Intrauterine Influences on Obesity and Insulin Resistance in Pre-pubertal Children

Oana Maftei

M.D., F.Rom.C.P.

Discipline of Public Health, School of Population Health and Clinical Practice

Discipline of Obstetrics and Gynaecology, School of Paediatrics and Reproductive Health

Faculty of Health Sciences, University of Adelaide

Australia

December 2011

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

“Truth lies all around us, but is only revealed to those who search for it.”

Nicolae Iorga (1871-1940)

This thesis is dedicated to my mother for her immense love, trust, support and encouragement not only through the PhD candidature years, but throughout my entire life. I have learnt from her wisdom that giving anything less than all I could give meant sacrificing a gift.

Table of contents

List of tables

List of figures

Abstract

Within the paradigm of developmental origins of health and disease, an intrauterine environment that stimulates fetal overnutrition has been found to contribute to the risk of subsequent obesity in the offspring. There is compelling epidemiological evidence for a positive association between maternal obesity prior to pregnancy, gestational diabetes (GD) or excessive gestational weight gain, and the development of childhood obesity (as measured by body mass index, BMI). However, the evidence is limited and inconsistent with respect to more specific measures of adiposity (body composition or fat pattern) and insulin resistance in children. Furthermore, the long-term effects of maternal borderline gestational glucose intolerance (BGGI) on the offspring have not been considered.

Therefore, I sought to examine whether maternal obesity prior to pregnancy, gestational glucose intolerance across the entire spectrum, and gestational weight gain have deleterious effects on the development of obesity (both global and specific measures of adiposity) and insulin resistance in pre-pubertal children. These associations are particularly important from a public health perspective as, once identified, they may point towards potential windows for prevention of childhood obesity and related metabolic disorders.

This project entailed a follow-up of an existing representative, prospective birth cohort study (Generation 1 Study, n=557) in Adelaide, South Australia, recruited during 1998-2000. At the 9-10 year follow-up, rigorous anthropometric measurements were conducted in 443 children (80% of the original cohort), of whom 163 consented to provide a fasting blood sample for the estimation of insulin resistance based on homeostasis model assessment (HOMA-IR). Information on intrauterine exposures and confounders was collected from the antenatal interviews and hospital records. Maternal age, parity, smoking, pregnancy-induced hypertension, and education at the time of pregnancy were considered as potential confounders for all the associations of interest, and child current BMI z-score as a potential mediator on the pathway between the intrauterine exposures and child insulin resistance. Data were analysed using multiple linear regression and generalized linear models.

Maternal pre-pregnancy BMI was positively associated with all three obesity-related measures considered in the 9-10 year-old children (BMI z-score, percentage body fat estimated by bioelectrical impedance analysis, and waist-to-height ratio); these relationships were robust to adjustment for potential confounders (adjusted coefficients for each one kg/m^2 increase in maternal pre-pregnancy BMI were 0.08 (95% confidence interval 0.06, 0.10) for child BMI z-score, 0.44 (95% CI 0.31, 0.58) for percentage body fat and 0.002 (95% CI 0.002, 0.003) for waist-to-height ratio). There was no association between maternal pre-pregnancy BMI and HOMA-IR in children (with or without adjustment); however, when child current BMI z-score was included as a mediating variable, the relationship between maternal pre-pregnancy BMI and child HOMA-IR was inverse and significant (adjusted change in child HOMA-IR for each one kg/m^2 increase in maternal pre-pregnancy BMI was -0.83% (95% CI -1.63, -0.02)).

Intrauterine exposure to glucose intolerance during pregnancy (either BGGI or GD) was not associated with any of the three obesity-related measures in children at 9-10 years. Children of mothers who developed GD during the index pregnancy had a higher HOMA-IR; this relationship was robust to adjustment for potential confounders (adjusted change in child HOMA-IR if exposed to maternal GD was 42.9% (95% CI 20.9, 68.9)) and partly mediated by child current BMI z-score. No association was found between exposure to maternal BGGI and child HOMA-IR (with or without confounder adjustment); however, when child current BMI z-score was added as a potential mediator, exposure to BGGI was associated with a reduction in child HOMA-IR (adjusted change in child HOMA-IR if exposed to maternal BGGI was -17.9% (95% CI -29.9, -3.96)).

There were no significant associations between maternal gestational weight gain and any of the outcome measures of interest in unadjusted models. However, adjustment for pre-pregnancy BMI led to a positive association between gestational weight gain and child BMI z-score (adjusted changes in child BMI z-score for each one kg increase in maternal gestational weight gain was 0.032 (95% CI 0.007, 0.057)). Gestational weight gain was not associated with child insulin resistance, and this did not change when child current BMI z-score was included as a potential mediator on the pathway between gestational weight gain and child insulin resistance.

Potential two-way interactions between the main exposures were investigated in relation to all outcomes of interest. Two significant interactions were identified: maternal pre-pregnancy BMI and glucose tolerance status, and maternal pre-pregnancy BMI and gestational weight gain, with a synergistic effect on child waist-to-height ratio.

These results suggest that childhood obesity and insulin resistance have origins, at least in part, in intrauterine life, particularly in relation to maternal obesity at the time of pregnancy and GD. Further research to differentiate between genetic, environmental and intrauterine programming is recommended. That said, maternal pre-pregnancy BMI was the strongest predictor of child BMI z-score, while GD appeared to have an independent effect on child insulin resistance, and both clinical and public health actions to address these maternal factors are warranted for a range of reasons.

Declaration

I, Oana Maftei certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Oana Maftei Date: 21 December 2011

Acknowledgements

It goes without saying that the research detailed in this thesis could never have occurred, had it not been for the innumerable contributions of my supervisors, colleagues, study participants, friends and family.

I owe an immense debt of gratitude to Associate Professor Vivienne Moore, primary supervisor, who was willing to accept into her research group an overseas, head-strong Paediatrician with no experience in epidemiological research and biostatistics. I thank her for her patience in guiding me through important stages of the project, for supporting my professional development and for allowing me a great deal of independence, which I have come to value with time. Not only has her vast knowledge in so many and diverse areas of public health been an inspiration for me, but also her personal kindness.

Dr Melissa Whitrow, one of my co-supervisors, deserves a big thank you for providing feedback on all the drafts of this thesis. I have appreciated her structured way of thinking and her attention to detail.

Associate Professor Michael Davies, my other co-supervisor, has been of invaluable assistance, particularly with the theoretical underpinning of this project, stimulating critical conversations and providing feedback on the drafts of the thesis. I have admired his enthusiasm to discuss any aspects of reproductive epidemiology.

Thanks are also due to Kendall Smith, study co-ordinator, for her dedication in facilitating access to the cohort families, who were always welcoming. None of this project could have been conducted without the commitment of the families and their willingness to contribute to research, despite their busy and complicated lives. I am also thankful to the other fieldwork members (Stephanie Champion, Trish Malbon, Deb Roffe and Amanda Hillgrove) for their contribution to data collection. I thank Dr Miles DeBlasio for running the blood assays necessary for this research.

Special thanks go to Professor Phil Ryan, whose clarity in teaching biostatistics and ability to simplify complex statistical issues enabled me to conduct the analyses presented in this thesis. I gratefully acknowledge Dr Lynne Giles for backing up some of the statistical analyses contained in this thesis and also Suzanne Edwards for data cleaning and imputation of some missing data. My colleagues in the Life course and Intergenerational Health research group, all extraordinary people, Dr Emily Steele,

Dr Alice Rumbold, Dr Jennifer Marino, Dr Wendy March, and Malinda Steenkamp have contributed by constant emotional support.

I am indebted to Maria Gardiner, for mentoring me in the last year of my candidature, hence 'turbocharging' the writing of this thesis. I will always remember her words: 'writing is critical thinking'. I thank other current PhD students for their friendship and for valuable feedback on several drafts obtained from those involved in the Thesis Writing Group.

My gratitude also extends to Dr Alexia Pena, who was extremely generous in offering me a part time job in a clinical research project, believed in me at challenging times when not many other people did and encouraged me to follow my dreams despite my disillusions. Her 'can-do' attitude contributed considerably to finalising this project within a reasonable timeframe. I am likewise grateful to my best friend, Crina for her constant support.

I also acknowledge the University of Adelaide for granting me the Adelaide Scholarship International, which allowed me to have a decent life throughout my candidature.

For what I am today, I owe enormous gratefulness to my parents, Elena and Ion, for embodying in me the virtues of scholarship and for educating me to put my dreams into action in order to become successful in life. My greatest debt of appreciation is owed to my husband Bob, whose love, care, thoughtfulness and understanding empowered me to finalise this research. I cannot imagine how impoverished my existence would be without him.

Abbreviations and acronyms

%BF	percentage body fat
ACHOIS	Australasian Carbohydrate Intolerance Study in Pregnancy
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
ADIPS	Australasian Diabetes in Pregnancy Society
ALSPAC	Avon Longitudinal Study of Parents and Children
BGGI	borderline gestational glucose intolerance
BIA	bioelectrical impedance analysis
BMI	body mass index
BW	birth weight
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CT	computed tomography
DXA	dual energy X-ray absorptiometry
EPOCH	Exploring Perinatal Outcomes among Children
FFM	fat-free mass
FGIR	fasting glucose-to-insulin ratio
FM	fat mass
FSIVGTT	frequently sampled intravenous glucose tolerance test
FTO	fat mass and obesity associated gene
GD	gestational diabetes
GLM	generalised linear model
GWG	gestational weight gain
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA1c	haemoglobin A1c
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
IGF	insulin-like growth factor
IGT	impaired glucose intolerance
IL	interleukin

IOM	Institute of Medicine
IOTF	International Obesity Task Force
IQR	interquartile range
IR	insulin resistance
LDL	low-density lipoprotein
LMS	lambda-mu-sigma
MRI	magnetic resonance imaging
NDDG	National Diabetes Data Group
NGT	normal glucose tolerance
NZSSD	New Zealand Society for the Study of Diabetes
OGCT	oral glucose challenge test
OGTT	oral glucose tolerance test
OR	odds ratio
PAR	population attributable risk
PCOS	polycystic ovarian syndrome
QUICKI	quantitative insulin sensitivity check index
r	Pearson's correlation coefficient
RCT	randomised clinical trial
RR	relative risk
SD	standard deviation
SES	socio-economic status
SFT	skinfold thickness
TBW	total body water
TNF	tumour necrosis factor
TAFE	Training and Further Education
WHO	World Health Organization
WHtR	waist-to-height ratio

Conference presentations

1. **Maftei O**, Whitrow MJ, Moore VM, Davies MJ. *Intrauterine influences on offspring obesity in prepubertal children* - oral presentation, 7th World Congress on Developmental Origins of Health and Disease, Portland, Oregon, USA, 18-21 September 2011

2. **Maftei O**, Whitrow MJ, Moore VM, Davies MJ. *Intrauterine influences on insulin resistance in prepubertal children* - oral presentation (ranked in top 10%), 7th World Congress on Developmental Origins of Health and Disease, Portland, Oregon, USA, 18-21 September 2011

3. **Maftei O**, Whitrow MJ, Moore VM, Davies MJ. *Insulin resistance in prepubertal children in relation to intrauterine exposure to overnutrition* - oral e-poster presentation, 52nd Annual Meeting of the European Society for Paediatric Research, Newcastle, UK, 14-17 October 2011