

Factor V Leiden and adverse pregnancy outcome

Tracy Elizabeth Dudding

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

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Tracy Dudding

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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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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

Date

Signature

Prof. John Rostas
Deputy Head of Faculty (Research)
Faculty of Health

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A Thakkinstian

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Date 15th December 2011

Signature

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Date 16/12/2011

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■ Primary writing of the prepared manuscript under the supervision of Professor
John Attia and Professor Rodney Scott

DateDecember 5, 2011.....

Signature

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

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I, Ammarin Thakkinstian, attest that Research Higher Degree candidate Dr Tracy Dudding contributed the following to the publication entitled 'Factor V Leiden is associated with pre-eclampsia but not with fetal growth restriction: a genetic association study and meta-analysis'.

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Contributions:

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

Date

Signature

Prof. John Rostas
Deputy Head of Faculty (Research)
Faculty of Health

Table of Contents

Overview	1
Chapter 1	1
1.1 Introduction	4
1.2 Late intrauterine fetal death	4
1.2.1 The burden of late intrauterine fetal death	4
1.2.2 Mechanisms of late intrauterine fetal death	5
1.2.3 Aetiology of late intrauterine fetal death	5
1.2.4 Risk factors for late intrauterine fetal death	8
1.3 Fetal growth restriction	13
1.3.1 The burden of fetal growth restriction	13
1.3.2 Definition of small-for-gestational age versus fetal growth	15
1.3.3 Diagnosis of fetal growth restriction	16
1.3.4 Factors contributing to fetal growth restriction	21
1.4 Pre-eclampsia	25
1.4.1 Definition	25
1.4.2 Burden of illness of pre-eclampsia	26
1.4.3 Risk factors for pre-eclampsia	27
1.4.4 Pathological features of pre-eclampsia	29
1.4.5 Aetiology and pathophysiology of pre-eclampsia	30
1.5 Feto-maternal circulation	35
1.5.1 Normal blood supply to the uterus	35
1.5.2 Implantation and development of the placenta	36
1.5.3 Fetal blood supply to the placenta	40
1.6 Genetic factors involved in normal placentation	41
1.6.1 Proteins involved in the formation of normal placenta	41
1.6.2 The importance of imprinted genes	42
1.6.3 Immunological factors involved in normal placentation	43
1.7 Aetiology of placental insufficiency	44
1.7.1 Placental size	44
1.7.2 Abnormal placentation	45
1.7.3 Abnormal fetoplacental blood flow	45
1.8 The inherited thrombophilias as a potential cause of placental insufficiency	46
1.8.1 Normal haemostasis	46
1.8.2 Thrombophilias	46
1.8.3 Factor V Leiden	47
1.9 Summary	48
References	49

Chapter 2	68
2.1 Introduction	69
2.2 Maternal fVL and PGV and adverse pregnancy outcome	71
2.2.1 Definition of meta-analysis	71
2.2.2 Publication I and Publication II	
2.2.3 Subsequently published meta-analyses	72
2.2.4 Summary of subsequently published meta-analyses (until 2007)	81
2.3 Fetal fVL or PGV and adverse adverse pregnancy outcome: summary of the literature	90
2.3.1 Intrauterine fetal death	90
2.3.2. Fetal growth restriction	90
2.3.2 Pre-eclampsia	91
2.4 Conclusion	92
2.5 Hypothesis	94
References	95
 Chapter 3	 97
3.1 Introduction	98
3.2 Publication III	
 Chapter 4	 100
4.1 Introduction	101
4.2 Publication IV	
 Chapter 5 Conclusion	 104
5.1 Introduction	
5.2 Clinical scenarios	105
5.2.1 Group 1: Factor V Leiden positive women identified through cascade family testing with no history of adverse pregnancy outcome	
5.2.2 Group 2: Genetic testing for factor V Leiden in women with a history of first-trimester fetal loss	
5.2.3 Group 3: Genetic testing for factor V Leiden in women with a history of late (>20 weeks) fetal loss	
5.2.4 Group 4: Genetic testing for factor V Leiden in women with a history of pre-eclampsia or severe pre-eclampsia	
5.2.5 Group 5: Genetic testing for fVL in women with a previous history of fetal growth Restriction	
5.3 Design for proposed future research trial	116
 References	 121
 Appendices	 125
Chapter 3: Appendix 1. The Avon Longitudinal Study of Parents and Children: methodology	126
Chapter 3: Appendix 2. Rodger et al. The association of factor V leiden and prothrombin gene mutation and placenta-mediated pregnancy complications: a systematic review and meta-analysis of prospective cohort studies. PLoS Med;7:e10002 92. Figure 2. Odds of placenta-mediated pregnancy complications in FVL + women.	130

Chapter 5: Appendix 1. Inclusion and exclusion criteria for proposed research trial
Figure 2. Odds of placenta-mediated pregnancy complications in FVL + women

131

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.