Oral Presentations

1.1 NON-INVASIVE PRENATAL TESTING USING CELL FREE FETAL DNA IN MATERNAL PLASMA: AN AID TO PRENATAL SONOGRAPHIC DIAGNOSIS

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Cell free fetal DNA (cffDNA) circulates in low concentration in maternal plasma and is a source of genetic material for safe non-invasive prenatal testing (NIPT). It is in routine use in the UK for fetal *RHD* determination in RhD- mothers, for fetal sex determination in pregnancies at risk of sex-linked disorders and for some single gene disorders. In the US and UK private sector, it is used for aneuploidy testing in high risk women.

We reviewed all cases in our unit where NIPT had been requested to help with interpretation of unexpected sonographic findings and identified 16 cases (see Table).

Abstract 1.1 Table

Sonographic findings	N	Gene	Final Diagnosis
*Short ribbed skeletal dysplasia	4	FGFR3	Thanatophoric dysplasia (TD) (4)
3rd trimester short long bones	10	FGFR3	Achondroplasia (5), IUGR (5)
Abnormal skull and hands	1	FGFR2	Apert syndrome
Bowed femurs, female genitalia	2	SRY	Male fetus with campomelic dysplasia (2)
Multiple anomalies, abnormal genitalia	1	SRY	Smith Lemli Optiz syndrome
Bladder exstrophy	1	SRY	Male with bladder exstrophy
Ambiguous genitalia	1	SRY	Severe hypospadias

Use of NIPT allowed us to come to a definitve diagnosis without jeopardising the pregnancy in several fetuses with skeletal anomalies, and was particularly useful in the two sets of twins* discordant for TD. Determining fetal genetic sex informed the diagnosis and/or aided counselling in five cases.

Those offering sonographic diagnosis should be conversant with NIPT, particularly as the scope of this new and safer testing is increasing with technological developments and access to next generation sequencing.

1.2 AN ENHANCED, MIDWIFERY-LED ULTRASOUND SERVICE TO MONITOR FETAL GROWTH

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Objective Antenatal detection of intrauterine growth restriction (IUGR) is a key objective of maternity care. In 2009, 4 in 5 babies in Birmingham born with an SGA birthweight were not recognised as such antenatally, and most high-risk mothers were afforded only one third trimester scan. We set out to improve detection through an enhanced ultrasound screening service for higher risk mothers.

Methods The Community Growth Scanning service (CoGS, www.pi.nhs.uk/cogs) was established in clinics staffed by midwives trained in 3rd trimester ultrasound. Standardised protocols were agreed with all clinicians, for women requiring scans following abnormal fundal height measurement, or for serial scanning because of increased risk of IUGR. The new service started in Summer 2010 and evaluation included all women who attended and delivered by the end of Dec 2011.

Results 2,583 women were referred during the study period. The majority (57.1%) were for serial scans and constituted 79.7% of scans undertaken. High-risk mothers were more likely to receive serial scans (mode: 4 scans, 68.3% having 3+), compared to the 2009 baseline (mode: 1 scan; 73% had less than 2). Compared to a background SGA rate of 13.1%, the prevalence in mothers referred for serial ultrasound was 26.2%, with an antenatal detection rate of 47.7% (CI 42.7–52.7%). There were two perinatal deaths of normally formed IUGR babies within this cohort (0.8/1,000 births, CI 0.0–1.8).

Conclusion Enhanced provision of ultrasound resources to mothers at increased risk results in significant improvements in antenatal detection of IUGR.

1.3 DNA METHYLATION OF SOMATOTROPIC AXIS GENES IN RELATION TO POSTNATAL GROWTH AND METABOLISM FOLLOWING AD.VEGF TREATMENT OF GROWTH-RESTRICTED SHEEP FETUSES

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Introduction We previously showed that adenovirus (Ad) mediated overexpression of vascular endothelial growth factor (VEGF) in the uteroplacental circulation increases fetal growth velocity in the overnourished adolescent sheep paradigm of fetal growth restriction[1,2]. Lambs born following Ad.VEGF therapy also demonstrated accelerated lean tissue accretion and enhanced insulin secretion following glucose challenge[3]. Herein we examined for putative epigenetic changes underlying these postnatal effects by quantification of methylation at cytosine:guanine (CpG) dinucleotides.

Methods DNA was extracted from liver samples obtained at 82 ± 0.2d postnatal age in 29 lambs born after prenatal treatment with Ad.VEGF (n = 16: 8 × Male/8 × Female) or Saline (n = 13: 7 × Male/6 × Female). After incubation with sodium bisulphite, PCR was performed using custom-designed primers targeting 9 CpG islands across 5 genes: insulin, growth hormone, insulin-like growth factor (IGF)1, IGF2 and H19. Using pyrosequencing, methylation status was determined by quantifying cystosine:thymine ratios at 35 individual CpG sites. Plasma IGF1/insulin levels were measured by RIA.

Results There were no significant differences in DNA methylation between Ad.VEGF and Saline groups, except at 1 of 4 CpG dinucleotides preceding IGF2 exon-6 (3.8 ± 0.59 vs. 1.9 ± 0.60%, p = 0.029). Irrespective of treatment, insulin gene methylation was greater in males than females (88.7 ± 0.23 vs. 87.0 ± 0.50%, p = 0.007) and negatively correlated with fasting insulin levels (r = –0.431, n = 28, p = 0.022). By contrast, IGF1 methylation tended to be lower in males than females (84.3 ± 0.16 vs. 84.8 ± 0.22%, p = 0.053) and was unrelated to plasma IGF1 levels.

Conclusion Increased postnatal growth rates in Ad.VEGF-treated lambs most likely reflect their relative size advantage at birth rather than altered epigenetic status of key somatotropic genes.

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