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Maternal nutrition and developmental programming of offspring

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ABSTRACT

Developmental programming is the concept that 'stressors' during development (i.e. pregnancy, the perinatal period and infancy) can cause long-term changes in gene expression, leading to altered organ structure and function. Such long-term changes are associated with an increased risk of a host of chronic pathologies, or non-communicable diseases including abnormal growth and body composition, behavioural or cognitive dysfunction, metabolic abnormalities, and cardiovascular, gastro-intestinal, immune, musculoskeletal and reproductive dysfunction. Maternal nutrition during the periconceptual period, pregnancy and postnatally can have profound influences on the developmental program. Animal models, including domestic livestock species, have been important for defining the mechanisms and consequences of developmental programming. One of the important observations is that maternal nutritional status and other maternal stressors (e.g. environmental temperature, high altitude, maternal age and breed, multiple fetuses, etc.) early in pregnancy and even periconceptually can affect not only embryonic/fetal development but also placental development. Indeed, altered placental function may underlie the effects of many maternal stressors on fetal growth and development. We suggest that future directions should focus on the consequences of developmental programming during the offspring's life course and for subsequent generations. Other important future directions include evaluating interventions, such as strategic dietary supplementation, and also determining how we can take advantage of the positive, adaptive aspects of developmental programming.

Keywords: developmental programming, fetal programming, gene expression, maternal nutrition, organ function, organ structure, periconceptual, placental programming.

Introduction

Developmental programming, also known as fetal programming, is the concept that developmental stressors can alter gene expression in the developing fetus/neonate via epigenetic mechanisms. Such epigenetic alterations are thought to 'program' not only fetal and postnatal growth and development, but also to cause long-term changes in organ structure (e.g. altered number of nephrons in the kidney, altered pancreatic islet number or size, altered number of myofibres) and function (Barker 1990; Paneth and Susser 1995, 2004; Armitage *et al.* 2004; Wu *et al.* 2006; Caton and Hess 2010; Reynolds *et al.* 2010*a*, 2017, 2019, 2022; Reynolds and Caton 2012; Caton *et al.* 2019; Dahlen *et al.* 2021; Diniz *et al.* 2022). The consequences of developmental programming include preterm delivery, low birth weight and poor survival of newborns as well as a host of chronic pathologies in the offspring including abnormal growth and body composition, behavioural or cognitive dysfunction, metabolic abnormalities and cardiovascular, gastro-intestinal, immune, musculoskeletal and reproductive dysfunction (Barker 2004; Wu *et al.* 2006; Caton and Hess 2010; Reynolds *et al.* 2010*a*, 2017, 2019, 2022; Reynolds and Caton 2012; Reynolds and Vonnahme 2016; Caton *et al.* 2019; Cushman and Perry 2019; Dahlen *et al.* 2021). Additionally, chronically altered function of organ systems may contribute to aging and, importantly for livestock production, reduced

longevity and production (Zambrano *et al.* 2014, 2015, 2020, 2021; Du *et al.* 2015; Franke *et al.* 2017; Kuo *et al.* 2017, 2018; Pankey *et al.* 2017; Yang *et al.* 2017; Broadhead *et al.* 2019; Cushman and Perry 2019; Wang *et al.* 2019).

The concept of developmental programming was first articulated by Dr. David Barker and colleagues. They used epidemiological evidence in humans to show a strong association between low birth weight, poor postnatal environment, or other developmental insults, and the subsequent risk of developing the range of pathologies noted above (Barker 1990, 2004). These studies suggested that an adverse intrauterine environment can lead to a greater incidence of non-communicable diseases in the offspring and that poor maternal nutrition was '.. an obvious suspect (Barker 1990, 2004).' Subsequently, numerous epidemiological studies in humans, as well as many carefully controlled studies in various animal models, have confirmed the initial observations of Barker and colleagues, and some of the risk factors for developmental programming have been identified (Armitage *et al.* 2004; Wu *et al.* 2006; Caton and Hess 2010; Reynolds *et al.* 2010*a*, 2017, 2019, 2022; Reynolds and Caton 2012; Reynolds and Vonnahme 2017; Caton *et al.* 2019).

An additional, and important concept is that developmental programming must have entered and remained in the genome because of its adaptive advantages (Nettle *et al.* 2013; Bateson *et al.* 2014; Mueller *et al.* 2015). Whether we can take advantage of these adpatations to improve fitness and therefore productivity of the offspring is not known but should be kept in mind as we study various aspects of developmental programming (Reynolds *et al.* 2022).

Maternal nutrition

Maternal nutrition has a profound effect on fetal growth, as reflected by fetal weights in late pregnancy (Reynolds *et al.* 2019, 2022). For example, adolescent sheep that are overfed throughout pregnancy exhibit reduced fetal and placental weights similar to those of heat-stressed adult mothers. In this experimental paradigm, not only is placental vascular development reduced, but gravid uterine (maternal placental) and umbilical (fetal placental) blood flows are profoundly reduced, similar to that seen in heat-stressed pregnancies (Reynolds *et al.* 2019, 2022). Reduced placental blood flows are associated with altered placental vascular growth and development (Reynolds *et al.* 2006, 2010*a*, 2010*b*, 2019, 2022).

These observations are not surprising, as soon after implantation the placenta becomes the sole organ of exchange between the fetal and maternal systems. In other words, very early in pregnancy, the exchange of nutrients, oxygen and metabolic wastes between the maternal and fetal systems occurs solely via the placenta (Mayhew *et al.* 2004; Redmer *et al.* 2005, 2009; Vonnahme *et al.* 2007; Mayhew 2009; Reynolds *et al.* 2010*b*). Because it is primarily an organ of transport, the placenta also develops an extensive blood supply (i.e. it becomes highly vascular), which causes gravid uterine and umbilical blood flows (that represent the blood supplies to the maternal and fetal sides of the placenta, respectively) to increase exponentially throughout pregnancy. In fact, the increase in umbilical blood flow keeps pace with the exponential growth of the fetus (Reynolds and Redmer 1995; Reynolds *et al.* 2010*b*).

Many studies in livestock have shown that placental development and function are altered late in pregnancy in a variety of models of developmental programming, including maternal dietary intake (overfed or underfed), environmental heat stress, multiple pregnancies (singletons vs twins or triplets), maternal age (adolescent vs adult pregnancies), and maternal breed (Reynolds *et al.* 2019, 2022). These observations agree with those in other species, including humans (Mayhew *et al.* 2004; Reynolds *et al.* 2006; Mayhew 2009). In addition, defects in placental growth, including vascular defects, normally precede altered fetal growth and development (Reynolds *et al.* 2017, 2019).

We have shown in nutritionally-compromised pregnancies that placental vascular development is reduced very early in gestation (Grazul-Bilska *et al.* 2013, 2014; Vonnahme *et al.* 2013; Reynolds *et al.* 2014, 2019, 2022; Bairagi *et al.* 2016; McLean *et al.* 2017). Not only is placental vascular development altered by maternal nutrition during early pregnancy, but other aspects of placental function are affected as well. For example, placental expression of nutrient transporters and angiogenic factors is reduced in nutrient-restricted heifers during early pregnancy (Table 1). Similarly, maternal dietary restriction during early pregnancy profoundly affects gene expression in fetal liver, muscle and cerebrum (Table 1).

Because placental vascular growth and development are critical for normal placental function (Reynolds and Redmer 1995; Reynolds *et al.* 2010*b*, 2013, 2014; Bairagi *et al.* 2016), the observations described in the preceding paragraph have led to the concept of placental programming; i.e. that defects in placental growth and development underpin the altered fetal growth and organ development that is seen with developmental programming by maternal nutrition, and perhaps other 'stressors' such as *in vitro* production of embryos (see the next section of the manuscript; Reynolds *et al.* 2006; Vonnahme *et al.* 2013; Bairagi *et al.* 2016; Reynolds and Vonnahme 2017). Thus, despite the low metabolic demands of the conceptus in early pregnancy, these studies have confirmed that poor maternal diet can 'program' placental, and consequently fetal, development during their earliest stages (Diniz *et al.* 2021*a*, 2021*b*). In addition, maternal nutritional restriction is associated with effects, either directly or indirectly (e.g. via altered placental development and function) on gene expression in fetal organs (Table 1). Importantly, we also have shown that nutritional interventions (e.g. vitamin–mineral, energy and/or one-carbon

Table 1. Experimental paradigms of maternal nutrition in cattle and sheep and outcomes for placental vascularity, placental nutrient transporters and placental and fetal organ gene expression during early pregnancy.

Experimental paradigm[A]	Outcome[B]		
	Placental vascularity	Placental nutrient transporters	Placental or fetal organ gene expression
Nutrient restriction	↓ in COT	↓*SLC7A2* in ICAR; ↑SLC7A2 and ↓SLC7A5 in ENDO and ICOT; ↓SLC2A3 and SLC7A1 in DG; ↓SLC7A1 in MYO; ↓SLC7A1, SLC38A2 and SLC38A7 in all U-P tissues	↓*VEGF* in ICAR; mostly up-regulation in fetal liver (n = 125 genes), muscle (n = 106 genes), and cerebrum (n = 60 genes)
Vitamin–mineral and energy supplementation	No Effect in early pregnancy (but ↑ in COT at parturition)	–	Differential expression of many energy-metabolism and transport-related genes in CAR and COT
One-carbon metabolite supplementation	↑ in CAR and EG	–	–
Assisted reproduction/*in vitro* production of embryos	↓ in CAR & COT	–	↓*VEGF*, *FLT1*, *ANGPT1* and *TEK* in CAR, and ↓*VEGF*, *FLT1*, *ANGPT1/2* and *NOS3* in COT

[A]Outcomes for nutrient restriction, vitamin–mineral supplementation, and one-carbon metabolite supplementation paradigms were all for cattle at day 50 (0.18 [18%]) through day 84 (0.3) of gestation (Crouse *et al.* 2017, 2019, 2020, 2021; McLean *et al.* 2017; Diniz *et al.* 2021*a*, 2021*b*; Dávila Ruiz *et al.* 2022; Kanjanaruch C, Bochantin KA, Borowicz PP, Reynolds LP, Crouse MS, Caton JS, Dahlen CR, Navanukraw C and Ward AK, unpubl.); outcomes for assisted reproduction/*in vitro* production of embryos were for sheep on day 22 (0.15) of pregnancy (Grazul-Bilska *et al.* 2014).

[B]For outcomes: ↓, downregulated compared with control; ↑, upregulated compared with control.

Abbreviations for tissues: CAR, maternal caruncle; ICAR, maternal intercaruncular endometrium; COT, fetal cotyledon; ICOT, fetal intercotyledonary chorioallantois (these four represent placental tissues); U-P, utero-placenta; ENDO, maternal endometrium; EG, endometrial glands; DG, deep endometrial glands; MYO, maternal myometrium. The CAR and COT together comprise the placentome, which is the primary region of intervascular exchange between the maternal and fetal systems. The ICAR and ICOT contain uterine glands (ICAR), which produce and secrete histotroph (uterine milk), and the corresponding areolae (ICOT), which provide for absorption of the histotroph. For placental nutrient transporters or angiogenic factors, abbreviations in italics represent genes whereas non-italicised abbreviations represent proteins.

Abbreviations for nutrient transporters and angiogenic factors: SLC2A3 = GLUT3, Glucose transporter 3; SLC7A1 = CAT1, high affinity cationic amino acid transporter 1; SLC7A2 = CAT2, low affinity cationic amino acid transporter 2; SLC7A5 = LAT1, L-type amino acid transporter 1; SLC38A2 = SNAT2, sodium-coupled neutral amino acid transporter 2; SLC38A7 = SNAT7, putative sodium-coupled neutral amino acid transporter 7; VEGF, vascular endothelial growth factor; FLT1, VEGF receptor 1; ANGPT1 and ANGPT2, angiopoietin 1 and 2; TEK, angiopoietin receptor; and NOS3, nitric oxide synthase 3, endothelial nitric oxide synthase.

–, no data.

metabolite supplementation; Table 1) can 'rescue' placental vascular development.

An additional time during which maternal nutrition seems to be important is the periconceptual period; that is, immediately before and after conception. Perhaps one of the most dramatic examples of developmental programming involves maternal nutrient restriction of ewes for 60 days before until 30 days after mating, which results in delivery an average of 7 days early compared with normally fed ewes and results in '... all preterm lambs [dying] soon after birth' (Fig. 1; Bloomfield *et al.* 2003; Kumarasamy *et al.* 2005). Similarly, overfeeding or underfeeding of ewes for 8 weeks before collecting their oocytes results in poor rates of *in vitro* fertilisation and poor development of embryos *in vitro* (Fig. 2; Grazul-Bilska *et al.* 2012). These studies emphasise the importance of maternal nutritional status not only during early pregnancy but also during the periconceptual period.

As we have already mentioned, developmental programming must have entered and remained in the genome

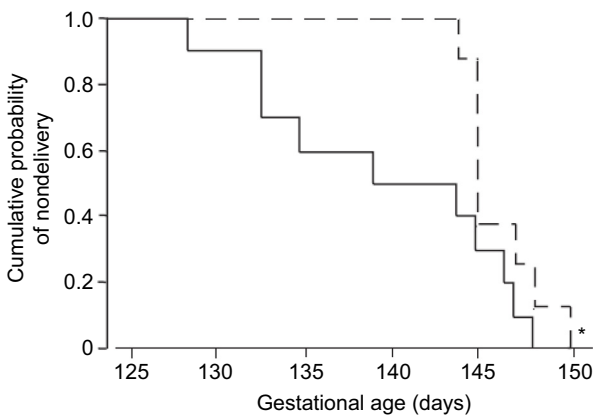

Fig. 1. Cumulative probability of nondelivery in sheep subjected to nutrient restriction (solid line) from 60 days before until 30 days after mating compared with controls (dashed line); normal time of delivery is approximately 145–150 days of gestation. In this paradigm, '... all preterm lambs died soon after birth' (Kumarasamy *et al.* 2005). Used, with permission, from Bloomfield *et al.* (2003).

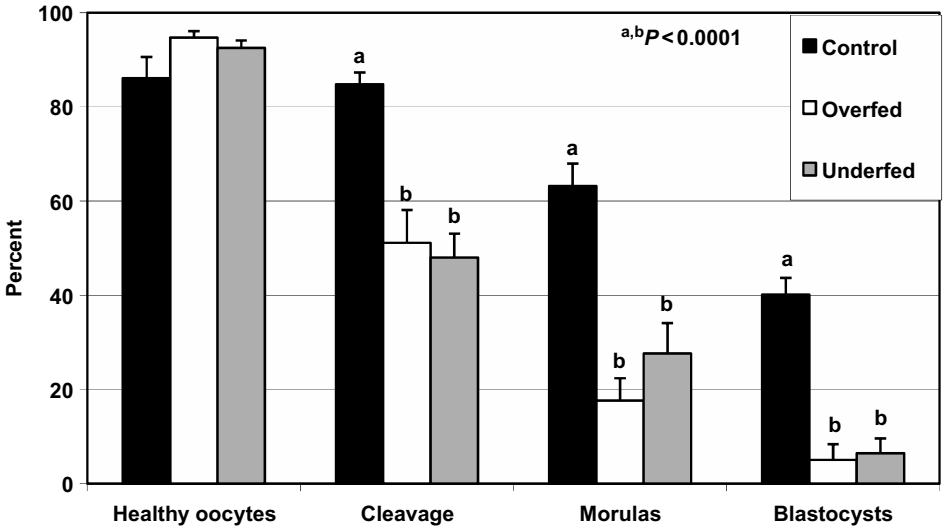

Fig. 2. Percentage of healthy oocytes collected, and cleaved oocytes, morulas and blastocysts after *in vitro* fertilisation and *in vitro* culture for control, overfed and underfed (for 60 days before *in vitro* fertilisation) in sheep. Taken, with permission, from Grazul-Bilska *et al.* (2012).

because of its adaptive advantages (Nettle *et al.* 2013; Bateson *et al.* 2014; Mueller *et al.* 2015), and taking advantage of these may improve fitness and therefore productivity of the offspring (Reynolds *et al.* 2022). For example, our studies of maternal nutritional status during the first 50 days of pregnancy in cattle showed that the vast majority of genes in fetal liver, muscle, and brain were upregulated in fetuses from nutrient-restricted dams (Table 1). Based on these observations, we have suggested that the upregulation of genes may represent an adaptive response to the maternal nutrient restriction (Crouse *et al.* 2019; Reynolds *et al.* 2022). This suggestion seems likely, as cattle under an extensive, pasture-based system, which is very common in regions with large areas of grassland such as the western region of the U.S., are often under nutritional stress during early pregnancy, which is typically in the fall, because of the declining yield and quality of pastures (Krysl *et al.* 1987; Wu *et al.* 2006; NASEM 2016; Caton *et al.* 2019, 2020). Thus, the adaptive response to limited maternal nutrient intake seems to involve upregulation of genes and even 'rewiring' of gene networks at the systems level (Caton *et al.* 2020; Diniz *et al.* 2021*b*).

In vitro production (IVP) of embryos

An instructive paradigm that is likely related to the nutritional, or perhaps more appropriately the environmental, status of the embryo during fertilisation and early development is that of *in vitro* production (IVP) of embryos. As shown by Loi *et al.* (2006) and subsequently many others, IVP by *in vitro* fertilisation or cloning results in a relatively low percentage (10–40%) of embryos surviving to term (Palmieri *et al.* 2008; Reynolds *et al.* 2013, 2014, 2019, 2022). Associated with the high rate of embryonic loss and poor pregnancy outcomes is poor embryonic and placental development very early in pregnancy (approximately 0.15, or 15%, of gestation; Arnold *et al.* 2006; Palmieri *et al.* 2007, 2008; Grazul-Bilska *et al.* 2013, 2014; Fidanza *et al.* 2014; Reynolds *et al.* 2014).

As shown in Table 2, poor embryonic and placental development after assisted reproductive technologies (ART) includes reduced fetal and placental growth; reduced placental vascularisation; reduced placental expression of a host of angiogenic factors, gap junctional connexins, and DNA methyl transferases; increased conceptus DNA methylation; and altered placental expression of oestrogen and progesterone receptors. All of these alterations would be expected to dramatically affect embryonic and placental growth and development and likely contribute to placental programming.

Observations in other mammalian species, including humans, have shown similar results after ART, including poor embryonic/fetal and placental development, poor pregnancy outcomes, and developmental programming of the offspring (Beaujean *et al.* 2004; Farin *et al.* 2006; Loi *et al.* 2006; Palmieri *et al.* 2007, 2008; Canovas *et al.* 2017; Coy *et al.* 2022). A promising approach to at least partially overcome the embryonic/fetal and placental defects seen with ART is the inclusion of oviductal or other reproductive fluids in the culture media. Inclusion of oviductal and other reproductive fluids improves the success of IVP and subsequent pregnancy rates and also reduces the effects of IVP on embryonic/fetal gene expression and DNA methylation status (Coy and Yanagimachi 2015; Canovas *et al.* 2017; Coy *et al.* 2022).

Table 2. Comparison of several processes and factors in maternal and fetal placenta during early pregnancy in sheep (day 22 after mating/fertilisation; approx. 0.15 of gestation) after application of ART (NAT-ET, naturally mated followed by embryo transfer; IVF, *in vitro* fertilisation; IVA, *in vitro* activation [i.e. parthenogenetic activation of embryonic development]) compared with control pregnancies achieved by natural mating and sampled on day 22.

Process	Factor	NAT-ET group		IVF group		IVA group	
		Maternal Placenta	Fetal placenta	Maternal Placenta	Fetal placenta	Maternal Placenta	Fetal placenta
Angiogenic factor mRNA	VEGF	↓	↓	–	↓	↓	↓
	PGF	↓	↓	–	↓	–	–
	FLT1	↓	↓	↓	↓	↓	↓
	KDR	–	–	–	–	–	–
	NP1	–	↓	–	↓	–	↓
	NP2	–	–	–	↓	–	↓
	ANGPT1	↓	↓	–	↓	–	↓
	ANGPT2	–	↓	–	↓	–	↓
	TEK	↓	–	↓	–	↓	–
	NOS3	–	↓	–	–	–	↓
	GUCY1B3	–	–	–	–	–	–
	HIF1A	–	↓	–	–	–	↓
	FGF2	–	↓	–	↓	–	↓
	FGFR	–	↓	–	↓	–	–
Global DNA methylation	DNMT1 mRNA	–	–	–	–	–	↑
	DNMT3a mRNA	↓	–	↓	–	↓	–
	DNMT3b mRNA	–	–	–	–	–	–
	5mC	NP	–	NP	↑	NP	↑
Steroid receptor mRNA	Nuclear P4	↓	–	↓	–	↓	–
	Membrane P4α	–	–	–	–	–	–
	Membrane P4β	–	–	–	–	–	–
	Membrane P4γ	–	–	–	–	–	–
	ERα	↓	–	↓	↑	↓	↑
	ERβ	–	–	–	–	–	-
Gap junctional connexin mRNA	Cx26	–	–	–	–	–	↑
	Cx32	↓	–	↓	–	↓	–
	Cx37	–	–	–	–	–	–
	Cx43	–	–	–	–	–	–
Vascularisation	Blood vessel number	↓	–	↓	↓	↓	↓
	Capillary size	–	NP	↓	NP	↓	NP
Tissue growth	Length of fetus	NA	↓	NA	↓	NA	↓
	Labelling index	↓	↓	↓	↓	↓	↓

ART, assisted reproductive technologies. Adapted from Reynolds *et al.* (2013, 2014). Compared to pregnancies from natural breeding (control): ↓, downregulated compared with control; ↑, upregulated compared with control; –, not different from control; NA, data not available; and NP, not performed. Table taken with permission from Reynolds *et al.* (2013).

Conclusions and future directions

As discussed in this review, maternal nutritional status, ART, and a host of other maternal 'stressors' can profoundly affect embryonic/fetal development and survival, and often result in 'programming' of gene expression and subsequently altered growth and development. Recent data have shown that programming of placental growth and development very early in pregnancy may underlie many of the defects in embryonic/fetal growth and development that lead to

poor outcomes during pregnancy and postnatally. In addition, maternal nutrition during the periconceptual period, that is, before and immediately after mating, also appears to program conceptus development.

Whether such early programming has long-lasting effects is unclear, but certainly epigenetic alterations occur, and there is every reason to believe they affect organ structure and function and will have lasting consequences throughout an individual's life. Nevertheless, an important direction for future research is investigating the consequences of early programming both for health and productivity of the offspring and subsequent generations.

Another important area of future research focus should be whether interventions, including some of those discussed in this review, such as strategic dietary supplementation or culture of embryos with reproductive fluids, can mitigate some of the negative consequences of developmental programming, or even enhance the fitness of the offspring and future generations. That is, whether some of the strategies currently being evaluated for their ability to overcome the negative consequences of developmental programming can actually take advantage of the positive effects of developmental programming. This is especially apropos since, as we have already mentioned, it seems clear that we need a much better understanding of whether changes in expression of fetal and placental genes are adaptive, and therefore positive, or maladaptive, and therefore detrimental in both the short and long term.

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