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THE FETAL ORIGINS HYPOTHESIS IN TWIN
CHILDREN: A METABOLIC EVALUATION

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ABSTRACT

This thesis explores whether low birth weight affects glucose homeostasis and other aspects of the metabolic syndrome in twin children. The key parameter studied is insulin resistance, and whether insulin resistance is also associated with abnormalities in blood pressure or other aspects of the metabolic syndrome. This thesis is a comparison of twins to singletons, rather than being a study of these traits within twin pairs.

The fetal origins hypothesis suggests that low birth weight ultimately is associated with adult onset diseases namely coronary heart disease, glucose intolerance and hypertension. All twins to a degree are born prematurely and with low birth weight. It is unclear whether their metabolism in later life reflects this, or alternatively reflects their uniqueness as twins irrespective of birth weight. This thesis reviews how adaptation for their unique fetal life has affected in particular, glucose homeostasis in twins.

Insulin resistance has been consistently identified prior to the onset of both type 2 diabetes mellitus and hypertension and is also the primary metabolic abnormality persisting from programming of the undernourished fetus. Both small-for-gestational-age and prematurely born infants are insulin resistant when examined in mid-childhood. It has been postulated that this represents an attempt of the fetus to salvage itself from a state of inadequate nutrition. Twins when examined in this thesis are also shown to be insulin resistant, or to have a reduction in insulin sensitivity. This insulin

resistance was independent of low birth weight and prematurity, and reflected a unique twin effect.

Examining blood pressure precisely revealed that twins had increased night-time blood pressure, a feature also seen in a variety of pre-hypertensive states. However, there was no association between low birth weight and any 24 hour blood pressure monitoring parameter in twins. Twins also had elevated leptin levels but reduced TNF-alpha levels in twins irrespective of birth weight or prematurity.

Twins have unique metabolic profiles which are not correlated with low birth weight, and twins should be considered an exception to the fetal origins hypothesis.

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AUTHOR'S PUBLICATIONS

The chapters of this thesis are based on the following publications.

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Jefferies CA, Hofman PL, Wong W, Robinson EM, Cutfield WS. Increased nocturnal blood pressure in healthy pre-pubertal twins. *J Hypertens* 2003; 21:1319; 21:1319-24.

Jefferies CA, Hofman PL, Keelan, JA, Robinson, EM, Cutfield WS. Insulin resistance is not due to persistently elevated serum tumour necrosis-alpha levels in small for gestational age, premature, or twin children. *Pediatr Diabetes*. 2004 Mar; 5(1):20-5.

Jefferies, CA, P Hofman, W Cutfield, *Starship Children's Hospital, New Zealand*. Book Chapter 3. Fetal Influences on Insulin Resistance in “Insulin Resistance in Children and Adolescents”. Editors: Denis Daneman and Jill Hamilton (The Hospital for Sick Children, University of Toronto) 2005. NOVA SCIENCE PUBLISHERS, INC.

Awards arising from these works.

- Jefferies C. Twin pressure on the fetal origins hypothesis. Royal Australasian College of Physicians and Paediatric Society Meeting, Auckland October 2001.

Winner of the RACP Young Investigator Award, 2001 Auckland, New Zealand

- Jefferies C. Pre-pubertal Twin Children are Insulin Resistant. Royal Australasian College of Physicians and Paediatric Society Meeting, Auckland October 2001.

Winner of the Paediatric Society Young Investigator Award 2001, Auckland, New Zealand.

- Jefferies C. Australasian Paediatric Endocrine Group (APEG) award 2000. Twins are insulin resistant.

Winner of the Young Investigator Award, November 2000, Sydney, Australia.

AUTHOR'S CONTRIBUTIONS

Chapter 4

I assisted in study design, attended the ethics application meeting and wrote the changes/rebuttals required, met with contacts from the New Zealand Multiple Birth Association and recruited all the subjects. I wrote and designed the successful grant which funded the study, performed the majority of the FSIGT tests and insulin assays, analysed the data with the biostatistician, and wrote the manuscript and rebuttal for successful publication.

Chapter 5

I wrote the successful grant for the ABPM monitors and recruited all the subjects. Programmed the ABPM cuffs, downloaded the traces, analysed the results with the biostatistician, and wrote the submission and rebuttals for successful publication.

Chapters 6& 7

I was involved in study design, sourcing of the TNF-alpha kits and liaising with the scientist to perform the assays, analysed the data with the biostatistician, and wrote the submission and rebuttals for successful publication. I sourced the leptin kits and organised the Auckland Hospital laboratory to perform the assays.

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ABBREVIATIONS

AIR	Acute Insulin Response
ABPM	Ambulatory Blood Pressure Monitoring
BMI	Body Mass Index
BP	Blood Pressure
DZ	Dizygotic
FOH	Fetal Origins Hypothesis
FSIGT	Frequently Sampled IV Glucose Tolerance Test
IUGR	Intrauterine Growth Retardation
K_G	Glucose Disposal Coefficient
MODY	Maturity Onset of Diabetes in the Young
MZ	Monozygotic
OGTT	Oral Glucose Tolerance Test
PPARγ	Peroxisome Proliferator Activated Receptor γ
SDS	Standard Deviation Score
SGA	Small-for-Gestational Age
S_G	Glucose effectiveness
S_I	Insulin Sensitivity
T2DM	Type 2 Diabetes Mellitus
TNF-α	Tumour Necrosis Factor Alpha
TTTS	Twin-Twin-Transfusion-Syndrome