Messing with metabolism: lessons from an IUGR fetus

Sarah J. Chapple* and Giovanni E. Mann

King's BHF Centre of Research Excellence, School of Cardiovascular Medicine & Sciences, Faculty of Life Sciences & Medicine, King's College London, 150 Stamford Street, London SE1 9NH, U.K.

*Corresponding Author Email: sarah.2.chapple@kcl.ac.uk and Tel: +44(0)207 848 4830

A wealth of evidence supports the developmental period as being an important determinant for future health status, as well as life expectancy. Intrauterine growth restriction (IUGR), or failure of the fetus to reach its full growth and developmental potential, can occur for many reasons. Abnormal or insufficiently small placental development can induce IUGR, with the latter often occurring secondary to maternal hypertensive disorders such as pre-eclampsia (PE). During pregnancy, the placenta has many roles including providing a functional interface between separate maternal and fetal circulatory systems to allow nutrient, waste and gas exchange. Consequently, poor placentation leads to a reduction in maternal-fetal transfer particularly of oxygen (O_2), impeding fetal growth and development.

Today IUGR remains a leading cause of perinatal mortality, morbidity and in the long-term, IUGR infants have an increased risk of developing later-life cardiometabolic complications including hypertension and Type 2 diabetes. Moreover, accumulating evidence suggests that IUGR and low birth weight lead to the early onset of markers of age-related decline or frailty, such as reduced grip strength and alterations in muscle fibre distribution associated with insulin resistance (Jensen *et al.*, 2007). As highlighted in this current issue of *The Journal of Physiology*, maternal-fetal hypoperfusion necessitates a hard choice; the sparing of critical fetal organs by limiting nutrient/O_2 delivery and utilisation by non-essential fetal tissue beds.

It is unsurprising that maintaining O_2 and nutrient delivery to the fetal heart and brain is paramount to fetal survival and normal development. Brain sparing is evident in response to both acute hypoxic challenge (Yaffe *et al.*, 1987) as well as chronic hypoxic conditioning (Allison *et al.*, 2016). In this issue, Rozance and colleagues utilised a well-validated sheep model of temperature-induced placental insufficiency to examine how fetal hindlimb blood flow, hormonal levels and metabolic substrate use correlate with muscle protein accretion in IUGR foetuses (Rozance *et al.*, 2017). In agreement with other published studies (Yates *et al.*, 2014), the authors report IUGR is associated with a lower daily fetal muscle mass growth rate, leading to a reduction in adrenergic and insulin-responsive Type I and IIa myofiber area. As Type IIa fibre area inversely correlates with fasting plasma glucose in adult low birth weight adult males (Jensen *et al.*, 2007), the phenotypic alterations reported by Rozance and colleagues may represent early adaptive changes in offspring, potentially priming them towards later insulin resistance.

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But what are the factor(s) limiting IUGR fetal muscle mass? Whilst the authors rule out enhanced protein catabolism as the cause of reduced muscle protein accretion, their most interesting findings attempt to address why muscle protein synthesis may be compromised in IUGR. As demonstrated in the current study, absolute blood flow, fetal arterial PaO_2, O_2 saturation, O_2 content and glucose levels are lower in IUGR. However, when considering blood flow relative to fetal hindlimb mass, blood flow, glucose uptake and lactate output are not different between healthy and IUGR fetuses. In contrast, O_2 delivery and O_2 consumption are significantly lower in IUGR fetuses, as is hindlimb total amino acid uptake relative to muscle mass. The authors further demonstrate a clear relationship between O_2 saturation, hindlimb glucose, amino acid uptake and hindlimb mass, however it is the reduction in the amino acid-O_2 quotient in IUGR rather than an alteration in glucose+lactate-O_2 quotient which reveals that amino acid uptake may be key to determining the rate of muscle protein synthesis.

The significance of this relationship should not be underestimated. Under normal conditions, as gestation progresses fetal O_2 demand increases to outpace uterine blood flow and placental exchange, leading to a modest reduction in fetal PaO_2 and potentially glucose levels. In IUGR, failure of the maternal uterine vessels and placenta to sufficiently adapt exacerbates this deficit. If growth in IUGR fetuses were to occur at the normal rate, the lower fetal O_2 saturation would cause oxidative metabolism to become compromised, initiating amino acid oxidation and protein catabolism to maintain its basal metabolic rate (Fig. 1).

Furthermore, the study by Rozance and colleagues implicates a critical role for Insulin-like growth factor-1 (IGF-1) in positively regulating fetal skeletal muscle growth. IGF-1 receptor mutations have previously been linked to the development of IUGR and as discussed by the authors, deletion of IGF-1 is associated with a reduction in murine muscle mass (Liu *et al.*, 1993), with IGF-1 also reported to exert anabolic actions in other target tissues. It has yet to be determined whether in IUGR, IGF-1 affects total amino acid uptake or if its actions may be more selective. Similarly, definitive evidence is needed to define whether previous associations observed between the rate of fetal liver perfusion via the ductus venosus and IGF-1 production translate to fetal skeletal muscle O_2 content and consequently amino acid transport, protein synthesis and muscle accretion. To conclude, studies of adverse pregnancy continue to improve our understanding of the physiological cues guiding fetal development and growth. As in the present study of IUGR, it is clear that messing with tissue-specific metabolic substrate supply and demand during pregnancy has developmental and long lasting consequences for the fetus.

Conflict of Interest.

The authors S.J.C & G.E.M declare no conflict of interest.

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Figure legend:

Fig. 1 IUGR is associated with lower skeletal muscle amino acid uptake and O_2 consumption leading to reduced muscle mass

Placental insufficiency reduces fetal O_2 supply, decreasing IGF-1 levels resulting in reduced muscle amino acid uptake, which matches a reduced muscle O_2 supply and O_2 consumption. Consequently, protein synthesis is reduced, leading to a lower muscle mass and loss of Type I and Type IIa fibre number in various skeletal muscle beds. As noted in *italics*, these alterations may be linked with brain sparing due to reduced liver perfusion, as more blood bypasses the liver via the ductus

venosus, which may also lead to lower IGF-1 production. Alterations in fetal skeletal muscle phenotype may increase its propensity to become insulin resistant in later-life.