PERSPECTIVES

'Placental programming': more may still be less

Pawel Borowicz[1] and Lawrence P. Reynolds[2]
[1]*Department of Animal Sciences, North Dakota State University, Fargo, ND 58102, USA*
[2]*North Dakota State University, Department 7630, Fargo, ND, 58108-6050, USA*

Email: pawel.borowicz@ndsu.edu

Malnutrition, mortality and morbidity: (a) malnutrition is the largest contributor to disease in the world; (b) childhood and maternal underweight alone are responsible for 138 million disability-adjusted life years lost or 9.5% of the global burden of disease; (c) in developing countries, diet-related risk factors for chronic disease are responsible for a large share of the burden of disease (http://www.unscn.org/layout/modules/resources/files/rwns5.pdf). The causes of diet-related fetal growth restriction are important and highly relevant, given the number of growth-restricted newborns (more than 20 million per year worldwide (http://www.who.int/making_pregnancy_safer/documents/9280638327/en/) and the profound influence of fetal development on life-long health and well-being of the resulting offspring (Barker, 2004). Fetal intrauterine growth retardation due to poor nutrition is closely linked to placental development and function.

In this issue of *The Journal of Physiology*, Coan *et al.* (2010) used a mouse model of maternal dietary restriction beginning early in pregnancy (day 3, or 0.14 of gestation) to address several emerging concepts concerning the mechanisms responsible for fetal growth restriction. Data presented by Coan *et al.* support the idea that small undernourished placentas may adapt their phenotype to be able to accommodate fetal nutrient demand and that this process may include either morphological or functional mechanisms acting during different stages of feto-placental development. The first concept addressed by the studies of Coan *et al.* is the idea that the placenta can be 'programmed' in response to a maternal 'stressor' such as maternal nutrient restriction. This concept has been articulated previously by this group, and it is supported by a body of literature in various animals including rodents and sheep (Fowden *et al.* 2006; Reynolds *et al.* 2009). Placental programming can lead in turn to altered nutrient transport to the fetus and hence to fetal growth restriction. Physiologically speaking, there are several ways in which placental nutrient transport can be altered, including changes in: (1) placental size and morphology, (2) placental nutrient transporter abundance or function, (3) placental vascular development, or (4) placental blood flow (Fowden *et al.* 2006; Borowicz *et al.* 2007; Reynolds *et al.* 2009). The second concept addressed by Coan *et al.* is that of a compensatory increase in placental function, as reflected in this case by nutrient transport. The authors demonstrate that although placental weight was reduced in late gestation (day 19, which represents 0.9 of gestation), there was a compensatory increase in placental glucose and amino acid transport and transporter expression in the nutrient-restricted mice compared with their control-fed counterparts. Fetal weight, however, was still reduced in spite of the increase in nutrient transporters, at least in part because placental surface area and capillary volume were also reduced in the nutrient-restricted dams. Thus, placental compensatory responses may not be enough to overcome the negative effects of placental programming. These observations also confirm the third concept, which is that the placental response to maternal stress is likely to be quite complex, and may depend on the type of stressor (e.g. nutrient restriction or excess, maternal age, maternal steroid exposure, maternal environmental stress such as high altitude or high ambient temperature and humidity, numbers of fetuses, etc.). This concept is supported by observations in several species (Reynolds *et al.* 2009). Moreover, Coan *et al.* show that the reduction in placental weight preceded fetal growth restriction, confirming that placental programming can lead to a reduction in fetal growth. The concept that reduced placental growth might, in some cases, lead to a compensatory increase in placental functional capacity in response to placental growth restriction is supported by previous studies in rodents (Fowden *et al.* 2006), sheep (Wallace *et al.* 2009), and other mammals (Reynolds *et al.* 2009). The fourth concept is that in addition to nutrient transport, altered placental angiogenesis, including in some cases a compensatory increase in vascularity, is also an important component of placental programming, as demonstrated not only by Coan *et al.* but also by numerous other studies in humans, rodents, pigs and sheep (Fowden *et al.* 2006; Reynolds *et al.* 2009). The fifth concept addressed by the study of Coan *et al.* is that a more complete understanding of the factors regulating placental growth, morphology, nutrient transporters, angiogenesis, and vascular function will require investigating these processes from the earliest stages of gestation using a variety of animal models. Using this comparative approach may eventually lead to clinically relevant therapeutic strategies designed to optimize placental growth and function, and thereby to minimize the negative consequences of placental programming on growth of the fetus and subsequent health of the resulting offspring.

References

Barker DJP (2004). *Philos Trans R Soc Lond B Biol Sci* **359**, 1359–1366.

Borowicz PP, Arnold DR, Johnson ML, Grazul-Bilska AT, Redmer DA & Reynolds LP (2007). *Biol Reprod* **76**, 259–267.

Coan PM, Vaughan OR, Sekita Y, Finn SL, Burton GJ, Constancia M & Fowden AL (2010). *J Physiol* **588**, 527–538.

Fowden AL, Ward JW, Wooding FPB, Forhead AJ & Constancia M (2006). *J Physiol* **572**, 5–15.

Reynolds LP, Borowicz PP, Caton JS, Vonnahme KA, Luther JS, Buchanan DS, Hafez SA, Grazul-Bilska AT & Redmer DA (2009). *Int J Dev Biol*; DOI: 10.1387/ijdb.082799lr.

Wallace JM, Milne JS & Aitken RP (2009). *Biol Reprod*; DOI: 10.1095/biolreprod.109.080069.

© 2010 The Author. Journal compilation © 2010 The Physiological Society
DOI: 10.1113/jphysiol.2009.185983

The Journal of Physiology