Factor V Leiden and adverse pregnancy outcome

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BMed FRACP

A thesis submitted for the degree of Doctor of Philosophy

School of Medicine and Public Health

Faculty of Health

University of Newcastle

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Declaration

The thesis 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 hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written word statement from each co-author; and endorsed by the Faculty Assistant Dean Professor John Rostas ,attesting to my contribution to the joint publications.

Tracy Dudding

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Publications included as part of thesis

Dudding TE, Attia J. The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis. Thromb Haemost. 2004 Apr; 91(4):700-11.

Attia J, Dudding T, Infante-Rivard C. Addendum to: The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis. Thromb Haemost. 2004 Aug; 92(2):434. No abstract available.

Dudding T, Heron J, Thakkinstian A, Nurk E, Golding J, Pembrey M, Ring SM, Attia J, Scott RJ. Factor V Leiden is associated with pre-eclampsia but not with fetal growth restriction: a genetic association study and meta-analysis. J Thromb Haemost. 2008 Nov; 6(11):1869-75.

Dudding TE, Attia J. Maternal factor V Leiden and adverse pregnancy outcome: deciding whether or not to test. J Matern Fetal Neonatal Med. 2011 Aug 19. [Epub ahead of print]

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I, John Attia, attest that Research Higher Degree candidate Dr Tracy Dudding contributed the following to the publication entitled 'The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis'.

Contributions:

- Literature review
- Data extraction
- Meta-analysis under the supervision of Professor John Attia
- Primary writing of the prepared manuscript under the supervision of Professor John Attia

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Contributions:

- Manuscript concept and objectives
- Literature review
- Primary writing of the prepared manuscript under the supervision of Professor John Attia

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Table of Contents

Abstract

Intrauterine fetal death, fetal growth restriction (FGR) and pre-eclampsia are major causes of fetal and maternal morbidity and mortality; and placental insufficiency is frequently proposed as the most important underlying mechanism. Given the importance of establishing and maintaining an adequate placental circulation, hereditary thrombophilias are postulated as a possible cause of placental insufficiency. Despite initial reports supporting an association between factor V Leiden (fVL) and adverse pregnancy outcomes, a number of other studies yielded conflicting results. A systematic review and meta-analysis of the literature up to January 2003 was undertaken to address the question of whether the common maternal fVL genotype is associated with an increased risk of adverse pregnancy outcomes (pre-eclampsia, fetal growth restriction and fetal loss). Subsequent meta-analyses were also evaluated. To address the shortfalls observed in the large number of small and possibility underpowered case-control studies, a decision was made to undertake a large nested case-control study within the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. The aim of this study was to evaluate the association between: 1) maternal fVL and intrauterine fetal death, fetal growth restriction and pre-eclampsia; 2) fetal fVL and intrauterine fetal death, fetal growth restriction; 3) maternal prothrombin gene variant (PGV) and intrauterine fetal death, fetal growth restriction and pre-eclampsia and 4) fetal PGV and intrauterine fetal death, fetal growth restriction and pre-eclampsia. Data from other published cohort studies was combined by meta-analysis to increase the power of detecting an association. Overall, the results of the study within the large ALSPAC cohort show no statistically significant association between maternal/fetal fVL or PGV, either alone or in combination with birth weight <10th centile. Furthermore, the FGR meta-analysis which pooled the results of this cohort study and other cohort studies found no evidence of an effect of maternal fVL on FGR. Given the size of the pooled sample, there was 80% power to detect an OR of 1.09, indicating that if an effect of fVL on FGR was missed by this meta-analysis, it would be quite small. The results of this study within the large ALSPAC cohort show no statistically significant association between maternal or fetal fVL or PGV, either

alone or in combination with pre-eclampsia. However, increasing the power by combining this study with other cohort studies by meta-analysis revealed a positive association between maternal fVL and pre-eclampsia with an OR of 1.49 (95% CI 1.13-1.96 p=0.003). A narrative review was subsequently published examining the translation from statistical association to change in clinical practice with respect to fVL and adverse pregnancy outcomes. The thesis concludes with a discussion of management in different clinical scenarios relating to fVL and adverse pregnancy outcomes, and the identification of future priority research areas.

Overview

Chapter One

Intrauterine fetal death, fetal growth restriction (FGR) and pre-eclampsia are major causes of fetal and maternal morbidity and mortality. Chapter One reviews the disease burden, underlying mechanisms, etiology, risk factors, optimal definition and diagnosis of each of these adverse pregnancy outcomes. Although each adverse pregnancy outcome has a complex etiology, placental 'insufficiency' is frequently proposed as the most important underlying mechanism.

The chapter includes a description of normal placental development as a benchmark to show the importance of adequate placental size, placentation and placental circulation. Given the importance of establishing and maintaining an adequate placental circulation, hereditary thrombophilias are postulated as a possible cause of placental insufficiency.

Chapter One concludes with a discussion of hereditary thrombophilias, with particular reference to factor V Leiden (fVL) and the conflicting results of a large number of studies that have investigated a possible association between fVL and adverse pregnancy outcomes.

Chapter Two

Despite initial reports supporting an association between factor V Leiden (fVL) and adverse pregnancy outcomes, a number of other studies yielded conflicting results. Publication I is a systematic review and meta-analysis of the literature up to January 2003 addressing the question of whether the common maternal fVL genotype is associated with an increased risk of adverse pregnancy outcomes (pre-eclampsia, fetal growth restriction and fetal loss). Publication II is addendum to Publication I.

The chapter progresses to a critical review of subsequently published meta-analyses (up to January 2007), evaluating possible associations between maternal fVL and

adverse pregnancy outcomes. During this process, a similar association between maternal prothrombin gene variant G20210A (PGV) and adverse pregnancy outcomes became evident. In light of this, it was apparent that including PGV in this review was important.

Chapter Two also reviews the literature with respect to possible associations between: 1) fetal fVL and adverse pregnancy outcomes; and 2) fetal PGV and adverse pregnancy outcomes. It concludes with the study hypotheses to be tested.

Chapter Three

Chapter Three is Publication III which describes the methods, results and conclusions of a nested case-control study within the Avon Longitudinal Study of Parents and Children (ALSPAC). In this study, 6755 mother/infant pairs were genotyped to determine whether maternal or fetal fVL or PGV, either alone or in combination is associated with FGR or pre-eclampsia. The results of this cohort study are also added to previous cohort studies using meta-analysis.

Chapter Four

This chapter is Publication IV, a narrative review examining the translation from statistical association to change in clinical practice with respect to fVL and adverse pregnancy outcomes.

Chapter Five

Chapter Five integrates results relating to fVL and analysis of the concurrent research to discuss possible management in the different clinical scenarios relating to pregnancy outcomes. The thesis concludes with the identification of future priority research areas.