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Altered biomechanical stimulation of the developing hip joint in presence of hip dysplasia risk factors

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A B S T R A C T

Fetal kicking and movements generate biomechanical stimulation in the fetal skeleton, which is important for prenatal musculoskeletal development, particularly joint shape. Developmental dysplasia of the hip (DDH) is the most common joint shape abnormality at birth, with many risk factors for the condition being associated with restricted fetal movement. In this study, we investigate the biomechanics of fetal movements in such situations, namely fetal breech position, oligohydramnios and primiparity (firstborn pregnancy). We also investigate twin pregnancies, which are not at greater risk of DDH incidence, despite the more restricted intra-uterine environment. We track fetal movements for each of these situations using cine-MRI technology, quantify the kick and muscle forces, and characterise the resulting stress and strain in the hip joint, testing the hypothesis that altered biomechanical stimuli may explain the link between certain intra-uterine conditions and risk of DDH. Kick force, stress and strain were found to be significantly lower in cases of breech position and oligohydramnios. Similarly, firstborn fetuses were found to generate significantly lower kick forces than non-firstborns. Interestingly, no significant difference was observed in twins compared to singletons. This research represents the first evidence of a link between the biomechanics of fetal movements and the risk of DDH, potentially informing the development of future preventative measures and enhanced diagnosis. Our results emphasise the importance of ultrasound screening for breech position and oligohydramnios, particularly later in pregnancy, and suggest that earlier intervention to correct breech position through external cephalic version could reduce the risk of hip dysplasia.

1. Introduction

Fetal movements during pregnancy are a natural part of the development process, and are detectable from 10 gestational weeks using ultrasound (de Vries and Fong, 2006). Sudden changes in fetal movements are known to be a strong predictor of fetal health, particularly approaching term, where decreases in fetal movements have been linked to poor fetal outcomes, such as low birth weight or preterm delivery (Dutton et al., 2012; O'Sullivan et al., 2009), and even stillbirth (Efkarpidis et al., 2004; Whitworth et al., 2011). Fetal movements are also known to play a significant role in normal development of the musculoskeletal system (reviewed in Nowlan, 2015). In cases of neuromuscular disorders with severely reduced or absent fetal movement, patients present with skeletal malformations such as joint fusions, craniofacial abnormalities and hypo-mineralised bones (Aronsson et al., 1994; Rodríguez et al., 1988a; Rodríguez et al., 1988b). Clinical evidence for the importance of fetal movements for skeletal development has been reinforced by studies of animal models, with abnormal joint conditions arising in both immobilised chick embryos and mutant mouse embryos with reduced or absent muscle activity (Kahn et al., 2009; Nowlan et al., 2010a, 2010b, 2014; Roddy et al., 2011). Indeed, a recent bioreactor study demonstrated

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that there is a dose-dependent relationship between movement and joint shape development in the chick embryo (Chandaria et al., 2016). Furthermore, a study of muscle-less mouse embryos observed down-regulation of key developmental regulatory genes in fetal skeletal rudiments when muscle forces were absent (Rolfe et al., 2014). Taken together, this evidence demonstrates that mechanical forces generated by fetal movements are required for normal prenatal musculoskeletal development, especially in the case of joint shape.

A relatively common developmental joint abnormality, observed in approximately 1.3 per 1000 live births, is known as developmental dysplasia of the hip (DDH) (Leck, 2000), and is indicated by instability, malformation or dislocation of the joint formed by the femoral head and the acetabulum of the pelvis (Weinstein, 1987). DDH has major implications for patient health, necessitating use of a harness postnatally, or possibly even surgery, to correct the shape. There are additional long term implications of the condition, as joint shape is strongly linked to risk of osteoarthritis in later life (Sandell, 2012). Despite known genetic risk factors for DDH, such as female gender and positive family history (Homer and Hickson, 2000), the other major risk factors relate to a more restrictive intra-uterine environment for fetal movements. The primary environmental risk factors are fetal breech position (Muller and Seddon, 1953), low amniotic fluid volume (oligohydramnios) (Hinderaker et al., 1994), and neuromuscular disorders (Homer and Hickson, 2000). Furthermore, breech position was recently linked to lower bone mineral content in neonates, persisting in hip up to 4 years of age (Ireland et al., 2018). While not an abnormal intra-uterine condition, primiparous (first-born) pregnancies also carry a significantly greater risk of DDH when compared to subsequent pregnancies (Chan et al., 1997; de Hundt et al., 2012; Stein-Zamir et al., 2008; Yiv et al., 1997), which may be related to greater uterine muscle tone in primiparity (Wilkinson, 1963). Interestingly, despite less available uterine space in twin pregnancies, the incidence of DDH in twins is no higher than in singletons (De Pellegrin and Moharamzadeh, 2010; Dezateux and Rosendahl, 2007). However, little is known of how the biomechanics of fetal movements change with intra-uterine environment or fetal position.

Recent advancements in MRI technology provide a novel method through which movements of an entire fetus can be directly observed, known as cine-MRI scans (Guo et al., 2006; Hayat et al., 2011). By tracking normal fetal movements from this type of scan and by applying a series of computational techniques, including finite element (FE) analysis and musculoskeletal modelling, we previously quantified fetal kick force and associated intramuscular forces for the first time (Verbruggen et al., 2016), and characterised the changes in biomechanical stress and strain in the fetal skeleton over gestation (Verbruggen et al., 2018). In this study, we investigate biomechanical stimuli in the developing hip joint for intra-uterine situations that increase the risk of DDH, as well as for twins, which counterintuitively don't have an increased risk of the condition. We hypothesise that fetal kicking, and the resulting stress and strain in the fetal skeleton, are altered in conditions associated with increased risk of DDH when compared to normal intrauterine conditions.

2. Materials and methods

2.1. Data acquisition

A database of fetal cine-MRI scans acquired from archived data of previous pregnancies at Hammersmith Hospital and St. Thomas' Hospital (both London, UK) was retrospectively analysed for those which included clear in-plane extension-flexion fetal kicks in a range of conditions (Fig. 1). A total of 341 scans from different individuals were examined, of which the following were chosen at 20 weeks gestational age: breech position ($n = 5$) and twin pregnancies ($n = 5$). Two groups of healthy, cephalic singletons ($n = 5$ each) were also analysed at 20 and 30 weeks, with these groups reported in our previous study (Verbruggen et al., 2018). Separately, a group of nine oligohydramnios scans at approximately 30 weeks were obtained, with kick movements observed in three scans ($n = 3$). Scans from each of these conditions can are shown in Fig. 2. Finally, a group of first-born fetuses ($n = 6$) was selected from the larger cohort of 341 scans and compared to a group of second, third or fourth born fetuses ($n = 6$), all at approximately 20 weeks gestational age. All women had given prior consent for scans to be used in research as part of larger ethically approved trials (Hammersmith Hospital Research Ethics Committee/MHRA approval for IEH award 102431).

Separately, post mortem MR scans of fetal leg bones at approximately 20 and 30 weeks gestational age were obtained from the radiology information system (RIS) at Great Ormond Street Hospital (London, UK), as detailed previously (Verbruggen et al., 2018). The sample sizes and controls used for each intra-uterine situation under investigation are described in Table 1.

2.2. Computational methods

Stress and strain in the fetal skeleton were quantified using a previously developed computational pipeline, as shown in Fig. 1. Firstly, the movements of individual joints *in utero* were tracked from cine-MR scans. Uterine dimensions and uterine wall deflection due to fetal kicking were also measured. Secondly, the reaction force generated by a fetal kick against the uterine wall was calculated using an FE model of the intra-uterine mechanical environment (Verbruggen et al., 2017). Thirdly, these results were applied as inputs for a scaled musculoskeletal model of the fetal lower limb developed in OpenSim (Version 2.4) (Delp et al., 2007; Verbruggen et al., 2016, 2018), with muscle forces outputted from OpenSim alongside their lines of action (van Arkel et al., 2013). Finally, the biomechanical stimulation (i.e. stress and strain) of the fetal lower limb during kicking *in utero* was predicted using a pair of FE models of the fetal leg bones at 20 and 30 weeks gestational age, generated from post-mortem MR scans, as described previously (Verbruggen et al., 2018). Stress and strain values within the hip joint (proximal femur and acetabulum) were recorded as the 95th percentile values.

2.3. Statistical analysis

Depending on uterine condition and availability of data, three (oligohydramnios), five (breech, healthy cephalic) or six (first-born, non-firstborn) cine-MR scans were analysed. The predicted muscle forces for each cine sequence were then applied to two fetal skeletal geometries, resulting ($n = 6$, 10 or 12 data points per group). All data are expressed as mean ± standard deviation. Normality was checked and statistical differences between groups were determined using an ANOVA analysis and a Tukey's post-hoc test, with statistical significance defined as $p < 0.05$ (SPSS, IBM, New York, U.S.).

3. Results

The findings of the current study are described by intra-uterine situation in this section. The average fetal femur and tibia lengths, uterine dimensions and kick durations for each scenario are given in Table 2.

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