CHIEF SCIENTIST OFFICE

CODE: PCL/21/05

RESEARCH PROJECT BRIEFING

Cardiovascular risk in early onset hypogonadism

AIMS

Over 1 in 300 baby boys are born with hypospadias, a condition where the opening for passing urine is not at the tip of the penis. This occurs because of low levels of the male hormone testosterone during early development (also known as early onset hypogonadism). Boys born with hypospadias may be at increased risk of high blood pressure and poor heart and blood vessel (vascular) health as they grow up. It is not known why this is the case although it may be due to a build of up of unstable molecules (free radicals) in the body (oxidative stress). Currently these boys and men are not routinely follow-up after their surgical repairs.

To be able to improve clinical care and long-term health for such children, this project aimed to:

1) identify those at greatest risk of early blood vessel problems
2) investigate whether oxidative stress also increases the risk of surgical complications after the hypospadias is repaired

KEY FINDINGS

- Up to 20% of males with early onset hypogonadism have high blood pressure at clinic.
- Boys with other forms of early onset hypogonadism, such as Klinefelter Syndrome (an XXY karyotype), also have evidence of pre-clinical early blood vessel problems.
- Treatment with antioxidants (medications to lower the number of free radicals in the body) improves wound healing in skin cells from boys with hypospadias.

WHAT DID THE STUDY INVOLVE?

This project involved 3 studies:

1) Project 1: Blood pressure in boys with Differences of Sex Development

Assessing blood pressure readings from individuals with a male karyotype via review of routinely collected global clinical data using international collaboration with the International Registries for Rare Conditions Affecting Sex Development and Maturation (sdmregistries.org).

2) Project 2: The vascular phenotype in children with early onset hypogonadism

Inviting boys with hypospadias and Klinefelter Syndrome, as 2 separate models of early onset hypogonadism, as well as healthy boys, to attend for a clinical visit to see if blood vessel problems are due to low testosterone early in life and not secondary to whatever has caused the hypospadias. Assessments included blood pressure (BP), carotid intima media thickness ((CIMT) for fat in the blood vessels), pulse wave velocity (for stiff blood vessels) and flow mediated dilatation (FMD) for blood vessel function).

3) Project 3: The role of antioxidants in wound healing in hypospadias

Measuring wound closure rates and cell proliferation in genital skin cells in the presence and absence of antioxidants.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

1) Project 1: Blood pressure in boys with XY DSD

In total BP readings from 208 individuals with 46,XY DSD were available from 22 centres worldwide. Of these, 77 (37%) cases ≥16 years of age. In total, 10% of the adults and 20% of the children had high clinic BP. This was not associated with other risk factors for high BP such as gestation at birth or birthweight and there were no clear predictors regarding who would have high BP. These rates are higher than you would expect normally.

2) Project 2: The vascular phenotype in children with early onset hypogonadism

Twenty-two boys with conditions associated with hypogonadism and 11 healthy controls (average age 14.5 yrs) were recruited. Blood pressure was higher in boys with early onset hypogonadism compared to controls. CIMT and pulse pressure were also increased in boys with early onset hypogonadism compared to controls, showing that there was more fat in the blood vessels and the vessels were stiffer, both of which are risk factors for cardiovascular disease. There were no differences in body mass index or blood vessel function. Boys with early onset hypogonadism had evidence of high levels of oxidative stress in their urine.

3) Project 3: The role of antioxidants in wound healing in hypospadias

Twenty four boys with hypospadias and 28 controls (average age 1.7 yrs to coincide with timing of surgical procedures) were recruited. Cells from boys with hypospadias did not move and regenerate as well as cells from controls. This correlated with how severe their hypospadias phenotype was. Exposure to antioxidants improved wound closure and cell regeneration.

WHAT IMPACT COULD THE FINDINGS HAVE?

- Through highlighting the increased risk of early problems with blood vessel and heart health, these projects should encourage the assessment of blood pressure and cardiovascular risk factors in boys and men with early onset hypogonadism, changing clinical care to reduce future health burden.
- This project also demonstrates that antioxidants may represent a therapeutic target to reduce surgical complications in boys with hypospadias, pending further translational research. It also leads to the question of whether antioxidants may help other issues in hypospadias too, so may result in future studies in this field.

HOW WILL THE OUTCOMES BE DISSEMINATED?

These results have been presented at national and international meetings in 2024 including ENDO in Boston, USA; the European Society for Paediatric Urology in Naples, Italy, the International Disorders of Sex Development Symposium in Stockholm, Sweden and the European Society for Paediatric Endocrinology in Liverpool, UK. In addition, they have been discussed to patients and their families at a West of Scotland family day for boys with hypospadias.

The first manuscript is now available in the Journal of Pediatric Urology (PMID: 40133121) with further manuscripts under peer review for publication.

CONCLUSION

Boys and men born with hypospadias are at increased risk of certain conditions long-term including impaired wound healing and hypertension. There is a need therefore to ensure affected individuals have long-term follow-up into adulthood so that any complications are identified and managed accordingly.

RESEARCH TEAM & CONTACT

Dr Angela Lucas-Herald
Developmental Endocrinology Research Group
University of Glasgow, Glasgow, UK

Angela.lucas-herald@glasgow.ac.uk

Additional Information
NES/CSO Clinical Lectureship funded August 2021-2024