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Insulin-like growth factor levels during pregnancy in the cow are affected by protein supplementation in the maternal diet

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Abstract

To determine if dietary protein supplementation in early pregnancy alters total circulating insulin-like growth factor (IGF) levels, genetically similar heifers were fed diets containing different levels of protein in the first and second trimesters of gestation. The groups were: low/low (L/L), fed a diet containing 7% crude protein (CP) per kg/DM (low protein) in the first and second trimesters; high/high (H/H), fed a diet containing 14% CP per kg/DM (high protein) in the first and second trimesters; low/high (L/H), fed low protein in the first trimester and high in the second trimester and vice versa for the high/low (H/L) group. At day 62 of gestation, there was a significant difference ($P < 0.01$) in IGF I concentrations between the high and low protein groups (149 versus 119 ng/ml, S.E. 5.9). There was a strong effect ($P < 0.001$) of protein levels in the second trimester on IGF I levels on days 119, 153, and 183 of gestation but not at day 257. Mean IGF I levels for high and low nutrition in the second trimester were 157 and 97 (S.E. 6.6) for days 119, 191, and 88 (S.E. 12.6) for days 153 and 160, and 67 (S.E. 7.7) for day 183. At day 257, there was a significant interaction ($P < 0.01$) between treatments with the means being 98^{ab}, 110^{b}, 116^{b} and $79^{a\gamma}$ (means followed by a letter in common do not differ significantly, $P < 0.05$) (S.E. 7.5) for H/H, H/L, L/H, and L/L, respectively. There was a significant ($P < 0.05$) effect of protein supplementation in the first trimester on calf IGF I levels at birth with means being 42 and 25 (S.E. 5.2) for high and low protein supplementation, respectively. There was a significant ($P < 0.01$) effect of protein supplementation in second trimester upon IGF II levels and a significant ($P < 0.05$) negative

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correlation between calf birth weight and IGF II levels.

Keywords: Cattle-pregnancy; Insulin-like growth factors; Dietary protein

1. Introduction

The effects of low protein intake during pregnancy are pertinent to the cattle industry as protein is the most deficient nutrient in the Australian rangelands. Further, high dystocia rates in heifers are reported in the Brigalow–Belah belt of Australia in some years more than others. This appears to be dependent upon the level of medic (Medicago genus of the family Leguminosae) growth available to the heifer during gestation. This plant may dominate pasture in the winter, when there is sufficient rain, causing dietary crude protein (CP) levels to rise to a maximum level of around 20% (Pullman and Hughes, 1986). It has been shown in earlier work that nutrition in the third trimester of pregnancy had little effect on the size of the calf produced (Rasby et al., 1990) and our own observations in previous years support this. Hence, this work has concentrated on the effect of protein in the first two trimesters of pregnancy.

It is thought that foetal birth weight is partially regulated by the insulin-like growth factor (IGF) system. IGF I promotes the growth of major foetal organs in vivo (Lok et al., 1996). DeChiara et al. (1990) and Liu et al. (1993), using mice with null mutations of the genes for IGF I, IGF II and the type 1 IGF receptor demonstrated that these growth factors are essential for normal foetal growth. It is thought that IGFs determine the partitioning of nutrients, as more receptors are found in the tissues, which are critical for survival. Intrauterine growth retardation, whether by carunclectomy, maternal fasting or other means, results in reduced foetal serum IGF I (Jones et al., 1988; Dwyer and Stickland, 1992a; Kind et al., 1995). Dwyer and Stickland (1992a), working with guinea pigs found that if the mother is on a restricted diet, levels of IGF I and II in the foetal blood were reduced. This corresponds with earlier work in which restriction of maternal diet resulted in a 35% reduction in foetal and placental weights and a 20–25% reduction in foetal fast muscles development (Dwyer and Stickland, 1992b). In rats, Pilistine et al. (1984) also found that maternal protein deprivation, for the last two-thirds of gestation, reduced concentrations of both IGF I and II in foetal rat plasma. In sheep, the foetal IGF axis can be altered by maternal nutrient restriction in early to mid gestation (Brameld et al., 2000).

Long-term restriction of total nutrient supply is accompanied by sustained reduction in IGF I and II concentrations in the rat, whilst administration of IGF I in late pregnancy promotes the growth of major foetal organs. It has been suggested that changes in circulating IGFs in response to altered substrate supply may well contribute to changes in foetal growth (Owens, 1991 and Schoknect et al., 1995). Both IGFs increase protein and glycogen synthesis in foetal tissues but it is thought that IGF I may have a more prominent role in modulating cell proliferation in specific endocrine and nutritional conditions in utero whereas IGF II provides a general stimulus for cell growth in utero and may also be responsible for developmental and tissue-specific changes in cell differentiation (Fowden, 1995). A strong

positive correlation has been reported between IGF I levels in the foetus and foetal size in late gestation (Jones et al., 1988; Dwyer and Stickland, 1992a; Carr et al., 1995).

Treatment of rodents with IGF I overcomes maternal constraints on foetal growth and alters the usual close correlation between foetal and placental size (Gluckman et al., 1992) and suggests that maternal IGF I directly or indirectly affects placental function (Gluckman and Harding, 1994). Kind et al. (1995) showed that restriction of placental growth reduces circulating levels of IGF I in the sheep foetus and reduces the capacity for the production of IGF I in a number of tissues suggesting that altered production of IGF I in various tissues may contribute to retarded foetal growth. In pregnant ewes infused with IGF I, the consequent suppression of maternal insulin led to greater glucose availability and an increase in placental amino acid nitrogen uptake (Harding et al., 1994a). In foetal sheep, infusion with IGF I reduced foetal protein catabolism, increased foetal glucose consumption and reduced placental lactate production (Harding et al., 1994b), suggesting that IGF I in foetal blood could influence foetal growth by endocrine regulation of placental function. When nutrient restricted ewes (fed only 50–60% of their energy requirement between 28 and 77 days gestation) are subsequently fed to fully meet their maintenance energy requirements for the remainder of pregnancy, this results in a larger placenta at term and lambs with a longer crown-rump length (Heasman et al., 2000).

It can be seen that an important role for IGFs has been established in sheep and small rodents. However, the impact of varied nutrition on placental growth and function and on foetal growth and the role of the IGF system in this has been little explored in large animals particularly those of agricultural importance.

This paper reports on a study of the effect of the level of protein in the maternal diet on maternal and newborn calf IGF levels.

2. Materials and methods

2.1. Animals and treatments

Genetically similar Hereford heifers were oestrus synchronised and artificially inseminated to a Hereford bull with a known estimated breeding value (EBV) for birth weight. Forty-five days after AI, the pregnant heifers ($n = 16$) were allocated at random to four treatment groups designated: high/high (H/H), high/low (H/L), low/high (L/H) and low/low (L/L)—the first word referring to maternal nutrition in the first trimester (day 0–90 of gestation) and the second word to nutrition in the second trimester (day 91–180). The high diet contained CP at 14% of dry matter (DM), which was achieved by individually feeding a daily supplement of 1420 g (wet weight) of cotton seed meal (CSM) to each heifer in addition to dry pasture and sorghum hay. The low diet of pasture and sorghum hay contained 7% CP. It should be noted that because of the welfare considerations of the animals and the facilities available to us, it was impossible to add extra protein to the diet of a ruminant without increasing energy. The CSM contained only a small amount of energy but increasing available protein to the ruminant would have enabled it to increase its intake of ad lib hay and therefore increase available energy to the animal. The diet of all groups in the third trimester consisted of grass pasture containing some medics with an average 10% CP.

2.2. Blood sampling and hormone assays

At 15, 62, 89, 119, 153, 183, and 257 days of gestation plasma samples were collected from each heifer. Immediately post calving, plasma was taken from each heifer and its calf prior to suckling and both were also weighed. Blood was collected via jugular venipuncture into lithium heparin vacutainers. The vacutainers were kept on ice until centrifugation, after which the plasma was stored at −18 °C until processing for IGF concentrations.

Concentrations of IGF I and II were measured by RIA (Owens et al., 1994) after IGF proteins were dissociated and separated from their binding proteins by semi-automated size exclusion chromatography HPLC of plasma at pH 2.5. This method is detailed by Owens et al. (1994).

One heifer in the H/H group was excluded from analysis as she had twin calves.

2.3. Statistical analysis

Data collected on day 15 provided the baseline for subsequent measurements. A one-way analysis of variance was used to assess the effect of nutrition in the first trimester on heifer liveweight and IGF I and II levels in the first trimester (days 62 and 89). Liveweight on day 15 was included as a covariate in all analyses of liveweight. Liveweight on day 15 and the respective IGF levels on day 15 were considered as potential covariates in the analysis of IGF levels. As these were not significant ($P > 0.05$), no covariates were included in the analyses of IGF I and II levels. A two-way analysis of variance was used to assess the effects of nutrition in the first and second trimesters and their interaction on heifer liveweight and plasma IGF levels in the second and third trimesters and at calving, as well as on calf birth weight and calf plasma IGF levels.

Pearson correlation coefficients were calculated to assess relationships between liveweight and plasma IGF levels at each time of measurement.

3. Results

Results for liveweight and IGF plasma levels for the full set of four treatments are presented graphically in Figs. 1–3. Details of significance of the main effects and their interaction, together with main effect means are presented in the text.

3.1. IGF I

During first trimester, despite there being no effect of diet on the weight of the heifers, there was a significant difference ($P < 0.01$) in IGF I levels between the high and low protein groups at day 62 of gestation. Mean IGF I levels on day 62 were 149 and 119 (S.E. 5.9) for high and low nutrition in the first trimester, respectively. Data showing the mean values and standard errors of IGF I during the trial are shown in Fig. 1.

Dietary protein levels in the first trimester had no significant effect on IGF I levels in the second or third trimester.

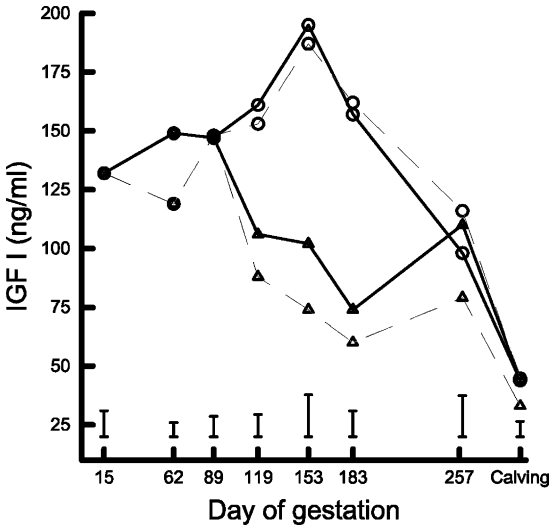

Fig. 1. Mean IGF I levels during gestation for H/H (●, solid line); H/L (△, solid line); L/H (○, dashed line); and L/L (△, dashed line) treatments. The vertical bars represent the standard error of the means.

There was a strong effect ($P < 0.001$) of protein levels in the second trimester on IGF I levels on days 119, 153, and 183 of gestation but not at day 257. Mean IGF I levels for high and low nutrition in the second trimester were 157 and 97 (S.E. 6.6) for day 119, 191, and 88 (S.E. 12.6) for day 153 and 160 and 67 (S.E. 7.7) for day 183. At day 257, there

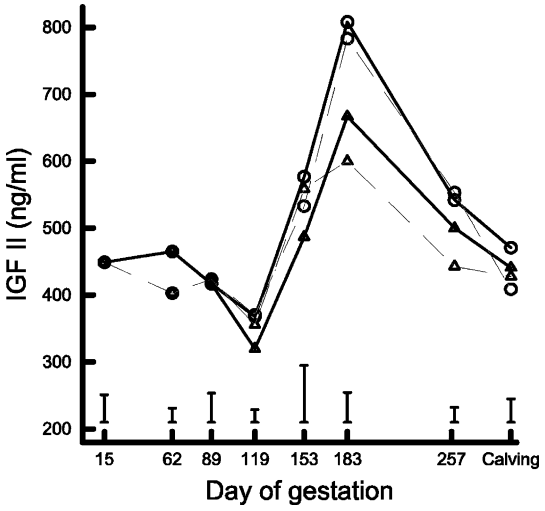

Fig. 2. Mean IGF II levels during gestation for H/H (●, solid line); H/L (△, solid line); L/H (○, dashed line); and L/L (△, dashed line) treatments. The vertical bars represent the standard error of the means.

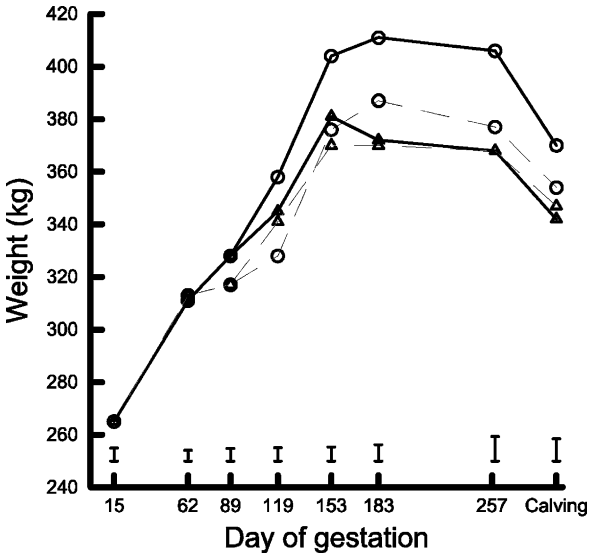

Fig. 3. Mean heifer weights during gestation for H/H (●, solid line); H/L (△, solid line); L/H (○, dashed line); and L/L (△, dashed line) treatments. The vertical bars represent the standard error of the means.

was a significant interaction ($P < 0.01$) between treatments with the means being 98^{ab}, 110^{b}, 116^{b}, and $79^{a\gamma}$ (means followed by a letter in common do not differ significantly, $P < 0.05$, S.E. 7.5) for H/H, H/L, L/H, and L/L, respectively.

There was a significant ($P < 0.05$) effect of protein supplementation in the first trimester on calf IGF I levels at birth with means being 42 and 25 (S.E. 5.2) for high and low protein supplementation, respectively.

IGF I concentrations rose during the first half of gestation in heifers supplemented with protein in the second trimester and gradually fell until calving. In the heifers that were unsupplemented in the second trimester concentrations fell away sharply after 90 days of gestation, rising a little in the third trimester to drop again at calving (mean 41.5, S.E. 4.4).

3.2. IGF II

There was no effect of diet in first trimester on plasma IGF II concentrations in any stage of gestation or in the newborn calf (Fig. 2). There was a significant ($P < 0.01$) effect of protein supplementation in the second trimester on IGF II concentrations at day 183 and 257. Mean IGF II for high and low protein in the second trimester were 796 and 633 (S.E. 31.7), respectively for day 183, and 547 and 472 (S.E. 15.6), respectively for day 257. IGF II concentrations in the heifer at calving and in the newborn calf were not affected by the diets, overall means being 437 (S.E. 23.1) and 374 (S.E. 62.9), respectively.

Fig. 2 shows that IGF II concentrations were fairly stable in the first trimester but rose sharply in the second trimester and fell again by the end of the third trimester. The rise of IGF II in the second trimester is significantly lessened by low protein in the unsupplemented

Table 1
Mean calf IGF I, IGF II and weight at birth

Treatment	IGF I	IGF II	Weight (kg)
H/H	44.6	378	33.9
H/L	39.4	319	33.9
L/H	27.2	431	33.3
L/L	22.9	370	35.4
S.E.	7.3	100	1.6

Table 2
Correlations between liveweight and levels of IGF I and II

	First trimester			Second trimester		Third trimester		At calving	
	15	62	89	119	153	183	257	Heifer	Calf
IGF I vs. wt.	−0.15	−0.05	0.12	−0.16	0.42	0.51*	0.30	0.21	−0.35
IGF II vs. wt.	0.36	0.35	0.07	0.05	0.05	0.31	0.27	0.39	−0.60*

* $P < 0.05$.

groups as seen in the L/L and H/L groups as compared to other two groups on high nutrition in the second trimester.

3.3. *Weight (Fig. 3)*

There was no effect of diet in the first trimester on weight of the heifers in the first trimester. A significant ($P < 0.01$) effect was noted in the second trimester regardless of diet content in the second trimester until day 183. Means for high and low nutrition in the first trimester were 352 and 334 (S.E. 3.6) for day 119 and 393 and 373 (S.E. 3.8) for day 153. Supplementation during the second trimester also had a significant ($P < 0.05$) effect on weight during the third trimester. Means for high and low nutrition in the second trimester were 399 and 371 (S.E. 4.4) for day 183 and 392 and 368 (S.E. 6.6) for day 257. At calving there were no differences between the treatment groups in heifer liveweight; overall mean being 353 (S.E. 5.6) or calf birth weight; overall mean 34.1 (S.E. 1.1). Calf weights and IGF I and II levels at birth are shown in Table 1.

Correlations between liveweight and IGF I and II are shown in Table 2. In general, liveweight and plasma IGF levels were not correlated, the only exception being IGF I and weight on day 183 ($r = 0.51$; $P = 0.05$) and calf IGF II with calf birth weight ($r = -0.06$; $P < 0.05$).

4. Discussion

From the data collected, it is evident that protein supplementation during gestation effects IGF concentrations in the maternal circulation Whether this influences foetal growth is difficult to assess with the small number of animals we had available to us. Similar observations

have been made for other species that foetal IGF I levels are decreased in undernourished animals (Dwyer and Stickland, 1992a). Schoknect et al. (1995) showed that sows fed a protein restricted diet in the second half of gestation had reduced plasma IGF I concentrations and smaller piglets at birth. Intravenous provision of exogenous IGF I enhanced their growth. Therefore, if the effects of IGFs in the bovine are similar to other species studied, we can assume that protein restriction would affect the growth of the foetus, although birth weight in the present study did not show this.

There is some work to suggest that the bovine is dissimilar to other species in the effects of nutrition on plasma concentrations of IGF I. Lacasse et al. (1994) found that plane of nutrition (ad lib versus 80% of ad lib feeding) had no effect on plasma IGF I concentrations in heifers from 1 year of age until just prior to calving. McGuire et al. (1991) also found that nutrition had no effect on IGF concentrations in lactating cows, although this study used relatively mild feed restrictions for only 16 days. In this study, we found that IGF I was influenced by protein levels during the first two trimesters of pregnancy with the second trimester being particularly affected in this regard. This concurs with work reported by Clemmons and Underwood (1991), and Thissen et al. (1994) where food deprivation caused a rapid decline in levels of IGF I in humans, pigs, and sheep. Breier et al. (1986) found that feed restriction in steers also decreased IGF I levels.

A role for IGF II as a determinant of prenatal growth is also indicated by studies in mice (DeChiara et al., 1990; Baker et al., 1993) but the role of nutrition in regulation of IGF II is less clear. Soliman et al. (1986) found that chronically malnourished children had reduced IGF II concentrations while short-term (5 days) food deprivation in humans appeared to have no effect (Davenport et al., 1988) whereas 2 days of feed deprivation in pigs modestly decreased circulating IGF II (Buonomo et al., 1988). In our studies, circulating IGF II during the last trimester was significantly effected by diet during the second trimester. This may suggest that IGF II is more sensitive to changes in nutrition later in gestation in cattle.

It should be noted here that, even though the IGF I and II were extracted from their binding proteins prior to assay, the effect of different levels of IGF binding proteins remain an unknown variable in this study as we did not have the resources to measure these.

Studies in rats and mice (Gluckman et al., 1992) have shown that maternal IGF I affects foetal growth by altering some aspects of placental function. Unfortunately, placental production and transfer of IGF was unable to be measured in this study. Positive associations observed between foetal plasma IGF I and the weight of foetal rats, (Unterman et al., 1993) sheep, and guinea pigs (Jones et al., 1988) also suggest that IGF I is an important influence on intrauterine growth in several species. Kind (1995) found that the concentration of IGF I in foetal blood at 120 and 127 days gestation could potentially account for 87 and 71%, respectively of the variation in foetal weight at 130 days gestation. However, Heasman et al. (2000) found that in nutrient restricted ewes the IGF axis was disrupted such that there was only a positive correlation between birth weight and IGF I levels in control lambs. In this study, there was no significant effect of treatment on IGF I concentrations in the newborn calf, although the small number of treatment animals could have mitigated against achieving significant results.

In conclusion, this study shows that dietary protein in the first and second trimester of pregnancy affects IGF I and II. IGF I appears to be particularly sensitive to dietary protein levels during second trimester of gestation. Considering the importance of IGF

concentrations in the development of the foetus (Gluckman et al., 1992; Brameld et al., 2000), these may represent one of the mechanisms by which foetal development is affected by protein levels in pasture. From our studies, the level of protein in the diet that can be produced by medic pasture is clearly sufficient to influence IGF concentrations in the heifers.

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