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Review

The case for pre-parturient selenium and iodine supplementation of ewes for improving lamb survival

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Abstract. Lamb survival is an issue of high relevance to the Australian sheep industry, as lamb-survival rates have direct bearing on overall reproductive performance of the sheep, and also constitute a main concern from an animal welfare perspective (Mellor and Stafford 2004). Both genetic and management factors play an important role in this complex issue (Hinch and Brien 2014). Ewe nutrition is of particular relevance as the intrauterine growth conditions prepare the lamb for the crucial transition to life outside the uterus. Effects of body condition of the ewe during various stages of the pregnancy have been investigated in detail, yet much less is known about the critical role of micronutrient provision to the ewe. Although several risk factors for selenium (Se) and iodine (I) subclinical deficiencies exist for sheep on pasture in Australia, determining micronutrient status in sheep or pasture is not straightforward. Several studies have separately found effects of Se and I supplementation on lamb survival. Studies investigating the interaction of Se and I supplementation have been few but results have demonstrated an interaction between Se and I. With increased twinning rates as a result of increased selection of numbers of lambs weaned, nutritional demands during pregnancy across flocks are increasing, and effects of micronutrients on lamb health and survival have greater impact. New opportunities in nutritional research are encouraging new studies into the effects of Se and I supplementation on lamb survival.

Additional keywords: goitre, growth, lamb mortality, management, neonate, pregnancy, reproduction, sheep, thermoregulation, thyroid.

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Introduction

Production losses due to lamb mortality are a major part of reproductive wastage in the sheep industry, and have been estimated to be ~30% when pregnancy scanning rates are compared with weaning rates (Hinch and Brien 2014). Despite ongoing selection for reproductive success by many sheep producers, survival rates have changed only incrementally over decades (Dwyer *et al*. 2015). Current industry targets in Australia for Merino ewes assume 10% and 30% mortality for single- and twin-born lambs, respectively (Anon 2008; Hinch and Brien 2014). Increased twin survival has been highlighted as one area of potentially high gains (Young *et al*. 2014*b*), with a recent study estimating the benefit from a 25% reduction of mortality of twin lambs in a self-replacing Merino wool flock with 30% twin pregnancy rate to be between AU\$1.25 and AU\$2.55/ewe (Young *et al*. 2014*a*). Improved management of pregnant Merino ewes has been shown to lift survival rates in singles from 84% to 95%, and in twins from 40% to 69% (Hocking Edwards *et al*. 2011), demonstrating the impact improved nutritional management can have on lamb survival. Micronutrients play an important role in ruminant nutrition; selenium (Se) supplementation has long been identified as being beneficial to the productive and reproductive efficiency of sheep, even where there is no sign of clinical deficiency, and iodine (I) intake was early identified as key to the function of the thyroid (Underwood 1966). Although micronutrients have been investigated in the past for their role in lamb survival, data on their effects, and in particular of I and Se, on lamb survival in Australian flocks are sparse. In the following, we will investigate whether there is a case for I and Se supplementation to improve lamb survival.

Factors contributing to lamb survival

The majority of lamb losses occur in the first 48 h of life (Brien *et al*. 2009), and the majority of those are generally attributed to a dystocia–mismothering–starvation–exposure complex (Nowak and Poindron 2006; Geenty *et al*. 2014). Peri-natal mortality is often attributed to mismothering, in particular in primiparous ewes, leading to absence or insufficient suckling of the lamb, which in turn also leads to vulnerability to exposure (Hinch and Brien 2014). In research flocks, the dystocia–mismothering–starvation complex accounted for the majority of lamb losses, while in comparison, exposure and predation both had a prevalence of less than 10% (Brien *et al*. 2009; Geenty *et al*. 2014; Hinch and Brien 2014). This indicates that exposure and predation might play a lesser role than commonly assumed, although effective counter-measures for both can be important in specific localities (Hinch and Brien 2014; Young *et al*. 2014*a*).

Significant differences in weaning success among sheep breeds as well as within breeds demonstrate the relevance of the genetic component; however, estimated heritabilities are low for survival to weaning (Safari *et al*. 2007; Brien *et al*. 2014; Everett-Hincks *et al*. 2014), indicating the multifactorial nature of the trait, and highlighting the importance of environmental, and in particular management, factors. Genetic factors of lamb survival have been recently reviewed in depth (Brien *et al*. 2014), and will not be further discussed here.

Ewe nutrition from conception to parturition is well recognised as an important factor for lamb health and survival (Kleemann *et al*. 1993; Brien *et al*. 2014; Hinch and Brien 2014; Rooke *et al*. 2015). Effects of maternal nutrition on fetal growth and lamb birth and weaning weights during different stages of pregnancy have been extensively studied and reviewed (Mellor 1983; Kenyon 2008; Greenwood and Bell 2014; Kenyon and Blair 2014). Maternal undernutrition in the last third of pregnancy appears to be most critical: a range of studies, reviewed by Rooke *et al*. (2015), have showed that lamb birthweight and subsequent lamb vigour and survival were consistently reduced with maternal undernutrition in the order of 50–85% of maintenance requirements, and the effects are considered specific to nutrition. In particular for twins, careful management of ewe body condition score has been reported to be a crucial management component in lowering lamb losses (Everett-Hincks and Dodds 2008), with optimum body condition score between 2.0 and 3.0 (Kenyon *et al*. 2012) At the same time, oversupply of energy, and resulting increased birthweights, could lead to dystocia and associated birth trauma, as supported by the observation of increased mortality for Merino lambs either under 3 kg or over 5 kg of birthweight, regardless of birth type (Hatcher *et al*. 2009).

Meeting ewe energy requirements peri-parturition is important for adequate colostrum on set and production (Banchero *et al*. 2004*a*, 2004*b*). Onset of lactation can be delayed in twin-bearing ewes (Hall *et al*. 1990; McNeill *et al*. 1998), so increased energy availability to the ewe may be of particular benefit for twin pregnancies. In turn, volume and consistency of colostrum can affect suckling behaviour, in particular of twin lambs (Holst *et al*. 1996), which might affect ewe–lamb bonding, and energy provision to the lamb.

The transition to life outside the womb is a complex process (Fig. 1) that includes a finely tuned exchange between ewe and lamb, to which both ewe and lamb contribute (Dwyer and Lawrence 1998). Feed restriction in pregnant Blackface ewes led to poor maternal behaviour after delivery (Dwyer *et al*. 2003), and the negative effect of undernutrition on maternal behaviour might affect lamb survival (Dwyer *et al*. 2010). In particular, prolonged birth events can interfere with the willingness of the ewe to care for the lamb (Dwyer *et al*. 2003); hence, factors leading to dystocia will likely also affect ewe–lamb bonding. Immediately after birth, both lamb and ewe have to learn to recognise each other, and the lamb alone is responsible for initiating suckling, processes which rely on cognitive function (Poindron *et al*. 2007), and hence, factors negatively affecting cognitive function might be disruptive to the bonding process.

In the immediate period following birth, the lamb has to be able to thermoregulate, stand, find the udder, suckle and follow the ewe. Thermoregulation in the neonatal lamb is supported by brown fat or non-shivering thermogenesis, a highly energy-efficient process that turns the energy stored in brown adipose tissue directly into heat (Clarke and Symonds 1998). In the following, we will examine the biological roles of micronutrients Se and I and their potential roles for lamb survival through cognitive, immune and thermo-

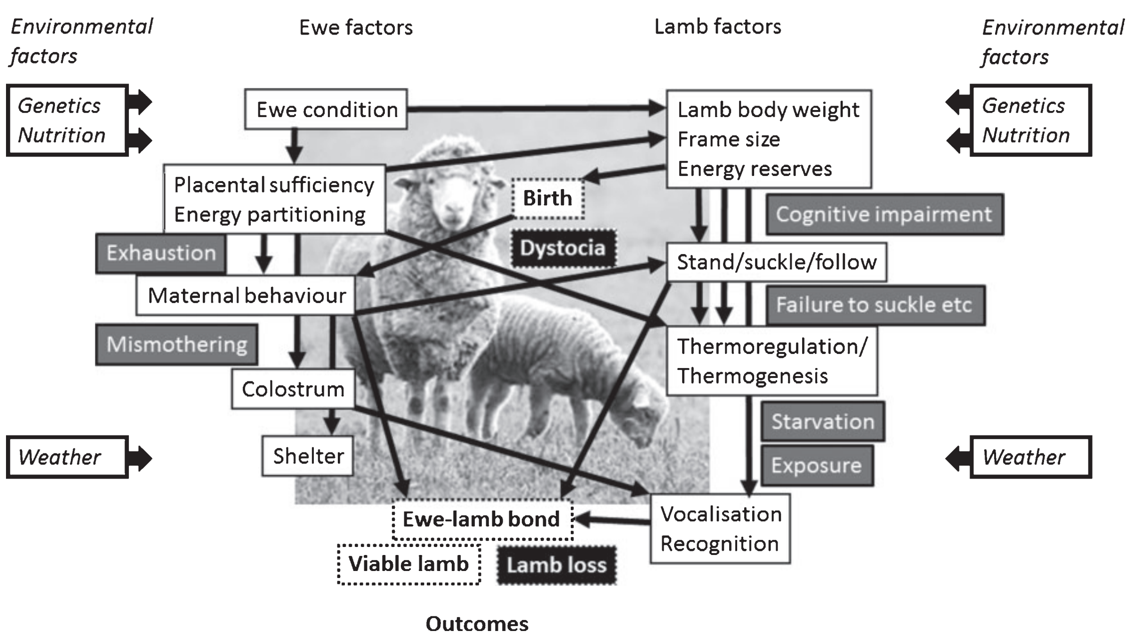

Fig. 1. Factors influencing lamb survival. Ewe factors are on the left, lamb factors are on the right. Physiological factors are black on white background, factors leading to lamb loss are white on grey background. Outcomes have dotted outlines.

regulatory functions, before examining the status of Se and I in Australia.

Biological roles of Se and I

Selenium is normally present biologically in the form of selenomethionine (SeMet) and selenocysteine (SeCys). In blood, the main species of Se is SeCys (Whanger 2002). Seleno-cysteine is used specifically to produce selenoproteins, which have the following three main classes of action (Rooke *et al*. 2004), all of which may play a role in lamb survival: in complex with the glutathione peroxidases (GPx), selenoproteins act as antioxidant reductases; as iodothyronine deiodinases, metabolising thyroxine (T_4) to the more biologically active thyroid hormone (T_3); and as thioredoxin reductases, involved in cellular proliferation, apoptosis and redox reactions. These selenoproteins are all present in the plasma and contribute to selenium homeostasis. Iodine is present in animal tissues as T_4 and T_3; however, some proportion of absorbed I circulates in plasma in its ionic form.

Cognitive function

The effect of Se on cognitive function might at least in part be mediated through the effects of Se on the thyroid (Sher 2001). Iodine has been well recognised for its role in brain development and cognitive function, and brain retardation is now considered as the main effect of the global issue of I deficiency (Li and Eastman 2012). Selenoproteins are centrally important but poorly recognised for neurological development and function (Schweizer *et al*. 2004), including brain development (Pitts *et al*. 2014). Declining Se concentrations and cognitive function have been linked in the elderly (Rita Cardoso *et al*. 2014), indicating the important role of Se in brain functionality.

It is well established that moderate levels of I deficiency cause brain damage, and even mild levels of I deficiency are suspected to impair cognitive function (Delange 2001). Cognition is a central process in maternal offspring bonding; hence, deficit in Se and/or I might impair cognition in lambs and ewes. The improved latency, duration and frequency of standing behaviour in newborn lambs from Se-supplemented dams reported by Muñoz *et al*. (2008*b*) may be associated with improved cognitive function, as well as vigour.

Effects on the immune system

Selenium and iodine have complex and sometimes contradictory influences on the immune status of newborn lambs. Selenium promotes the lamb immune response in several ways (reviewed by Rooke *et al*. (2004)). The metabolism of GPx and thioredoxin reductases in neutrophils and macrophages allows them to produce superoxide and hydrogen peroxide to kill bacterial infections via the so-called ‘respiratory burst’ mechanism. Glutathione peroxidases (GPx) activate the enzymes that catalyse the synthesis of pro-inflammatory and immuno-suppressive eicosanoids. Maternal Se supplementation of deficient ewes increases lamb plasma GPx content, and immune status, as indicated by zinc sulfate turbidity (Muñoz *et al*. 2008*a*). It is proposed that pre-natal supplementation with Se improved the offspring’s ability to absorb IgG from the small intestine (Rock *et al*. 2001). Late-gestation supranutritional supplementation of ewes with inorganic Se did not affect lamb IgG absorption efficiency nor serum IgG concentration (Boland *et al*. 2005).

Selenium has a complex interaction with vitamin E in immune function, since some of its effects are aligned, and some are counter to the effects of selenium (Rooke *et al*. 2004). Vitamin E is a chain-breaking anti-oxidant that scavenges lipid hydroperoxidase radicals, using enzymes that are part of the Se-dependent thiol-reductase cycle (Rooke *et al*. 2004). The requirement for vitamin E is variable and depends on dietary levels of polyunsaturated fatty acids, antioxidants, sulfur amino acids and selenium (Lee *et al*. 2002). Vitamin E is not stored in tissues in appreciable amounts, so all requirements must be met from the diet.

Dietary supplementation of ewes with high levels of I has been shown to decrease newborn-lamb serum IgG concentration and inhibit IgG absorption efficiency (Aumont *et al*. 1989; Guinan *et al*. 2005; Rose *et al*. 2007). High levels of maternal I supplementation do not affect the IgG concentration of colostrum, and it appears that uptake, rather than supply, is inhibited (Boland *et al*. 2008). Uptake of vitamin E by the newborn lamb is also reduced with maternal I supplementation (Boland *et al*. 2008). Rose *et al*. (2007) identified several unknowns about this mechanism, whereby increased maternal I intake is associated with reduced lamb circulating IgG and vitamin E concentrations. These include questions about how I affects (1) the time that the gut is open to macro-molecule transport, (2) the efficiency of that transport, (3) the rate of uptake, (4) the rate of IgG turnover and (5) the extent of redeposition of Ig in the gut and lymphatic systems. Proteomic and metabolomic studies may offer insights into this mechanism and help set the limits of its action.

Effects on lamb thermogenesis

Non-shivering thermogenesis plays an important role in newborn-lamb homeostasis (Alexander and Williams 1968). The thyroid hormones T_4 and T_3 both contain I, and are vitally important regulators of the energy metabolism, and affect basal metabolic rate, body temperature, heart rate and body growth (Towery 1953). The conversion of T_4 to T_3 is essential specifically for brown adipose tissue (BAT) function (Bianco and Silva 1987). The selenoenzyme deiodinase iodothyronine Type II (D2) is responsible for the T_4–T_3 conversion in BAT and BAT thermogenesis (de Jesus *et al*. 2001), proving a mechanistic link for Se and I function. Brown adipose fat is mobilised in response to stimulation by adrenergic cold receptors, and maximal heat production is positively correlated with lamb plasma T_4 concentrations at birth, but there is no relationship with plasma T_3 concentration until 3–36 h after birth (Kerslake *et al*. 2010). Although T_3 has an undisputed role in BAT metabolic heat production, the mechanism of its action is still uncertain (Gereben *et al*. 2008).

Positive associations between ewe I supplementation and lamb thyroid hormone concentrations (Rose *et al*. 2007), and between the latter and lamb thermogenesis have been established; however, a clear link between maternal I supplementation or lamb I status and lamb thermogenesis remains elusive. Lamb rectal temperature at birth has not been successfully linked to maternal I supplementation (Donald *et al*. 1994; Kerslake *et al*. 2010). However, maternal supplementation has significant positive effects on newborn-lamb base-heat production, and triplet lambs born to I-supplemented ewes had greater glucose and IgG concentrations at 24–36 h of age than did triplet lambs born to non-supplemented ewes (Kerslake *et al*. 2010). Lamb thermogenesis in response to short periods of cold stress was not affected by ewe supplementation with I (Kerslake *et al*. 2010); however, it tended to increase when ewes were co-supplemented with both I and Se (Donald *et al*. 1994).

Selenium and iodine in perinatal lamb mortality

An overview of studies on the effects of supplementation of ewes with Se and I on productive performance of ewes and neonatal lambs is given in Table 1. In a landmark study of ewes grazing on Se-deficient soils, Se supplementation increased lamb survival at a stocking rate of 12.5 ewes/ha (Langlands *et al*. 1991*b*). Later studies of the same group on subclinical deficiencies of Se and I could not replicate significant effects on lamb survival; however, they conclusively demonstrated the physiological interaction of Se and I, and also demonstrated the effect of ewe Se supplementation on birth and weaning weight, and on the growth rate of the lamb (Donald *et al*. 1993). Interestingly, Merinos in particular appeared to be vulnerable to Se deficiency (Langlands *et al*. 1991*a*). If breed differences could be confirmed, this would have important ramifications for the interpretation of studies in other breeds.

Supplementing ewes with selenised yeast in the pre-conception period up to mid-pregnancy affected vigour and survival behaviours in newborn lambs. Lambs from Se-marginal dams supplemented with organic Se were quicker to attempt and successfully stand than lambs from unsupplemented ewes (Muñoz *et al*. 2008*b*). Although lamb birthweight was not affected by Se supplementation of dams, supplemented ewes weaned lambs on average 2 kg heavier than controls due to higher growth rates (Muñoz *et al*. 2008*a*). Supplementing ewes with I has not shown a consistent response in reducing perinatal lamb mortality, and pasture I status is a poor indicator of the mortality response to I supplementation (Clark *et al*. 1998). Lambs with an increased thyroid weight, born from unsupplemented ewes, generally had an increase in perinatal lamb mortality compared with those from their supplemented peers. Those authors tentatively identified a thyroid : bodyweight ratio of 0.40 g/kg as the critical threshold of perinatal mortality effects (Clark *et al*. 1998). Research from western Queensland found an interaction of I supplementation with maternal plane of nutrition (Knights *et al*. 1979). Neonatal mortality as a result of starvation was halved (from 36%) in ewes on a low plane of nutrition given I supplementation. Unsupplemented ewe I status was considered marginal in this case.

Selenium and iodine status

Recommendations for the requirement of Selenium (Se) in ewes and lambs are inconsistent as a result of the wide range of tested administration rates and methods, bioavailability (depending on source) and the physiological status of the sheep. Selenium concentration in blood of less than 0.02 μg Se/mL has been suggested as a threshold for Se-deficiency (Langlands *et al*. 1991*a*) but no firm concentrations have been established. Tissue glutathione peroxidase content is often used as an indicator of Se status in preference to tissue Se content; however, its responsiveness reaches a plateau above a level of 0.23 mg Se/kg diet (NRC 1985).

In its organic forms, Se can form complexes with methionine and cysteine to form seleno-methionine and seleno-cysteine, with SMet being the most common species of Se in cereal grains and herbaceous legumes (Whanger 2002). However, while animals are unable to synthesise SeMet from inorganic Se (Whanger 2002), rumen microbes can either degrade SeMet into its inorganic forms, trans-selenate it into SeCys or incorporate dietary SeMet directly into microbial protein (Van Ryssen *et al*. 1989). Inorganic Se can be incorporated by microbes and ruminants into SeCys, excreted in urine or reduced to insoluble forms (Donald *et al*. 1994; Hall *et al*. 2012). Once reduced, elemental Se has low bioavailability, particularly in ruminants (Donald *et al*. 1994).

A simple selenite salt is the most common form of Se administered to animals as supplements and in mineral mixes (Van Ryssen *et al*. 1989; Whanger 2002), but they are considered to be less bioavailable and have a considerably shorter half-life in tissue (Whanger 2002) than do organic Se compounds from, for example, yeasts (Hall *et al*. 2012) and algae (Rodinova *et al*. 2008).

Absorption of Se occurs in the intestine, and is not regulated to meet a specific requirement (Rayman *et al*. 2008). Selenite diffuses freely across the intestinal wall, but there are active transport mechanisms for selenate and seleno-amino acids (Mehdi *et al*. 2013). Uptake of SeMet is non-specific, since it is interchangeably incorporated into proteins including haemoglobin and albumin in the place of Met (Hall *et al*. 2012), and these proteins act as endogenous reservoirs of Se for times of negative Se-balance (Mehdi *et al*. 2013). When these proteins are catabolised, SeMet is trans-selenated into SeCys for use in selenoproteins, or else excreted. Further research is needed into the signalling processes that initiate and regulate the mobilisation and turnover of these endogenous Se stores so that Se supply meets demand.

Iodine is present in animal tissues as covalently bound T_4 and its more active form, T_3, with some proportion of the absorbed I circulating in plasma in its ionic form. It is typically administered to plants and animals as iodine salts in the form of potassium iodide (KI) or potassium iodate (KIO_3). Iodine concentrations in animals are typically assessed indirectly by measurement of the I-containing thyroid hormones thyroxine and triiodothyronine.

Selenium and iodine availability

Throughout Australia and New Zealand, the soil content of Se and I is deficient in several sheep-growing areas. About 30% of soils in New Zealand are considered to be Se deficient (Wichtel 1998). In Australia, areas of subclinical deficiency are thought to be widely spread (Langlands *et al*. 1991*a*), and include several key sheep-raising districts throughout Victoria and New South Wales, as well as large areas of south-west Western Australia

Table 1. Effects of supplementation of ewes with selenium (Se) and iodine (I) on productive performance of ewes and neonatal lambs
GPA, glutathione peroxidase activity

Treatment	Animals and age	Performance of ewes (treatment effects)	Performance of lambs (treatment effects)	References
		Selenium		
Ewes on Se-deficient pasture were supplemented with Fe-Se intra-ruminal pellets before mating, and grazed in two stocking densities (6.3 and 12.5 ewes/ha)	75 Merino and 86 Border Leicester × Merino ewes of 14 or 40 months	Stocking density effect on Se in not supplemented ewes. Merino ewes lower Se than crossbreds. All ewes at 12.5 ewes/ha Se deficient (<0.2 µg/mL). Plasma Se positively correlated with rainfall during preceding 12 months	*Se supplementation increased lamb survival at 12.5 ewes/ha*. Se supplementation increased survival of Merino singles but there was no difference for crossbred singles. Se supplementation increased survival of crossbred twins but not in Merinos	Langlands *et al*. (1991*b*, 1991*a*)
Ewes fed Se-deficient (<0.02 ppm Se) total mixed ration; 0.3 ppm Se from sodium selenite (Se_i) or selenised yeast (Se-y)	21 Rambouillet × Polypay ewes	Se_i and Se-y increased whole blood Se, T_3 and T_4, GPA. Colostrum Se increased. Serum IgM increased	Se_i and Se-y supplementation increased liver and blood Se concentration and glutathionie peroxidase activity. Lamb absorption of IgG increased. No effect on thermometabolism observed	Rock *et al*. (2001)
Corn and soybean meal basal diet supplemented with 0.2, 4, 8, 12, 16, and 20 mg Se/kg DM as sodium selenite during pregnancy and lactation for 2 lambing seasons	33 4-year-old Rambouillet ewes	Milk Se concentration increased with supplementation	Placental transfer of Se, and unsuckled lamb plasma Se increased with supplementation at 20 mg Se/kg DM	Davis *et al*. (2006*a*, 2006*b*)
Ewes housed and fed basal mixed diet, with 0 or 0.5 mg organic Se/ewe.day, from –14 to 90 days after mating. After 90 days of gestation, all ewes offered a standard mineral mix until lambing	82 multiparous crossbred (Greyface and Texel × Greyface) ewes	Se supplementation increased glutathione peroxidase activity and plasma Se. No effects on maternal behaviour	Se supplementation increased glutathione peroxidase activity, plasma Se concentration and immune status 24 h after birth. Lambs showed faster progression to stand, but no other behavioural changes. *Perinatal lamb mortality reduced*	Muñoz *et al*. (2008*b*)
Ewes on pasture supplemented with grass hay and lucerne hay until Week 15, then housed and fed lucerne hay and shelled corn. Ewes supplemented with weekly Se drenches at 4.9, 14.7 and 24.5 mg Se/week.sheep, from Na-selenite, Na-selenate (4.9 mg/week.sheep only) and organic Se-yeast, with a no-supplement control	240 mature, pregnant ewes of Polypay, Suffolk and crossbred genotypes	Organic Se-yeast: effect on whole blood Se and colostrum Se. Se: colostral IgG concentration increased	No treatment effect on birthweight or survival. Se supplementation increased whole-blood and serum Se concentrations at birth. Organic Se supplementation: more efficiency Se transfer to lambs than inorganic Se. Transfer of colostral IgG in Polypay lambs increased with increasing organic Se supplementation, but decreased with inorganic Se supplementation	Hall *et al*. (2012); Stewart *et al*. (2012*a*, 2012*b*, 2013)
		Iodine		
Factorial experiment. Ewes on pasture (mid pregnancy), then penned and fed lucerne hay (late pregnancy) to reach high or low plane of nutrition. For each group, 5 and 20 ewes given 50 and 20 mg KI twice weekly by oral drench, respectively; 25 ewes received no supplement	100 mature pregnant Merino ewes	Unsupplemented ewes showed marginally depressed T_4	*I supplementation increased birthweight and survival* (84% *v*. 64%). Changes were more profound in low plane of nutrition group. No change in body composition	Knights *et al*. (1979)
Grazing ewes supplemented with long-acting dose of 1 mL iodised oil i.m.	1022 Romney ewes, grazed as a single flock over two years	I: increased lambing rate by 21% and 14% in Year 1 and Year 2	*I supplementation increased lamb survival*, particularly during wet conditions	Sargison *et al*. (1998)

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Table 1. (*continued*)

Treatment	Animals and age	Performance of ewes (treatment effects)	Performance of lambs (treatment effects)	References
Treated groups injected intra-muscularly with 400 mg of iodised oil, 2–3 weeks before mating. Both groups grazed together in each trial	10 trials using Merino, Romney and Coopworth ewes, treatment groups of 500 or more	In 2 trials, litter size increased by 14% and 21% in treated ewes	*In 3 trials significant reduction in perinatal lamb mortality*. Lambs from unsupplemented ewes, with a mean thyroid W : body W ratio of >0.40 g/kg had increased perinatal mortality. Pasture I, serum T_4 and T_3 concentrations poorly predicted litter size and perinatal mortality	Clark *et al*. (1998)
Factorial experiment with ewes grazed either pasture exclusively, or pasture + brassica in late gestation; and supplemented with intra-muscular long-acting barium selenate + iodised oil (48 mg Se and 400 mg I)	350 Romney ewes	Increased serum I for 127–206 days	Thyroid weight: Birthweight ratio range was 0.09–0.70, mean 0.35 g/kg in the supplemented group; and 0.21–8.5, mean 1.61 g/kg in the unsupplemented group. Values near 40 g/kg were associated with goitre	Knowles and Grace (2007)
Ewes housed and fed concentrate meal, 0.2, 5.0, 9.9, 14.8 or 21.0 mg I/kg DM. Lambs prevented from suckling and fed fixed quantity of artificial colostrum	60 Mule twin-bearing ewes	No measurements in ewes	I supplementation increased T_3 and T_4 concentrations at birth. Plasma I concentrations 24 h *postpartum* decreased with increasing ewe I supplementation	Rose *et al*. (2007)
Basal diet of grass silage *ad libitum* and 190 g/kg protein concentrate. Supplemented with 0 (C); 26.6 mg I/day for final 3 weeks of pregnancy (I-3); or 26.6 mg I/day for final 1 week of pregnancy (I-1)	60 twin-bearing ewes, breed unknown	I-3: higher colostrum yield at 10 h, but not at 1 h or 18 h *postpartum*. I-1: lower IgG and yield at 10 h, but not at 1 h or 18 h *postpartum*	No effect of I-3 on serum IgG, vitamin E or T_4 at 1 h *postpartum*. I-3 reduced serum T_3 concentrations. I-3 and I-1 decreased IgG absorption efficiency and serum IgG concentration	Boland *et al*. (2008)
Grazing pasture *ad libitum*, supplemented with 1.5 mL iodised peanut oil (26% I w/w), 35 days before mating	16 twin- and 14 triplet-bearing Romney ewes	Increased plasma I concentration throughout pregnancy	No effect on rectal temperature, T_3 concentration, or maximal heat production	Kerslake *et al*. (2010)
		Selenium and Iodine		
Factorial experiment. Ewes grazing Se deficient pastures at two stocking densities (7.4 and 14.8 ewes/ha) and supplemented with intraruminal Se pellets, potassium isothiocyanate pessaries (KCSN) and oral potassium iodine solution (I)	216 Merino ewes	Se supplementation: higher whole blood Se concentrations during pregnancy and lactation. Increased T_3 and decreased T_4 concentrations, affecting $T_4 : T_3$ ratio	Heavier lambs at birth and weaning with faster growth rates (176 vs 144 g/day), increased plasma T_3 and reduced $T_4 : T_3$ ratio	Donald *et al*. (1993)
		I supplementation: higher T_4 and T_3 concentrations, but $T_4 : T_3$ unchanged	Reduced T_3 and increased $T_4 : T_3$	
Factorial experiment. Ewes grazing Se deficient pastures, Se supplementation 0, 0.01, 0.04, 0.15, 0.5, 2.0 or 8.0 mg (sodium selenite), I supplementation 0 or 100 mg (KI), both every 14 days	70 perinatal Merino ewes	Se supplementation: increased blood (11–224 µg/L) and plasma (6–111 µg/L) Se concentrations	Increased blood and plasma Se, reduced T_4, and increased T_3 concentrations and decreased $T_4 : T_3$ ratio. No effect on birthweight or rectal temperature during cold stress. No interaction with I supplementation	Donald *et al*. (1994)
		Iodine supplementation: No response of ewe blood or plasma Se concentration	Tended to increase rectal temperature during cold stress (n. s.). No effect of I on plasma T_3 or T_4 concentration or $T_4 : T_3$ ratio	

(*continued next page*)

Table 1. (*continued*)

Treatment	Animals and age	Performance of ewes (treatment effects)	Performance of lambs (treatment effects)	References
Basal diet of *ad libitum* grass silage, supplemented with multi-minerals excluding Ca, P, Mg, Na, Zn, Se (sodium selenite), I, Mn, Co, vitamin E individually for the last 6 weeks of pregnancy. Se supplementation 0.45 g/ewe.day. I supplementation 0.06 g/ewe.day	108 twin-baring ewes of mixed age and parity	No effect of Se on colostral IgG yield or concentration.No effect on colostral IgG yield or concentration	Se supplementation: no effect of on colostral IgG intake, serum IgG concentration or IgG absorption efficiency. Iodine supplementation: reduced serum IgG concentration and colostral IgG absorption efficiency at 24 h. No effect on colostral IgG intake	Boland *et al*. (2005)

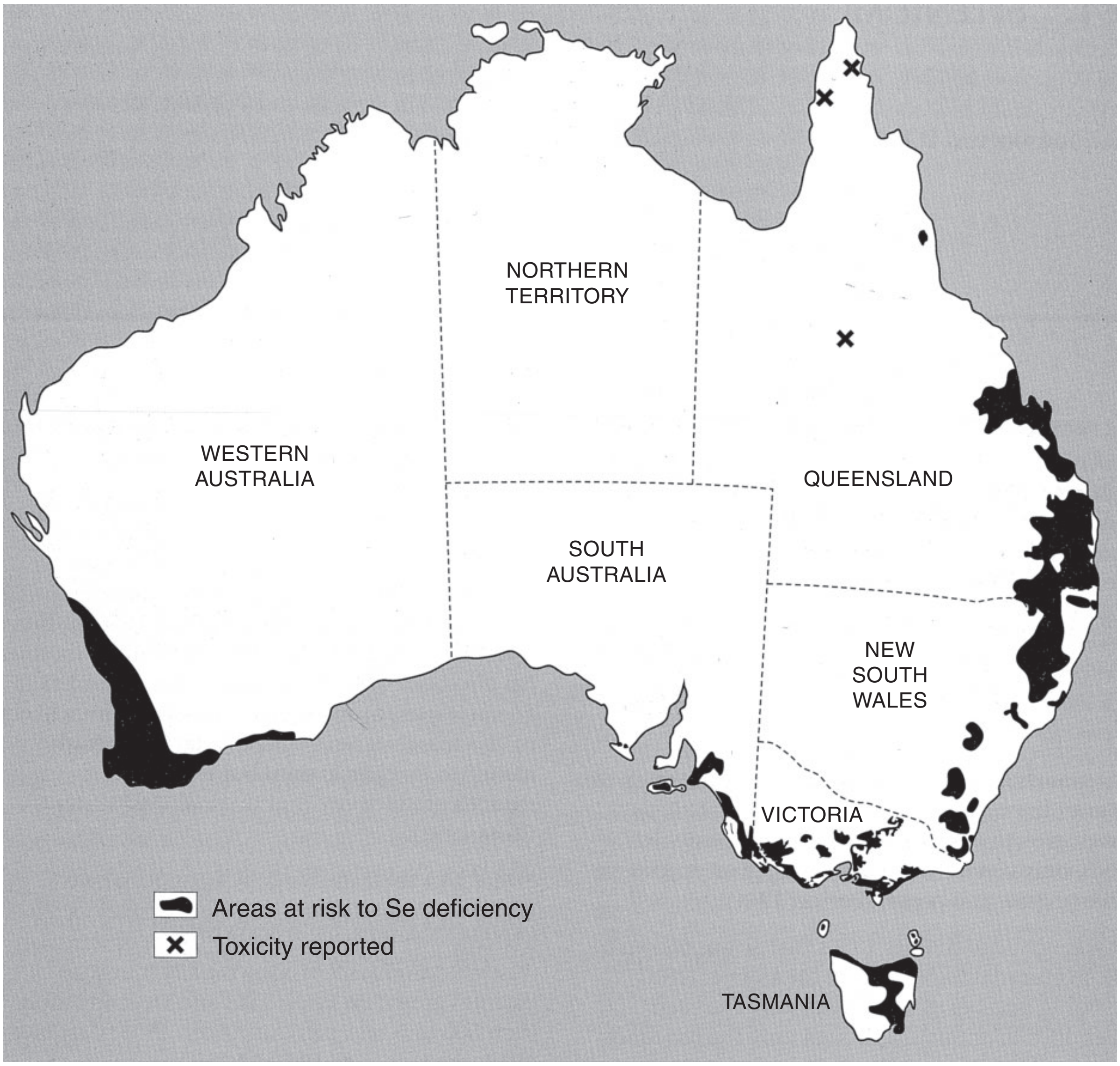

Fig. 2. Selenium (Se) levels in Australian soils (reproduced from Judson and Reuter 1999, with permission).

(Fig. 2; fig. 24.1 in Judson and Reuters 1999), although areas where flocks exhibit clinical signs of Se deficiency are rare, and highly localised (Caple *et al*. 1980). Poor Se nutrition is most likely to occur in wheat crops grown (Lyons *et al*. 2005) or sheep flocks grazing (Caple *et al*. 1980) in high-rainfall or sandy-soiled areas (where Se is easily leached from the soil), igneous (granite)-derived soils (which are low in Se (Dhillon and Dhillon 2003)), acidic soils (where more Se is present in forms unavailable to plants (selenides and ionic Se)), after use of high sulfur-containing fertilisers such as gypsum and superphosphate through competition of Se with sulfur for uptake in plants leading to decreased plant Se content, and in Australia's coastal areas where there may be high and competing levels of S- deposition from rainfall (Caple *et al*. 1980; Lyons *et al*. 2005). Dilution caused by rapid plant growth is another possible cause of Se deficiency (Caple *et al*. 1980), and could be a risk factor for pregnant ewes grazing improved pasture, particularly those lambing in spring.

In Australia, there have been no extensive surveys of soil I content, and no soil maps are available; however, it is commonly known that several regions are deficient. Iodine deficiency in soils has been inferred indirectly from studies such as the Australian National Iodine Nutrition Study, showing that school-age children in New South Wales and Victoria are mildly I deficient, and those in South Australia are borderline deficient (Li *et al*. 2008). Meta-analysis of several studies on estimated I intake of pregnant and breastfeeding women conducted in New South Wales, Victoria and Tasmania concluded that I supplementation was necessary in all studied areas (Mackerras and Eastman 2012). Iodine deficiency in humans used to be judged by the incidence of goitre only; however, in recent years, a paradigm shift has occurred that now judges I deficiency as a global public-health problem affecting most countries, with the most important consequence being brain damage causing mental retardation in children (Li *et al*. 2008; Li and Eastman 2012). In grazing animals, cognitive function is vital during the first hours of mother–offspring bonding (Nowak *et al*. 2007), and I deficiency during critical stages of brain development might lead to brain damage interfering considerably with this critical process. Marginal and deficient I status in grazing animals can be due to low concentration or availability in soil, or the presence of I agonists in the pasture. Thiocyanates, which are present in high concentrations in brassica species, linseed and white clover (among others), act as inhibitors of I uptake by the thyroid gland. Pastures with high concentrations of thiocyanate precursors can cause I deficiency, even if dietary supply is appropriate (Sargison *et al*. 1998).

Intake recommendations

Selenium

The significance of Se in nutrition was first identified through its role as a toxicant. Later, its essentiality was determined and the thresholds of Se deficiency were described. More recently, an understanding of the role of supranutritional supplementation with Se has emerged (Stewart *et al*. 2012*a*, 2012*b*). Current NRC requirements for Se are 0.1–0.2 mg Se/kg DM (NRC 1985). Typical Se intakes in New Zealand are ~1/10 of recommended intakes, yet the low incidence of clinical symptoms of Se-deficiency, such as white muscle disease and reproductive disorders, indicates that factors such as nutrition and management may either reduce the requirement for Se or the effects of deficiency (Wichtel 1998).

Aumont *et al*. (1989) identified a minimum intake of 0.12 mg I/kg DM in pregnant ewes to prevent deficiency in ewes, their fetuses and newborn lambs. Recommended dietary I requirements for pasture-fed sheep range from 0.3 mg I/kg DM (Grace 1994) to 0.5 mg I/kg DM (ARC 1980). However, a reliable indicator of animal I status has not yet been identified (Grace and Knowles 2012). The NRC (1985) suggested a maximum tolerable intake of I of 50 mg/kg DM; however, ewe intakes above 9 mg I /kg DM impaired IgG absorption in their newborn lambs (Aumont *et al*. 1989).

Mineral supplementation of ewes

Long-acting rumen boluses and intra-muscular injections of Se and I have practical application for extensively managed grazing flocks. Intra-ruminal selenium–iron boluses and intra-muscular barium selenate depot injections have effective durations of 12–18 months (Wichtel 1998; Grace and Knowles 2012). Long-acting injectable barium selenate delivering 36–60 mg of Se administered 4 weeks before mating was sufficient to maintain Se concentrations in ewe and lamb blood at five times the threshold of deficiency at lambing (Grace *et al*. 2006). Intramuscular injection of iodised oil has a long-acting effect on ewe I status, and a single 2 mg injection of I given to lactating ewes showed an increase in milk I concentration up to 16 months and two pregnancies after the initial administration, while the effect from the same dose administered as oral drench disappeared within 23 h (Azuolas and Caple 1984).

Some antihelmentic drenches contain trace elements such as Se, copper or cobalt. As a supplementation strategy for Se, this kind of drench can deliver 5–6 weeks of efficacy, limiting their practicality (Grace and Knowles 2012). Trace-mineral supplementation using self-administration techniques, such as lick blocks, have high variabilities in individual intakes by sheep (Ducker *et al*. 1981). Since trace minerals act within a range delimited by deficiency and toxicity, self-administered supplements may affect a single flock at both ends of this spectrum.

The bioavailability of dietary Se supplements strongly affects effectiveness. Selenium-yeast is manufactured by fermenting yeast in Se-enriched medium, so that inorganic Se becomes organically bound to the yeast, typically as SeMet (Rayman *et al*. 2008).

An alternative option to administer trace elements to flocks is by surface application to pastures in the form of fertiliser. Selenium in fertiliser has widespread use in New Zealand and Finland, where it is mandated (Dhillon and Dhillon 2003). Surface application of potassium iodide and potassium iodate fertilisers have significant effects on pasture I levels, up to 19 weeks after application (Smith *et al*. 1999).

Transfer of minerals to lambs in utero

Maternal plasma Se is not readily transferred across the placenta to the fetus, even when ewe tissue concentrations are high. The ratio of Se concentrations in maternal plasma to fetal plasma is ~12 : 1 for singletons and 22 : 1 for twins (Hidiroglou 1980). The range of ewe supplementation levels at which responses are seen in lambs is more restricted with inorganic Se than organic sources as a result of the more efficient placental transfer of Se from ewes to offspring when ewes are supplemented with organic Se (Rock *et al*. 2001; Stewart *et al*. 2012*b*).

As pregnancy advances, the trace-mineral status of ewes declines as minerals are transferred across the placenta to the fetus, and this effect is even stronger in twin-bearing ewes. Plasma concentrations of Se, I, T_3 and T_4 decrease from 90 days of pregnancy (Abdollahi *et al*. 2013). The implication of this is that one-off administration of short-acting Se at mating will be insufficient for fetal development throughout gestation (Hidiroglou 1980). Twinning reduces ewe plasma concentrations of Zn, Mn, I and T_4 at all stages of pregnancy; however, it is only in late gestation that twinning has a greater effect on ewe plasma Se and T_3 concentrations than have singletons (Abdollahi *et al*. 2013).

Iodine is transferred bi-directionally across the placenta as an inorganic ion (Hidiroglou 1980), and plasma inorganic I concentrations in the newborn reflect those of the dam (McCoy *et al*. 1997). Iodine transfer across the placenta correlates with fetal thyroid development; however, there is no mechanism to transfer I in organic forms or as thyroid hormones (Aumont *et al*. 1989), and I stored in the thyroid of the ewe is unavailable to her fetus (Azuolas and Caple 1984). If a ewe has adequate thyroid hormone stores, then dietary deficiency may not be apparent, although there may not be sufficient circulating ionic I for fetal thyroid development and function (Azuolas and Caple 1984). Ewe thyroid hormone concentrations may, therefore, be a poor indicator of deficiency or lamb thyroid status (Sargison *et al*. 1998). When ewes are experiencing hypothyroidism as a result of dietary I deficiency, their own thyroid uptake of I may be upregulated, resulting in lower transplacental I transfer to their offspring; however, this has not been confirmed experimentally (Sargison *et al*. 1998).

Transfer of trace minerals via colostrum

After *in utero* transfer of trace minerals, colostrum is a second source of improved mineral status of newborn lambs. Supplementation of dams with I increases the inorganic I content of colostrum (McCoy *et al*. 1997). Selenium supplementation of ewes can improve lamb Se status by passive transfer of Se, incorporated as SeMet into milk proteins, and as an increased concentration of immunoproteins. Supplementation with Se at adequate (Rock *et al*. 2001) and supranutritional (Stewart *et al*. 2012*b*) concentrations increases Se concentrations in ewe colostrum, and the transfer efficiency from blood to colostrum is five-fold when supplemented with adequate organic Se-yeast compared with sodium selenite (Stewart *et al*. 2012*b*).

Conclusions

Despite a large body of work on the effects of overall ewe nutrition on lamb production values including lamb survival, there is a dearth of clear recommendations for requirements of micronutrients during gestation, including Se and I. In Australia, both Se and I deficiency levels as such are likely to be subclinical but wide-spread across production systems due to risk factors such as competition with other minerals, in particular on superphosphate-improved pasture, and through grazing of plants containing inhibitors of uptake. However, supra-requirement supplementation can have negative effects as demonstrated by the finding of high levels of iodine supplementation decreasing lamb serum IgG concentration, emphasising the need for clear guidelines for ewe supplementation during pregnancy.

The biological roles of Se and I are intrinsically connected, with Se and I deficiency being implicated in cognitive impairment, and impaired growth and development. It is possible that supplementation of one without the other might not have the desired outcomes; however, few studies have addressed the question. Under restricted feed-availability conditions, Se and I supplementation become particularly important and effective. In multiple pregnancies, where nutritional availability for each fetus is limited, the role of micronutrients is likely to be more pronounced as several studies have indicated. Twin survival is one of the most important and promising areas for improvement in Merino production (Young *et al*. 2014*b*).

This review has shown that, although there is a broad theoretical metabolic rationale linking ewe Se and I status with cognitive, immune and thermogenic capacity of newborn lambs, the production effects of Se and I on lamb survival or viability are not clearly established. Part of this is a result of experimental variability in supplemental Se availability, existing Se and I status, and interactions with breed, nutrition, weather and twinning. Studies aiming to link ewe supplementation and lamb survival are challenged by the need for large, costly experiments to overcome natural variation and establish clear effects on lamb survival. In addition, both Se and I blood concentrations are usually measured indirectly, adding another variable to each study. A more productive approach to lamb survival may be one that focuses on the management conditions that contribute to mineral deficiencies arising and affecting production. Future research trying to establish whether there is a causal relationship between Se and I status and lamb survival may be more successful if it focuses on the linking metabolic transactions that drive lamb viability and are based around Se and I metabolism. For instance, the application of metabolomic analysis to the effects of Se and I status in pregnant ewes might advance our understanding of how to address the problem of lamb survival substantially, and complement emerging research on the interaction between temperament and energy metabolism (Henry *et al*. 2010) in sheep, which has implications for selection strategies based on observed behaviour such as maternal behaviour score. Novel data-driven approaches to nutritional research will add value to animal experiments and complement hypothesis-driven research methods such as metabolic hormone profiling. Resulting data will help underpin current management guidelines that feed into extension programs such as Lifetime Ewe Management, which are crucial tools for the ability of the sheep industry to fully realise the genetic potential of the Australian sheep flock.

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