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Impact of placental insufficiency on fetal skeletal muscle growth

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ABSTRACT

Intrauterine growth restriction (IUGR) caused by placental insufficiency is one of the most common and complex problems in perinatology, with no known cure. In pregnancies affected by placental insufficiency, a poorly functioning placenta restricts nutrient supply to the fetus and prevents normal fetal growth. Among other significant deficits in organ development, the IUGR fetus characteristically has less lean body and skeletal muscle mass than their appropriately-grown counterparts. Reduced skeletal muscle growth is not fully compensated after birth, as individuals who were born small for gestational age (SGA) from IUGR have persistent reductions in muscle mass and strength into adulthood. The consequences of restricted muscle growth and accelerated postnatal "catch-up" growth in the form of adiposity may contribute to the increased later life risk for visceral adiposity, peripheral insulin resistance, diabetes, and cardiovascular disease in individuals who were formerly IUGR. This review will discuss how an insufficient placenta results in impaired fetal skeletal muscle growth and how lifelong reductions in muscle mass might contribute to increased metabolic disease risk in this vulnerable population.

1. The effects of placental insufficiency on fetal skeletal muscle growth

1.1. Fetal adaptation to increased placental resistance

Placental insufficiency affects ~8% of all pregnancies and commonly begins early in pregnancy for a multitude of reasons, including maternal chronic disease (chronic hypertension, pregnancy-induced hypertension, and other vascular disorders), placental disorders (preeclampsia, abruption, infarcts), and idiopathic causes (Rozance et al., 2016). Maternal/placental conditions that obliterate small muscular arteries result in increased placental vascular resistance and decreased diastolic flow in the umbilical artery (demonstrated by a high pulsatility index) (Berkley et al., 2012). In response to reduced umbilical blood flow and decreasing fetal oxygenation, the fetal ductus venosus dilates to shunt oxygenated blood from the umbilical vein away from the liver to ensure an adequate supply of oxygen and nutrients to the heart and brain (Tchirikov et al., 2006). The middle cerebral artery also dilates (demonstrated by a low pulsatility index) to maximize blood flow to the brain; providing nutrients and oxygen that spare brain growth restriction relative to overall fetal growth. Doppler velocimetry abnormalities in the umbilical artery are the gold standard for defining placental insufficiency-induced IUGR status (ACOG, 2013). This is opposed to either the population-based term small for gestational age (SGA), which refers to infants born <10% on standard intrauterine growth charts, or low birth weight (LBW) at term gestation, which refers to neonates born with a birthweight of <2500 g. Most human epidemiological studies to date use these terms to represent IUGR status. However, it should be noted that these terms will include IUGR neonates as well as those normal neonates born constitutionally small.

Redistribution of blood flow to the vital organs such as the brain occurs at the expense of nutrient and oxygen delivery to the periphery (Tchirikov et al., 1998; Yajnik, 2004) (Fig. 1). These selective reductions in blood flow and oxygen supply to the peripheral musculature likely contribute to 25–40% reductions in muscle mass observed in IUGR fetuses and neonates when compared to their appropriate for gestational age (AGA) counterparts (Baker et al., 2010; Beltrand et al., 2008; Larciprete et al., 2005; Padoan et al., 2004; Yau and Chang, 1993). However, even "brain sparing" is incomplete, as head circumference in IUGR infants is frequently below the 10th percentile for gestational age (Kramer et al., 1989)

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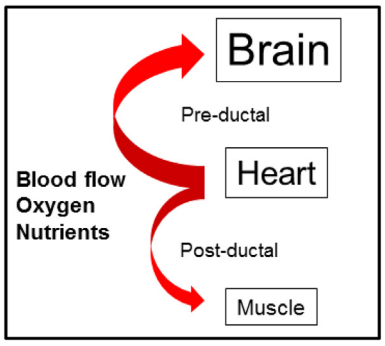

Fig. 1. Redistribution of blood flow in IUGR. Dilation of the ductus venosus and middle cerebral artery shunts oxygen and nutrients from the umbilical vein directly to the heart and brain and away from skeletal muscle (diagram modified from Yajnik, 2004).

with reduced brain volume (Toft et al., 1995) and higher risk of poor neurodevelopmental outcome (Arcangeli et al., 2012; De Jesus et al., 2013; Guellec et al., 2015; von Beckerath et al., 2013).

1.2. Myogenesis

In severe cases of placental insufficiency, onset occurs as early as the second trimester of human pregnancy (De Jesus et al., 2013) with progressive reduction in nutrient and oxygen delivery to the fetus and subsequent development of growth factor deficiencies. Understanding fetal skeletal muscle development (myogenesis) across gestation is important in order to investigate how placental insufficiency and chronic nutrient restriction impact skeletal muscle growth.

Much of what we know about the timing and regulation of myogenesis comes from animal models, notably livestock (sheep, cows) in which the timing of myogenesis is similar to humans (Du et al., 2010; Romero et al., 2013) (Fig. 2). The primary (embryonic) stage of muscle fiber formation occurs by the end to end fusion of myogenic precursor cells into primary myotubes and begins at 0.2 of gestation (Wilson et al., 1992). Primary myotubes form the scaffold for subsequent myotube formation. The secondary (fetal) stage of myogenesis involves rapid proliferation of myoblasts that differentiate and fuse to form multinucleated myotubes and secondary myofibers, beginning at 0.2 of gestation and peaking around 0.6 of gestation (Fahey et al., 2005b). Based on environmental signals, such as insulin like-growth factors (Ren et al., 2010), myoblasts either proliferate for self-renewal or align to differentiate into myotubes (Yan et al., 2013). Pax transcription factors (Pax3, Pax7) in myogenic precursors regulate the progressive expression of highly conserved myogenic regulatory factors (MRFs), including Myf5 and MyoD, which are considered determination factors, and myogenin (MyoG), which signifies terminal differentiation (Bentzinger et al., 2012).

Muscle grows primarily by myofibrillar protein synthesis and hypertrophy of myofibers during the final third of gestation, though this process includes continued proliferation and fusion of myoblasts into established myofibers (McCoard et al., 2001; Stickland, 1981). The postnatal (adult) stage of myogenesis involves maintenance of satellite cells that reside around the muscle fibers in a quiescent state and are activated during muscle growth, regeneration, and repair (Wang et al., 2014; Zammit et al., 2006). The stages of myogenesis are similar among vertebrates, though secondary myogenesis in humans, sheep, and cows occurs earlier in gestation than in rodents (Du et al., 2010) and is more complex with successive generations of myotubes (tertiary) adding to the scaffold (McLennan, 1994; Wilson et al., 1992).

1.3. Impact of placental insufficiency on myoblast proliferation

The concept that chronic fetal undernutrition in utero may disrupt normal myogenesis was introduced over 40 years ago by Elsie Widdowson, a pioneer of child nutrition and growth (Widdowson et al., 1972). Her statements were based on several studies which showed muscle fiber number to be set at birth (Rowe and Goldspink, 1969, Stickland et al., 1975; Widdowson et al., 1972; Wigmore and Stickland, 1983). In a variety of species, maternal nutrient restriction during pregnancy limits fetal myoblast cell cycle activity, reduces myonuclei per myofiber, and reduces myofiber number in offspring (Bayol et al., 2004; Costello et al., 2008; Dwyer et al., 1995, Dwyer and Stickland, 1992, Fahey et al., 2005a, b; Greenwood et al., 1999, 2000; Osgerby et al., 2002; Prakash et al., 1993; Wilson et al., 1988). Though less well studied, placental insufficiency independent of maternal nutrient intake also results in decreased proliferative capacity of fetal myoblasts, as measured by decreased expression of proliferating cell nuclear antigen (PCNA) and reduced rates of replication *in vitro* (Yates et al., 2014).

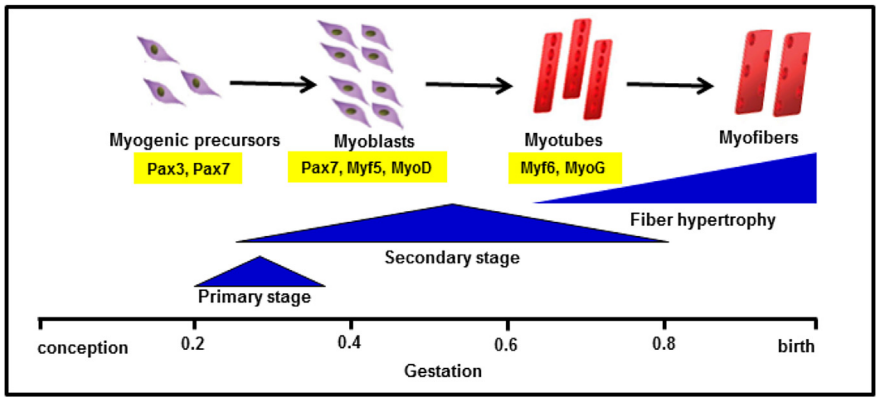

Fig. 2. Schematic representation of fetal myogenesis during pregnancy. The fraction of gestation when primary (embryonic) and secondary (fetal) stages of myogenesis occur are based on studies from sheep, cow, and human (Du et al., 2010; Romero et al., 2013; Wilson et al., 1992). Pax transcription factors Pax3 and Pax7 define the progenitor cell population during fetal myogenesis (Wang et al., 2010). Pax7 is expressed in fetal myoblasts, in addition to Myf5 and MyoD which commit cells to the myogenic program. Myotubes express the terminal differentiation genes Myf6 (also known as Mrf4) and MyoG (Bentzinger et al., 2012). Myofibers grow by hypertrophy late in gestation and in postnatal life.