INFO #: 18738065

CustID: 6339
Virbac Australia Pty Limited
Paul Martin
R&D
Locked Bag 1000
Peakhurst NSW, Australia 1000

Document Delivery

The role of essential trace elements in embryonic and fetal development in livestock

Chris E. Hostetler*, Ron L. Kincaid, Mark A. Mirando

Department of Animal Sciences and Center for Reproductive Biology, Washington State University, Pullman, WA 99164, USA

Abstract

This review addresses the concept that essential trace minerals play a vital role in many enzymatic and metabolic pathways that are critical for conceptus development during pregnancy in livestock species. The conceptus relies entirely on the maternal system for a sufficient supply of trace minerals and other nutrients needed for normal development. If this supply is inadequate, growth and/or health of the conceptus can be affected adversely, and many of these effects carry over into the neonatal period. Information, accumulated in our laboratory and presented herein, indicates that zinc, copper and manganese are among the trace minerals that have the greatest impact on reproduction. For example, levels of zinc, copper and manganese were several fold greater in the conceptus than in other reproductive tissues, indicating that the conceptus preferentially accumulates these minerals, an action that may be important for conceptus development, growth and survival. Moreover, some recent results indicate that increasing the biological availability of zinc, copper and manganese, by attachment to short peptide chains (i.e., proteinated trace minerals) can enhance reproductive performance of swine. Mineral concentrations in conceptuses from female pigs consuming proteinated trace minerals were greater than those from females that consumed only inorganic mineral salts. Elucidating the mechanisms whereby conceptus development and survival are enhanced by essential trace minerals may lead to development of specific feeding programs to increase the number and health of offspring at parturition, thereby allowing for further improvements in production efficiency in animal agriculture.
© 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Mineral; Nutrition; Utilization; Reproduction; Pregnancy

1. Introduction

Important links between nutrition and reproduction were clearly established many years ago. For example, Bennetts and Chapman (1937) established that enzootic neonatal ataxia (swayback) in newborn lambs was the result of ewes grazing copper deficient pastures. These and subsequent researchers (Allcroft et al., 1959) demonstrated that copper supplementation of the ewe during gestation could prevent this disease. Since that time, studies have shown the importance of numerous trace elements for support of normal reproduction in many animal species; however, nutrition and reproduction traditionally have been studied as separate disciplines.

Most early studies altered a nutrient concentration in the diet and then measured the outcome (e.g. litter size, birth weight, birth defects, etc.). In recent years, studies have focused more on cellular mechanisms by which nutrition affects fetal development. However, much of this work was conducted using the rodent model, making it necessary to extrapolate the findings to practical livestock nutritional. Many controlled nutritional studies need to be conducted to determine if the same effects that are observed in rodents also occur in livestock. With newer technology and more sensitive assays available, the disciplines of nutrition and reproduction can be investigated together more readily.

Hidiroglou and Knipfel (1981) stated that the fetus is completely dependent on the dam for its supply of nutrients, including essential trace elements. Inadequate transfer of these elements results in a mineral deficiency in the fetus, causing impaired fetal growth and abnor-

*Corresponding author.

E-mail addresses: chostetler@wsu.edu (C.E. Hostetler), rkincaid@ wsu.edu (R.L. Kincaid), mmirando@reeusda.gov (M.A. Mirando).

malities to the central nervous system, skeleton and metabolism (Widdowson et al., 1974). Additionally, newborn offspring of dams with insufficient mineral intake during pregnancy have low body reserves and are susceptible to trace mineral deficiencies in early life (Weiss et al., 1983). For example, selenium (Se) supplementation of cows during the last 60 days of gestation not only greatly increases endogenous Se reserves of newborn calves, but the improved Se status is still present in calves at 42 days of age (Abdelrahman & Kincaid, 1995). The mechanisms that control nutrient utilization during pregnancy are not well defined. By understanding these mechanisms, animal management practices can be developed to increase the number of viable offspring at parturition, as well as enhance other commercially important aspects of reproductive performance. Additionally, by knowing the time during pregnancy when an essential trace element is most needed, precise feeding plans can be formulated such that urinary or fecal excretion of the element are reduced, thereby reducing the release of heavy metals into the environment from intensive animal production operations. This article reviews the available information on the roles of essential trace elements in development of the embryo and fetus during pregnancy.

2. Early pregnancy

2.1. Maternal recognition of pregnancy and embryonic mortality in livestock

Conception rates, as determined by the presence of cleaved embryos in the oviduct, are relatively high in livestock and occur at a rate of 90–95% (Coffey & Britt, 1993; Pope, 1988; Robertson et al., 1951). However, the rate of embryonic mortality during the first 30 days of pregnancy is approximately 30% (Marlow & Smith, 1971; Perry & Rowlans, 1962; Pope, 1988, 1992), although the causes of early embryonic death in livestock are largely unknown. Factors that directly or indirectly influence conceptus growth and development are likely to also alter the rate of embryonic survival or development, thereby influencing the number and size of offspring at parturition. The essential trace minerals (ETM) copper (Cu), iodine (I), iron (Fe), manganese (Mn), Se and zinc (Zn) are known to influence embryonic and fetal survival, as well as other aspects of reproductive performance and growth in mammals (Davis & Mertz, 1987; Hambidge et al., 1986; Hidiroglou, 1979; Hurley & Keen, 1987). Thus, inadequacies in tissue concentrations of ETM may contribute to the high incidence of early embryonic mortality in livestock.

Much of the embryonic loss is thought to occur during that period of corpus luteum (CL) rescue (Moore, 1985; Wilmut et al., 1986a) termed 'maternal

recognition of pregnancy' (Short, 1969). Bazer et al. (1988, 1991a,b, 1994) extensively reviewed the mechanisms of maternal recognition of pregnancy in food-producing animals. Briefly, female livestock have uterine-dependent estrous cycles because the luteolysin, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is released from the endometrium, enters the uterine vasculature and causes demise of the CL (Kieborz et al., 1991; McCracken et al., 1999; Mirando et al., 1996; Goding, 1974). In cyclic female ruminants, oxytocin is released from the CL and, to a lesser extent, from the anterior pituitary in a pulsatile manner and travels through the systemic circulation to the uterus where it binds to its endometrial receptors to stimulate $PGF_{2\alpha}$ release (Flint & Sheldrick, 1986; Hooper et al., 1986). Pulsatile release of $PGF_{2\alpha}$ ensues as the endometrium attains responsiveness to oxytocin through increased endometrial expression of oxytocin receptors during the late luteal phase (Mirando et al., 1993b; Stevenson et al., 1994). Through this mechanism, $PGF_{2\alpha}$ is released in a pulsatile fashion with approximately five pulses in 24 h being required to lyse the CL (Schramm et al., 1983; Zarco et al., 1988). The female returns to estrus as progesterone production from the regressing CL wanes and follicular estrogen production increases. In pigs, more oxytocin is apparently released from the neurohypophysis than from the CL (Kotwica et al., 1990), although the endometrium is probably the most significant source of oxytocin in this species (Boulton et al., 1996; Trout et al., 1995; Vallet et al., 1998). Many aspects of luteolysis and pregnancy recognition differ between pigs and ruminants, although numerous similarities also exist (McCracken et al., 1999; Mirando et al., 1996).

In pregnant animals, the signal for maternal recognition of pregnancy results in rescue of the CL such that progesterone secretion continues and maintains the uterine environment in a favorable condition to support embryonic growth and development (Bazer & First, 1983). Pregnancy recognition occurs on approximately days 12–13 in sheep (Moor & Rowson, 1966; Rowson & Moor, 1967) and days 15–17 in cattle (Betteridge et al., 1980; Northey & French, 1980) and goats (Gnatek et al., 1989). In pregnant ruminants, the molecular signal responsible for maintenance of the CL is interferon-τ (Godkin et al., 1982; Martal et al., 1979). In the pig, the maternal recognition of pregnancy occurs on days 12–13 (Dhindsa & Dzuik, 1968) and the signal for pregnancy recognition is estrogen (Bazer & Thatcher, 1977), which is secreted by the conceptuses between days 10 and 16 of gestation (King & Ackerley, 1985), in association with a period of dramatic embryo elongation (Bazer, 1989). Estradiol must be present during days 11–15 to maintain the CL beyond day 30 of gestation (Geisert et al., 1987).

Because the majority of conceptus loss occurs during the critical period of pregnancy recognition (Pope,

1988), it is an important physiological event to study. Moreover, little is known about the causes of early embryonic mortality, although nutritional factors have been implicated as a cause (Ashworth & Antipatis, 2001; McArdle & Ashworth, 1999; Wilmut et al., 1986a). Trace minerals may have a direct effect on conceptus growth and development, thereby influencing their stage of development relative to that of the uterine environment and consequently, their survival.

3. Essential trace minerals

3.1. Major functions of ETM

Essential trace minerals are minerals that are required for normal growth and development of animals; however, ETM are normally present in minute quantities in the animal's body and are required in low concentrations in the diet. Although the nutritional requirements for these elements are small, these nutrients can greatly affect reproduction. The list of ETM includes cobalt (Co), Cu, chromium (Cr), Fe, I, Mn, Se and Zn. Of these, Cu, I, Mn, Se and Zn seem to have the greatest impact on reproduction and have been studied most extensively. In general, trace minerals are required for synthesis of many proteins and activate a vast array of enzyme systems. Metalloenzymes, of which ETM are constituents, are important in bone formation (Leach, 1967), lipid metabolism (Cunnane et al., 1993), glucose utilization (Jovanovic-Peterson & Peterson, 1996), iron transport (Raub et al., 1985), DNA synthesis and transport (Townsend et al., 1994) and free radical metabolism (deHaan et al., 1994). Through one or more of these mechanisms, ETM may directly affect embryonic and fetal development.

Essential trace minerals also influence the immune system (Chandra, 1999; Galyean et al., 1999; Madsen et al., 1991) and once pregnancy is established, conceptus growth may be controlled, in part, by the maternal immune system. Macrophages, natural killer cells and T lymphocytes are recruited to the uterus during early pregnancy in pigs, sheep, mice and humans (Bazer & Johnson, 1989; Croy et al., 1987, 1988; Keys & King, 1990; Lee et al., 1988; Starkey et al., 1988;) and it was proposed that cytokines secreted by these immune cells stimulate growth of the fetal-placental unit (Bazer & Johnson, 1989; Starkey et al., 1988). Further, interferon secretion is initiated by conceptuses of ruminants and swine at about the time of rapid conceptus morphogenesis and elongation (Cross & Roberts, 1989; Imakawa et al., 1987; Mirando et al., 1990; Stewart et al., 1987). Interferons are known to be potent regulators of cell growth and modulators of immune cell function. Thus, a deficiency in tissue concentrations of ETM could alter embryonic growth, signaling for pregnancy recognition or immune function and, therefore, contribute to the high incidence of early embryonic mortality in livestock.

3.2. Copper

Copper was first shown to be an ETM in 1928 (Hart, 1928). Cu deficiency in ruminants can occur through either low Cu concentrations in pastures (Saba et al., 2000) or due to molybdenum and sulfur in the forage and the formation of thiomolybdates in the rumen resulting in decreased availability of Cu (Grace et al., 1999; Unny et al., 2002). Enzootic neonatal ataxia in lambs has been known for many years to be a result of pregnant ewes grazing on Cu deficient pastures (Bennetts & Chapman, 1937). Subsequent studies confirmed this finding (Smith et al., 1977) and expanded it to include neonatal ataxia in other species (Joyce, 1955; O'Sullivan, 1977; Toolan, 1990; Wilkie, 1959). Evidence indicates that this disorder is caused by low brain Cu concentrations leading to a deficiency in cytochrome oxidase in the motor neurons and resulting aplasia of the myelin surrounding these neurons (Fell et al., 1965; Keen et al., 1998; Mills & Williams, 1962). In addition to the effect on neuronal development, Cu-deficient fetuses and neonates have characteristic cardiac hemorrhages (Tinker & Rucker, 1985) thought to be a result of decreased elastin content and cross-linking integrity because of reduced lysyl oxidase activity (Rucker et al., 1998). The decrease in lysyl oxidase activity in Cu-deficient fetuses has been implicated in lung abnormalities seen in rats (O'Dell et al., 1978), chickens (Harris, 1986) and rabbits (Abdel Mgeed et al., 1994), but this work has not yet been conducted in livestock species.

The alterations described above occur in utero but changes in Cu concentrations in female reproductive tissues throughout gestation have yet to be fully described for all species. Abdelrahman and Kincaid (1993) quantified Cu levels in fetal tissues at different stages of pregnancy in cattle, and found that stage of gestation did not affect Cu concentrations in the fetal liver or kidney. In contrast, others have determined that there is an accumulation of Cu by the ovine fetal liver as gestation advances (Grace et al., 1986; Langlands et al., 1982). Gooneratne and Christensen (1989) reported that Cu concentrations in bovine fetal liver were higher than maternal liver Cu concentrations. Similarly, concentrations of Cu were substantially greater in conceptus tissue than in the uterine endometrium or ovary of pigs on days 12–30 of gestation (Hostetler et al., 2000). These results may indicate an increased demand for Cu by the conceptus such that the maternal system shunts Cu to the developing embryo and fetus.

Copper functions as an activator of enzyme systems associated with Fe metabolism and is required for normal hematopoiesis. Ceruloplasmin is a Cu-containing

(6–7 Cu atoms) enzyme required for oxidation of Fe, from the ferrous to the ferric state, so that it can be utilized for erythrocyte formation (McArdle, 1992). Beguin and co-workers (1985) found that Cu, Fe and ceruloplasmin activity were significantly decreased in plasma and liver from pregnant female rats fed 1.3 ppm vs 11.1 ppm Cu, but they did not measure these factors in the fetus. A receptor for ceruloplasmin was isolated from human placental vesicles (Hilton et al., 1995) indicating that Cu is transported within the placenta. Because uteroferrin, a protein secreted by the endometrium of pigs during pregnancy (Raub et al., 1985), was shown to be active in the transport of ferric Fe to the conceptus (Raub et al., 1985), it is tempting to speculate that Cu may play a role in activation of uteroferrin secretion. Copper uptake by trophoblast cells has been demonstrated using human term placenta (Tong & McArdle, 1995) and appears to involve a membrane bound protein that binds ceruloplasmin. The uptake mechanism for Cu has been characterized for placental vesicles (Hilton et al., 1995). Copper may be important in oxidative defense systems as part of superoxide dismutase (SOD) because rat embryos cultured under Cu-deficient conditions develop abnormally (Hawk et al., 1998). It has been suggested that normal rat gestation diets should contain 5 ppm Cu (Anonymous, 1977), and typically ranges from 5.3 (Barone et al., 1998) to 18 ppm (Lewis et al., 1993). Beguin et al. (1985) reported that female rats fed diets containing either 1.3 or 11.1 ppm Cu had comparable numbers of implantation sites and fetuses appeared normal on day 11 of gestation; however, some fetuses were necrotic and reabsorbed by day 13 in the females fed the low Cu diet. There have been several reports that feeding high levels of Cu to sows during lactation can improve weaning weights and piglet survival (Roos & Easter, 1986; Thacker, 1991; Wallace et al., 1966). Lillie and Forbish (1978) fed 15, 30 or 60 ppm Cu to sows through four gestation–lactation cycles and demonstrated that pig birth weights, weaning weights and survival to weaning were increased with increasing Cu concentrations. Cromwell et al. (1993) reported that sows fed very high levels of Cu (i.e., 250 ppm) for an extended period of time had increased litter size. The exact mechanism by which feeding pharmacological levels of Cu to gestating sows manifests its beneficial effects on fetal development and subsequent piglet growth and survival has not been defined.

3.3. Iodine

Iodine was determined to be an ETM in the early 1900s through work that demonstrated that iodine could prevent goiter in humans (Merke, 1984). A deficiency of iodine is characterized by several reproductive problems in adult females including fetal resorption, abortion, stillbirths, irregular estrous cycles and suppressed estrus. The highest concentration of iodine is found in the thyroid gland where iodinated amino acids link with other amino acids to form thyroglobulin; the major storage form of iodine in the gland. While thyroglobulin represents roughly 90% of the iodine in the thyroid, iodine is also found as a constituent of thyroxine (T_4) and triiodothyronine (T_3). Regulation of these thyroid hormones occurs through the actions of thyroid releasing hormone, secreted from the hypothalamus, which enters the portal blood of the anterior pituitary where it stimulates the synthesis and release of thyroid stimulating hormone (TSH). Under the influence of TSH, thyroid cells actively transport iodine from the blood plasma to the colloid space where it is rapidly oxidized and bound to tyrosyl amino acid residues of thyroglobulin to form monoiodotyrosine and diiodotyrosine. Monoiodotyrosine and diiodotyrosine are subsequently coupled to form T_4 and T_3. Taurog (1996) provided a thorough review of the thyroid hormone biosynthetic pathway. Thyroxine, the major inhibitor of TSH secretion, provides a negative feedback action at the level of the anterior pituitary. While T_4 is the major secretory product of the thyroid gland, T_3 accounts for the majority of the biological activity. Most T_3 is produced by the reductive deiodination of the phenolic ring of T_4 by the type I, type II and type III $5'$-deiodinase enzymes. Inactivation of T_4 and T_3 occurs by deiodination of iodotyrosines at the tyrosyl ring to yield T_{3r}. Under low dietary intake of iodine, T_4 is not produced in adequate quantity to provide this negative feedback and TSH levels rise, thereby causing the classic symptom of iodine deficiency, goiter. Under influence of TSH, plasma T_3 levels are maintained during initial iodine deficiency because of intrathyrodial deiodination of T_4 to yield T_3. Interestingly, the deiodinase enzymes are reported to be Se-dependent (Arthur et al., 1993; Behne et al., 1990; Kohrle, 1999) and molecular cloning has revealed the presence of the UGA base sequence in the $3'$-untranslated region that codes for the insertion of selenocysteine in the context of a hairpin loop common to all Se-containing enzymes (Berry et al., 1991a, 1991b; Buettner et al., 1998, Kohrle, 1999). Therefore, poor Se nutrition can exacerbate problems associated with low dietary iodine intake (Arthur et al., 1990, 1999; Meinhold et al., 1993). The iodothyronine deiodinases show tissue specificity with type I located in the thyroid, liver and kidney and being responsible for production of plasma T_3 (Richard et al., 1998). Local production of T_3 is mediated in the brain, pituitary and brown adipose tissue by type II deiodinase and in the brain, skin, intestine and placenta by type III deiodinase (Richard et al., 1998).

In addition to the three iodothyronine deiodinases, selenoperoxidases and the Se-dependent enzyme, thioredoxin reductase, help to protect the thyroid gland from oxidative damage resulting from H_2O_2 produced during

formation of T_4 and T_3 (Arthur et al., 1999) providing another potential mechanism for the interaction between Se and iodine. The vast majority of investigations into the effects of combined iodine and Se deficiency have been conducted in the rat. Few studies in livestock have been conducted to confirm these findings, however, Zagrodzki et al. (1998) found that iodine deficient cows and their calves had increased thyroidal type I deiodinase and cytosolic glutathione peroxidase activity allowing them to appear clinically normal because of these compensatory mechanisms in T_3 production. Lambs born of ewes fed diets low in Se but supplemented with iodine tended to have reduced plasma T_3 levels (Donald et al., 1993; Rock et al., 2001). Decreased plasma T_3 levels were also observed in kid goats from iodine and Se deficient does even when iodine was supplemented to the kids after birth (Wichtel et al., 1996). Mee and Rogers (1996) addressed the practical aspect of iodine and Se deficiency in beef cattle and determined that, although iodine and Se deficiency have been associated with perinatal calf mortality, restoring maternal thyroid hormone balance through iodine and Se supplementation did not reduce calf mortality. Much work remains to be done to determine the effects of combined iodine and Se deficiency on fetal development in livestock species.

Iodine is supplied to the fetus by two mechanisms. First, the endometrium concentrates iodine by an active process during late pregnancy and makes it available for the fetus (Peterson & Young, 1952). Second, the serum of the fetus has a specific thyroxine-binding protein that increases in concentration in late term fetuses (Osorio & Myant, 1958). This fetal thyroxine-binding protein has a higher affinity for thyroxine than the thyroxine-binding protein present in the maternal plasma (Osorio & Myant, 1960). Experimental studies indicate that reproductive failure in iodine deficiency is mediated by a combination of maternal and fetal hypothyroidism (Burrow et al., 1994; Fisher et al., 1972; Potter et al., 1982). McIntosh et al. (1979) reported the effects of iodine deficiency on fetal brain development were more severe when thyroidectomy was performed on fetal sheep at 50–60 days of gestation. Fetal thyroidectomy later in gestation (i.e., after day 98) reduced the severity of the effects of iodine deficiency (McIntosh et al., 1982; Potter et al., 1986). More recently, several experiments were conducted in the laboratory of Morreale de Escobar to investigate the importance of maternal thyroid hormones during fetal brain development. They found that thyroid hormones from the maternal system are available to the developing fetus, but after development of the fetal thyroid, T_4 and T_3 are of both fetal and maternal origin (reviewed by Morreale de Escobar et al., 1993). Additionally, the fetus requires a supply of maternal T_4 to support early brain development (Burrow, 1990; Roti et al., 1983) and this information is compiled in several excellent reviews (Burrow et al., 1994; Calvo et al., 2002; Polk, 1995).

3.4. Manganese

Manganese was first classified as an ETM in 1931 (Orent & McCollum, 1931; Waddell et al., 1931). A deficiency of Mn results in poor growth and impaired reproduction, which is characterized by testicular atrophy in males (Hurley & Doane, 1989), impaired ovulation in females (Wilson, 1952) and small litters of weak, ataxic piglets (Plumlee et al., 1956).

Transport of Mn is facilitated by α_2-macroglobulin and occurs rapidly to all tissues where it is localized in the mitochondria of the cell (Maynard & Cotzias, 1955). The tissue most responsive to dietary intake of Mn is bone, where it is essential for formation of chondroitin sulfate as a component of mucopolysaccharides in the matrix of organic bone (Leach, 1967, 1976). Thus, Mn may play a key role in fetal bone formation during organogenesis. Several studies have demonstrated that Mn crosses the placenta to the fetus (Gamble et al., 1971; Newland & Davis, 1961) and fetal storage of Mn seems to be dependent on maternal dietary intake (Hansard, 1972; Hostetler et al., 2000; Howes & Dyer, 1971; Langlands et al., 1982; Rojas et al., 1965). In contrast to several other trace minerals, the fetus does not preferentially accumulate Mn in the liver during gestation and fetal liver Mn concentrations tend to be lower than adult liver Mn concentrations (Meinel et al., 1979). Rate of fetal accumulation of Mn is estimated to be 0.3 mg/day between 190 and 270 days of gestation (House & Bell, 1993), which is consistent with the finding that samples of fetal liver taken at different gestational ages did not show differences in Mn concentrations (Graham et al., 1994; Kincaid et al., 1993). Further, Mn levels in porcine embryos and fetuses were 2- to 12-fold greater than those in the endometrium or ovary during the first month of gestation (Hostetler et al., 2000). However, the mechanism of Mn transfer from the dam to the conceptus has yet to be determined.

One of the three main isozymes of SOD found in humans is Mn-SOD, which is located in the mitochondria (Weisiger & Fridovich, 1973a, 1973b). Studies with a fibroblast cell line demonstrated that Mn-SOD promotes cellular differentiation (St. Clair et al., 1994), an effect that may be extremely important during early fetal development. In fact, preimplantation bovine embryos were shown to transcribe and express Mn-SOD under culture conditions (Lequarre et al., 2001). Other functions attributed to Mn include actions as a cofactor for an enzyme that converts mevalonic acid to squalene and stimulates synthesis of cholesterol (Olson, 1965). Squalene is a precursor in steroid hormone production; thus, Mn may have a role in initiating estradiol secretion by the conceptus as the signal for pregnancy recognition in

pigs. Alternatively, Mn may play a role in progesterone secretion because concentrations of Mn in the CL of ewes increased between 4 and 11 days (Hidiroglou & Shearer, 1976) and sub-optimal progesterone concentration has been implicated as a cause of early embryonic loss (Wilmut et al., 1986b; Wright et al., 1982). Moreover, several studies have reported that supplementation of cattle and sheep diets with Mn improved pregnancy rates (Egan, 1972; Everson et al., 1959; Wilson, 1966), although the mechanisms behind the beneficial effects of Mn on reproductive performance have not been elucidated.

3.5. Selenium

Selenium was first determined to be an ETM by Schwarz and Foltz (1957) when it was reported that Se prevented liver necrosis in rats. Subsequently, Muth et al. (1958) prevented nutritional muscular dystrophy in lambs by supplementation of Se and Rotruck et al. (1973) reported that glutathione peroxidase contains Se, thereby establishing a specific biological function for Se.

Soil concentrations of Se vary greatly depending on geographical region and this, along with variations in soil pH, leads to variation in the Se content of animal feeds grown on these soils (Allaway, 1972). Most absorption of dietary Se occurs in the small intestine (Wolffram et al., 1986) from which it is transported to the liver, kidney and muscle, tissues that contain the largest amount of Se in the body. Selenium, as selenomethionine, can be incorporated nonspecifically into body proteins; however, Se is present as selenocysteine in selenoproteins (Behne & Kyriakopoulos, 2001). Among the most well-known selenoproteins are glutathione peroxidases, deiodinases and thioredoxin reductases (Allan et al., 1999). Through its association with these enzymes, Se is involved in the catabolism of peroxides generated during lipid oxidation (Burk, 1991). Thus, Se plays an important role in maintaining the integrity of the cell and the organelles within the cell, and may act through this mechanism to protect the early fetus from mortality due to oxidative damage.

Signs of Se deficiency include nutritional muscular dystrophy in lambs, poultry, calves and pigs, liver necrosis in rats and pigs, and exudative diathesis in poultry (Ullrey, 1974). Hill and co-workers (2001) successfully created fatal myopathy in guinea pigs by feeding the dams a diet deficient in both Se and vitamin E. Se-responsive problems include impaired fertility (Segerson et al., 1977) and abortion (Hedstrom et al., 1986; Taylor et al., 1979; Yamini & Mullaney, 1985). While many field studies have reported that poor reproduction in livestock is improved after Se supplementation (Hartley & Grant, 1961; Mudd & Mackie, 1973; Scales, 1974; Vipond, 1984), there are few properly controlled studies to support these findings (Davies, 1966; Hartley, 1963;

Segerson et al., 1977). Buck et al. (1981) reported a preferential accumulation of Se in some maternal reproductive tissues, as well as in the fetal pituitary and adrenal glands. These fetal tissues are very important in the induction of parturition and insufficient dietary Se may impair parturition or other aspects of reproductive performance. Conception rate in dairy cattle was improved when barium selenate was injected (Taskar et al., 1987) or given orally as a bolus to beef cattle (Allan et al., 1993). The improvement in conception rate seen in some studies but not others (reviewed by Harrison & Hancock, 1999) may be due to a down-stream effect resulting from the reduction of retained placenta, reduced incidence of metritis and fewer days to insemination and conception following Se supplementation (Harrison & Hancock, 1999). Mahan et al. (1974), and Chavez and Patton (1986) demonstrated an improvement in litter size when Se was supplemented in diets of gestating sows. In contrast, Se supplementation (0.1–0.3 ppm) of gilt diets did not alter the number of live-born pigs (Mahan & Kim, 1996; Mihailovic et al., 1982; Mutetikka & Mahan, 1993) but did reduce the number of stillborn pigs (Mihailovic et al., 1982). Kim and Mahan (2001) fed diets containing up to 10 ppm Se to gilts and found a decrease in litter size with increasing Se concentration. However, Poulsen et al. (1989) fed 16 ppm Se to sows during gestation and lactation but failed to detect a decrease in litter size. The discrepancy in litter size observed in the above studies could arise from many factors including maternal age, timing and duration of supplementation, level of Se in the basal diet, the level of Se supplementation or the source of Se. Clearly, more work needs to be conducted to fully describe the effects of Se on pregnancy outcome in the pig, but a gestation ration containing 0.1–0.3 ppm Se should be adequate to support normal reproduction.

Placental transfer of Se has been documented for ruminants (Jacobsson & Oksanen, 1966; Koller et al., 1984) and dietary supplementation of cows and ewes during late gestation significantly increases Se in the newborn (Abdelrahman & Kincaid, 1995; Rock et al., 2001). The mechanism by which Se crosses the placenta is reported to be by anion exchange with sulfur (Boyd & Shennan, 1986; Shennan, 1988). Although this mechanism has not yet been shown to occur in food animals, it is probably an evolutionarily conserved pathway. Because many of the Se deficiency cases occur in newborn animals, either placental transfer of Se is a relatively inefficient process or the newborn animal has a higher Se requirement than older animals. Van Saun et al. (1989) found that the concentration of Se in maternal and fetal liver, whole blood and serum were highly correlated. More recently, Abdelrahman and Kincaid (1993) demonstrated that fetal liver concentrations of Se increased initially and then decreased as gestation advanced. Gooneratne and Christensen (1989) reported that, in

general, fetal liver Se concentrations were higher than in the dam. When pregnant ewes were fed diets low in Se, not only were Se reserves reduced in the newborn lambs and the concentration of Se in colostrum reduced, but the lambs absorbed less IgG from the colostrum (Rock et al., 2001). Considerable work remains to elucidate the role of Se in the development of the fetus and a more mechanistic approach may yield the best results.

3.6. Zinc

Zinc, established as an ETM in 1934 (Todd et al., 1934), is found in highest concentrations in liver, bone, kidney and muscle (Schell & Kornegay, 1996), where it functions as a constituent of numerous metalloenzymes (Hambidge et al., 1986). Absorption of Zn, at a rate of 5–40% of dietary intake, occurs in the small intestine, where Zn is then rapidly distributed to tissues via the blood (Hambidge et al., 1986). Zinc deficiency is marked by growth retardation, anorexia, parakeratosis and hypogonadism (Tucker & Salmon, 1955).

The fetus requires Zn for normal growth and development (Vallee & Falchuk, 1993). Additionally, Zn deficiency results in fetal teratogenesis, prolonged gestation, difficult labor, low birth weight, and weak offspring (Bedwal & Bahuguna, 1994; Favier, 1992). Although the specific requirement for Zn during reproduction has not been well established, it is probably higher than for other life stages due to nutrient demand for fetal growth, stress of parturition and milk synthesis during lactation (National Research Council, 1998). In addition, levels of Zn in porcine conceptuses were 1.7- to 8.7-fold greater than those in the endometrium or ovary between days 12 and 30 of gestation (Hostetler et al., 2000), which is further indicative of increased uptake and/or utilization by the developing conceptus. In contrast, (Widdowson et al., 1974) reported that human fetal hepatic Zn stores decreased with gestational age, whereas Abdelrahman and Kincaid (1993) detected no change during gestation in cattle. However, neither of these latter studies examined conceptuses in the early stages of development when early embryonic mortality is greatest.

Expression of Cu/Zn-SOD and glutathione peroxidase activity was shown to be elevated in organs of developing fetuses (deHaan et al., 1994). These enzymes are active in scavenging free oxygen radicals, thereby protecting cell membranes from oxidative damage. Zinc was shown to play a role in the configuration of RNA and DNA (Chesters, 1978), primarily by formation of zinc fingers that are essential to the binding of the steroid–receptor complex to DNA (Freedman, 1992). The steroid responsive elements on DNA then turn on genes active in protein synthesis that may be important during early pregnancy when the conceptus and uterus are producing proteins, under the influence of gonadal

steroids, that serve as biochemical signals between the conceptus and dam. Zinc also is an important cofactor in DNA synthesis and gene transcription (Chesters, 1978, 1991). Zinc is involved in the formation of prostaglandins because Zn enzymes control the arachidonic acid cascade (Chanmugam et al., 1984; Sakuma et al., 1996, 1999; Wauben et al., 1999). Prostaglandins are required for maintenance of pregnancy because $PGF_{2\alpha}$ secretion into the uterine lumen, and away from the uterine vasculature, is increased in pregnant pigs (Bazer & Thatcher, 1977) and inhibition of $PGF_{2\alpha}$ synthesis prevents establishment of pregnancy in mice and swine (Kraeling et al., 1985; Lau et al., 1973), whereas indomethacin-induced blockade of pregnancy in mice is reversed by administration of $PGF_{2\alpha}$ (Lau et al., 1973). Thus, Zn may enhance conceptus development through its effects on $PGF_{2\alpha}$ synthesis. Prostaglandin $F_{2\alpha}$ is also important at parturition to initiate uterine contractions required for expulsion of the fetus (Thorburn, 1991, 1992).

Another potential pathway for Zn to influence pregnancy is by modulating the action of insulin-like growth factors (IGFs) at the cellular level. Insulin-like growth factors are known to be potent stimulators of tissue differentiation and cell proliferation (Zapf & Froesch, 1986). These growth factors are present in high levels within the uterus of several livestock species during early pregnancy (Geisert et al., 1991; Ko et al., 1991; Simmen et al., 1992) and may be important in uterine remodeling during the time of embryonic implantation (IGF-I) and fetal development (IGF-II), as well as for conceptus growth in general. The responsiveness of cells to IGF is mediated by the type and number of IGF receptors present on the cell surface (LeRoith et al., 1995) and by IGF-binding proteins (IGFBP), which are secreted by cells and inhibit IGF binding to cell surface receptors (Clemmons et al., 1991). In vitro studies using transformed cell lines have demonstrated that Zn decreases the binding affinity of IGF to IGFBP (Sackett & McCusker, 1998) and increases IGF binding affinity for Type 1 IGF receptors on the cell surface (McCusker et al., 1998). In addition, IGF-1 levels are lowered during Zn deficiency (MacDonald, 2000). Therefore, if more Zn is available, more IGF may be transferred from IGFBP to cell surface IGF receptors to promote growth and differentiation. Although the actions of Zn in fetal growth and development have not yet been defined, these results may provide one possible mechanism for the action of Zn during early pregnancy.

3.7. Factors affecting bioavailability of ETM

Bioavailability, as defined by Levander (1983), is a quantitative measure of the utilization of a nutrient in a food, meal or diet under specific conditions to support normal structural and physiological processes occurring

in the body. Absorption, availability and utilization of ETM may be limited by many factors including competing ions, valance state of the minerals ingested, pH of the intestinal contents, ruminal fermentation, chelation to form insoluble mineral salt complexes, saturation of mineral transport mechanisms, and limited duration of retention. Evidence exists that, at least under certain conditions, organic forms of some trace minerals can have greater bioavailability than inorganic salt forms. For example, more Se is absorbed from selenomethionine (selenized yeast) than sodium selenite, resulting in greater concentrations of Se in blood of newborns and higher concentrations of Se in colostrum (Awadeh et al., 1998; Rock et al., 2001) and milk (Knowles et al., 1999). Similarly, attaching minerals to amino acids and short peptide chains enhances retention of Cu, Zn and Mn (Hostetler et al., 2000; Hostetler & Mirando, 1998; Kegley & Spears, 1994; Mirando et al., 1993a; Smith et al., 1994; Ward et al., 1996; Wright & Spears, 2001; Wright et al., 2001). Covalent linking of minerals to amino acids or peptides may provide ETM with multiple routes for absorption from the intestine. Some absorption could occur through normal mineral transport mechanisms. Alternatively, uptake may occur via transport proteins for amino acids, di-peptides and tri-peptides, in the intestinal mucosa (Munck, 1981; Schultz, 1986; Stevens & Wright, 1987; Wolffram et al., 1989). Additionally, attaching ETM to amino acids or peptides may also serve to limit the ability of a mineral to form insoluble complexes with other minerals or dietary factors (e.g., phytic acid, thiomolybdates, etc.) in the digestive tract that render the ETM unavailable to the animal (Ward et al., 1996).

In contrast to the reports indicating increased bioavailability of organic ETM, others have found little or no difference in the bioavailability of organic ETM compared to inorganic sources (Mahan et al., 1999; Wedekind et al., 1994; Whitaker et al., 1997; Olson, 1999; Wolter et al., 1999). Wedekind et al. (1994) reported that the general trend in bioavailability of Zn from different sources was: zinc sulfate > zinc methionine > zinc oxide > zinc lysine. Olson et al. (1999) found no difference in liver Zn and Mn, but higher Cu concentrations in beef cattle fed supra-nutritional levels of organic ETM compared to those fed an equivalent amount of inorganic ETM. It was also reported that organic minerals increased the days to conception during the first year but not in the second year of the trial (Olson et al., 1999). Others reported that feeding organic Se to pigs has little effect on growth performance or carcass quality when compared to inorganic sources of Se (Mahan et al., 1999; Wolter et al., 1999). However, differences between ruminants and nonruminants in mineral absorption make comparison across species very difficult. Furthermore, there is considerable variation among commercially available trace element prod-

ucts (proteinates, chelates, etc.) and some may be effective in a particular species and feeding situation, while others are not (Spears, 1996). Further studies are required to better define the conditions where feeding organic trace minerals may improve animal performance and to determine the mechanism of action whereby animal performance is enhanced.

Two studies demonstrated increased bioavailability of proteinated ETM to the developing fetus in swine. When only 25% of the dietary Cu, Mn and Zn were supplemented in the proteinated form (OPTiMINS; DuCoa, Highland, IL, USA) with the remaining 75% in the inorganic salt form, pregnancy rate on day 30 of gestation was improved (Mirando et al., 1993a). Although ovulation rate and the average number of fetuses did not differ between pregnant sows receiving proteinated ETM or inorganic ETM, the number of live fetuses was greater and mean number of degenerating fetuses was less on day 30 of gestation for sows fed the proteinated ETM (Mirando et al., 1993a). These latter results are indicative of a decrease in the early embryonic loss that occurs at a high rate in swine (Pope, 1988, 1992). Subsequently, gilts fed proteinated or inorganic ETM had a similar number of embryos on day 12 of gestation, but by day 15, the total mass of embryonic tissue was approximately 70% greater in gilts fed diets containing proteinated ETM (Hostetler & Mirando, 1998), although the number of conceptuses was not specifically determined in that study. Again, ovulation rate was unaltered. Whether greater total mass of embryonic tissue in gilts fed proteinated ETM represents more embryos or larger conceptuses may not be particularly important because it has been reported that larger, more advanced conceptuses are more likely to survive (Xie et al., 1990a, 1990b), presumably because of the reduced asynchrony of development (Pope, 1988; Pope et al., 1990). Moreover, the onset of a difference in mass of embryonic tissue between days 12 and 15 is consistent with the timing of early embryonic mortality in pigs (Pope, 1988), further indicating that these changes may be indicative of increased conceptus survival in pregnant pigs (Hostetler & Mirando, 1998; Mirando et al., 1993a).

Concentrations of Cu, Mn and Zn were all significantly greater in conceptuses collected on day 12 of pregnancy from pigs fed the proteinated ETM diet (Hostetler et al., 2000). Moreover, the increases in conceptus mineral levels were extraordinarily large; Cu was increased 6-fold, Mn was increased 7-fold, and Zn was increased 4-fold compared to conceptuses from gilts that were not fed proteinated ETM. However, by days 15–30 of gestation, only Cu was increased in conceptuses of pigs fed the proteinated ETM (Hostetler et al., 2000). Importantly, the increase on day 12 in ETM in conceptuses from gilts fed proteinated ETM (Hostetler et al., 2000) preceded the increase in mass of conceptus

tissue that was detected on day 15 (Hostetler & Mirando, 1998) and the reduced conceptus death observed on day 30 (Mirando et al., 1993a). This indicates that increases in conceptus levels of ETM could have contributed to increased conceptus survival. The high embryonic and fetal levels of Cu, Mn and Zn, compared to other tissues, are further indicative of the role for ETM in embryonic and fetal development. While the results concerning the beneficial effects of proteinated minerals in swine may be considered somewhat preliminary, there is ample merit to investigating this practice as a method for increasing absorption and utilization of ETM in livestock.

4. Summary and conclusions

The necessity of ETM for support of life is largely unquestioned; however, their requirement for reproduction has not been as extensively studied. Many experiments conducted to investigate the interaction of reproduction and nutrition utilized the rat as a biological model. Thus, much of the information must be extrapolated to livestock species. Additionally, early research conducted to establish nutritional requirements for livestock measured the end result (e.g., conception rate, litter size, birth weight, weaning weight, etc.) but not the mechanism behind the improvement noted when minerals are fed above deficiency levels. Mechanisms whereby conceptus development and fetal survival are enhanced by ETM have not been investigated. Elucidating these mechanisms will allow for greater improvements in production efficiency in commercial enterprises that produce food animals.

References

Abdel Mgeed, A.B., Welti, R., Oehme, F.W., Pickrell, J.A., 1994. Perinatal hypocuprosis affects synthesis and composition of neonatal lung collagen, elastin, and surfactant. American Journal of Physiology 267, L679–L685.

Abdelrahman, M.M., Kincaid, R.L., 1993. Deposition of copper, manganese, zinc, and selenium in bovine fetal tissue at different stages of gestation. Journal of Dairy Science 76, 3588–3593.

Abdelrahman, M.M., Kincaid, R.L., 1995. Effect of selenium supplementation of cows on maternal transfer to fetal and newborn calves. Journal of Dairy Science 78, 625–630.

Allaway, W.H., 1972. An overview of distribution patterns of trace elements in soils and plants. Annals of the New York Academy of Science 199, 17–25.

Allan, C.L., Hemingway, R.G., Parkins, J.J., 1993. Improved reproductive performance in cattle dosed with trace element/vitamin boluses. The Veterinary Record 132, 463–464.

Allan, C.B., Lacourciere, G.M., Stadtman, T.C., 1999. Responsiveness of selenoproteins to dietary selenium. Annual Reviews Nutrition 19, 1–16.

Allcroft, R., Clegg, F.G., Uvarov, O., 1959. Prevention of swayback in lambs. Veterinary Record 71, 884–889.

Anonymous, 1977. Report of the American Institute of Nutrition Ad Hoc Committee on Standards for Nutritional Studies. Journal of Nutrition 107, 1340–1348.

Arthur, J.R., Beckett, G.J., Mitchell, J.H., 1999. The interactions between selenium and iodine deficiencies in man and animals. Nutrition Research Reviews 12, 55–73.

Arthur, J.R., Nicol, F., Beckett, G.J., 1993. Selenium deficiency, thyroid hormone metabolism, and thyroid hormone deiodinases. American Journal of Clinical Nutrition 57 (Suppl.), 236S–239S.

Arthur, J.R., Nicol, F., Beckett, G.J., 1990. Hepatic iodothyronine 5′-deiodinase: the role of selenium. Biochemical Journal 272, 537–540.

Ashworth, C.J., Antipatis, C., 2001. Micronutrient programming of development throughout gestation. Reproduction 122, 527–535.

Awadeh, F.T., Kincaid, R.L., Johnson, K.A., 1998. Effect of level and source of dietary selenium on concentrations of thyroid hormones and immunoglobulins in beef cows and calves. Journal of Animal Science 76, 1204–1215.

Barone, A., Ebesh, O., Harper, R.G., Wapnir, R.A., 1998. Placental copper transport in rats: effects of elevated dietary zinc on fetal copper, iron and metallothionein. Journal of Nutrition 128, 1037–1041.

Bazer, F.W., 1989. Establishment of pregnancy in sheep and pigs. Reproduction Fertility and Development 1, 237–242.

Bazer, F.W., First, N.L., 1983. Pregnancy and parturition. Journal of Animal Science 57 (Suppl. 2), 425–460.

Bazer, F.W., Johnson, H.M., 1989. Actions of lymphokines and cytokines on reproductive tissue. Progress in Neurology, Endocrinology and Immunology 2, 50–54.

Bazer, F.W., Thatcher, W.W., 1977. Theory of maternal recognition of pregnancy in swine based on estrogen controlled endocrine versus exocrine secretion of prostaglandin $F_{2\alpha}$ by the uterine endometrium. Prostaglandins 14, 397–401.

Bazer, F.W., Ott, T.L., Spencer, T.E., 1994. Pregnancy recognition in ruminants, pigs and horses: signals from the trophoblast. Theriogenology 41, 79–94.

Bazer, F.W., Simmen, R.C.M., Simmen, F.A., 1991a. Comparative aspects of conceptus signals for maternal recognition of pregnancy. Annals of the New York Academy of Sciences 622, 202–211.

Bazer, F.W., Thatcher, W.W., Hansen, P.J., Mirando, M.A., Ott, T.L., Plante, C., 1991b. Physiological mechanisms of pregnancy recognition in ruminants. Journal of Reproduction and Fertility 43 (Suppl.), 39–47.

Bazer, F.W., Vallet, J.L., Harney, J.P., Gross, T.S., Thatcher, W.W., 1988. Comparative aspects of maternal recognition of pregnancy between sheep and pigs. Journal of Reproduction and Fertility 37 (Suppl.), 85–87.

Bedwal, R.S., Bahuguna, A., 1994. Zinc, copper and selenium in reproduction. Experientia 50, 626–640.

Beguin, D.P., Kincaid, R.L., Hargis, A.M., 1985. Fetal death in copper-deficient rats. Nutrition Reports International 31, 991–999.

Behne, D., Kyriakopoulos, A., 2001. Mammalian selenium-containing proteins. Annual Reviews Nutrition 21, 453–473.

Behne, D., Kyriakopoulos, A., Meinhold, H., Kohrle, J., 1990. Identification of type I iodothyronine 5′-deiodinase as a selenoenzyme. Biophysical Research Communications 173, 1143–1149.

Bennetts, H.W., Chapman, F.E., 1937. Copper deficiency in sheep in western Australia: a preliminary account of the aetiology of enzootic ataxia of lambs and anemia of the ewe. Australian Veterinary Journal 13, 138–149.

Berry, M.J., Banu, L., Chen, Y., Mandel, S.J., Kieffer, J.D., Harney, J.W., Laresn, P.R., 1991a. Recognition of UGA as a selenocysteine codon in type-I deiodinase requires sequences in the 3′ untranslated region. Nature 353, 273–276.

Berry, M.J., Banu, L., Laresn, P.R., 1991b. Type-I iodothyronine deiodinase is a selenocysteine-containing enzyme. Nature 349, 438–440.

Betteridge, K.L., Eaglesome, M.D., Randall, G.C., Mitchell, D., 1980. Collection, description and transfer of embryos from cattle 10–16 days after oestrus. Journal of Reproduction and Fertility 59, 205–216.

Boulton, M.I., McGrath, T.J., Goode, J.A., Broad, K.D., Gilbert, C.L., 1996. Changes in content of mRNA encoding oxytocin in the pig uterus during the oestrous cycle, pregnancy, at parturition and in lactational anoestrous. Journal of Reproduction and Fertility 108, 219–227.

Boyd, C.A.R., Shennan, D.B., 1986. Sulphate transport into vesicles prepared from human placental brush border membranes; inhibition by trace element oxides. Journal of Physiology 379, 367–376.

Buck, E.L., Schmitz, J.A., Swanson, L.V., 1981. Incorporation of ^{75}Se into endocrine glands and reproductive tissues of the prepartum ewe and fetus. In: Spallholz, J.E., Martin, J.L., Ganther, H.E. (Eds.), Selenium in Biology and Medicine. AVI Publishing Co, Westport, CT, USA, pp. 514–520.

Buettner, C., Harney, J.W., Larsen, P.R., 1998. The 3′-untranslated region of human type 2 iodothyronine deiodinase mRNA contains a functional selenocysteine insertion sequence element. Journal of Biological Chemistry 273, 33374–33378.

Burk, R.F., 1991. Molecular biology of selenium with implications for its metabolism. FASEB Journal 5, 2274–2279.

Burrow, G.H., 1990. Thyroid status in normal pregnancy. Journal of Clinical Endocrinology and Metabolism 71, 274–275.

Burrow, G.N., Fisher, D.A., Larsen, P.R., 1994. Maternal and fetal thyroid function. New England Journal of Medicine 331, 1072–1078.

Calvo, R.M., Jauniaux, E., Gulbis, B., Asuncion, M., Gervy, C., Contempre, B., Morreale de Escobar, G., 2002. Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. Journal of Clinical Endocrinology and Metabolism 87, 1768–1777.

Chandra, R.K., 1999. Nutrition and immunology: from the clinic to cellular biology and back again. Proceedings of the Nutrition Society 58, 681–683.

Chanmugam, P., Wheeler, C., Hwang, D.H., 1984. The effect of zinc deficiency on prostaglandin synthesis in rat testes. Journal of Nutrition 114, 2066–2072.

Chavez, E.R., Patton, K.L., 1986. Response to injectable selenium and vitamin E on reproductive performance of sows receiving a standard commercial diet. Canadian Journal of Animal Science 66, 1065–1074.

Chesters, J.K., 1978. Biochemical functions of Zn in animals. World Review Nutrition Dietetics 32, 135–164.

Chesters, J.K., 1991. Trace element-gene interactions with particular reference to zinc. Proceedings of the Nutrition Society 50, 123–129.

Clemmons, D.R., Camacho-Hübner, C., Jones, J.I., McCusker, R.H., Busby, W.H., 1991. Modern conceptus of insulin-like growth factors. In: Spencer, E.M. (Ed.), Insulin-like Growth Factor Binding Proteins: Mechanisms of Action at the Cellular Level. Elsevier Science, New York, pp. 475–486.

Coffey, M.T., Britt, J.H., 1993. Enhancement of sow reproductive performance by beta-carotene or vitamin A. Journal of Animal Science 71, 1198–1202.

Cromwell, G.L., Morgan, H.J., Stahly, T.S., 1993. Long-term effects of feeding high copper diet to sows during gestation and lactation. Journal of Animal Science 71, 2996–3002.

Cross, J.C., Roberts, R.M., 1989. Porcine conceptuses secrete an interferon during the preattachment period of early pregnancy. Biology of Reproduction 40, 1109–1118.

Croy, B.A., Waterfield, A., Wood, W., King, G.J., 1988. Normal murine and porcine embryos recruit NK cells to the uterus. Cellular Immunology 115, 471–480.

Croy, B.A., Wood, W., King, G.J., 1987. Evaluation of intrauterine immune suppression during pregnancy in a species with epitheliochorial placentation. Journal of Immunology 139, 1088–1095.

Cunnane, S.C., Yang, J., Chen, Z.Y., 1993. Low zinc intake increases apparent oxidation of linoleic and α-linolenic acids in the pregnant rat. Canadian Journal of Physiology and Pharmacology 71, 205–210.

Davies, H.L., 1966. The effect of selenium and vitamin E on reproduction in Merino sheep in South Western Australia. Journal of Australian Institute of Agriculture Research 32, 216–217.

Davis, G.K., Mertz, W., 1987. Copper, 5th ed.. In: Mertz, W. (Ed.),. Trace Elements in Human and Animal Nutrition, vol. 1. Academic Press, San Diego, pp. 301–364.

deHaan, J.B., Tymms, M.J., Cristiano, F., Kola, I., 1994. Expression of copper/zinc superoxide dismutase and glutathione peroxidase in organs of developing mouse embryos, fetuses, and neonates. Pediatric Research 35, 188–196.

Dhindsa, D.S., Dzuik, P.J., 1968. Influence of varying the proportion of uterus occupied by embryos on maintenance of pregnancy in the pig. Journal of Animal Science 27, 668–672.

Donald, G.E., Langlands, J.P., Bowles, J.E., Smith, A.J., 1993. Subclinical selenium insufficiency. 4. Effects of selenium, I, and thiocyanate supplementation of grazing ewes on their selenium and iodine status, and on the status and growth of their lambs. Australian Journal of Experimental Agriculture 33, 411–416.

Egan, A.R., 1972. Reproductive responses to supplemental zinc and manganese in grazing Dorset Horn ewes. Australian Journal Experimental Agriculture Animal Husbandry 12, 131–135.

Everson, G.J., Hurley, L.S., Geiger, J.F., 1959. Manganese deficiency in the guinea pig. Jounal of Nutrition 68, 49–56.

Favier, A.E., 1992. The role of zinc in reproduction: hormonal mechanisms. Biological Trace Element Research 32, 363–382.

Fell, B.F., Mills, C.F., Boyne, R., 1965. Cytochrome oxidase deficiency in the motor neurons of copper-deficient lambs: a histochemical study. Research in Veterinary Science 6, 170–177.

Fisher, D.A., Dussault, J.H., Erenberg, A., Lam, R.W., 1972. Thyroxine and triiodothyronine metabolism in maternal and fetal sheep. Pediatric Research 12, 894–899.

Flint, A.P.F., Sheldrick, E.L., 1986. Ovarian oxytocin and the maternal recognition of pregnancy. Journal of Reproduction and Fertility 76, 831–839.

Freedman, L.P., 1992. Anatomy of the steroid receptor zinc finger region. Endocrine Reviews 13, 129–145.

Galyean, M.L., Perino, L.J., Duff, G.C., 1999. Interaction of cattle health/immunity and nutrition. Journal of Animal Science 77, 1120–1134.

Gamble, C.T., Hansard, S.L., Moss, B.R., Davis, D.J., Lidvall, E.R., 1971. Manganese utilization and placental transfer in pregnant gilts. Journal of Animal Science 32, 84–87.

Geisert, R.D., Lee, C.Y., Simmen, F.A., Zavy, M.T., Fliss, A.E., Bazer, F.W., Simmen, R.C.M., 1991. Expression of messenger RNAs encoding insulin-like growth factor-I, -II and insulin-like growth factor binding protein-2 in bovine endometrium during the estrous cycle and early pregnancy. Biology of Reproduction 45, 975–983.

Geisert, R.D., Zavy, M.T., Wettemann, R.P., Biggers, B.G., 1987. Length of pseudopregnancy and pattern of uterine protein release as influenced by the time and duration of oestrogen administered in the pig. Journal of Reproduction and Fertility 79, 163–172.

Gnatek, G.G., Smith, L.D., Duby, R.T., Godkin, J.D., 1989. Maternal recognition of pregnancy in the goat: effects of conceptus removal on interestrus intervals and characterization of conceptus protein production during early pregnancy. Biology of Reproduction 41, 655–663.

Goding, J.R., 1974. The demonstration that $PGF_{2\alpha}$ is the uterine luteolysin in the ewe. Journal of Reproduction and Fertility 38, 261–271.

Godkin, J.D., Bazer, F.W., Moffat, J., Sessions, F., Roberts, R.M., 1982. Purification and properties of a major low molecular weight

protein released by the trophoblast of sheep blastocysts at day 13–21. Journal of Reproduction and Fertility 65, 141–150.

Gooneratne, S.R., Christensen, D.A., 1989. A survey of maternal copper status and fetal tissue concentrations in Saskatchewan bovine. Canadian Journal of Animal Science 69, 141–150.

Grace, N.D., Rounce, J.R., Knowles, S.O., Lee, J., 1999. Effect of increasing elemental sulphur and copper intakes on the copper status of grazing sheep. Proceedings of the New Zealand Grassland Association 60, 271–274.

Grace, N.D., Watkins, J.H., Martinson, P.L., 1986. Accumulation of minerals by the fetus(es) of single and twin bearing ewes. New Zealand Journal of Agriculture Research 29, 207–222.

Graham, T.W., Thurmond, M.C., Mohr, F.C., Holmberg, C.A., Anderson, M.L., Keen, C.L., 1994. Relationship between maternal and fetal liver copper, iron, manganese and zinc concentrations and fetal development in California Holstein dairy cows. Journal of Veterinary Diagnostic Investigation 6, 77–87.

Hambidge, K.M., Casey, C.E., Krebs, N.F., 1986. Zinc, 4th ed.. In: Mertz, W. (Ed.),. Trace Elements in Human and Animal Nutrition, vol. 2. Academic Press, San Diego, pp. 1–37.

Hansard, S.L., 1972. Physiological behavior of manganese in gravid cattle, sheep and swine. In: Isotope Studies on the Physiology of Domestic Animals. International Atomic Energy Agency, Vienna, pp. 351–364.

Harris, E.D., 1986. Biochemical defect in chicken lung resulting from copper deficiency. Journal of Nutrition 116, 252–258.

Hart, E.B., 1928. Copper as a supplement to iron for hemoglobin building in the rat. Journal of Biological Chemistry 77, 797–812.

Hartley, W.J., 1963. Selenium and ewe fertility. Proceedings of the New Zealand Society of Animal Production 23, 20–27.

Hartley, W.J., Grant, A.B., 1961. A review of selenium responsive diseases of New Zealand livestock. Federation Proceedings 20, 679–688.

Harrison, J.H., Hancock, D., 1999. The role of selenium and vitamin E deficiency in postpartum reproductive diseases of the bovine. In: Hogan, J. (Ed.), A.L. Moxon Honorary Lectures, Special Circular 167-99. Ohio Agriculture Research and Development Center, pp. 83–95.

Hawk, S.N., Uriu-Hare, J.Y., Daston, G.P., Jankowski, M.A., Kwik-Uribe, C., Rucker, R.B., Keen, C.L., 1998. Rat embryos cultured under copper-deficient conditions develop abnormally and are characterized by an impaired oxidant defense system. Teratology 57, 310–320.

Hedstrom, O.R., Maas, J.P., Hultgren, B.D., Lassen, E.D., Wallner-Pendelton, E.A., Snyder, S.P., 1986. Selenium deficiency in bovine, equine, and ovine with emphasis on its association with chronic diseases. In: Proceedings of the 29th Annual Meeting of the American Association of Veterinary Laboratory Diagnosticians, pp. 101–126.

Hidiroglou, M., 1979. Manganese in ruminant nutrition. Canadian Journal of Animal Science 59, 217–236.

Hidiroglou, M., Knipfel, J.E., 1981. Maternal fetal relationships of copper, manganese and sulfur in ruminants. A review. Journal of Dairy Science 64, 1637–1647.

Hidiroglou, M., Shearer, D.A., 1976. Concentration of manganese in the tissues of cycling and anestrous ewes. Canadian Journal of Comparative Medicine 40, 306–309.

Hill, K.E., Motley, A.K., May, J.M., Burk, R.F., 2001. Combined selenium and vitamin E deficiency causes fatal myopathy in guinea pigs. Journal of Nutrition 131, 1798–1802.

Hilton, M., Spenser, D.C., Ross, P., Ramsey, A., McArdel, H.J., 1995. Characterization of the copper uptake mechanism and isolation of the ceruloplasmin receptor/copper transporter in human placental vesicles. Biochimica et Biophysica Acta 1245, 153–160.

Hooper, S.B., Watkins, W.B., Thorburn, G.D., 1986. Oxytocin, oxytocin associated neurophysin, and prostaglandin $F_{2\alpha}$ concen-

trations in the utero-ovarian vein of pregnant and nonpregnant sheep. Endocrinology 119, 2590–2597.

Hostetler, C.E., Cronrath, J.D., Becker, W.C., Mirando, M.A., 2000. Dietary supplementation of proteinated trace minerals (OPTiMIN) in sows and replacement gilts increases mineral concentrations in reproductive tissues. Abstracts 14th International Congress Animal Reproduction 1, 272, Abst.

Hostetler, C.E., Mirando, M.A., 1998. Dietary supplementation of proteinated trace minerals influences reproductive and growth performance of replacement gilts. Journal of Animal Science 76 (Suppl. 1), 274, Abst.

House, W.A., Bell, A.W., 1993. Mineral accretion in the fetus and adnexa during late gestation in Holstein cows. Journal of Dairy Science 76, 2999–3010.

Howes, A.D., Dyer, T.A., 1971. Diet and supplemental mineral effect on manganese metabolism in newborn calves. Journal of Animal Science 32, 141–145.

Hurley, W.L., Doane, R.M., 1989. Recent development in the roles of vitamins and minerals in reproduction. Journal of Dairy Science 72, 784–804.

Hurley, L.S., Keen, C.L., 1987. Manganese, 5th ed.. In: Mertz, W. (Ed.),. Trace Elements in Human and Animal Nutrition, vol. 1. Academic Press, San Diego, pp. 185–223.

Imakawa, K., Anthony, R.V., Kazemi, M., Marotti, K.R., Polites, G.H., Roberts, R.M., 1987. Interferon-like sequence of ovine trophoblast protein secreted by embryonic trophectoderm. Nature 330, 377–379.

Jacobsson, S.O., Oksanen, H.E., 1966. The placental transmission of selenium in sheep. Acta Veterinary Scandinavia 7, 66–76.

Jovanovic-Peterson, L., Peterson, C.M., 1996. Vitamin and mineral deficiencies which may predispose to glucose intolerance of pregnancy. Journal of the American College of Nutrition 15, 14–20.

Joyce, J.M., 1955. Posterior paralysis in pigs. Summary of Northland survey 1954. New Zealand Veterinary Journal 3, 157–158.

Kegley, E.B., Spears, J.W., 1994. Bioavailability of feed-grade copper sources (oxide, sulfate or lysine) in growing cattle. Journal of Animal Science 72, 2728–2734.

Keen, C.L., Uriu-Hare, J.Y., Hawk, S.N., Jankowski, M.A., Daston, G.P., Kwik-Uribe, C.L., Rucker, R.B., 1998. Effect of copper deficiency on prenatal development and pregnancy outcome. American Journal of Clinical Nutrition 67 (Suppl.), 1003S–1011S.

Keys, J.L., King, G.J., 1990. Microscopic examination of porcine conceptus–maternal interface between days 10 and 19 of pregnancy. American Journal of Anatomy 188, 221–238.

Kieborz, K.R., Silvia, W.J., Edgerton, L.A., 1991. Changes in uterine secretion of prostaglandin F2 alpha and luteal secretion of progesterone in response to oxytocin during the porcine estrous cycle. Biology of Reproduction 45, 950–954.

Kim, Y.Y., Mahan, D.C., 2001. Prolonged feeding of high dietary levels of organic and inorganic selenium to gilts from 25 kg body weight through one parity. Journal of Animal Science 79, 956–966.

Kincaid, R.L., Abdelrahman, M.M., Cronrath, J.D., 1993. Maternal transfer of trace elements in the bovine. In: Anke, M., Meissner, D., Mills, C.F. (Eds.), TEMA 8: Proceedings of the Eighth International Symposium on Trace Elements in Man and Animals. Verlag Media Touristik, Gersdorf, pp. 337–340.

King, G.J., Ackerley, C.A., 1985. Demonstration of oestrogens in developing pig trophectoderm and yolk sac endoderm between days 10 and 16. Journal of Reproduction and Fertility 73, 361–367.

Knowles, S.O., Grace, N.D., Wurms, K., Lee, J., 1999. Significance of amount and form of dietary selenium on blood, milk, and casein selenium in grazing cows. Journal of Dairy Science 82, 429–437.

Ko, Y., Lee, C.Y., Ott, T.L., Davis, M.A., Simmen, R.C.M., Bazer, F.W., Simmen, F.A., 1991. Insulin-like growth factors in sheep uterine fluids: concentrations and relationship to ovine trophoblast

protein-1 production during early pregnancy. Biology of Reproduction 45, 135–142.

Kohrle, J., 1999. Local activation and inactivation of thyroid hormones: the deiodinase family. Molecular and Cellular Endocrinology 151, 103–119.

Koller, L.D., Whitbeck, G.A., South, P., 1984. Transplacental transfer and colostral concentration of selenium in beef cattle. American Journal of Veterinary Research 45, 2507–2510.

Kotwica, G., Dusza, L., Ciereszko, R., Okrasa, S., Schams, D., 1990. Oxytocin plasma levels during spontaneous and cloprostenol-induced luteolysis in sows. Animal Reproduction Science 22, 109–119.

Kraeling, R.R., Rampacek, G.B., Fiorello, N.A., 1985. Inhibition of pregnancy with indomethacin in mature gilts and prepubertal gilts induced to ovulate. Biology of Reproduction 32, 105–110.

Langlands, J.P., Bowles, G.E., Donald, G.E., Smith, A.J., Paull, D.R., Davies, H.I., 1982. Deposition of copper, manganese, selenium and zinc in the ovine fetus and associated tissues. Australian Journal of Agricultural Research 33, 591–605.

Lau, I.F., Saksena, S.K., Chang, M.C., 1973. Pregnancy blockade by indomethacin, an inhibitor of prostaglandin synthesis: its reversal by prostaglandins and progesterone in mice. Prostaglandins 4, 795–803.

Leach, R.M., 1967. Role of manganese in the synthesis of mucopolysaccharides. Federation Proceedings 26, 118–120.

Leach, R.M., 1976. Metabolism and function of manganese. In: Prasad, A.S., Oberleas, D. (Eds.), Trace Elements in Human Health and Disease, vol. 2. Academic Press, New York, pp. 235–248.

Lee, C.S., Gogolin-Ewens, K., Brandon, M.R., 1988. Identification of a unique lymphocyte subpopulation in the sheep uterus. Immunology 63, 157–164.

Lequarre, A.S., Feugang, J.M., Malhomme, O., Donnay, I., Massip, A., Dessy, F., van Langendonckt, A., 2001. Expression of Cu/Zn and Mn superoxide dismutase during embryo development:influence of in vitro culture. Molecular Reproduction and Development 58, 45–53.

LeRoith, D., Werner, H., Beitnerjohnson, D., Roberts, C.T., 1995. Molecular and cellular aspects of the insulin-like growth factor I receptor. Endocrinology Review 16, 143–163.

Levander, O.A., 1983. Considerations in the design of selenium bioavailability studies. Federation Proceedings 42, 1721–1725.

Lewis, R.D., Johnson, M.A., Dengal, D.R., Jones, M.T., Norton, K.I., 1993. The effects of maternal training on plasma copper, magnesium and zinc in rats. Nutrition Research 13, 771–778.

Lillie, R.J., Forbish, L.T., 1978. Effect of copper and iron supplements on performance and hematology of confined sows and their progeny through four reproductive cycles. Journal of Animal Science 46, 678–685.

MacDonald, R.S., 2000. The role of zinc in growth and cell proliferation. Journal of Nutrition 130, 1500s–1508s.

Madsen, F.C., Rompala, R.E., Miller, J.K., 1991. Essential trace minerals: requirements altered by disease, stress, management, etc. Large Animal Veterinarian (March/April), 32–36, see also p. 40.

Mahan, D.C., Cline, T.R., Richert, B., 1999. Effects of dietary levels of selenium-enriched yeast and sodium selenite as selenium sources fed to growing-finishing pigs on performance, tissue selenium, serum glutathione peroxidase activity, carcass characteristics, and loin quality. Journal of Animal Science 77, 2172–2179.

Mahan, D.C., Kim, Y.Y., 1996. Effect of inorganic or organic selenium at two dietary levels on reproductive performance and tissue selenium concentration in first-parity gilts and their progeny. Journal of Animal Science 74, 2711–2718.

Mahan, D.C., Penhale, L.H., Cline, J.H., Moxon, A.L., Fetter, A.W., Yarrington, J.T., 1974. Efficacy of supplemental selenium in reproductive diets on sow and progeny performance. Journal of Animal Science 39, 536–543.

Marlow, T.J., Smith, J.H., 1971. Early prenatal death loss in pigs. Journal of Animal Science 33, 203, Abst.

Martal, J., Lacroix, M.-C., Loudes, C., Saunier, M., Wintenberger-Torres, S., 1979. Trophoblastin, an antiluteolytic protein present in early pregnancy in sheep. Journal of Reproduction and Fertility 56, 63–73.

Maynard, L.S., Cotzias, G.C., 1955. The partition of manganese among organs and intracellular organelles of the rat. Journal of Biological Chemistry 214, 489–495.

McArdle, H.J., 1992. The transport of iron and copper across the cell membrane: different mechanisms for different metals? Proceedings of the Nutrition Society 51, 199–209.

McArdle, H.J., Ashworth, C.J., 1999. Micronutrients in fetal growth and development. British Medical Bulletin 55, 499–510.

McCracken, J.A., Custer, E.A., Lamsa, J.C., 1999. Luteolysis, A neuroendocrine-mediated event. Physiological Reviews 79, 263–323.

McCusker, R.H., Kaleko, M., Sackett, R.L., 1998. Multivalent cations and ligand affinity of the Type 1 insulin-like growth factor receptor on P_2A_2-LISN muscle cells. Journal of Cellular Physiology 176, 392–401.

McIntosh, G.H., Baghurst, K.I., Potter, B.J., Hetzel, B.S., 1979. Fetal thyroidectomy and brain development in the sheep. Neuropathology and Applied Neurobiology 5, 102–114.

McIntosh, G.H., Potter, B.J., Hetzel, B.S., Hua, C.H., Cragg, B.G., 1982. The effects of 98-day fetal thyroidectomy on brain development in the sheep. Journal of Comparative Pathology 92, 599–607.

Mee, J.F., Rogers, P.A.M., 1996. Relevance of I, selenium, copper and cobalt deficiencies on Irish cattle farms. Irish Veterinary Journal 49, 529–537.

Meinel, B., Bode, J.C., Koenig, W., Richter, F., 1979. Contents of trace elements in the human liver before birth. Biology of the Neonate 36, 225–232.

Meinhold, H., Campos-Barros, A., Walzog, B., Köhler, R., Müller, F., Behne, D., 1993. Effects of selenium and iodine deficiency on Type I, Type II and Type III iodothyronine deiodinases and circulating thyroid hormones in the rat. Experimental and Clinical Biology 101, 87–93.

Merke, F., 1984. History of endemic cretinism. In: Merke, F. (Ed.), History and Iconography of Endemic Goiter and Cretinism. Hans Huber Publishers, Bern, pp. 195–223.

Mihailovic, M., Pavlovic, A., Radetic, P., Vlatkovic, M., Tomic, V., 1982. Influence of feed supplementation with selenium and vitamin E on glutathione peroxidase activity and reproduction in pigs. Acta Veterinaria (Beograd) 32, 275–282.

Mills, C.F., Williams, R.B., 1962. Copper concentrations and cytochrome-oxidase and ribonuclease activities in the brains of copper deficient lambs. Biochemistry Journal 85, 629–632.

Mirando, M.A., Harney, J.P., Beers, S., Pontzer, C.H., Torres, B.A., Johnson, H.M., Bazer, F.W., 1990. Onset of secretion of proteins with antiviral activity by pigs conceptuses. Journal of Reproduction and Fertility 88, 197–203.

Mirando, M.A., Peters, D.N., Hostetler, C.E., Becker, W.C., Rompala, R.E., 1993a. Dietary supplementation of proteinated trace minerals influences reproductive performance of sows. Journal of Animal Science 71 (Suppl. 1), 358, Abst.

Mirando, M.A., Becker, W.C., Whiteaker, S.S., 1993b. Relationships among endometrial oxytocin receptors, oxytocin-stimulated phosphoinositide hydrolysis and prostaglandin $F_{2\alpha}$ secretion in vitro, and plasma concentrations of ovarian steroids before and during corpus luteum regression in cyclic heifers. Biology of Reproduction 48, 874–882.

Mirando, M.A., Uzumcu, M., Carnahan, K.G., Ludwig, T.E., 1996. A role for oxytocin during luteolysis and early pregnancy in swine. Reproduction in Domestic Animals 31, 455–461.

Moor, R.M., Rowson, L.E., 1966. Local maintenance of the corpus luteum in sheep with embryos transferred to various isolated

portions of the uterus. Journal of Reproduction and Fertility 12, 539–550.

Moore, N.W., 1985. The use of embryo transfer and steroid hormone replacement therapy in the study of prenatal mortality. Theriogenology 23, 121–128.

Morreale de Escobar, G., Obregon, M.J., Calvo, R., Escobar del Rey, F., 1993. Effects of iodine deficiency on thyroid hormone metabolism and the brain in fetal rats: the role of the maternal transfer of thyroxin. American Journal of Clinical Nutrition 57 (Suppl.), 280S–285S.

Mudd, A.J., Mackie, I.L., 1973. The influence of vitamin E and selenium on ewe prolificacy. Veterinary Record 93, 197–199.

Munck, B.G., 1981. Intestinal absorption of amino acids. In: Johnson, L.R. (Ed.), Physiology of the Gastrointestinal Tract. Raven Press, New York, pp. 1097–1122.

Mutetikka, D.B., Mahan, D.C., 1993. Effect of pasture, confinement, and diet fortification with vitamin E and selenium on reproducing gilts and their progeny. Journal of Animal Science 71, 3211–3218.

Muth, O.H., Oldfield, J.E., Remmert, L.F., Schubert, J.R., 1958. Effects of selenium and vitamin E on white muscle disease. Science 128, 1090.

National Research Council, 1998. Nutrient Requirements of Swine, Tenth ed., National Academy of Science, Washington, DC.

Newland, H.W., Davis, G.K., 1961. Placental transfer of Manganese in swine. Journal of Animal Science 20, 15–17.

Northey, D.L., French, L.R., 1980. The effect of embryo removal and intrauterine infusion of embryonic homogenates on the lifespan of the bovine corpus luteum. Journal of Animal Science 50, 298–302.

O'Dell, B.L., Kilburn, K.H., McKenzie, M.S., Thurston, R.J., 1978. The lung of the copper deficient rat. American Journal of Pathology 91, 413–432.

Olson, J.A., 1965. The biosynthesis of cholesterol. Reviews of Physiology Biochemistry and Experimental Pharmacology 56, 173–215.

Olson, P.A., Brink, D.R., Hickok, D.T., Carlson, M.P., Schneider, N.R., Deutscher, G.H., Adams, D.C., Colburn, D.J., Johnson, A.B., 1999. Effects of supplementation of organic and inorganic combinations of copper, cobalt, manganese and zinc above nutrient requirement levels on postpartum two-year-old cows. Journal of Animal Science 77, 522–532.

Orent, E.F., McCollum, E.V., 1931. Effects of deprivation on manganese in the rat. Journal of Biological Chemistry 92, 651–678.

Osorio, C., Myant, N.B., 1960. The passage of thyroid hormone from mother to foetus and its relation to foetal development. British Medical Bulletin 16, 159–164.

Osorio, C., Myant, N.B., 1958. Thyroxine binding protein in the serum of rabbit foetuses. Nature 182, 866–867.

O'Sullivan, B.M., 1977. Enzootic ataxia in kid goats. Australian Veterinary Journal 53, 455–456.

Perry, J.S., Rowlans, I.W., 1962. Early pregnancy in the pig. Journal of Reproduction and Fertility 4, 175–188.

Peterson, R.R., Young, W.C., 1952. The problem of placental permeability for thyrotrophin, propylthiouracil and thyroxine in the guinea pig. Endocrinology 50, 218–225.

Plumlee, P.M., Thrasher, D.M., Beeson, W.M., Andrews, F.N., Parker, H.E., 1956. The effect of a manganese deficiency upon the growth, development, and reproduction of swine. Journal of Animal Science 15, 352–367.

Polk, D.H., 1995. Thyroid hormone metabolism during development. Reproduction Fertility and Development 7, 469–477.

Pope, W.F., 1992. Embryogenesis recapitulates oogenesis in swine. Proceedings of the Society for Experimental Biology and Medicine 119, 273–281.

Pope, W.F., 1988. Uterine asynchrony: a cause of embryonic loss. Biology of Reproduction 39, 999–1003.

Pope, W.F., Xie, S., Broermann, D.M., Nephew, K.P., 1990. Causes and consequences of early embryonic diversity. Journal of Reproduction and Fertility 40, 250–260.

Potter, B.J., Mano, M.T., Belling, G.B., McIntosh, G.H., Hua, D., Cragg, B.G., Marshall, J., Wellby, M.L., Hetzel, B.S., 1982. Retarded fetal brain development resulting from severe dietary iodine deficiency in sheep. Neuropathology and Applied Neurobiology 8, 303–313.

Potter, B.J., McIntosh, G.H., Mano, M.T., Baghurst, P.A., Chavadej, J., Hua, D., Cragg, B.G., Hetzel, B.S., 1986. The effect of maternal thyroidectomy prior to conception on fetal brain development in sheep. Acta Endocrionology 112, 93–99.

Poulsen, H.D., Danielsen, V., Nielsen, T.K., Wolsturp, C., 1989. Excessive dietary selenium to primiparous sows and their offspring; I. Influence on reproduction and growth. Acta Veterinaria Scandinavia 30, 371–378.

Raub, T.J., Bazer, F.W., Roberts, R.M., 1985. Localization of the iron transport glycoprotein, uteroferrin, in the porcine endometrium and placenta by using immunocolloidal gold. Anatomy and Embryology 171, 253–258.

Richard, K., Hume, R., Kaptein, E., Sanders, J.P., van Toor, H., de Herder, W.W., den Hollander, J.C., Krenning, E.P., Visser, T.J., 1998. Ontogeny of iodothyronine deiodinases in human liver. Journal of Clinical Endocrinology and Metabolism 83, 2868–2874.

Robertson, G.L., Casida, L.E., Grummer, R.H., Chapman, A.B., 1951. Some feeding and management factors affecting age at puberty and related phenomena in Chester White and Poland China gilts. Journal of Animal Science 10, 841–866.

Rock, M.J., Kincaid, R.L., Carstens, G.E., 2001. Effects of prenatal source and level of dietary selenium on passive immunity and thermometabolism of newborn lambs. Small Ruminant Research 40, 129–138.

Rojas, M.H., Dyer, I.A., Cassatt, W.A., 1965. Manganese deficiency in bovine. Journal of Animal Science 24, 664–667.

Roos, M.A., Easter, R.A., 1986. Effect of sow and piglet performance of feeding a diet containing 250 ppm copper during lactation. Journal of Animal Science 63 (Suppl. 1), 115, Abst.

Roti, E., Gnudi, A., Braverman, L.E., 1983. The placental transport, synthesis and metabolism of hormones and drugs which affect thyroid function. Endocrine Reviews 4, 131–149.

Rotruck, J.T., Pope, A.L., Ganther, H.E., Swanson, A.B., Hafeman, D.G., Hoekstra, W.G., 1973. Selenium: biochemical role as a component of glutathione peroxidase. Science 179, 588–590.

Rowson, L.E.A., Moor, R.M., 1967. The influence of embryonic tissue homogenate infusion into the uterus, on the life-span of the corpus luteum in the sheep. Journal of Reproduction and Fertility 13, 539–550.

Rucker, R.B., Kosonen, T., Clegg, M.S., Mitchell, A.E., Rucker, B.R., Uriu-Hare, J.Y., Keen, C.L., 1998. Copper, lysyl oxidase, and extracellular matrix protein cross-linking. American Journal of Clinical Nutrition 67 (Suppl.), 996S–1002S.

Saba, L., Bombik, T., Bombik, A., Nowakowicz-Debek, B., 2000. Mineral deficiency in dairy cows. Medycyna Weterynaryjnia 56, 125–128.

Sackett, R.L., McCusker, R.H., 1998. Multivalent cations depress ligand affinity of insulin-like growth factor-binding proteins-3 and -5 on human GM-10 fibroblast cell surfaces. Journal of Cellular Biochemistry 69, 364–375.

Sakuma, S., Fujimoto, Y., Kitao, A., Sakamoto, H., Nishida, H., Fujita, T., 1999. Simultaneous measurement of prostaglandin and arachidonoyl CoA formed from arachidonic acid in rabbit kidney medulla microsomes: the roles of Zn^{2+} and Cu^{2+} as modulators of formation of the two products. Prostaglandins, Leukotrienes and Essential Fatty Acids 61, 105–112.

Sakuma, S., Fujimoto, Y., Miyata, Y., Ohno, M., Nishida, H., Fujita, T., 1996. Effects of $Fe^{2+}, Zn^{2+}, Cu^{2+}$ and Se^{4+} on the synthesis and catabolism of prostaglandins in rabbit gastric antral mucosa.

Prostaglandins, Leukotrienes and Essential Fatty Acids 54, 193–197.

Scales, G.H., 1974. Reproductive performance of Merino ewes dosed with selenium prior to mating. Proceedings of the New Zealand Society of Animal Production 34, 103–113.

Schell, T.C., Kornegay, E.T., 1996. Zinc concentration in tissues and performance of weanling pigs fed pharmacological levels of zinc from ZnO, Zn-methionine, Zn-lysine, or $ZnSO_4$. Journal of Animal Science 74, 1584–1593.

Schramm, W., Bovaird, L., Glew, M.E., Schramm, G., McCracken, J.A., 1983. Corpus luteum regression induced by ultra-low pulses of prostaglandin $F_{2\alpha}$. Prostaglandins 26, 347–364.

Schultz, S.G., 1986. Ion-coupled transport of organic solutes across biological membranes. In: Andreoli, T.E., Hoffman, J.F., Fanestil, D.D., Schultz, S.G. (Eds.), Physiology of Membrane Disorders. Plenum Publishing, New York, pp. 283–294.

Schwarz, K., Foltz, C.M., 1957. Selenium as an integral part of factor 3 against dietary necrotic liver degeneration. Journal of the American Chemical Society 79, 3292–3293.

Segerson, E.C., Murry, F.A., Moxon, A.L., Redman, D.R., Conrad, H.R., 1977. Selenium/vitamin E: role in fertilization of bovine ova. Journal of Dairy Science 60, 1001–1005.

Shennan, D.B., 1988. Selenium (selenate) transport by human placental brush border membrane vesicles. British Journal of Nutrition 59, 13–19.

Short, R.V., 1969. Implantation and the maternal recognition of pregnancy. In: Wolstenholme, G.E.W., O'Connor, M. (Eds.), Foetal Autonomy. J.A. Churchill Ltd, London, pp. 2–31.

Simmen, F.A., Simmen, R.C.M., Geisert, R.D., Martinat-Botte, F., Bazer, F.W., Terqui, M., 1992. Differential expression, during the estrous cycle and pre- and post-implantation conceptus development, of messenger ribonucleic acids encoding components of the pig uterine insulin-like growth factor system. Endocrinology 130, 1547–1556.

Smith, M.O., Sherman, I.L., Miller, L.C., Robbins, K.R., 1994. Bioavailability of manganese from different sources in heat distressed broilers. Poultry Science 73 (Suppl. 1), 163, Abst.

Smith, R.M., Fraser, F.J., Russell, G.R., Robertson, J.S., 1977. Enzootic ataxia in lambs: appearance of lesions in the spinal cord during foetal development. Journal of Comparative Pathology 87, 119–128.

Spears, J.W., 1996. Organic trace minerals in ruminant nutrition. Animal Feed Science and Technology 58, 151–163.

St. Clair, D.K., Oberely, T.D., Muse, K.E., St. Clair, W.H., 1994. Expression of manganese superoxide dismutase promotes cellular differentiation. Free Radicals in Biology and Medicine 16, 275–282.

Starkey, P.M., Sargent, I.L., Redman, C.W., 1988. Cell populations in human early pregnancy decidua: characterization and isolation of large granular lymphocytes by flow cytometry. Immunology 65, 129–134.

Stevens, B.R., Wright, E.M., 1987. Kinetics of the intestinal brush border proline (imino) carrier. Journal of Biological Chemistry 262, 6546–6551.

Stevenson, K.R., Riley, P.R., Stewart, H.J., Flint, A.P.F., Wathes, D.C., 1994. Localization of oxytocin receptor mRNA in the ovine uterus during the oestrous cycle and early pregnancy. Journal of Molecular Endocrinology 12, 93–105.

Stewart, H.J., McCann, S.H., Barker, P.J., Lee, K.E., Lamming, G.E., Flint, A.P., 1987. Interferon sequence homology and receptor binding activity of ovine trophoblast antiluteolytic protein. Journal of Endocrinology 115, R13–R15.

Taskar, J.B., Bewick, T.D., Clark, R.G., Fraser, A.J., 1987. Selenium response in dairy cattle. New Zealand Veterinary Journal 35, 139–140.

Taylor, R.F., Puls, R., MacDonald, K.R., 1979. Bovine abortions associated with selenium deficiency in Western Canada. In:

Proceedings of the 22nd Annual Meeting of the American Association of Veterinary Laboratory Diagnosticians, pp. 77–84.

Taurog, A., 1996. Hormone synthesis and secretion. In: Braverman, L.E., Utiger, R.D. (Eds.), Werner and Ingbar's The Thyroid, 7th ed.. Lippincott-Raven, Philadelphia, pp. 47–81.

Thacker, P.A., 1991. Effect of high levels of copper or dichlorvos during late gestation and lactation on sow productivity. Canadian Journal of Animal Science 71, 227–232.

Thorburn, G.D., 1991. The placenta, prostaglandins and parturition: a review. Reproduction Fertility and Development 3, 277–294.

Thorburn, G.D., 1992. The placenta, PGE_2 and parturition. Early Human Development 29, 63–73.

Tinker, D., Rucker, R.B., 1985. Role of selected nutrients in synthesis, accumulation, and chemical modification of connective tissue proteins. Physiology Reviews 65, 605–657.

Todd, W.R., Elvehjem, C.A., Hart, E.B., 1934. Zinc in the nutrition of the rat. Americian Journal of Physiology 107, 146–156.

Tong, K.K., McArdle, H.J., 1995. Copper uptake by cultured trophoblast cells isolated from human term placenta. Biochimica et Biophysica Acta 1269, 233–236.

Toolan, D.P., 1990. Enzootic ataxia (swayback) in kid goats. Irish Veterinary Journal 43, 27–28.

Townsend, S.F., Briggs, K.K., Krebs, N.F., Hambridge, K.M., 1994. Zinc supplementation selectively decreases fetal hepatocyte DNA synthesis and insulin-like growth factor II gene expression in primary culture. Pediatric Research 35, 404–408.

Trout, W.E., Smith, G.W., Gentry, P.C., Galvin, J.M., Keisler, D.H., 1995. Oxytocin secretion by the endometrium of the pig during maternal recognition of pregnancy. Biology of Reproduction 52 (Suppl. 1), 189, Abst.

Tucker, H.F., Salmon, W.D., 1955. Parakeratosis or zinc deficiency disease in the pig. Proceedings of the Society for Experimental Biology in Medicine 88, 613–616.

Ullrey, D.E., 1974. The selenium deficiency problem in animal agriculture. In: Hoekstra, W.G., Suttie, J.W., Ganther, H.E., Mertz, W. (Eds.), Trace Element Metabolism in Animals, vol. 2. University Press, Baltimore, pp. 275–293.

Unny, N.M., Pandey, N.N., Dwivedi, S.K., 2002. Biochemical studies on experimental secondary copper deficiency in goats. Indian Journal of Animal Sciences 72, 52–54.

Vallee, B.L., Falchuk, K.H., 1993. The biochemical basis of zinc physiology. Physiology Reviews 73, 79–118.

Vallet, J.L., Christenson, R.K., Trout, W.E., Klemcke, H.G., 1998. Conceptus, progesterone, and breed effects on uterine protein secretion in swine. Journal of Animal Science 76, 2657–2670.

Van Saun, R.J., Herdt, T.H., Stowe, H.D., 1989. Maternal and fetal selenium concentrations and their interrelationships in dairy cattle. Journal of Nutrition 119, 1128–1137.

Vipond, J.E., 1984. Effects of a single oral dose of a commercial selenium cobalt and vitamin preparation on ewe fertility. Veterinary Record 114, 519–521.

Waddell, J., Steenbock, H., Hart, E.B., 1931. Growth and reproduction on milk diets. Journal of Nutrition 4, 53–65.

Wallace, H.D., Houser, R.H., Combs, G.E., 1966. High level copper supplementation of the sow during the farrowing and early lactation period. In: Florida Animal Science Mimeograph Series No. 6612. University of Florida, Gainesville.

Ward, J.D., Spears, J.W., Kegley, E.B., 1996. Bioavailability of copper proteinate and copper carbonate relative to copper sulfate in cattle. Journal of Dairy Science 79, 127–132.

Wauben, I.P., Xing, H.C., Wainwright, P.E., 1999. Neonatal dietary zinc deficiency in artificially reared rat pups retards behavioral development and interacts with essential fatty acid deficiency to alter liver and brain fatty acid composition. Journal of Nutrition 129, 1773–1781.

Wedekind, K.J., Lewis, A.J., Giesemann, M.A., Miller, P.S., 1994. Bioavailability of zinc from inorganic and organic sources for pigs

fed corn-soybean meal diets. Journal of Animal Science 72, 2681–2689.

Weisiger, R.A., Fridovich, I.J., 1973a. Mitochondrial superoxide dismutase. Site of synthesis and intramitochondrial localization. Biological Chemistry 248, 4793–4796.

Weisiger, R.A., Fridovich, I., 1973b. Superoxide dismutase. Organelle specificity. Journal of Biological Chemistry 248, 3582–3592.

Weiss, W.P., Colendrander, V.F., Cunningham, M.D., Callahan, C.J., 1983. Selenium/vitamin E: role in disease prevention and weight gain of neonatal calves. Journal of Dairy Science 66, 1101–1107.

Whitaker, D.A., Eayres, H.F., Aitchison, K., Kelly, J.M., 1997. No effect of a dietary zinc proteinate on clinical mastitis, infection rate, recovery rate and somatic cell count in dairy cows. Veterinary Journal 153, 197–204.

Wichtel, J.J., Thompson, K.G., Craigie, A.L., Williamson, N.B., 1996. Effects of selenium and iodine supplementation on the growth rate, mohair production, and thyroid status of Angora goat kids. New Zealand Journal of Agricultural Research 39, 111–115.

Widdowson, E.M., Dauncey, J., Shaw, J.C.L., 1974. Trace elements in foetal and early postnatal development. Proceedings of the Nutrition Society 33, 275–284.

Wilkie, W.J., 1959. Mineral deficiencies in pigs. Australian Veterinary Journal 35, 209–216.

Wilmut, J.M., Ashworth, C.J., Sales, D.I., 1986a. The influence of progesterone profile on embryo loss in ewes. In: Diskin, M.G., Sreenan, J.M. (Eds.), Embryonic Mortality in Farm Animals. Martinus Nijhoff, Dordrecht, pp. 135–141.

Wilmut, I., Sales, D.I., Ashworth, C.J., 1986b. Maternal and embryonic factors associated with prenatal loss in mammals. Journal of Reproduction and Fertility 76, 851–864.

Wilson, J.G., 1952. Herd functional infertility, with reference to nutrition and mineral intake. Veterinary Record 64, 621–623.

Wilson, J.G., 1966. Bovine functional infertility in Devon and Cornwall: response to manganese therapy. Veterinary Record 79, 562–566.

Wolffram, S., Anliker, E., Scharrer, E., 1986. Uptake of selenate and selenite by isolated intestinal brush border membrane vesicles from pig, sheep, and rat. Biological Trace Element Research 10, 293–306.

Wolffram, S., Berger, B., Grenacher, B., Scharrer, E., 1989. Transport of selenoamino acids and their sulfur analogues across the intestinal brush border membrane of pigs. Journal of Nutrition 119, 706–712.

Wolter, B., McKeith, F.K., Miller, K.D., Mahan, D.C., 1999. Influence of dietary selenium source on growth performance, and carcass and meat quality characteristics in pigs. Canadian Journal of Animal Science 79, 119–121.

Wright, C.L., Spears, J.W., 2001. Effects of zinc source and dietary level on zinc metabolism in Holstein bull calves. Journal of Animal Science 79 (Suppl. 1), 86, Abst.

Wright, C.L., Failla, M.L., Spears, J.W., 2001. Uptake and transport of zinc from zinc sulfate and zinc proteinate by Caco-2 cells. Journal of Animal Science 79 (Suppl. 1), 86, Abst.

Wright, L.J., Feinstein, A., Heap, R.B., Saunders, J.C., Bennett, R.C., Wang, M.-Y., 1982. Anti-progesterone monoclonal antibody blocks implantation in mice. Nature 295, 415–417.

Xie, S., Broermann, D.M., Nephew, K.P., Bishop, M.D., Pope, W.F., 1990a. Relationship between oocyte maturation and fertilization on zygotic diversity in swine. Journal of Animal Science 68, 2027–2033.

Xie, S., Broermann, D.M., Nephew, K.P., Geisert, R.D., Pope, W.F., 1990b. Ovulation and early embryogenesis in swine. Biology of Reproduction 43, 236–240.

Yamini, B., Mullaney, T.P., 1985. Vitamin E and selenium deficiency as a possible cause of abortion in food animals. In: Proceedings of the 28th Annual Meeting of the American Association of Veterinary Laboratory Diagnosticians, pp. 131–144.

Zagrodzki, P., Nicol, F., McCoy, M.A., Smyth, J.A., Kennedy, D.G., Beckett, G.J., Arthur, J.R., 1998. Iodine deficiency in cattle: compensatory changes in thyroidal selenoenzymes. Research in Veterinary Science 64, 209–211.

Zapf, J., Froesch, R., 1986. Insulin-like growth factors/somatomedins: structure, secretion, biological actions and physiological role. Hormone Research 24, 121–130.

Zarco, L., Stabenfeldt, G.H., Basus, S., Bradford, G.E., Kindahls, H., 1988. Modification of prostaglandin $F_{2\alpha}$ synthesis and release in the ewe during initial establishment of pregnancy. Journal of Reproduction and Fertility 83, 527–536.