (intervention by 1 person without use of mechanical assistance); and 3 = severe dystocia (includes the use of mechanical extraction).
Loyacano et al. (2002)	Beef	Various crossbred	Infection or health	Controls were not treated for gastrointestinal nematodes or liver flukes whereas experimental groups were either treated for gastrointestinal nematodes, liver fluke, or both gastrointestinal nematodes and liver fluke.
Lundborg et al. (2003)	Dairy	Swedish Red & White or Swedish Holstein	Infection or health	Observational study investigating associations between clinical mastitis (yes or no), somatic cell count, and disease in the dam during gestation on offspring.
Notter et al. (1978)	Beef	Various	Birth	Parturitions classified as "difficult" or "not difficult."
Reyes et al. (2007)	Dairy	Holstein	Environment	Dams given either access to shade and a cooling system or only access to shade during last 60 d before calving.
Stott and Reinhard (1978)	Dairy	Holstein	Birth	Parturition classified as eutocal (no assistance required) or dystocial (if a mechanical calf-puller was used to complete parturition).
Vermorel et al. (1989)	Dairy	Holstein–Friesian	Birth	Parturitions classified as eutocal (no assistance required) or dystocial (difficult = when 2 or 3 people pulled; very difficult = 3 people pulled with mechanical assistance or surgical removal).
Waldner & Rosengren (2009)	Beef	Various	Birth	Parturitions classified as nonassisted or assisted.
White et al. (2010a)	Beef	Various	Environment	Observational study investigating associations between drought 5 mo before parturition and the birth of calves suffering from congenital chondrodystrophy of unknown origin.
Wittum et al. (1994)	Beef	Various	Birth	Parturitions classified as nonassisted or assisted.

event that occurs as a routine cattle husbandry practice is pregnancy diagnosis per rectum, during which the uterus and its contents are palpated. For economic and management reasons, the diagnostic aim is to identify "nonpregnant" animals earlier than 50 d after insemination (Franco et al., 1987). Palpating the amnion or fetal membranes might, however, injure the conceptus. Moreover, the process of pregnancy diagnosis typically involves restraining cattle in a "crush" or "squeeze chute" often in the presence of a number of people (some of whom are novel), which might in itself be distressing for cows (Pilz et al., 2012). Our SR failed to identify any studies examining offspring outcomes from dams as affected by rectal palpation; however, Franco et al. (1987) reported significantly greater fetal death among dairy cows palpated per rectum at a time of gestation frequently used by veterinary practitioners for early pregnancy diagnosis (between 42 and 46 d after insemination). The impairment of fetal survival could represent the most extreme conceptus effect, but there could be more subtle long-term offspring consequences that remain to be examined. It also is likely that the timing of palpation has important implications for progeny development. For example, Paisley et al. (1978) found that fetal death rates did not differ when dairy cows were palpated in early gestation (5.8 and 6.0% when palpated <35 d and 36 to 46 d, respectively) but were significantly less (0.8%) when palpated at a later stage (>46 d). Because of the economic necessity for pregnancy diagnosis, the timing could provide a means to minimize any potential adverse effects on the developing progeny.

A study by Gianola and Tyler (1974) demonstrated that breeding management can have consequences for offspring. Calves from early bred dairy cows (breeding at first estrus postpartum) were significantly lighter (by 1.2 kg) than offspring from cows bred later (first heat after 74 d postpartum). Moreover, there was an effect of parity, with calves from heifers being lighter than those from second- and third-parity cows. More studies are warranted to investigate how husbandry practices and management decisions influence pregnant cattle and their offspring.

Environmental Variables

Our review identified 3 studies (Collier et al., 1982; Andreoli et al., 1988; Reyes et al., 2007) examining the effects of environmental conditions on offspring birth weight. During the last trimester of pregnancy, Andreoli et al. (1988) either maintained beef dams in a thermoneutral environment (12°C) or exposed them to ambient winter weather conditions (ambient temperature and wind velocity were obtained at hourly intervals from a nearby weather station and used to calculate wind chill, which

fell below –7°C on occasions but did not exceed the LCT for dry, pregnant, beef cattle). Dams of both groups were fed a complete diet formulated to meet calculated nutrient requirements, with those exposed to ambient winter weather receiving additional dietary energy (when average weekly wind chill fell below 6.7°C) to ensure that both groups maintained similar body condition. Calves from dams exposed to winter weather were lighter than controls, highlighting the negative effects of chronic cold stress on offspring. The fact that dams were above LCT during this experiment suggests that even greater effects might be detected when ambient conditions drop below this threshold, a scenario that has been documented in out-wintered beef cattle (Morgan et al., 2009). Effects on birth weight have implications for welfare. For example, low birth weight is associated with high neonatal morbidity and mortality rates, particularly under adverse climatic conditions (e.g., Azzam et al., 1993). Furthermore, in terms of production efficiency, low birth weight can impair postnatal growth, performance, and carcass traits (reviewed by Greenwood et al., 2010b).

Heat stress also can adversely affect offspring. Collier et al. (1982) found that offspring from dairy cows exposed to heat stress during the last third of gestation were significantly lighter at birth whereas Reyes et al. (2007) documented a trend for decreased birth weight in calves from dairy cows with no access to cooling during the last 60 d of gestation.

Drought

Some major cattle-producing regions are at risk of drought, the incidence or severity of which is expected to increase in the foreseeable future (e.g., Hennessey and Mpelasoka, 2007). In pregnant cattle, drought is predicted to result in quantitative and qualitative feed restriction as a result of restricted pasture growth and decreased quantity of pasture cover (White et al., 2010a). Moreover, drought also might alter the nutrient uptake of pasture species further affecting maternal nutrition (Whitehead, 2000). When these adverse conditions coincide with critical periods of gestation they could have profound effects on offspring development.

Drought during gestation has been associated recently with a particularly severe health problem in Australia of neonatal beef calves termed congenital chondrodystrophy of unknown origin (**CCUO**; White et al., 2010a). This condition is characterized by a failure of long bone growth as a result of lesions affecting the epiphyseal growth plates (McLaren et al., 2007). Affected calves suffer from disproportionate dwarfism, with signs including shortened and rotated limbs, shortening of the upper jaw, and spinal deformities (Cave et al., 2008). Breathing difficulties, resulting from deformities

of the trachea and nasal turbinates, often occur and can lead to perinatal death, with most affected calves not being viable in the long term (McLaren et al., 2007). The incidence of CCUO in Australia has been increasing, with farmers anecdotally reporting an association between very dry periods during gestation and the birth of affected calves. In support of this anecdotal association, White et al. (2010a) found significant negative correlations between both average monthly and 3-mo average rainfall 5 mo before birth and cases of CCUO calves. Furthermore, when the 3-mo average rainfall was in the lowest decile 5 mo before the birth of calves, the risk of CCUO was increased 3.3 times. Therefore, a period of drought within the second trimester of pregnancy was associated with an increased likelihood of calves being born with CCUO.

Drought results in a maternal nutritional deficiency (e.g., Mee, 2001; McLaren et al., 2007), and White et al. (2010b) found an association between CCUO calves and inadequate pastures. It therefore seems that periods of drought within the second trimester of pregnancy, at a time of rapid fetal and placental growth, contributes to the birth of CCUO calves through an effect on maternal nutrition. It is suggested that farmers might benefit from providing improved nutrition to pregnant cows during the first two-thirds of gestation when rainfall is deficient and pasture quality and quantity are inadequate. It seems highly likely that other detrimental offspring outcomes of drought during pregnancy remain to be quantified. Given that climate change models predict an increasing incidence of drought in the future, this seems an appropriate area of research.

Infectious Environment and Maternal Health Status

Studies in laboratory animals have shown that stimulation of the maternal immune system can cause variation in offspring biology, including brain development and behavior (reviewed by Boksa, 2010). A particularly pertinent question for the cattle industry is the degree to which disease or pain experienced by the dam during pregnancy can have consequences for developing offspring. An observational study of Swedish dairy farms highlights the importance of this (Lundborg et al., 2003), finding effects of dam health status on heifer calves monitored from birth until 90 d of age. Calf size at birth was decreased if the dam had clinical mastitis during the 49-d period before calving, and there was a trend for decreased calf size if the dam had a high somatic cell count (>124,000 cells/mL) during lactation. No associations were observed between dam-related factors and risk of diarrhea in the calves; however, calves born to cows that had a disease from conception to 50 d before calving had a greater risk of developing respiratory

disease as did those from dams with a increased somatic cell count (>34,500 cells/mL) during lactation. Moreover, calves whose mothers experienced disease had a decreased growth rate, a finding widely reported by others (e.g., Thomas et al., 1978; Ganaba et al., 1995; Virtala et al., 1996; Donovan et al., 1998). Similarly, Lents et al. (2008) reported that dry cow treatment of beef cows with intramammary antibiotics improved calf growth during the subsequent lactation whereas Loyacano et al. (2002) found that failure to treat dams for gastrointestinal nematodes or liver fluke during gestation resulted in decreased offspring birth and weaning weights. Therefore, in addition to the welfare concerns of disease, there also are important economic consequences for performance in terms of decreased growth rates.

These studies clearly demonstrate that disease in the dam during gestation has implications for the health, welfare, and performance of her offspring; however, more work is clearly needed to verify the extent of these effects in detail and to identify mechanisms of action. For example, maternal–offspring immune communication might be important, or more generally, poor maternal health status might have an effect on offspring function as a result of indirect mechanisms (e.g., maternal condition or stress). One particularly pertinent question for many farm animals is whether pain experienced by the mother, for instance as a consequence of lameness, could act as a significant stressor affecting offspring development. In sheep, Wassink et al. (2010) found that 17 extra lambs were reared per 100 ewes in flocks where ewes were treated for foot rot. It should be noted, however, that in addition to alleviating pain, successful treatment of foot rot also is likely to improve feed intake. Also working with sheep, Sargison et al. (1995) identified a significant decrease in birth weight of lambs born to ewes that had experienced an acute outbreak of sheep scab during pregnancy. Thus, alleviating suffering during gestation is likely to be beneficial not only to the dam but also to her offspring.

Artificial Challenges

Glucocorticoids are thought to mediate many of the effects of maternal stress on the fetus (Harris and Seckl, 2011), passing across the placenta and having the potential to affect the maturation of the fetal HPA, which might have implications for HPA function later in life. Artificial models of prenatal stress involving exogenous manipulation of HPA axis function (e.g., administration of exogenous glucocorticoids or ACTH during pregnancy) to stimulate a maternal stress response have been developed (e.g., in pigs; Kranendonk et al, 2008). This method has the advantage of enabling a standardized, quantifiable stressor to be applied, but it has the disad-

vantage that altering HPA function does not fully replicate the complete range of physiological changes that might be associated with exposure to natural stressors.

In addition to the transportation treatment discussed earlier, Lay et al. (1997b) also included a treatment group taking the ACTH model approach and reported that calves from dams receiving repeated injections of ACTH on d 60, 80, 100, 120, and 140 of gestation had increased stress reactivity compared with controls, in terms of their cortisol response to restraint at 150 d of age. In addition, during a cortisol clearance test at 180 d of age, calves from ACTH-treated dams cleared cortisol at a slower rate than controls. Comparing ACTH injections and transportation of dams, the cortisol response to restraint at 10 d of age was greater in calves from transported dams whereas the cortisol clearance rate of these calves was slower than that of ACTH calves. Taken together, these results indicate that ACTH injection was intermediate between control and transport treatments in its ability to alter the response of calves to stress. It was suggested that the ACTH injections might not have increased plasma cortisol concentrations in the dam to the same degree or duration as that caused by transportation stress. It also is the case that factors other than glucocorticoids (or more generally HPA axis activation) could be mediating some of the changes that occur during prenatal stress.

Parturition Issues: Dystocia

Dystocia, defined as delayed or difficult parturition (Lombard et al., 2007), is a stressful event for both mother and offspring, with potentially lifelong consequences. Extended periods of labor, contractions, and trauma during difficult parturitions increase hypoxia and acidemia in the neonate (Massip, 1980; Hoyer et al., 1990). The studies outlined in Table 2 clearly demonstrate that dystocia has wide-ranging and significant effects on offspring. Three general causes of dystocia are fetal–maternal size mismatch, fetal malpresentation, and maternal-related causes (Zaborski et al., 2009). Our review concentrates on the offspring consequences of dystocia rather than causes although a number of studies in Table 2 highlight the fetal–maternal size mismatch problem as evidenced by a positive association between birth weight and dystocia (e.g., Laster and Gregory, 1973; Notter et al., 1978; Adams et al., 1995; Bellows and Lammoglia, 2000; Civelek et al., 2008).

The most obvious detrimental offspring outcome of dystocia in cattle is the birth of dead or dying calves. Although there is some uncertainty as to whether we should judge death before birth as a welfare issue (Mellor and Diesch, 2006), it can still be viewed as an ethical issue (Yeates, 2010) and certainly represents an economic inefficiency. Results of studies document an increase in perinatal calf mortality (dead at birth or within the first 24 h of life) as a result of dystocia in both dairy (Barnouin et al., 1992; Lombard et al., 2007) and beef cattle (Laster and Gregory, 1973; Notter et al., 1978; Wittum et al., 1994). Moreover, studies also indicate a detrimental effect of dystocia on later mortality. For example, Lombard et al. (2007) found a significant increase in later mortality (alive at 24 h after calving but dead by 120 d of age) for heifer calves from dairy cows experiencing severe dystocia. Furthermore, the same study calculated survival curves to 30 d of age, finding a significant decrease in survival probability for calves experiencing severe dystocia. Similarly, Wells et al. (1996) found that calves exposed to forced extractions were at increased odds of dying within 21 d of birth. Moreover, a recent study (Henderson et al., 2011) highlighted that dystocia can negatively influence survival to maturity, in that an increasing calving difficulty score was associated with greater mortality in dairy heifers in a replacement rearing unit. In contrast, other studies have failed to find an effect of dystocia on later mortality. For example, Wittum et al. (1994) found no difference in neonatal mortality (from 12 h to 45 d of age) between beef calves that experienced dystocia or were born without assistance, as also reported by Notter et al. (1978).

Only 1 study (Adams et al., 1995) identified by our SR specifically examined the effects of dystocia on calf growth rate and failed to find a relationship with growth between birth and 3 wk of age. Nonetheless, because calves experiencing dystocia weighed more at birth and would therefore be expected to gain more BW during this growth period (Adams et al., 1995), equal BW gains might represent decreased performance in the dystocia-affected calves. Negative effects of dystocia on performance also are to be expected given that others have reported detrimental effects on offspring health and immunity (Table 2). Although not the focus of this review, further research is clearly needed to quantify the effects of dystocia on aspects of offspring performance. Recent research has demonstrated, for instance, that dairy heifers born after a difficult parturition subsequently displayed decreased milk yields during their first lactation (Eaglen et al., 2011).

Dystocia has negative consequences for offspring health. For example, in their large observational study of dairy cows, Lombard et al. (2007) found an association between dystocia score and morbidity. Heifer calves experiencing dystocia were more likely to succumb to respiratory and digestive diseases during the first 120 d of life. Similarly, Wittum et al. (1994) documented an increased risk of neonatal morbidity (from 12 h to 45 d of age) in beef calves experiencing dystocia. Decreased transfer of passive immunity has been documented in

Table 2. Summary of results from dystocia[1] studies

Dystocia at parturition	Industry sector	Birth WT	Growth	Mortality	Physiology	Offspring outcomes[2]				
						Immunity	Behavior	Health	Blood constituents	Other
Adams et al. (1995)	Beef	↑	NS average BW gain between birth & 3 wk of age		↑ RT, ↓ pulse, NS respiratory rate at 10 min of age ↑ plasma lactate (10min, 1 and 4 h), ↑ plasma glucose (1-h sample)	NS IgG, IgM	↑ interval to stand ↑ interval to nurse			
Barnouin et al. (1992)	Dairy			↑ PCM						
Beam et al. (2009)	Dairy	↑				↑ FPT				
Bellows and Lammoglia (2000)	Beef				↑ serum glucose, NS cortisol, NS RT at 30 min of age, NS serum glucose, ↓ cortisol, ↓ RT during cold exposure test		NS shivering score during cold exposure test			
Civelek et al. (2008)	Dairy	↑		↑ LaM	↑ plasma cortisol, ↑ plasma glucose, ↑ cholesterol after birth				↓ Vitamin A, ↓ Vitamin C, ↓ β-carotene after birth NS creatinine, triglycerides	
Henderson et al. (2011)	Dairy			↑						
Hickson et al. (2008)	Beef						↑ time to attempt to stand ↑ time to successfully stand ↑ time to suckling			
Laster and Gregory (1973)	Beef	↑		↑ PCM						

Table 2. Continued.

Dystocia at parturition	Industry sector	Birth WT	Offspring outcomes[2]							
			Growth	Mortality	Physiology	Immunity	Behavior	Health	Blood constituents	Other
Lombard et al. (2007)	Dairy			↑ PCM ↑ LaM ↑ TM ↓ 30-d survival probability				↑ overall morbidity ↑ respiratory morbidity ↑ digestive morbidity		
Notter et al. (1978)	Beef	↑		↑ PCM NS LaM ↑ TM						
Stott and Reinhard (1978)	Dairy				↓ serum cortisol at birth, NS serum cortisol at 4 h	NS serum IgG, IgM, IgA (at 16 & 24 h)				
Vermorel et al. (1989)	Dairy				↑ RT at birth, ↓ total & resting heat production, ↓ blood pH, ↑ serum lactate during first d of life, ↑ serum glucose (birth and 2 h), ↓ plasma T_3 & T_4 (birth and 2 h)	↓ serum immunoglobulin during d 1 of life			↑ plasma alanine, NS plasma glutamate, NS plasma NEFA during first d of life	↓ colostral consumption at 12-h meal
Waldner and Rosengren (2009)	Beef					↓ serum IgG (sampled between 2 & 8 d old)				
Wittum et al. (1994)	Beef		NS average BW gain between birth & 3 wk of age	↑ PCM NS LaM				↑ overall morbidity ↑ neonatal enterotoxaemia or sudden death ↑ weak calf NS neonatal diarrhea or respiratory disease		

[1]Dystocia definition: delayed or difficult parturition (Lombard et al., 2007).

[2]↑ = increase; ↓ = decrease; NS = no statistically significant effect; PCM = perinatal calf mortality (dead at birth or dead within first 24 h of life); LaM = later mortality (death after first 24 h of life); TM = total mortality (all deaths, including still births, from birth onwards); RT = rectal temperature; FPT = failure of passive transfer of immunity; T_3 = triiodothyronine; T_4 = thyroxine.

dystocia-affected calves (Vermorel et al., 1989; Beam et al., 2009; Waldner and Rosengren, 2009) and provides a potential mechanism for decreased survival and increased disease incidence. In the study by Vermorel et al. (1989), calves were removed from dams after parturition and fed pooled colostrum, thereby removing dam-related effects on acquiring passive immunity.

Important physiological changes also occur in calves experiencing dystocia. For instance, initial rectal temperatures after birth were greater in dystocia-affected dairy (Vermorel et al., 1989) and beef calves (Adams et al., 1995), but later temperatures were less than in eutocial calves. Furthermore, Vermorel et al. (1989) found that heat production during the first day of life was significantly less in dystocial calves as were plasma thyroid (triiodothyronine and thyroxine) hormone concentrations. These findings suggest that dystocia compromises neonatal thermoregulation, which is supported by the work of Bellows and Lammoglia (2000), who observed lower rectal temperatures for dystocial beef calves during a cold exposure test. Dystocia also has effects on stress physiology, as evidenced by increased serum cortisol concentrations in dystocial calves after birth (Civelek et al., 2008) together with decreased cortisol concentrations during a cold exposure test (Bellows and Lammoglia, 2000). Moreover, Adams et al. (1995) found that meconium staining, a sign of intrauterine stress, was more common in dystocia-affected calves whereas plasma lactate concentrations, indicative of anaerobic challenge, were significantly greater (Vermorel et al., 1989; Adams et al., 1995).

Glucose homeostasis also is affected by dystocia, with studies reporting initially increased concentrations after birth (Vermorel et al., 1989; Adams et al., 1995; Bellows and Lammoglia, 2000; Civelek et al., 2008). Hyperglycemia typically follows a stressful event but the duration of hyperglycemia depends on hepatic glycogen stores. Therefore, calves exposed to a stressful dystocial birth might become hypoglycemic more rapidly, particularly as they may have a decreased intake of colostrum (Vermorel et al., 1989). Dystocia also has been shown to influence a number of other important blood constituents. For example, Civelek et al. (2008) found that dystocial calves had decreased concentrations of vitamins A and C as well as β-carotene immediately after parturition. These are important antioxidants with potential health-promoting benefits, including decreasing the effects of dystocia-induced stress (Sathya et al., 2007).

Few studies have investigated the effect of dystocia on offspring behavior. Indeed, our SR only identified 3 studies (Adams et al., 1995; Bellows and Lammoglia, 2000; Hickson et al., 2008) that considered behavioral effects. Hickson et al. (2008) showed that dystocial Angus calves took longer to attempt to stand, to suc-

cessfully stand, and to suckle than calves that did not require assistance at parturition. In agreement with these findings, Adams et al. (1995) also reported that dystocial beef calves took longer to stand and suckle. These results highlight that neonatal calf behavior is unfavorably affected by dystocia. Moreover, this altered behavior is likely to have consequences for colostral intake (e.g., Vermorel et al., 1989), with downstream effects on morbidity and performance. In addition, the increased time taken for dystocial calves to stand and suckle could partly explain the findings of decreased survival and impaired thermogenesis and immunoglobulin absorption. Research is warranted to examine the behavioral effects of dystocia in more detail and over a longer time period. Areas that could be investigated include emotional reactivity, learning, cognition, and pain sensitivity.

Parturition Issues: Induced Parturition

One additional aspect of calving management that has the potential to affect offspring welfare is whether parturition is induced early or allowed to proceed naturally. For example, Field et al. (1989) found that calves from cows induced to calve 2 wk before term (with PG or dexamethasone) had decreased serum IgG concentrations 24 h after birth compared with a control group, with all calves having been tube-fed similar volumes of colostrum within 1 h of birth. The decreased serum IgG concentrations for induced calves were in the range representative of partial failure of passive transfer of immunity. Preterm calves exhibit morphological and functional immaturity of the gastrointestinal tract (e.g., Bittrich et al., 2004), which could have implications for intestinal IgG uptake, as has been demonstrated in preterm pigs (Sangild et al., 2002). There also was a trend for induced dams to have decreased IgG concentrations in their colostrum. These results suggest that calves born to cows induced to calve early are at an increased risk of failure of passive transfer of immunity, which has implications for health and performance.

Lammoglia et al. (1999) also demonstrated the potential for compromised welfare in beef calves born to dams that had been induced to calve 2 wk before term. During a cold stress test (calves placed in a 9°C cold chamber for 200 min) these offspring were less cold tolerant, as evidenced by their lower rectal temperature and a more pronounced decline in rectal temperature. Furthermore, they had decreased plasma glucose concentrations throughout the cold stress test. As such, it seems that induced early parturition has the potential to compromise offspring cold tolerance, possibly as a result of impaired shivering or brown adipose tissue thermogenesis (Casteilla et al., 1987). Because hypothermic deaths are a major cause of mortality in some regions, particu-

larly in suckler cow systems (Bellows et al., 1987; Azzam et al., 1993), a decreased ability to cope with thermal stress is a significant welfare concern. In contrast to the results of these studies, when Bellows et al. (1988) induced cows to calve 3 d early (with flumethasone) there was no apparent effect on offspring vigor, and calf mortality was actually less in the group of calves from induced dams compared with controls from natural parturitions; however, this study did not investigate effects on cold tolerance or passive immunity.

Conclusions

Results from the studies that have been conducted clearly demonstrate that prenatal stress in beef and dairy cattle has implications for offspring welfare and performance. Furthermore, numerous studies show the effect that a difficult birth (as the end of the prenatal period) can have on offspring well-being. Dairy cattle spend a large proportion of their postpubertal life pregnant, and many of the factors that are known to affect cow welfare (e.g., health states such as lameness or mastitis, housing conditions, and quality of stock handling) have substantial potential to affect the developing fetal offspring in a manner that influences their postnatal welfare. Beef cattle face a similar list of possible hazards and when reared extensively might face additional challenges relating to environmental conditions and the frequency and quality of human contact. The possibility exists that prenatal conditions could be a hidden risk factor for some negative health and welfare outcomes in cattle. In addition to possible effects on welfare, prenatal conditions also could affect the purely economic aspects of cattle performance, and this area also deserves study, particularly as efforts to improve the efficiency of livestock production increase. Another largely unanswered question for farmed species is the extent that offspring sex affects the outcomes of a maternal stressor. The present review failed to uncover any important sex differences in how cattle respond to prenatal stress; however, evidence from laboratory animals suggests that important differences can exist (e.g., Weinstock, 2007).

Our review provides a novel categorical framework into which studies involving prenatal challenges can be placed. Serving as a useful starting point to clarify current knowledge, it also provides a means to develop further understanding of the welfare and economic effects of prenatal stress in cattle. Several important sources of prenatal stress in cattle were identified, and these stressors have important detrimental offspring consequences with implications for animal welfare and performance. There are, however, considerable gaps in our knowledge and understanding of the effects of prenatal stress in cattle. For example, to date, no studies have examined the role of the social environment or housing system during pregnancy on offspring welfare-relevant outcomes. Compared with work from other farmed and laboratory species, research is scarce. More research is needed both to quantify the offspring responses to dam stressors applied at a severity representative of commercial practice and to examine the mechanisms responsible. Furthermore, at present, many studies involve calves remaining with their dams after birth, and more work is therefore needed to separate and quantify prenatal and postnatal effects. Research also should investigate whether some cattle breeds are more resistant to prenatal stressors than others.

The importance of prenatal stress for farm animal welfare should not be neglected in the future, especially as there is potential for its prevalence to increase. For example, it is possible that pregnant cattle will be transported more frequently or for longer distances (perhaps as a result of climate change) whereas changing husbandry practices could result in less frequent human contact and potentially greater stress when handling occurs. It also should be possible to mitigate potential sources of early life stress, perhaps by selecting for certain dam traits including temperament, stress reactivity, and calving ease.

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