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Prepared by: Julie Owens, Dr Karen Kind

University of Adelaide

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On farm manipulation of bioactives Nature and nurture impact on bioactivity

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Executive summary

Fetal bovine serum is a complex natural product, containing a mix of biomolecules with both growth promoting and growth inhibitory actions. FBS is used in cell culture to support cell proliferation and maintenance. As a natural product, the composition of serum is highly variable however, introducing batch to batch variation in the ability to support cell growth, a problem for high yield cell culture.

It is envisaged that genetic and physiological differences between the donor animals which underlie this variation could be exploited to the benefit of the whole value chain, with producers and processors able to make the biggest contribution and therefore claim a significant share of this benefit.

Candidate bioactives have been identified from the literature, based on those required for cell growth and maintenance and those which varied with FBS bioactivity, with the priority candidates being: the insulin-like growth factors (IGFs) and their binding proteins (IGFBPs), the fibroblast growth factors (FGFs), transforming growth factor-β (TGF-β), the epidermal growth factors (EGF) and the neuregulins (NRGs).

The evidence for both “nature and nurture” (genetics and environment) being able to affect these candidate and other biochemical factors in fetal bovine serum, which are able to impact cell growth and protein production, was then reviewed. The literature relating to other species was also reviewed.

The review aimed to address three questions:

1. What is the evidence that breed of cattle or of sheep can influence biochemicals in blood serum, likely to influence growth of developing cells or of mammalian cell culture?
    - Specific intersubspecies crosses can substantially influence fetal IGF-I, depending upon sex of the fetus.
    - The effects of breed and genetics on fetal plasma levels of other candidate bioactives are unknown.

2. What is the evidence that environmental factors such as nutrition, temperature, season, drought can result in biochemical changes in blood serum likely to influence growth of developing cells or of mammalian cell culture?
    - The effects of these environmental factors on fetal plasma levels of other candidate bioactives are unknown in the bovine.
    - Nutrition and oxygen can alter fetal plasma levels of IGFs or related factors (ovine).
    - Certain maternal micronutrients can substantially alter plasma IGF-2 in neonates (rodents).
3. What is the evidence that physiological condition such as age, gender, pregnancy, size of animal, stress, can result in biochemical changes in blood serum likely to influence growth of developing cells or of mammalian cell culture?
    - Increasing gestation substantially increases fetal plasma levels of candidate bioactives, including IGF-I, IGF-2, as well as other growth promoting hormones.
    - Increasing fetal weight increases plasma IGF-I, but not IGF-2, in late gestation.
    - The effects of gestation, fetal size and stress on fetal plasma levels of other candidate bioactives are unknown.

There is evidence for major effects of genetics, environment and gestation on fetal bovine serum levels of one (IGF-I) or more of the major bioactives, able to influence cell growth and survival. There are major gaps in knowledge about the presence and/or modulation of levels of most candidate bioactives by such factors, however, and in whether these can account for the observed variations in bioactivity of batches of FBS. There is the opportunity to cost effectively address these gaps through identification of relevant past, current or future projects or the design of on farm and harvesting projects to provide samples for investigation.

The future applications of such knowledge may take the form of modifications to on-farm and/or harvesting practices, including the development of new manipulations to mimic effects of IVF on fetal serum IGF-1 to produce product specifically for FBS.

Recommendations

1. The effects of intersubspecies crosses, gestation, fetal sex and weight and maternal weight and condition on fetal serum levels of candidate bioactives (Tables 1, 2; prioritising IGFs and related factors) be investigated (multiplex assays are available for most of these candidate bioactives).
2. The feasibility of defining the effects of genetic, environmental and physiological factors on fetal serum bioactives be investigated by survey of
    a. MLA supported projects and other relevant projects in the bovine to identify those which offer archived samples for analysis.
    b. On farm and harvesting practices, which would enable collection of samples classified according to some factors.
3. Concentrations of candidate bioactives be measured in batches of FBS and correlated with bioactivity in various culture systems.
4. The effects of IVF on fetal serum concentrations of candidate bioactives and bioactivity in different culture systems be determined and correlated.
5. The effects of selected micronutrient supplementation of the mother and its timing (targeting epigenetic state) on fetal serum concentrations of candidate bioactives and bioactivity in different culture systems be determined and correlated.

Contents

1 Background

The background for this literature review was provided by Meat and Livestock Australia in the Terms of Reference for Project Number A.Bit.0002, Nature and Nurture Impact on Bioactivity – On Farm Manipulation of Bioactives.

The red meat bioactives industry in Australia is estimated to be worth $200mpa. MLA is aiming to increase the profitability of the red meat industry by supporting the growth of the bioactives industry. Our strategy is to facilitate growth by a combination of identifying new opportunities, identifying new technologies and co-investing in R&D with potential value adders. Our priority is to maximise the share of the added value that can be realised by the red meat producers and processors.

The largest sector of the Australian red meat bioactives industry currently is blood products, valued at $100m pa, which includes serum, plasma, fatty acids and growth factors. The greatest potential for significant impact on the red meat industry in the short to medium term is therefore seen to lie in growth of this sector.

The highest value blood products are those used by the pharmaceutical industry for the manufacture of therapeutic and diagnostic chemicals. This is an expensive and capital intensive production process and it is known that there is natural variation in the efficacy of sera in these applications. The conventional solution by serum manufacturers to this variability is to combine many batches of blood in order to “even-out” the variation. The opportunity exists however to take advantage of this natural variation, and even to exploit it, in order to create products of greater value to the pharmaceutical and diagnostic manufacturers.

It is envisaged that genetic and physiological differences between the donor animals which underlie this variation could be exploited to the benefit of the whole value chain, with producers and processors able to make the biggest contribution and therefore claim a significant share of this benefit. It is recognised that only by developing products of real value to the pharmaceutical and diagnostic manufacturers can profitability of the red meat bioactives industry be developed. Before investing in the development of this capability, it is necessary to objectively assess both the potential for impact and the likely value of the impact on pharma manufacturers.

2 Project aims

This project aimed to investigate the potential for on farm manipulation of genetic, environmental or physiological factors to influence levels of bioactive factors in blood serum. In particular this project focused on the blood product, **fetal bovine serum**, as this was identified as a major red meat bioactive of interest.

Therefore, the evidence for both “nature and nurture” (genetics and environment) being able to affect biochemical factors in fetal bovine serum which are able to impact cell growth and protein production was reviewed.

The review aimed to address the following questions, as detailed in the Terms of Reference for Project Number A.Bit.0002, Nature and Nurture Impact on Bioactivity – On Farm Manipulation of Bioactives provided by Meat and Livestock Australia:

- What is the evidence that breed of cattle or of sheep can influence biochemicals in blood serum, likely to influence growth of developing cells or of mammalian cell culture?
- What is the evidence that environmental factors such as nutrition, temperature, season, drought can result in biochemical changes in blood serum likely to influence growth of developing cells or of mammalian cell culture?
- What is the evidence that physiological condition such as age, gender, pregnancy, size of animal, stress, can result in biochemical changes in blood serum likely to influence growth of developing cells or of mammalian cell culture?

3 Bioactive compounds present in Fetal Bovine Serum

3.1 Identity of candidate bioactive factors that impact on cell growth

Fetal bovine serum is a complex natural product, and as such contains a complex mix of biomolecules with both growth promoting and growth inhibitory actions (Coecke et al. 2005; Zheng et al. 2006). FBS is used in cell culture to support cell proliferation and maintenance. To provide a basis for the “nature vs nurture” literature review a list of known or candidate bioactive compounds, important for mammalian cell culture and present in FBS was required.

Information relating to candidate bioactive components of FBS was researched and provided by Associated Stephen Mahler and Mrs Vicki Snelson, through Project A.Bit.0003. This information formed the basis for the review of factors that may influence the levels of these bioactives in fetal blood, and is therefore also included here.

Table 1: Important components of FBS for mammalian cell culture

Component	Function
Albumin (major protein component of serum)	Provides buffering capacity; protection against shear; transport of fatty acids, steroids and fat soluble vitamins; neutralization of toxic compounds such as metal ions.
Growth factors	Modulators of cell growth
Trace elements – including iron, zinc and selenium	
Metal transporters – including transferrin and ceruloplasmin	Provide transport for metals
Protease inhibitors - including alpha-1-antitrypsin and alpha-2-macroglobulin (both broad spectrum)	Prevent proteolysis of cells and secreted proteins
Attachment factors – including fibronectin, fetuin and laminin	Involved in binding of anchorage dependent cells to th substratum
Polyamines – including putrescin, ornithine and spermidine	Required for cell growth, ion channel modulators
Lipids – including cholesterol, linoleic acid and steroids	Involved in energy production, cell membrane structure, and signalling
Vitamins	Required for essential metabolic reactions

Additional information as to the specific growth factors present in FBS and of importance for culture of mammalian cells was also provided. Growth factors were identified by Project Project A.Bit.0003 as the most important modulators of cell growth.

Table 2. Growth factors and their target cells

Growth Factor	Major target cells
Interleukins	Various, mainly cells mediating immunity and inflammation.
Interferon-γ	Mainly lymphocytes and additional cells mediating immunity and inflammation.
Colony stimulating factors	Mainly haematopoietic stem cells
Erythropoietin	Erythroid precursor cells
Thrombopoietin	Mainly megakaryocytes
Neurotrophic factors	Several, but mainly neuronal cell populations.
Insulin	Various
Insulin-like growth factors	A very wide range of cells found in various tissue types.
Epidermal growth factor	Various, including epithelial and endothelial cells and fibroblasts.
Platelet-derived growth factor	Various, including fibroblasts, glial cells and smooth muscle cells.
Fibroblast growth factors	Various, including fibroblasts, osteoblasts, and vascular endothelial cells
Transforming growth factors –α, β	Various
Leukemia inhibitory factor	Mainly haematopoietic stem cells.

(Walsh, Biopharmaceuticals, Biochemistry and Biotechnology, Wiley, Second Edition, 2003)

3.2 Variation in bioactive components between batches of fetal bovine serum

As a natural product, the composition of serum is variable. This introduces batch-to-batch variation in the ability of the serum supplement to support cell growth. This variation in the quality, type and concentration of components within FBS has been identified as a problem for high yield cell culture (Coecke et al. 2005; Zheng et al. 2006). An understanding of the key components that vary between batches of FBS of differing quality could provide an insight into 1) the bioactive compounds that are important for cell growth and 2) the bioactive compounds with the greatest variation potentially attributable to genetic, physiological or environmental factors.

The literature was therefore searched to identify studies characterising the variation in composition of batches of FBS. Routine screening procedures used for FBS batches does

include analysis of pH, total protein, albumin, immunoglobulin, and haemoglobin levels and tests for endotoxin or viral contamination. However, surprisingly, there has been limited study of the specific bioactive compounds that vary between FBS batches.

One study (Zheng *et al*. 2006) investigated variation between three batches of FBS, in terms of ability to support growth of adult retinal epithelial pigment cells, and compared protein composition of the batches. TGFβ1, Glial growth factor (neuregulin-1), preproIGFI, bFGF and IGFBP4 were detected in the FBS batch that supported the highest cell growth rate.

Two studies, published in the 1970s, comparing batches of FBS were identified. These studies investigated serum components in general, rather than specific bioactive components. Bittles *et al*. (1974) identified marked differences in levels of total protein, haemoglobin and inorganic phosphate across 3 commercial batches of FBS. Concentrations of individual amino acids, including taurine, glycine, cystine, histidine and arginine, also varied. Honn *et al.* (1975), analysed chemical and hormone levels in 7 batches of FBS. In contrast to the previous report (Bittles *et al*. 1974) they observed little variation in phosphate levels, but significant variation in potassium levels between FBS batches. Cholesterol levels varied from 29-165 mg/dl, glucose varied from 249-382 mg/dl and protein varied from 3.04-8.49 g/dl. Variation was also observed in levels of a range of hormones, including thyroxine, growth hormone, cortisol, insulin and glucagon between batches of FBS. The methods for analyses of these chemicals and hormones have advanced significantly since the 1970s, and techniques for collecting and processing FBS may also now vary significantly. However, these studies suggest that factors in addition to the known bioactives may also vary considerably between batches of FBS.

3.3 Bioactive growth factors chosen for the Nature vs Nurture literature review

Based on the information provided by the study of Zheng et al (2006) and the understanding of the importance of the growth factors for maintenance of cell growth, a subset of growth factors of interest was generated to form the basis for the literature review. These growth factors are summarised below.

3.3.1 Insulin-like growth factors-1 and –2 and their associated binding proteins

The insulin-like growth factors, IGF-1 and IGF-2, are peptide growth factors that influence metabolism, proliferation and differentiation of a wide range of cell types (Stewart & Rotwein, 1996). The majority of actions of the IGFs are mediated via the Type 1 IGF receptor. An additional IGF receptor, the Type 2 IGF receptor (IGF2R) preferentially binds IGF-2. The IGFs circulate bound to one of 6 IGF binding proteins. The IGFBPs can both inhibit and enhance the

actions of the IGFs, through modulation of the circulating concentrations of free IGF available to bind tissue IGF receptors, and regulation of tissue delivery of the IGFs (Stewart & Rotwein, 1996). Both IGFs are produced by a wide range of tissues in the fetus, and a number of tissues may contribute to circulating concentrations of the IGFs. IGF-2, in particular, is present in high abundance in fetal tissues and fetal blood (Owens *et al*. 1994; Kind *et al*. 1995). An essential role for the IGFs in regulating fetal growth has been demonstrated in transgenic mouse models, where deletion of IGF-1, IGF-2 or the Type 1 receptor is associated with significant fetal growth retardation, while deletion of the IGF2R is associated with increased blood levels of IGF-2 and fetal overgrowth (Stewart & Rotwein, 1996). Fetal, placental and birth weights correlate with plasma IGF-I in late gestation and term and with IGF-2 in some species (Owens, 1991). Variations in fetal weight may therefore serve as a marker of the abundance of IGF-I in fetal serum.

3.3.2 Fibroblast growth factors

Fibroblast growth factors are a family of polypeptide growth factors, consisting of at least 22 members. FGF-2, also known as basic FGF, was one of the earliest FGFs characterised (Bottcher & Niehrs, 2005; Ornitz & Itoh, 2001). FGF-2 has mitogenic and angiogenic properties, and FGFs are involved in a range of cell processes including differentiation, cell migration and apoptosis (Bottcher & Niehrs, 2005; Ornitz & Itoh, 2001). Although FGF-2 lacks a signal peptide sequence, suggesting it is not a secreted protein, it does leave the cell and is localised predominantly to the cell surface and extracellular matrix, where it binds with high affinity to heparin sulphate proteoglycans. FGF-2 is produced by many tissues in the human and rat fetus, including the endothelium of arterial and venous blood vessels (Gonzalez et al, 1990; 1996). The source of FGF-2 in fetal blood is not known, but the placenta and the vascular endothelium are possible sources (Gonzalez et al. 1996; Hill et al. 1995a, b, 1997). In human pregnancy, FGF-2 in both maternal and umbilical cord serum is increased in diabetic pregnancies, and levels of FGF-2 in cord serum correlate with fetal and placental weight (Arany & Hill, 1998; Hill *et al*, 1995a,b, 1997). This adds to the evidence for fetal weight serving as a potential marker for the abundance of candidate bioactives in fetal serum.

3.3.3 Transforming growth factor-β

Members of the transforming growth factor-β (TGF-β) family are cytokines with biological roles in growth and development, inflammation and repair and host immunity (Clark and Coker, 1998). They elicit a range of actions including proliferation and differentiation, adhesion and cell migration, and apoptosis in a range of cell types (Ingman and Robertson, 2002). TGF-β1, β2 and β3 are alternative isoforms encoded by individual genes. In addition, the TGFβ superfamily

contains more than 30 proteins with 30-80% sequence homology, including TGFβ, activins, inhibins, bone morphogenic proteins, and growth differentiation factors (Kitisin *et al*. 2007). TGFβ is released from tissues in an inactive form, bound to a latency-associated peptide. Release of bioactive TGF-β from the latency peptide requires proteases, such as plasmin, and differs depending on whether the latent peptide is bound to extracellular matrix, or is associated with cell membrane associated mannose-6-phosphate receptor. The TGFβs are expressed in a range of fetal tissues in the mouse (Pelton *et al*. 1989, Wilcox & Derynck, 1988), with expression varying across the different isoforms, and have roles in various functions including bone and lung development, vasculogenesis and haematopoiesis.

3.3.4 Epidermal growth factor family

The EGF family consists of peptide growth factors that bind to the EGF family of receptors. The EGF family includes epidermal growth factor (EGF), transforming growth factor-α (TGF-α), heparin binding EGF like growth factor (HB-EGF), amphiregulin (AR), epiregulin (EPR) and the neuregulins (NRGs). These proteins all contain an EGF-like sequence, and are mostly produced as transmembrane proteins, requiring proteolytic processing to produce their mature forms. The EGF receptor family consists of four members, ErbB1, ErbB2, ErbB3 and ErbB4, with actions of TGFα and EGF exerted by binding ErbB1 and those of neuregulins via ErbB3 and ErbB4 (Dreux *et al*. 2006).

Epidermal growth factor and transforming growth factor-α

Epidermal growth factor was originally detected based on its ability to accelerate tooth eruption and eyelid opening in the newborn rat and was purifed from salivary glands, its most abundant site of EGF protein in the rodent. EGF influences proliferation and differentiation, with effects demonstrated in the skin, and epithelial tissues of the lung and cornea (Carpenter and Cohen, 1979). Transforming growth factor-α, has a wider distribution in adult tissues, compared to EGF, and has demonstrated roles in a range of biological processes, including angiogenesis, wound healing, and bone resorption (Lee *et al*. 1995). TGF-α and EGF are produced as integral membrane proteins, requiring cleavage to produce the soluble form. The EGF receptor is widely distributed in fetal tissues. It is suggested that TGF-α may be the major ligand for the receptor in the fetus, although functions of EGF in the fetus, including effects on lung maturation are implicated. TGF-α is expressed within a range of tissues in the fetal rat and human, including brain, kidney, liver, gastrointestinal tract and lungs (Ruocco *et al*. 1996; Miettinen, 1993; Wilcox & Derynck, 1988).

Neuregulins

Neuregulins are signalling proteins that mediate cell-cell interactions in the nervous system, heart, breast and other organ systems (Falls, 2003). The Neuregulin family has four members (*NRG1, NRG2, NRG3, NRG4*). Most studies have concentrated on NRG1. The NRGs signal by binding to the extracellular domain of the Erb3 or Erb4 receptors. At least 15 different mRNA isoforms are produced from the human NRG1 gene. The isoforms differ in the type of EGF-like domain they contain, the N-terminal sequence (type I, II or II), and whether the isoform is initially synthesised as a transmembrane or non-membrane protein, and this variation influences their biological properties. Most NRGs are synthesized as transmembrane proteins, and it is likely that they are proteolytically cleaved to act via paracrine signalling. One isoform, NRG II-β3 or glial growth factor-2, may however, be produced as a soluble protein and be secreted from cells.

4 Fetal bovine serum – collection and processing

4.1 Collection procedures and processing

Information on current practices for collection and processing of FBS is essential to the understanding of potential sources of variation, and whether potential on-farm manipulations would be compatible with the subsequent processing. Interviews conducted by the Project teams of A.Bit.0003 and 4 (Stephen Mahler, Vicki Snelson, John Friend) with FBS suppliers (Moregate Biotech, SAFC Biosciences, Hyclone) provided important information as to the processes used for collection of FBS. Current practice involves collection of batch sizes of 1000-2000 L of serum. An individual fetus contributes from 200 ml to 2 litres of blood depending on the age and size at the time of slaughter. Blood is collected into bags with an 800 ml capacity, and all bags are filled. Therefore each bag may contain blood from between 1 to 3 fetuses. Following centrifugation the serum is pooled into 4.5 litre bottles, filtered and pooled. Therefore, at least 220 x 4.5 L bottles will contribute to each 1000 L batch, containing serum from greater than 1000 fetuses (http://www.moregatebiotech.com). Blood is stored on ice at the abattoirs before transport to the processing facilities. Variation in the processing time and in the handling procedures could therefore contribute to differences in levels of peptide growth factors and hormones.

A bovine fetus of 90 days gestation yields approximately 300 ml of blood and 150 ml of FBS (Jochems 2002). Therefore, most fetuses contributing to the FBS pool could be estimated to be of 90 days gestation or greater. It appears that no distinction is made between fetuses of differing age, breed or indeed sex, and that even the bags of blood (of 800 ml capacity) may contain samples collected from fetuses of diverse gestational age.

5 Potential environmental, physiological and genetic influences on the levels of bioactives in fetal bovine serum

Environmental, physiological and genetic factors that could 1) regulate the levels of the chosen growth factors in fetal bovine serum, and 2) contribute to the variation between batches in the levels of the chosen growth factors in fetal bovine serum were considered.

In particular the following were considered as potential factors that could contribute to variation in fetal blood levels of bioactives

- Developmental stage and age
- Environmental — Nutrition (level, quality and composition); Temperature; Stress; Seasonal; Circadian
- Genetic — Breeds and EBVs
- Epigenetic — ART; Othe r

A comprehensive literature search was conducted for studies reporting on the blood levels and the regulation of each of the identified growth factors of interest in the bovine fetus (Search Strategies are summarised in Appendix 1). Limited numbers of papers were identified that had investigated the concentrations of, or variation in, levels of circulating bioactive growth factors in the bovine fetus. Of the chosen growth factors only the insulin-like growth factors have been studied in the bovine fetus. The search strategy and literature assessment was therefore also extended to include information on variation in the levels of major hormones and metabolites in the bovine fetus. Information relevant to the bovine fetus is summarised in the following sections and Table 1.

5.1 Developmental stage and age

Fetal growth and birthweight in the cow are influenced by breed and genotype of sire, breed of dam, calf sex, length of gestation, and physiological state of the dam, including parity, age, weight (Holland and Odde, 1992). Highest rates of fetal growth occur around day 232 of

gestation. As discussed above, fetuses from 90 days gestation to term are likely to contribute to the FBS pool.

Developmental stage and age is likely to contribute to FBS variation, and categorising fetuses according to gestational age, as determined by fetal weight, should reduce the variation. Five studies reporting analysis of fetal plasma hormones and growth factors in the bovine fetus throughout gestation were identified and are summarised below (Table 1).

5.1.1 Insulin-like growth factors

Highest plasma levels of IGF-I and IGF-2 in the bovine fetus are reported between 200 to 250 days gestation (Holland *et al*. 1997) (Table 1). IGF-I and IGF-2 increase throughout gestation to peak at day 232 of gestation and decline again to lower levels by day 274. Levels of IGF-2 in bovine fetal serum are 2 to 10 times higher than IGF-I.

In fetuses of crossbred beef cows mean serum IGF-I during the second trimester was 29.8 ng/ml, and 71.3 ng/ml during the third trimester. Serum IGF-I levels are ~20 ng/ml prior to day 100. The peak level of IGF-I was ~100 ng/ml at 232 days gestation and IGF-I decreased to ~ 65 ng/ml after day 250 gestation. Fetal serum IGF-I correlated positively with fetal body weight.

Mean serum IGF-2 levels were 238 $\pm$ 55 ng/ml during the second trimester and 321 $\pm$ 70 during the third trimester. Serum IGF-2 levels are ~200-240 ng/ml prior to day 100 gestation. The peak level of IGF-2 was ~360 ng/ml at 232 days gestation and IGF-2 levels decreased to ~320 ng/ml after day 250 gestation. Fetal serum IGF-2 correlated positively with fetal body weight. Mean umbilical serum venous-arterial differences for IGF-2 tended to increase with gestation, when measured from 148 days, suggesting a possible placental source for fetal IGF-2.

5.1.2 Insulin

Reynolds et al. (1990) report no significant difference in plasma insulin at different gestational ages (days 137, 180, 226, 250) in the bovine fetus (Table 1). Insulin levels in plasma collected from the fetal vein ranged from 5.8 $\pm$ 0.6 μU/ml at day 137 to 8.4 $\pm$ 1.3 μU/ml at day 250.

5.1.3 Growth hormone

Reynolds et al (1990) report higher concentrations of GH in fetal venous plasma at days 226 and 250 gestation, than at days 137 and 180 in the bovine fetus (Table 1). GH values measured in fetal plasma ranged from 23.9 ± 5.5 ng/ml at day 137 to 58.5 ± 4.0 ng/ml at day 226 gestation.

5.1.4 Other hormones

Levels of placental lactogen were reported not to vary across gestation in the bovine fetus (Holland et al.1997) (Table 1), although others report that placental lactogen decreases with gestation, with values ranging from ~15 ng/ml at 110 days gestation to ~5 ng/ml at 230-270 days gestation (Byatt et al. 1987).

Levels of prolactin in fetal serum increased from 4 ng/ml at 90 days, to 43 ng/ml at 180 days and 61 ng/ml at 260 days (Oxender et al. 1972).

Levels of thyroxine (T_4) increased throughout gestation from 2.2 μg/dl at 90 days, to 11.7 μg/dl at 180 days and 17.2 μg/dl at 260 days (Hernandez et al. 1972).

Levels of testosterone are higher in male fetuses than female fetuses (5-10 x higher) and decreased from 2.7 to 0.3 ng/ml between 90 and 260 days gestation (Mongkonpunya *et al*. 1975).

5.1.5 Other blood metabolites

Levels of glucose were reported not to change across gestation by Reynolds *et al*. (1990). Levels of potassium (4.19 mEq/l, range 2.85-6.65), sodium (140 mEq/L, range 117-156), chloride (97.2 mEq/l, range 87.8-111), total calcium (10.79, mg/dl, range 7.78-12.79), total magnesium (4.5 mg/dl, range 3.10-6.40) and inorganic phosphorus (4.24 mg/dl, range 2.93-6.10) have been measured in bovine fetuses from day 208 to 269 gestation. Potassium and phosphorus levels increased close to term, but levels of sodium, chloride or magnesium did not vary (Wilson *et al,* 1977a, b).

Summary:

- There are major increases in fetal serum IGF-I, IGF-2, insulin, GH, Prolactin, T_4 from mid to late gestation, but not in fetal serum placental lactogen, while electrolytes were usually unchanged.
- Fetal serum IGF-I and in some, but not all studies, IGF-2, increase with fetal weight.

5.2 Environmental factors - Nutrition

The majority of studies of nutrition in the cow focus on birth weight, lactation or time to subsequent conception as outcome measures. No studies directly manipulating maternal nutrition and investigating the effects on levels of metabolites, growth factors or hormones in bovine fetal blood were identified.

5.2.1 Insulin-like growth factors – effect of nutrition

Holland *et al.* (1997) report that maternal body weight was moderately correlated with fetal serum IGF-I and IGF-2 ($r=0.44$, 0.36 respectively, $P<0.01$), in crossbred beef cows maintained on native pasture in the USA and supplemented with alfalfa hay. This supports a positive influence of maternal nutrition on IGFs in the bovine fetus. However, studies directly manipulating maternal nutrition and investigating the effects on fetal blood levels of the IGFs were not identified in the bovine.

Summary:
No studies reporting the direct effects of maternal body condition or nutrition on IGFs or any other bioactive compounds in fetal blood were identified.

5.3 Environmental factors - Other environmental measures

Summary:
No studies were identified investigating the effects of Temperature, Stress, Season, or Circadian cycles on blood composition in the bovine fetus.

5.4 Genetic and Epigenetic factors

In this section studies assessing the effects of genetic or potential epigenetic effects on IGFs were assessed.

5.4.1 Genetic variation

Birth weight varies significantly between cattle breeds. Whether this is associated with differences in levels of bioactive compounds in fetal blood, between fetuses of different size within breeds, has not been studied. In other species, levels of growth factors, such as IGF-I, are correlated with fetal size in late gestation (Owens *et al*. 1994), suggesting that there may be some variation between levels of IGF-I in bovine fetuses of differing growth potential. This has been little studied.

Birthweight is one of the variables incorporated in the BREEDPLAN estimated breeding values (http://breedplan.une.edu.au/). Therefore, it is possible to choose sires with an expected progeny difference in birthweight. One study has assessed levels of IGF-I in fetal blood following breeding from sires with expected progeny differences of high or low birthweight. Holland *et al.* (1997) used semen of Polled Hereford sires with expected progeny differences of high and low birthweight. Fetal genotype effects were detected for fetal blood levels of IGF-I, but not IGF-2, with low growth potential fetuses (due to paternal genotype) having higher concentrations of IGF-I than high growth potential fetuses. This was significant in the third, but not second trimester.

IGF-I is also moderately heritable (Moore *et al*. 2005). IGF-I has been suggested as a potential marker for net feed efficiency. However, the aim of these breeding programs is to select for low levels of IGF-I. Whether selection for IGF-I would influence fetal levels of IGF-I has not been investigated.

One study has investigated variation in IGF-I in fetal blood from different breeds and crossbreeds. Gore *et al*. (1994) compared three genotypes (Angus x Angus, Angus x Chiana, Chiana x Chiana) and observed no differences in IGF-I in fetal blood between genotypes.

In crossbreeding programs, birthweight is also influenced by whether the genetics is inherited from the paternal or maternal genome. For example, Brahman x Hereford calves are significantly heavier at birth, than Hereford x Brahman calves, indicating that differences exist depending on whether the Brahman genes are inherited from the sire or dam (Ellis *et al*. 1965; Amen *et al*. 2007). Whether these differences in fetal growth determined by the maternal or paternal genotype are associated with differences in the levels of bioactive compounds in fetal blood has not been studied. A subset of genes, known as imprinted genes, are differentially expressed depending on whether they are inherited from the mother or father (Ferguson-Smith & Surani, 2001). IGF-2 and its receptor are imprinted genes in several species, including the bovine (Long & Cai, 2007; Khatib *et al.* 2007). Whether variation in IGF-2 levels contributes to the differences in fetal growth in the cross breeds has not been examined.

A recent preliminary report has described major effects of intersubspecies matings between Brahman (Bos primigenius indicus, Bi) and Angus (B. p. taurus, Bt) on plasma IGFs and growth in the fetus in late gestation (Hiendleder *et al* 2008). These effects are seen only when a male Bi is mated with a Bt female, which causes fetal overgrowth and increased plasma IGF-I (+ 40%) that is most pronounced in males (d150 gestation, term ~ 280 days). This intersubspecies mating did not affect growth at mid-gestation, suggesting that the alterations in growth factor abundance and growth emerge in the second half of gestation, although the precise timing is unclear. Fetal plasma IGF-2 in late gestation did not vary with intersubspecies matings, while fetal plasma IGFBPs and other growth factors or bioactives were not reported. Overall, this indicates that genetic factors can strongly influence fetal plasma IGF-1 in late gestation, with marked sex specific effects evident and that fetal growth is a marker of this endocrine impact.

5.4.2 Assisted Reproductive Technologies (in vitro embryo production)

Plasma levels of IGF-1 at day 150 of gestation are higher in bovine fetuses generated via somatic cell nuclear transfer (30.3 $\pm$ 2.3 ng/ml), compared with artificial insemination (19.1 + 5.5 ng/ml) or in vitro embryo production (24.2 + 2.5 ng/ml) (Ravelich *et al*. 2004).

Others report increased levels of IGF-I (~28 ng/ml) at day 80 gestation in fetuses developed following in vitro fertilisation, compared with artificial insemination (~19 ng/ml) (Hiendleder *et al*. 2006). Similar increases were observed in plasma levels of glucose (~34 mg/dl vs ~19 mg/dl), creatinine (~0.9 mg/dl vs ~0.7 mg/dl) and potassium (~10 mmol/l vs ~8mmol/l) (Hiendleder *et al*. 2006). These differences were dependent on the media used for embryo culture, however, as no differences were observed in fetal blood parameters when the serum content of the media was reduced from 10% estrous cow serum, to 5%.

Bovine fetal overgrowth, referred to a large offspring syndrome (LOS) can be induced by a range of embryo manipulations in assisted reproductive technology, including in vitro fertilisation (IVF), somatic cell nuclear transfer and cloning (Hiendleder et al 2008). These treatments are considered to potentially alter expression and abundance of bioactives that are epigenetically regulated, such as IGF-2, but also IGF-I, and certain IGFBPs and receptors (IGF2R). Epigenetic state refers to modifications to DNA that do not change the nucleotide sequence, but do alter expression of genes. IVF increased fetal plasma IGF-I and IGFBP-4, compared to SCNT and control fetuses and fetal plasma soluble IGF2R, compared to controls, at the end of the first trimester. This indicates that major perturbation of the periconceptional environment markedly alters fetal plasma IGF-I and circulating IGFBPs, early in gestation. IVF also alters expression of IGF-II in a tissue specific manner compared to SCNT fetuses, but whether plasma IGF-II is

altered is not known. Whether these responses of the bovine fetus to ART persist into late gestation is also not known.

Summary:

- Some intersubspecies hybrids substantially alter fetal plasma IGF-I in late gestation, but not IGF-2 and in males only.
- IVF alters fetal plasma IGF-I and certain IGFBPs in early to mid gestation, but not IGF-2.

5.5 Immune responses

The bovine fetus can respond to an antigenic stimulus from around 120 days gestation (Schultz *et al*. 1973). Viral or bacterial infections may therefore alter the immunoglobulin and antibody profile of fetal serum. Fetal bovine serum batches are routinely tested for major viruses, such as bovine viral diarrhoea virus (BVDV), and for antibodies to the virus (information provided by S Mahler & V Snelson). BVDV is an infectious disease of cattle caused by a single-stranded RNA virus, a member of the *Pestivirus* genus. BVDV infection of a pregnant cow results in fetal infection. Fetuses infected in early gestation will either die, or will become a persistently infected carrier of the virus, depending on the form of the virus they are infected with. Infection in later gestation, however, results in the formation of antibodies to the BVDV (Bolin & Ridpath, 1998; Brown *et al.* 1979). Batches contaminated with BVDV or its antibodies are excluded from use.

Few studies have investigated cytokines in fetal bovine blood. Levels of macrophage colony stimulating factor (M-CSF) of 8.8 $\pm$ 1.4 ng/ml have been reported in fetal bovine sera collected at 152-278 days of gestation. Serum levels in the fetus were higher than in the postnatal calves (2.7 $\pm$ 1.5 ng/ml) (Yoshihara *et al*. 2003). Increased expression of IFN-γ, tumour necrosis factor-α and interleukin-10 has been reported in the spleen of bovine fetuses exposed experimentally to a protozoan parasite at 140 days gestation, indicating that a cytokine response to infections occurs (Almeria *et al.* 2003). Whether fetal serum levels of cytokines are altered following infection has not been investigated. Whether altered levels of cytokines would contribute to between batch variation in the maintenance of cell growth could be considered.

Summary:

Fetal bovine serum contains macrophage colony stimulating factor, but the presence of other cytokines remains largely uninvestigated.

5.6 Overall summary

Potential environmental, physiological and genetic influences on the levels of bioactives in fetal bovine serum.

- No studies were identified reporting natural or manipulated variation in transforming growth factor-β, the fibroblast growth factors, epidermal growth factor, transforming growth factor-α or the neuregulins in the bovine fetus.
- There are major increases in fetal serum IGF-I, IGF-2, insulin, GH, Prolactin, T_4 from mid to late gestation, but not in fetal serum placental lactogen, while electrolytes were usually unchanged.
- Categorising fetuses according to gestational age could reduce some variation in levels of the IGFs. Fetal weight can provide a surrogate marker of gestational age.
- Fetal weight may also provide a marker of the abundance of certain bioactives such as the IGFs. This may confound use of fetal weight as a marker of gestational age.
- No studies reporting the direct effects of maternal body condition or nutrition on IGFs or any other bioactive compounds in fetal blood were identified.
- No studies were identified investigating the effects of Temperature, Stress, Season, or Circadian cycles on blood composition in the bovine fetus.
- Perturbation of the periconceptional environment can influence fetal growth, and alter fetal plasma IGF-I and certain IGFBPs in early to mid gestation, but not IGF-II.
- Genetics in terms of intersubspecies matings and parent specific genotype has major effects on fetal plasma IGF-I in late gestation and in males.
- Fetal bovine serum contains macrophage colony stimulating factor, but the presence of others remains largely uninvestigated.

5.7 Recommendations

1. The effects of intersubspecies crosses, gestation, fetal sex and weight and maternal weight and condition on fetal serum levels of candidate bioactives (Tables 1, 2; prioritising IGFs and related factors) be investigated.
2. The feasibility of defining the effects of genetic, environmental and physiological factors on fetal serum bioactives be investigated by survey of
    a. MLA supported projects and other relevant projects in the bovine to identify those which offer archived samples for analysis.
    b. On farm and harvesting practices, which would enable collection of samples classified according to some factors.
3. Concentrations of candidate bioactives be measured in batches of FBS and correlated with bioactivity in various culture systems.
4. The effects of IVF on fetal serum concentrations of candidate bioactives and bioactivity in different culture systems be determined and correlated.
5. The effects of selected micronutrient supplementation of the mother and its timing (targeting epigenetic state) on fetal serum concentrations of candidate bioactives and bioactivity in different culture systems be determined and correlated.

6 Evidence from other species – effects of environmental, physiological, and genetic influences on the levels of bioactives in the ovine fetus

Limited information was available on the circulating levels of bioactive growth factors in the bovine fetus. Therefore, a literature search was also conducted for the ovine fetus. Literature was searched for information on the chosen growth factors in ovine fetal blood, with the aim of identifying physiological and environmental factors that influence circulating levels of the bioactive factors. As for the bovine fetus, studies were identified that investigated variation in the levels of the IGFs and their binding proteins in fetal sheep. However, no appropriate studies could be identified assessing fetal blood levels of any of the other candidate growth factors.

6.1 Developmental Age and Stage – ovine fetus

Levels of IGF-I were highest from 120 days gestation in the fetal sheep (term = 150 days) (Table 2). Carr *et al*. (1995) reported higher levels of IGF-2 from 80 days of gestation in the fetal sheep. Levels of the IGF binding proteins were also assessed. Highest levels of IGFBP-2 were observed at 120 days gestation (Carr *et al*. 1995). Levels of IGFBP-4 increased linearly from day 45 to day 145 pregnancy (Carr *et al*. 1995). Therefore, studies in the sheep also indicate that levels of the IGFs will be highest in the last third of pregnancy. This is consistent with findings in the bovine.

6.2 Environmental factors – ovine fetus

6.2.1 Nutrition

The effects of nutritional perturbations on blood levels of the IGFs and their binding proteins have been assessed in a number of studies. The majority of these studies have been conducted under laboratory conditions, and are not on-farm studies.

Restriction of maternal feed intake can reduce the levels of IGF-I in fetal blood by between 13 to 50% (Table 3). Many of these studies impose a substantial reduction in available nutrition for the mother. Fetal plasma IGF-I is reduced (-32%) following restriction of pregnant ewes to 25% of nutritional requirements for 20 days in late gestation (Bauer *et al*. 1995), and by 3-5 days maternal starvation in late gestation (-30 to -50%) (Gallaher *et al*. 1998; Lee *et al*. 1997; Oliver *et al*. 1996; Bassett *et al*. 1990). Some variation between studies is reported with one study reporting no reduction in fetal plasma IGF-I in late gestation following restriction of ewes to 50% metabolisable energy requirements from conception (Rae *et al* 2002). Undernutrition induced

reductions in fetal plasma IGF-I do not necessarily persists, as nutrient restriction in mid gestation (0.5 metabolisable energy requirements from day 28-77 gestation) followed by adequate nutrition in late gestation did not alter fetal blood levels of IGF-I.

The effects of nutrient restriction in blood levels of IGF-2 in the fetus have been assessed in fewer studies compared to IGF-1 and appear more variable, but reductions of between 17 to 27% have been reported (Table 3). IGF-2 concentrations in fetal blood were reduced (-27%) following 3 or 5 days maternal fasting in late gestation (Oliver et al 1996). Fetal plasma IGF-2 concentrations also tend to be lower (-25%) following restriction of maternal intake by 75% for 20 days in late gestation (Bauer et al 1995).

In fetal sheep, plasma levels of IGF-1 and -2 vary considerably between studies. For example levels of IGF-2 range across studies from 1400 to 375 ng/ml. This is likely to reflect the assays used, rather than variation between breeds. Molecular sieving under acid conditions to remove IGF binding proteins is required to prevent their interference in the IGF assay, and to provide accurate assessment of IGF proteins levels (Owens *et al*. 1995).

Some studies have assessed the effect of nutrition on IGF binding proteins in the ovine fetus. Maternal nutrient restriction or starvation consistently increases plasma levels of IGFBP-1 (Lee *et al*. 1997; Gallaher *et al*. 1994; Osborn *et al*. 1992). Increased levels of IGFBP-2 in fetal plasma were also reported following 72 h maternal starvation (Gallaher *et al*. 1994); however, no differences in IGFBP-2 levels were reported in 3 other studies of maternal starvation or undernutrition (Gallaher *et al*. 1998; Lee *et al*. 1997; Osborn *et al*. 1992). Levels of IGFBP-3 in fetal blood were reduced by maternal feed restriction or starvation in 2 studies (Gallaher *et al*. 1998; Gallaher *et al*. 1994), but no differences were reported in 2 other studies following 3-5 days maternal starvation (Osborn *et al*. 1992; Lee *et al*. 1997) (Table 3).

Summary:

- Undernutrition reduces fetal plasma IGF-I (-13 to -50%), IGF-2 (-17 to -27%) and IGFBP-3, but increases levels of the other IGFBPs, including IGFBP-1 (30 to 250%) in the ovine fetus.
- Manipulation of maternal nutrition or use of markers of this, such as body condition, may enable collection of FBS according to differing bioactivity.

6.2.2 Hypoxia or hyperthermia

The effect of maternal hypoxia on fetal plasma levels of the IGFs has also been assessed (Table 4). While this environmental factor may be of little on-farm relevance, acute hypoxia may be of relevance at the time of collection of the fetal serum.

Acute maternal hypoxia (3 hours) reduced fetal plasma IGF-I (-23%), but not IGF-2 (Iwamoto *et al*. 1992). Non-significant reductions in IGF-I and IGF-2 were observed following 24 hours of restricted uterine blood flow (McLellan *et al*. 1992). However, the restriction in uterine blood flow was associated with a significant increase in fetal plasma levels of IGFBP-1 (75%) and a significant decrease in plasma levels of IGFBP-2 (-40%). Hence, fetal plasma levels of IGFBPs may be altered by short term changes in oxygen supply to the fetus.

No differences in fetal plasma levels of IGF-I were observed following exposure of pregnant ewes to hyperthermic conditions (35-40^{O}C, compared to 20^{O}C) (De Vrijer *et al*. 2006).

Summary:

- Hypoxia reduces fetal plasma IGF-I and increases IGFBP-1.

6.2.3 Intrauterine growth restriction

Restriction of placental size reduces nutrient supply and restricts fetal growth in the sheep (Table 5). Plasma levels of IGF-I are significantly reduced in growth restricted fetal sheep and correlate with fetal size (Owens *et al*. 1994; Kind *et al*. 1995). Plasma levels of IGF-2 were also significantly reduced, but only in late gestation, in growth-restricted fetal sheep (Owens *et al*. 1994). This is consistent with findings in the bovine, that fetal weight is a marker of the abundance of fetal serum IGFs.

Summary:

- Hypoxia reduces fetal plasma IGF-I and increases IGFBP-1.
- Length of fetal hypoxia during collection of FBS may alter levels of IGF related bioactives.

6.3 Overall summary

Potential environmental and physiological influences on the levels of bioactives in fetal ovine serum.

- No studies were identified reporting natural or manipulated variation in transforming growth factor-β, the fibroblast growth factors, epidermal growth factor, transforming growth factor-α or the neuregulins in the ovine fetus.
- Studies that have investigated EGF in the ovine fetus have focused predominantly on administration of EGF to the fetus to enhance wool follicle development or fetal growth, and were therefore not included in the review.
- Studies of the effects of these influences in the ovine fetus have focused on the IGFs and the IGFBPs.
- Restriction of nutrition of the pregnant ewe, by starvation or general restriction of maternal feed intake, reduces fetal plasma levels of IGF-1 (-13 to -50%) and of IGF-2 (-17 to -27%). Restriction of maternal nutrition increases fetal plasma levels of IGFBP-1 (30 to 250%). Results obtained for IGFBP-3 and IGFBP-2 are variable. Some studies report a decrease in plasma levels of IGFBP-3 and an increase in levels of IGFBP-2 following maternal nutrient restriction.
- Hypoxia reduces fetal plasma IGF-I and increases IGFBP-1. Length of fetal hypoxia during collection of FBS may alter levels of IGF related bioactives.
- Fetal plasma levels of IGF-I are reduced in growth restricted fetal sheep, following restriction of placental size. Plasma levels of IGF-2 are reduced in late gestation in the growth-restricted fetus. Fetal weight provides an indicator of levels of IGF related bioactives in fetal plasma

7 Evidence from other species – effects of environmental, physiological and genetic influences on the levels of bioactives in the rodent fetus

7.1 Nutrition

The effects of nutritional perturbations such as maternal protein restriction or maternal starvation in late gestation or of fetal oxygen deprivation by hypoxia or uterine artery ligation on blood levels of the IGFs have been assessed in a number of studies in the rat. Maternal protein restriction or starvation in late gestation reduces fetal plasma IGF-I in the rat fetus by 31 to 35% (Table 6) (Muaku et al 1995; Bernstein et al 1991). Fetal hypoxia induced by bilateral uterine artery ligation, but not maternal hypoxia, also reduces fetal plasma IGF-I and by about 46% (Table 6) (Unterman et al 1993; Tapanainen et al 1994).

We have also recently described the effect of maternal folate supplementation from before and throughout pregnancy on plasma IGF-2 in offspring from early in postnatal life (Owens JA, personal communication). Plasma IGF-2 was increased by ~250% in offspring at day 7, suggesting a major influence of maternal methyaltion status on neonatal IGF-2 production (Owens JA, personal communication). If present before birth, this would identify the supply of methyl groups for DNA methyaltion and control of epigenetic state and expression of labile genes as a major influence over this and other imprinted or epigenetically labile genes for bioactives.

Summary:

- Undernutrition reduces fetal plasma IGF-I (-30%) in the rodent fetus.
- Fetal hypoxia also reduces fetal plasma IGF1 and to a more limited extent, IGF-2, in the rodent fetus.
- Maternal folate supplementation increases plasma IGF-2 by 250% in the neonatal rat.

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TABLE 1. Bovine fetal serum metabolites and hormones according to development stage

Active compoun	Stage of pregnancy (term ~ 280 days)				Breed	Assay	Other comment	Gender	Ref.
	Day <100	Day 100-200	Day 200-250	Day >250					
Glucose (mM)		2.5 (d137) 2.2 (d180)	2.1 (d226)	2.1 (d250)	Hereford	RIA for insulin and GH	Catheterised fetuses, fetal vein results reported here, values for uterine artery also in paper GH highly		Reynolds et al. 1990
Insulin (uU/ml)		5.8 (d137) 6.3 (d180)	6.2 (d226)	8.4 (d250)					
Growth Hormone (ng/ml)		23.9 (d137) 37.8 (d180)	58.5 (d226)	49.3 (d250)					
IGF-1 (ng/mll)	20	20-70 (steady increase)	Peak of 100 ng/ml at day 232	65	Crossbred beef heifers semen from Polled hereford (semen selected to give High or Low genetic potential for growth)	Acid column extraction, RIA	No correlation fetal with maternal levels, IGF-2 umb vein conc.> umb artery. (placental source?) IGF-I and –2 correlated with fetal size measures. No correlation maternal breed with fetal hormones, maternal body	No effects of fetal gender on IGFs	Holland et al. 1997.
IGF-2 (ng/ml)	240	200-280	320-360	320					
Placental lactogen (ng/ml)	27	24-19	20-15	20-15					

Active compound	Stage of pregnancy (term ~ 280 days)				Breed	Assay	Other comments	Gender	Ref.
	Day <100	Day 100-200	Day 200-250	Day >250					
IGF-I (ng/ml)	Day 100 = 76 (LSM)	Day 200 = 114 (LSM)			Angus x Angus Chianina x Chianina	Acid ethanol extraction RIA	No differences according to genotype.		Gore et al. 1994
Prolactin ng/ml	4 (d90)	43 (d180)		61 (d260)	Holstein	RIA	Thoracic artery at 90 days, umbilical artery and vein at other ages, not catheterised		Oxender et al. 1972
Growth hormone ng/ml	42 (d90)	65 (d180)		103 (d260)					
LH ng/ml	3 (d90)	1.28 (d180)		0.85 (d260)					
Thyroxine (T_4) μg/100 ml	2.2 (d90)	11.7 (d180)		17.2 (d260)	Holstein	RIA	Same as Oxender et al 1972.	Serum T_4 higher in female fetuses at each age	Hernandez et al.1972

LSM = least squares mean, values in brackets represent specific gestational ages at which measurements were made, RIA = radioimmunoassay.

TABLE 2. Ovine fetal serum hormones according to development stage

Active compound	Stage of pregnancy (term ~150 days)								Breed	Assay	Other comments	Ref
	D45	D60	D80	D95	D120	D130	D140	D145			Samples collected from cord blood at PM or from indwelling umbilical catheters	
IGF-1 (ng/ml)		22	40	43	98	68	98	98	Not given	Acid column RIA	IGF-1 correlates positively with fetal weight, circulating IGFBP-3 and -4. Values are mean estimates	Carr et al 1995
IGF-2 (ng/ml)		253	547	425	625	483	385	620		Acid column RIA	IGF-2 correlates positively with circulating IGFBP-2. Values are mean estimates	
IGFBP-3 (ug/ml)	0.7	0.5-0.9	0.6-1.5	0.8-1.2	0.7-1.6	0.6-1.6	0.7-1.3	1.0-1.4		RIA	Values are mean estimates from 2-3 plotted values.	
IGFBP-2 and IGFBP-4										Western ligand blot	IGFBP-2 and IGF-BP-4 were assessed by western ligand blotting. IGFBP-2 increased throughout pregnancy to peak at 120 d. IGFBP-4 increased linearly throughout pregnancy from 45 to 145	

Active compound	Stage of pregnancy				Breed	Assay	Other comments	Ref
	d 50-80	d 90-110	d 110-130	d 140-150				
IGF-1 (U/ml)	0.29 ± 0.15	0.5	0.65	0.79 ± 0.18	Romney-Suffolk	Acid Ethanol/RIA	Samples collected from indwelling catheters	Gluckman & Butler 1983
IGF-2 (U/ml)	2.8	3.1	3.0	2.6		Acid Ethanol/RRA		
		d110-114	d127-130	d142-145				
IGF-1 (ng/ml)		57 ± 2	57 ± 10	54 ± 7	Welsh Mountain	Acid column RIA	Samples collected from indwelling arterial catheters or from umbilical artery at PM	Li et al 1996
Insulin (ng/ml)			0.26		Mixed Western breed		Samples collected from indwelling arterial catheters at 126-134 d gestation. Effects of IGF-I also assessed in this study. Values presented here represent preIGF-I infusion.	De Zegher et al 1988
Growth hormone (ng/ml)			172 ± 35					

PM = post mortem, h= hours, d= days

TABLE 3. Ovine fetal serum hormones studies involving environmental alterations – restricted maternal nutrition

Active compound				Breed	Assay	Other comments	Ref
	Ad libitum feeding	**Nutrient restricted groups**					
Glucose (mM)	1.1 ± 0.08	0.79 ± 0.05 **	**Restricted nutrition** Ewes fed 25% nutritional requirements d 100-120 gestation # p<0.06 * p<.05 ** p<.01		YSI Glucose oxidase	Samples collected from indwelling arterial and venous catheters at 120 days gestation.	Bauer et al 1995
Insulin (ng/ml)	1.8	0.8 **			RIA		
GH (ng/ml)	60	105 *			RIA		
IGF-1 (ng/ml)	95	65 *			Acid ethanol cryoprecipitation /RIA		
IGF-2 (ng/ml)	1400	1050			Acid column / RIA		
Placental lactogen (ng/ml)	14	9 #			Homologous RIA		
Free fatty acids (umol/l)	13 ± 2	16 ± 2					
Glucose (mM)	1.08 ± 0.11	0.83 ± 0.07 * after 72 h starvation	**Maternal starvation** 72h maternal starvation * p<0.05	Romney - Suffolk	Glucose oxidase (Beckman glucose analyser	Samples collected from indwelling arterial catheter at 130-135 days gestation. Infusion of glucose to the ewe restored fetal levels of IGF-I	Bassett et al 1990
IGF-1 (ng/ml)	176.1 ± 15.2	124 ± 10.3 * after 72h starvation			acid ethanol cryoprecipitation / RIA		
IGF-1 (ng/ml)	~120 ng/ml	~60 ng/ml	**Restricted nutrition** Undernourished for 60 d prior to mating then 30 d after conception. From 105 -115 d gestation nutrient restriction to achieve maternal blood glucose of 60% ad lib fed	Coopworth - Border	Acid Ethanol / cryoprecipitation	Values are mean values in the ad lib fed and feed restricted group at 115 d gestation, independent of preconception nutrition. No effect of preconception undernutrition (UN) on IGF levels at d 105. Preconception UN group had a greater decrease in IGF-I and BP-3 levels	Gallaher et al 1998
IGFBP-3 (ng/ml)	~1200 ng/ml	~500 ng/ml			RIA		
IGFBP-2 (ng/ml)	463	466			RIA		

Active compound				Breed	Assay	Other comments	Ref
	Ad libitum feeding	**Nutrient restricted**					
IGF-2 receptor		IGF-2 receptor was decreased by 30% by maternal starvation, returned to 90% of baseline values by fetal glucose infusion or maternal refeeding	**Maternal starvation followed by glucose infusion** 72 h maternal starvation starting d 125-130 gestation. Followed by iv infusion of 10% glucose into the fetus.	Coopworth-Dorset	Western ligand blot	Samples collected from indwelling catheters.	Gallaher et al 1994
IGFBP-1		IGFBP-1 increased by 30% by maternal starvation, restored to normal levels by fetal glucose infusion or			Western ligand blot		
IGFBP-2		IGFBP-2 increased by 20% by maternal starvation, restored to normal levels by fetal glucose infusion or			Western ligand blot		
IGFBP-3		IGFBP-3 decreased by ~18% by maternal starvation, no effect of fetal glucose infusion, restored			Western ligand blot		
Glucose (mM)	1.35 ± 0.10	1.74 ± 0.20	**Restricted nutrition** 1.2 x metabolizable energy requirements (ME) vs 0.5 x ME from d 28 to 77 gestation. Measurements	Welsh Mountain	Enzymatic methods	Samples collected from umbilical artery at PM at 145 d gestation. Also measured cortisol, T3 and T4, norepinephrine, epinephrine. No significant	Heasman et al 2000
Non-esterified fatty acids (mM)	0.09 ± 0.01	0.06 ± 0.01 *					
IGF-1 (nM)	12.58 ± 1.39	13.49 ± 0.93			ELISA OCTEIA IGFs removed from binding		

			adequate nutrition from d77 to 145. * (p<0.05)		proteins by IDS Release Reagent		
Active compound				**Breed**	**Assa**	**Other comments**	**Re**
	Ad libitum feeding	**Nutrient restricted groups**					
IGF-1 (ng/ml)	69.2 ± 6.9 - d 90 104.8 ± 14 -d 135	61.4 ± 5.9 - d 90 90.5 ± 13.3 - d 135	**Restricted nutrition & starvation** Reduced nutrition from d 83, starved from d 85 to d 90, then refed, measurements made at d 90 & 135	Welsh Mountain	Ethanol-acetone-acetic acid extraction, then RIA	Samples collected by cardiac puncture at PM at either d 90 or d 135 gestation. No effect of restricted nutrition on IGF-I or insulin in this study.	McMullen et al 2005
Insulin (ng/ml)	0.23 ± 0.02 - d 90 0.19 ± 0.02 -d 135	0.22 ± 0.02 -d 90 0.17 ± 0.01 -d 135			ELISA DRG Diagnostics		
Glucose (mM)	0.8 ± 0.1	0.5 ± 0.0 *	**Maternal starvation** 72 hours maternal starvation starting at d 125-130 gestation * p<0.05	Coopworth/ Border	YSI 2300 STAT glucose analyser	Samples collected from indwelling arterial and venous catheters. IGF-I and IGF-2 in fetal blood were reduced by 72 hour fasting.	Oliver et al 1996
IGF-1 (nM)	13.5 ± 1.5	7.9 ± 1.3 *			Acid ethanol cryoprecipitation /RIA		
IGF-2 (nM)	151.9 ± 8.4	111.5 ± 3.6 *			Acid ethanol cryoprecipitation /RIA		
Insulin (nM)	0.3 ± 0.0	0.1 ± 0.0 *			RIA		
Glucose (mg/100 ml)	24.18 ± 6.32	6.01 ± 1.00 *	**Maternal starvation** 72 hours maternal starvation starting at d 123-134 gestation		Glucose oxidase kit	Samples collected from indwelling arterial and venous catheters. Study also investigated the effect of restoring glucose by glucose infusion.	Osborn et al 1992
Insulin (ng/ml)	0.69 ± 0.16	0.37 ± 0.06 *			RIA		
IGFBP-1	2-3 fold increase in				Western ligand blot		
IGFBP-2	No significant effect				Western ligand blot		
IGFBP-3	No significant effect				Western ligand blot		

IGFBP-4	No significant effect				Western ligand blot		
IGF-2 receptor	No significant effect				Western ligand blot		
Active compound				**Breed**	**Assa**	**Other comments**	**Re**
	Ad libitum feeding	**Nutrient restricted groups**					
IGF-1 (ng/ml)	45	27 *	**Maternal starvation** 5 d fast starting at ~130 days gestation * p<0.05		Formic acid/acetone extraction, then RIA	Samples collected from indwelling arterial, venous and umbilical vein catheters. Units for IGFBPs are arbitrary densitometric units. IGF-I and IGF-2 decreased by maternal starvation. IGFBP-1 was increased by maternal starvation,	Lee et al 1997
IGF-2 (ng/ml)	375	310 *			Formic acid/acetone extraction, then RIA		
IGFBP-1	120	155 *			Western ligand blot		
IGFBP-2	210	215			Western ligand blot		
IGFBP-3	150	140			Western ligand blot		
IGF-1 (ng/ml)	242 ± 14.9	213 ± 7.9	**Restricted nutrition** 50% metabolisable energy requirements from mating to d 119.	Scottish Blackface		Samples collected from indwelling arterial and venous catheters at d113 to 119 gestation.	Rae et al 2002
Insulin (uIU/ml)	18.3 ±1.15	19.2 ±1.76					
Triiodothyronine T3 (ng/ml)	0.24 ± 0.01	0.19 ± 0.02 *					
Thyroxine (ng/ml)	82.9 ± 5.2	72.4 ± 4.6					

TABLE 4. Ovine fetal serum hormones studies involving environmental alterations –hypoxia or hyperthermia

Active compound				Breed	Assay	Other comments	Ref
	Control	**Hypoxia**					
Glucose (mM)	0.96±0.17	1.11 ± 0.18 (30 min) 1.14 ± 0.23 (60 min) 1.26 ± 0.40 (120 min) * 1.23 ± 0.40 (180 min) *	**Acute hypoxia** Ewes made hypoxic for 3 hours		Glucose/lactate analyser (YSI)	114-124 days gestation. Samples collected from indwelling arterial catheter. Ewes made hypoxic by infusion of nitrogen to trachea. Acute hypoxia reduced fetal plasma IGF-I, but not IGF-2.	Iwamoto et al 1992
IGF-1 (ng/ml)	91 ±11	80 (30 min) * 85 (60 min) 75 (120 min) * 70 (180 min) *			Acid extraction, HPLC, RIA		
IGF-2 (ng/ml)	934±157	992 ± 219 (30 min) 952 ± 139 (60 min) 941 ± 151 (120 min) 873 ± 171 (180 min)			Acid extraction HPLC, RIA,		
	Control	**Hypoxia**					
IGF-1 (ng/ml)	43.1 ± 7.9 Range 14.0-72.5	60% of control values, (not significantly reduced)	**Hypoxia** 24h of hypoxia by restriction of uterine blood flow		Acid Chromatography / RIA	115-120 days gestation Samples collected from indwelling arterial catheter. Plasma IGF values expressed in the paper as % of baseline values.	McLellan et al 1992
IGF-2 (ng/ml)	444.7 ± 89.4 Range 97-775	75% of control values, (not significantly reduced)			Acid Chromatography / RIA		
Insulin (ng/ml)	0.7 ± 0.12	0.73 ± 0.17					
Lactate (mg/dl)	14	40-60 *					
IGFBP-1		Increased by 75%			Western ligand blot		
IGFBP-2		Decreased by 40%			Western ligand blot		
IGFBP-3		IGFBP-3 not altered			Western ligand blot		

IGFBP-4		IGFBP-4 not altered			Western ligand blot		
Active compound				**Breed**	**Assay**	**Other comments**	**Ref**
	Control	**Hyperthermic**					
Insulin (uU/ml)	0.24	0.12	**Maternal hyperthermia** Ewes maintained at 35-40^{o}C, compared to	Columbia-Rambouillet	Mercodia ELISA Extraction, then immunoradiometry	Samples collected from umbilical vein at post-mortem at d 90 gestation. Large variance in insulin values, decreased by	De Vrijer et al 2006
IGF-1 (ng/ml)	52	48					

TABLE 5. Ovine fetal serum hormones studies involving environmental alterations – intrauterine growth retardation

Active compound					Breed	Assay	Other comments	Ref
	Normal	**Growth retarded**	**Very Growth retarded**					
Glucose (mmol/l)	0.71 ± 0.06 (120 d) 0.65 ± 0.04 (127 d)	0.65 ± 0.15 (120 d) 0.51 ± 0.10 (127 d)	0.47 ± 0.07 (120 d) 0.40 ± 0.12 (127d)*	**Fetal growth retardation due to placental restriction** * p<0.05 compared to normal size at same age	Border/ Leicester	Enzymatic assay	Samples collected from indwelling arterial catheters Fetuses classified as normal, growth retarded (2-6 SD below mean) or very growth retarded (>6 SD below mean)	Owens JA et al 1994
IGF-1 (ng/ml)	140 ± 9 (120 d) 137 ± 13 (127 d)	95 ± 7 (120 d) * 74 ± 24 (127 d) *	38 ± 7 (120 d) * 16 ± 2 (127 d) *			Acid HPLC,RIA		
IGF-2 (ng/ml)	709 ± 206 (120 d) 1181 ± 290 (127 d)	1023 ± 269 (120 d) 910 ± 144 (127 d)	744 ± 157 (120 d) 385 ± 74 (127 d) *			Acid HPLC,RIA		
	Normal	**Growth retarded**						
IGF-1 (ng/ml)	157 ± 7	121 ± 10 *		**Fetal growth retardation due to placental restriction** * p<0.05	Dorset / Merino	Acid HPLC,RIA	Samples collected from indwelling arterial catheters	Kind KL et al 1995
IGF-2 (ng/ml)	663 ± 45	697 ± 45				Acid HPLC,RIA		
Insulin (pg/ml)	772 ± 132	564 ± 119				RIA		

TABLE 6. Rat fetal serum metabolites and hormones according to development stage, maternal nutritional treatment or oxygen deprivation

	Stage of pregnancy				Breed	Assay	Other comments	Ref
			d20		Wistar rats		**Nutritional Restriction**	
Glucose (mM)							**Effect of feeding a 20%(P20) vs 5% (P5)protein diet**	Muaku et al 1995
IGF-1 (ng/ml)			145±10 (P20)	100±1 (P5) *p* <0.01		Non-equilibrium RIA	IGF-1 decreased in low protein diet	
IGF-2 (ng/ml)						Non-equilibrium RIA	No change in IGF-II	
	d14		d21		Wistar rats		**Nutritional Restriction**	Fernandez - Twinn et al 2003
Glucose (mM)	5.9±0.22	2.8±0.16 (LP) *p*<0.0001	3.6±0.58	3.8±0.34 (LP)			**Dams fed 40% protein restricted diet (LP)**	
Insulin (pmol/l)			539±1231	417±64 (LP)			No effect in d21 fetus on leptin,prolactin, corticosterone,	
			d20		Sprague-Dawley		Rats fed 20% protein for first 10-11 days gestation, then isocaloric diet with 4% casein (LP)	Barone et al 1998
Total plasma protein (g/l)			21.6±1.5	13.6±1.0 (LP) P< 0.01			**Protein restriction** reduced plasma protein but not plasma albumin concentration.	
Plasma Albumin (g/l)			15±2.0	12±1.0				
			d21				Fed *ad libitum*, then starved from d18-d21	Bernstein IM et al
IGF-1 (ng/ml)			87.45±17.5	56.8±14.9 *p* <0.01		Acid chromatogr a phy, then RIA	**Maternal starvation** resulted in a marked reduction in fetal plasma IGF-1	

	Stage of pregnancy				Breed	Assay	Other comments	Ref
			d21		Sprague-Dawley		**Experimental intrauterine growth retardation** (IUGR) induced by hypoxia (d14-21 of	Tapanainen et al 1994
IGF-1 (ug / l)			59±9	54±7 (IUGR)		Acid chromatograp		
IGF-2 (ng/ml)			297±31	418±33 (IUGR)		Acid chromatograp hy, then		
			d21		Sprague-Dawley		Small for gestational age (SGA) model induced by bilateral uterine arterial ligation	Unterman et al 1993
Insulin (uU/ ml)			134±12	70±5 p <0.001		Double antibody immunoassay		
IGF-1 (ng/ml)			120±9	65±5 p <0.001		Acid extraction, HPLC, then RIA		
IGF-2 (ng/ml)			760±52	622±12		Acid extraction, HPLC, then RIA		

8.1 Appendix 1 Literature Survey Summary – bovine fetus

Search tools used

Web of Science
Current Contents
PubMed
Professional and scientific society conference/meeting proceedings

Journals with a focus on Animal Production were searched independently: Journal of Animal Science, Theriogenology, Australian Journal of Experimental Agriculture.

http://www.livestocklibrary.com.au/ The Livestock Library - developed and funded by the CRC for Beef Genetic Technologies, the Australian Sheep Industry CRC, funded by Australian Wool Innovation. Supported and hosted by the Dept. Agriculture and Food, Western Australia.

Due to the focus of the literature analysis being bovine fetal serum, an extensive review of all literature relating to the "bovine fetus" was undertaken.

- "Bovine" and "fetus" resulted in 5024 publications in PubMed.
- The majority of articles focus on pregnancy complications associated with viral or bacterial infections.
- Current Contents search results were compared to detect any articles not cited by PubMed.
- The list was reduced to 388 references with some relevance.
- 268 references of these were chosen for initial review of abstracts where available.
- 45 articles were obtained and reviewed and those that were relevant are included in the report.
- Additional literature was accessed to provide background information to the bioactive growth factors.

Literature Survey Summary – ovine fetus

A similar approach was taken to review the literature on the ovine fetus.
A summary of the literature accessed is provided below.

Search outcomes (number of references)

a.	Ovine and fetus	1563
b.	Sheep and fetus	2591
c.	IGF and fetus and sheep	121
d.	IGF and fetus and ovine	66
e.	Growth factor and fetus and sheep	242
f.	Growth factor and fetus and ovine	139
g.	Hormone and fetus and sheep	394
h.	Hormone and fetus and ovine	374
i.	Albumin and fetus and sheep	4
j.	Albumin and fetus and ovine	5
k.	Insulin and fetus and sheep	115
l.	Insulin and sheep and ovine	139
m.	EGF and fetus and sheep	5
n.	EGF and fetus and ovine	0
o.	FGF and fetus and sheep	7
p.	FGF and fetus and ovine	4

8.2 Appendix 2. Bovine fetus reference database

Generated and selected for initial review

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8.3 Appendix 3 - Ovine fetus reference database

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8.4 Appendix 4 - Rodent fetus reference database

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