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Comparing a fetus diagnosed with Prader-Willi-syndrome with non-affected fetuses during light and sound stimulation using 4_D_ultrasound

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"Just wondering if the fact he didn't react much was a sign of his low muscle tone or if was typical across the board with other babies too? I thought he was just lazy." (Mother of a PWS infant recalling her experience during ultrasound see Fig.1).

Prader-Willi syndrome (PWS) is a complex neuro-genetic disorder with estimated prevalence varying from 1 in 10,000 to 1 in 30,000 [1] with an equal number of males and females affected. A study of the incidence of PWS in France[2] reported thirty-eight infants were diagnosed at a median age of 18 days post birth. None of the cases were identified prenatally. The condition is complex[3] with fetal PWS phenotype including fetal hypo-mobility, polyhydramnios, intra-uterine growth restriction, and immobile flexed extremities with clenched hands or fists, symptoms which are not exclusively

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pathognomonic to PWS. Developmental characteristics associated post birth with PWS include significant cognitive and behavioural abnormalities. [1] Criteria which might identify PWS prenatally are nonspecific and can also be present in premature births not affected by PWS. . It is extremely important to find specific features alerting clinicians to the need for additional genetic testing.

In the present case study we examined the movement profile for a fetus postnatally diagnosed with PWS, and compared this movement profile to a non-affected group of fetuses. Our hypothesis is that assessing the rate of fine grained fetal movements will help to draw attention to differently behaving fetuses and therefore facilitate early diagnosis and immediate treatment. We examined these movements when fetuses were stimulated cross modally with sound and light. Our rationale is twofold: 1) prior research[4] has found that sound and light stimulation increases reactions in normally developing fetuses, and hence is an optimal condition for observing fetal facial reactions; 2) fetal reactions to stimulation can be interpreted as precursors of neurocognitive functioning[5] and muscle tone and, given the established neurocognitive deficits and hypotonia in PWS children, fetal reactions to stimulation are hypothesized to differ prenatally.

Participants were an opportunity sample of 23 healthy pregnant women, not on medication with healthy singleton fetuses, as assessed at their 20-week anomaly scan. All mothers were Caucasian, coming from the same catchment area in the North East of England and gave their fully informed written consent. Ethical permission was granted by Durham University (Dept of Psychology ethics committee; N Reissland 14/51). The PWS case was a male fetus scanned at 32 weeks, who had been assessed as healthy at the 20-week anomaly scan, with gestation at birth 36.5 weeks and Apgar scores of 8 at 1 min and 9 at 5 mins. The case was diagnosed after birth as PWS with deletion of part of chromosome 15. The PWS fetus was compared to a group of 22 healthy fetuses (9 boys, 13 girls), mean age at scan 32.3 weeks (range 31.5 and 34.5 weeks); gestation at birth mean age 40.2 weeks (range 38.1 and 42.5 weeks).

The stimuli applied consisted of light and sound visible and audible to fetuses at the ages observed gestation (see[4] for a detailed description of the stimuli and coding). The 4D ultrasound scans were then coded offline using the Fetal Observable Movement System[4] and Coders were blind to case-control status. Reliability tests were carried out by independent coders on 10% of observations with Cohen's Kappa mean = 0.93 (range 0.66 -0.99).

For each fetus we calculated the total number of mouth movements over the observation period divided by the total length of the codable scan resulting in the mean rate of mouth movement per minute of scan for each fetus. We examined these means both graphically and by using an independent samples t-test between the single case and the control group, after transforming to normality. Because a single case does not allow us to calculate a variance, we assumed the variance in the case and control groups to be equal. This provided a method to test whether the case observation was different to the reference group. The PWS fetus showed a rate per minute of 0.375 mouth movements compared with controls (female mean 7.37 rate; range 1.864- 14.03; male mean 9.49; range 4.62- 17.44). Mean observable fetal scan times for the male (602.17 seconds) and female (716.72 seconds) fetuses were slightly shorter than for the PWS case (798.82 seconds).

We then tested the difference between the case rate 0.37 and the control rate mean. A quantile plot of the rates showed non-normality of the control rate distribution therefore the rates were log- transformed. The independent samples t-test ($t= -5.543$, 21 df ($p<0.001$) indicates that the mouth movement rate for the PWS case is not consistent with the control distribution.

In summary, the current study is the first analysing the behavioural profile of a PWS fetus stimulated with sound and light. Results demonstrate significant behavioural differences between the PWS fetus and the control group in reaction to sound and light stimulation. This type of stimulation could serve as a prenatal test to indicate a differently developing fetus who needs additional attention, and prepare parents for the possible unfavourable outcome of the current pregnancy. The present study comparing a fetus affected by PWS and a non-affected group of fetuses during cross-modal

stimulation supports the hypothesis that the behavioural profile, could serve as an indicator that further genetic tests would be warranted.. Not only is recognition of the differently developing fetus is essential, since early diagnosis allows early intervention, it also might help parents to prepare and come to terms with a condition which has been reported to result in elevated parental stress levels. In this case study we tested one PWS fetus stimulated by light and sound against a group of healthy fetuses who had been exposed to the same stimuli. Future research needs to elucidate whether our findings of markedly different reactions to sound and light stimulation in the PWS fetus might serve as an universal marker to alert clinicians of possibly unfavourable outcome of the current pregnancy.

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Conflict of Interest:

None

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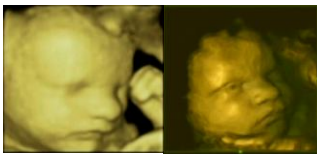
Fig 1 Comparison of Prader-Willi-Syndrome case and healthy fetus
32 weeks gestation



PWS | Healthy