MATERNAL FATTY ACIDS AND ANTIOXIDANTS IN PREGNANCIES COMPLICATED BY ASTHMA AND THEIR RELATIONSHIP TO FETAL GROWTH

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# Table of Contents

Table of Figures...........................................................................................................6
Table of Tables...............................................................................................................10
Abbreviations................................................................................................................13
Abstract..........................................................................................................................15
Declaration.......................................................................................................................17
Acknowledgements.........................................................................................................18
Published Works Arising From This Thesis...................................................................21
Conference Abstracts Arising From This Thesis...........................................................21
Chapter 1: Literature Review .........................................................................................22
  1.1 Asthma and pregnancy ............................................................................................23
      1.1.1 Asthma prevalence ..........................................................................................23
      1.1.2 Pathophysiology of asthma ..........................................................................24
      1.1.3 Asthma and oxidative stress .........................................................................26
      1.1.4 Pregnancy ......................................................................................................26
      1.1.5 Stress in pregnancy ......................................................................................27
      1.1.6 Oxidative stress in pregnancy ......................................................................28
      1.1.7 Maternal Smoking .......................................................................................28
      1.1.8 The effect of pregnancy on asthma ...............................................................31
      1.1.9 The effect of asthma on pregnancy ..............................................................33
      1.1.10 Management of asthma during pregnancy ...............................................34
  1.2 Fetal growth ............................................................................................................36
      1.2.1 Fetal growth and oxidative stress .................................................................36
      1.2.2 Fetal growth and the placenta .......................................................................38
      1.2.3 Fetal growth and systolic-diastolic ratio .......................................................39
      1.2.4 Fetal head growth parameters .....................................................................39
      1.2.5 Birth weight and birth weight centile .........................................................40
      1.2.6 Fetal growth and gender differences ...........................................................41
      1.2.7 Fetal growth and asthma .............................................................................42
      1.2.8 Fetal growth and asthma severity ...............................................................43
  1.3 Diet ..........................................................................................................................44
      1.3.1 Current Dietary Trends ..................................................................................44
      1.3.2 Maternal Diet and Fetal Growth .................................................................47
      1.3.3 Fatty acids ....................................................................................................48
          1.3.3.1 Fatty acid nomenclature .......................................................................48
          1.3.3.2 Fatty Acids Recommended Dietary Intake Levels ...............................51
          1.3.3.3 Fatty acids and diet ..............................................................................52
          1.3.3.4 Fatty acids and asthma .......................................................................55
          1.3.3.5 Fatty acids and fetal growth .................................................................56
      1.3.4 Antioxidants ....................................................................................................60
          1.3.4.1 Antioxidant nomenclature ...................................................................60
          1.3.4.2 Antioxidant recommended dietary intake levels ...............................62
          1.3.4.3 Antioxidants and diet ..........................................................................62
          1.3.4.4 Antioxidants and asthma .................................................................63
1.3.4.5 Antioxidants and fetal growth .......................................................65
1.4 Synopsis .........................................................................................66
1.5 Hypotheses .......................................................................................68
1.6 Aims ...............................................................................................69

Chapter 2: Study Design and General Methodology .........................................70
2.1 Participants .........................................................................................71
2.2 Inclusions ........................................................................................71
2.3 Exclusions .........................................................................................71
2.4 Blood collection ...............................................................................72
2.5 Assessment of maternal asthma severity, inhaled corticosteroid (ICS) use and smoking...72
2.6 Assessment of fetal growth ...................................................................73
2.7 24 hour dietary recall .........................................................................73
2.8 Biochemical Analyses .........................................................................73
  2.8.1 Maternal circulating levels of Fatty Acids .....................................73
  2.8.2 Maternal circulating levels of tocopherols and carotenoids ..........74
    2.8.2.1 Carotenoid standard preparation ..................................75
    2.8.2.2 Tocopherol standard preparation ................................76
2.9 Statistical analysis .............................................................................76

Chapter 3: Maternal, Fetal and Neonatal Characteristics ......................................78
3.1 Maternal general characteristics in pregnancies complicated by asthma and its severity.79
3.2 Maternal dietary intake classified by asthma severity ................................79
3.3 Fetal and birth anthropometry in pregnancies complicated by asthma and its severity ....80
3.4 Discussion .........................................................................................85

Chapter 4: Fatty Acids ...............................................................................88
4.1 Rationale ..........................................................................................89
4.2 Statistical Analysis ...........................................................................89
4.3 Results ............................................................................................90
  4.3.1 Cross-sectional analysis of asthma severity on maternal fatty acid dietary intake...90
    4.3.1.1 Total fat ........................................................................90
    4.3.1.2 Saturated fat ..................................................................90
    4.3.1.3 Monounsaturated fat ....................................................90
    4.3.1.4 Omega 6 fats .................................................................91
    4.3.1.5 Omega 3 fats .................................................................91
    4.3.1.6 Essential fatty acids .......................................................91
  4.3.2 Temporal analysis of asthma severity on maternal dietary intake of fat ...............91
    4.3.2.1 Total fats ........................................................................91
    4.3.2.2 Saturated fats .................................................................91
    4.3.2.3 Monounsaturated fats ....................................................92
    4.3.2.4 Omega 6 fats .................................................................92
    4.3.2.5 Omega 3 fats .................................................................92
    4.3.2.6 Essential fats ..................................................................92
  4.3.3 Cross-sectional analysis of asthma severity on maternal circulating levels of fatty
      acids ..........................................................................................92
    4.3.3.1 Total fatty acids .............................................................92
## Table of Contents

4.3.3.2 Saturated Fatty Acids ................................................................. 97  
4.3.3.3 Monounsaturated Fatty Acids .................................................. 97  
4.3.3.4 Omega 6 Fatty Acids ............................................................... 97  
4.3.3.5 Omega 3 Fatty Acids ............................................................... 98  
4.3.3.6 Essential fatty acids ............................................................... 99  
4.3.4 Temporal analysis of asthma severity on maternal circulating levels of fatty acids .................................................. 101  
4.3.4.1 Total fatty acids ................................................................. 101  
4.3.4.2 Saturated Fatty Acids ............................................................. 104  
4.3.4.3 Monounsaturated Fatty Acids ................................................. 104  
4.3.4.4 Omega 6 Fatty Acids ............................................................. 105  
4.3.4.5 Omega 3 Fatty Acids ............................................................. 105  
4.3.4.6 Essential fatty acids ............................................................. 106  
4.3.5 The effect of maternal inhaled corticosteroid use on maternal circulating levels of fatty acids .................................................. 108  
4.3.6 The effect of maternal smoking on maternal circulating levels of fatty acids .................................................. 108  
4.3.7 The relationship between maternal circulating fatty acid levels and fetal ultrasound and birth growth parameters in pregnancies complicated by asthma .................................................. 109  
4.3.7.1 Head Development .............................................................. 109  
4.3.7.2 Birth Weight Centile ............................................................. 112  
4.3.7.3 Placental Weight ................................................................. 112  
4.4 Discussion .................................................................................. 113  

Chapter 5: Antioxidants .................................................................. 119  
5.1 Rationale .................................................................................. 120  
5.2 Statistical Analysis .................................................................... 120  
5.3 Results ..................................................................................... 121  
5.3.1 Cross-sectional and temporal analysis of asthma severity on maternal antioxidant dietary intake .................................................. 121  
5.3.2 Cross-sectional analysis of asthma severity on maternal circulating plasma antioxidant levels .................................................. 122  
5.3.2.1 Tocopherols ................................................................. 122  
5.3.2.2 Carotenoids ................................................................. 123  
5.3.3 Cross-sectional analysis of asthma severity on maternal erythrocyte antioxidant levels. .................................................. 123  
5.3.3.1 Tocopherols ................................................................. 123  
5.3.3.2 Carotenoids ................................................................. 125  
5.3.4 Temporal analysis of asthma severity on maternal circulating plasma antioxidant levels .................................................. 126  
5.3.4.1 Tocopherols ................................................................. 126  
5.3.4.2 Carotenoids ................................................................. 127  
5.3.5 Temporal analysis of asthma severity on maternal erythrocyte antioxidants levels .................................................. 128  
5.3.5.1 Tocopherols ................................................................. 128  
5.3.5.2 Carotenoids ................................................................. 128  
5.3.6 The effect of maternal inhaled corticosteroid use on maternal plasma and erythrocyte antioxidant levels .................................................. 129
Table of Contents

5.3.6.1 Tocopherols........................................................................................................129
5.3.6.2 Carotenoids........................................................................................................130
5.3.7 The effect of maternal smoking on maternal plasma and erythrocyte antioxidant levels..............................................................................................................................131
5.3.7.1 Tocopherols........................................................................................................131
5.3.7.2 Carotenoids........................................................................................................133
5.3.8 The relationship between maternal circulating plasma antioxidant levels and fetal and birth growth parameters in pregnancies complicated by asthma..................................................135
5.3.8.1 Systolic-Diastolic Ratio.......................................................................................135
  5.3.8.1.1 Tocopherols.................................................................................................135
  5.3.8.1.2 Carotenoids.................................................................................................136
5.3.8.2 Head Development.........................................................................................136
  5.3.8.2.1 Tocopherols.................................................................................................136
  5.3.8.2.2 Carotenoids.................................................................................................138
5.3.8.3 Birth Weight Centile......................................................................................141
  5.3.8.3.1 Tocopherols.................................................................................................141
  5.3.8.3.2 Carotenoids.................................................................................................141
5.3.8.4 Placental weight.............................................................................................142
  5.3.8.4.1 Tocopherols.................................................................................................142
  5.3.8.4.2 Carotenoids.................................................................................................143
5.4 Discussion............................................................................................................143

Chapter 6: Final Discussion.......................................................................................148

Chapter 7: Appendix..................................................................................................160
  7.1 Ethics Approval......................................................................................................161
  7.2 Control participant information sheet and informed consent..............................163
  7.3 Asthmatic participant information sheet and informed consent............................170
  7.4 Participant Demographics..................................................................................178
  7.5 Asthma Control Questionnaire............................................................................180
  7.6 24 Hour Dietary Recall Questionnaire..................................................................181
  7.7 Maternal Dietary Intake......................................................................................182
  7.8 Maternal Circulating Fatty Acids..........................................................................199
  7.9 Maternal Circulating Antioxidants.......................................................................213

Chapter 8: References..............................................................................................221
Table of Figures

Figure 1.1. World prevalence of clinical asthma........................................................................................................................................23
Figure 1.2. Comparison of a normal airway (left panel) and an asthmatic airway (right panel).........................................................25
Figure 1.3. Structure and metabolism of n6 and n3 long chain polyunsaturated fatty acids.................................................................50
Figure 1.4. Percentage contribution of various food groups to polyunsaturated food intake in an adult Australian population........................................................................................................................................53
Figure 1.5. Structure of common carotenoids found in human plasma..................................................................................................................61
Figure 4.1. Maternal circulating plasma total fatty acids (mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................93
Figure 4.2. Maternal circulating plasma total saturated fatty acids (SFA; mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................94
Figure 4.3. Maternal circulating plasma total monounsaturated fatty acids (MUFA; mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................94
Figure 4.4. Maternal circulating plasma total omega (n)6 polyunsaturated fatty acids (n6PUFA; mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................94
Figure 4.5. Maternal circulating plasma total n3 polyunsaturated fatty acids (n3PUFA; mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................95
Figure 4.6. Maternal circulating plasma total n6-n3 polyunsaturated fatty acid ratio (mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................95
Figure 4.7. Maternal circulating plasma arachidonic acid (AA [20:4n6] mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................96
Figure 4.8. Maternal circulating plasma eicosapentaenoic acid (EPA [20:5n3] mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................98
Figure 4.9. Maternal circulating plasma docosahexaenoic acid (DHA [22:6n3] mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................99
Figure 4.10. Maternal circulating plasma linoleic acid (LA [18:2n6] mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................100
Figure 4.11. Maternal circulating plasma α-linolenic acid (αLNA [18:3n3] mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................100
Figure 4.12. Temporal analysis of maternal circulating plasma total fatty acids (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation........................................................................................................................................101
Table of Figures

Figure 4.13. Temporal analysis of maternal circulating plasma total saturated fatty acids (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.................................................................102
Figure 4.14. Temporal analysis of maternal circulating plasma total monounsaturated fatty acids (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................102
Figure 4.15. Temporal analysis of maternal circulating plasma total omega 6 fatty acids (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................103
Figure 4.16. Temporal analysis of maternal circulating plasma total omega 3 fatty acids (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................103
Figure 4.17. Temporal analysis of maternal circulating plasma n6:n3 fatty acid ratio in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................104
Figure 4.18. Temporal analysis of maternal circulating plasma arachidonic acid (AA [20:4n6] mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................105
Figure 4.19. Temporal analysis of maternal circulating plasma eicosapentaenoic acid (EPA [20:5n3] mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................106
Figure 4.20. Temporal analysis of maternal circulating plasma docosahexaenoic acid (DHA [22:6n3] mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................106
Figure 4.21. Temporal analysis of maternal circulating plasma linoleic acid (LA [18:2n6] mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................107
Figure 4.22. Temporal analysis of maternal circulating plasma α linolenic acid (αLNA [18:3n3] mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.......................................................................................................................107
Figure 4.23. Maternal circulating plasma total fatty acid levels (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) for non-smokers and smokers at G18, 30 and 36 weeks...........................................................................................................................................108
Figure 4.24. Relationship between maternal circulating n6:n3 fatty acid ratio and fetal ultrasound head circumference (USHC, mm) during mid (G30) and late pregnancy (G36) in mild asthmatic women..................................................................................................................................................109
Figure 4.25. Relationship between maternal circulating plasma omega 3 fatty acids (mg/L) and head growth in pregnancies complicated by moderate/severe asthma..................................................................................................................110
Figure 4.26. Relationship between maternal circulating plasma omega 6 fatty acids (mg/L) and birth HC in pregnancies complicated by moderate/severe asthma........................................................................................................111
Figure 4.27. Relationship between maternal circulating plasma total fatty acid levels (mg/L) and birth head circumference (BHC) in pregnancies complicated by moderate/severe asthma.....................................................................................................................112
Figure 5.1. Maternal circulating plasma total tocopherol levels (mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................122

Figure 5.2. Maternal circulating plasma α tocopherol levels (mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C).........................................................................................................................123

Figure 5.3. Cross-sectional analysis of maternal erythrocyte α tocopherol levels (mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C). .........................................................................................................................124

Figure 5.4. Cross-sectional analysis of maternal erythrocyte α tocopherol quinone levels (mg/L) in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C). .........................................................................................................................124

Figure 5.5. Cross-sectional analysis of maternal erythrocyte α tocopherol quinone-α tocopherol ratio in control, mild and moderate/severe asthmatic pregnancies at gestational week 18 (G18, panel A), G30 (panel B) and G36 (panel C). .........................................................................................................................125

Figure 5.6. Temporal analysis of maternal circulating plasma total tocopherol levels (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.........................................................................................................................126

Figure 5.7. Temporal analysis of maternal circulating plasma α tocopherol levels (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.........................................................................................................................127

Figure 5.8. Temporal analysis of maternal circulating plasma total carotenoids (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.........................................................................................................................127

Figure 5.9. Temporal analysis of maternal circulating plasma lutein (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) at 18, 30 and 36 weeks gestation.........................................................................................................................128

Figure 5.10. Maternal circulating plasma α tocopherol levels (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) for non-smokers and smokers at 18, 30 and 36 weeks gestation.........................................................................................................................133

Figure 5.11. Maternal circulating plasma lycopene levels (mg/L) in control pregnancies (panel A), mild (panel B) and moderate/severe asthmatic pregnancies (panel C) for non-smokers and smokers at G18, 30 and 36 weeks..................................................................................................................................................135

Figure 5.12. Relationship between maternal erythrocyte α tocopherols (mg/L) and fetal systolic-diastolic (SD) ratio at 36 weeks gestation in pregnancies complicated by moderate/severe asthma. ...........................................................................................................................................136

Figure 5.13. Relationship between maternal erythrocyte tocopherol levels (mg/L), α tocopherol quinone: α tocopherol ratio and fetal/birth head development in mild asthmatic women............137

Figure 5.14. Relationship between maternal erythrocyte tocopherol levels (mg/L), α tocopherol quinone:α tocopherol ratio and fetal/birth head development in pregnancies complicated by moderate/severe asthma. .........................................................................................................................138

Figure 5.15. Relationship between maternal circulating carotenoids levels (mg/L) and fetal head development in control pregnancies.........................................................................................................................139
Figure 5.16. Relationship between maternal circulating carotenoids levels (mg/L) and fetal head development in pregnancies complicated by mild asthma. ................................................................. 140
Figure 5.17. Relationship between maternal circulating lycopene levels (mg/L) and fetal/birth head development in pregnancies complicated by moderate/severe asthma. ........................................... 141
Figure 5.18. Relationship between maternal circulating plasma lycopene levels (mg/L) and birth weight centile (BWC) in pregnancies complicated by moderate/severe asthma................................. 142
Figure 5.19. Relationship between maternal erythrocyte α tocopherol quinone:α tocopherol ratio at G36 and placental weight (g) in pregnancies complicated by moderate/severe asthma. ......................... 143
Table of Tables

Table 1.1. Adequate and upper level intake of Linoleic Acid, alpha-linolenic acid and combined EPA, DPA and DHA for adults..........................................................52
Table 1.2. Adequate intake of Linoleic Acid, alpha-linolenic acid and combined EPA, DPA and DHA during pregnancy and lactation..........................................................52
Table 1.3. Adequate intake of vitamin E for adults..........................................................62
Table 2.1. Carotenoid standard preparation..................................................................75
Table 2.2. Final concentrations of Carotenoids used as standards..............................75
Table 2.3. Tocopherol standard preparation..................................................................76
Table 2.4. Final concentrations of Tocopherols used as standards..............................76
Table 3.1. Maternal general characteristics for pregnancies classified by asthma severity..........................................................81
Table 3.2. Maternal asthma treatment characteristics classified by asthma severity........82
Table 3.3. Fetal ultrasound characteristics classified by asthma severity........................83
Table 3.4. Neonatal characteristics classified by asthma severity..................................84
Table 5.1. Maternal circulating plasma levels of tocopherols (mg/L) as classified by inhaled corticosteroid (ICS) usage..........................................................129
Table 5.2. Maternal erythrocyte levels of tocopherols (mg/L) as classified by inhaled corticosteroid (ICS) usage..........................................................129
Table 5.3. Maternal circulating plasma levels of carotenoids (mg/L) as classified by inhaled corticosteroid (ICS) usage..........................................................130
Table 5.4. Maternal erythrocyte levels of carotenoids (mg/L) as classified by inhaled corticosteroid (ICS) usage..........................................................131
Table 5.5. Maternal plasma tocopherol levels (mg/L) as classified by smoking status........132
Table 5.6. Maternal erythrocyte tocopherol levels (mg/L) as classified by smoking status........132
Table 5.7. Maternal circulating plasma levels of carotenoids (mg/L) as classified by smoking status..........................................................133
Table 5.8. Maternal erythrocyte levels of carotenoids (mg/L) as classified by smoking status........134
Table 7.1. Maternal standard dietary intake at G18 classified by asthma severity........182
Table 7.2. Maternal standard dietary intake at G30 classified by asthma severity........183
Table 7.3. Maternal standard dietary intake at G36 classified by asthma severity........184
Table 7.4. Cross-sectional analysis of asthma severity on maternal total fatty acid dietary intake (g%)..........................................................185
Table 7.5. Cross-sectional analysis of maternal saturated fatty acid dietary intake (g%) at G18..........................................................186
Table 7.6. Cross-sectional analysis of maternal saturated fatty acid dietary intake (g%) at G30..........................................................187
Table 7.7. Cross-sectional analysis of maternal saturated fatty acid dietary intake (g%) at G36..........................................................188
Table 7.8. Cross-sectional analysis of asthma severity on maternal monounsaturated fatty acid dietary intake (g%)..........................................................189
Table 7.9. Cross-sectional analysis of asthma severity on maternal n6 fatty acid dietary intake (g)..........................................................190
Table 7.10. Cross-sectional analysis of asthma severity on maternal n3 fatty acid dietary intake (g%)..........................................................191
Table 7.11. Temporal analysis of asthma severity on maternal total fatty acid dietary intake (g%)..........................................................192
Table 7.12. Temporal analysis of asthma severity on maternal saturated fatty acid dietary intake (g%)..........................................................193
Table 7.13. Temporal analysis of asthma severity on maternal saturated fatty acid dietary intake (g/%) .......................................................... 194
Table 7.14. Temporal analysis of asthma severity on maternal monounsaturated fatty acid dietary intake (g/%) .......................................................... 195
Table 7.15. Temporal analysis of asthma severity on maternal n6 fatty acid dietary intake (g/%) .......................................................... 196
Table 7.16. Temporal analysis of asthma severity on maternal n3 fatty acid dietary intake (g/%) .......................................................... 197
Table 7.17. Maternal dietary intake of carotenoids (μg) as classified by asthma severity .......................................................... 198
Table 7.18. Cross-Sectional analysis of asthma severity on maternal circulating plasma total fatty acid levels (mg/L) .......................................................... 199
Table 7.19. Cross-sectional analysis of asthma severity on maternal circulating plasma saturated fatty acid levels (mg/L) at G18 and G30 .......................................................... 200
Table 7.20. Cross-sectional analysis of maternal circulating plasma saturated fatty acid levels (mg/L) at G36 .......................................................... 201
Table 7.21. Cross-sectional analysis of asthma severity on maternal circulating plasma monounsaturated fatty acid levels (mg/L) at 18 and 30 weeks gestation .......................................................... 202
Table 7.22. Cross-sectional analysis of asthma severity on maternal circulating plasma monounsaturated fatty acid levels (mg/L) at G36 .......................................................... 203
Table 7.23. Cross-sectional analysis of asthma severity on maternal circulating plasma n6 fatty acid levels (mg/L) at 18 and 30 weeks gestation .......................................................... 204
Table 7.24. Cross-sectional analysis of asthma severity on maternal circulating plasma n6 fatty acid levels (mg/L) at 36 weeks gestation .......................................................... 205
Table 7.25. Cross-sectional analysis of asthma severity on maternal circulating plasma n3 fatty acid levels (mg/L) at 18 and 30 weeks gestation .......................................................... 206
Table 7.26. Cross-sectional analysis of asthma severity on maternal circulating plasma n3 fatty acid levels (mg/L) at 36 weeks gestation .......................................................... 207
Table 7.27. Temporal analysis of asthma severity on maternal circulating plasma levels of total fatty acids (mg/L) .......................................................... 208
Table 7.28. Temporal analysis of asthma severity on maternal circulating plasma levels of saturated fatty acids (mg/L) .......................................................... 209
Table 7.29. Temporal analysis of asthma severity on maternal circulating plasma levels of monounsaturated fatty acids (mg/L) .......................................................... 210
Table 7.30. Temporal analysis of asthma severity on maternal circulating plasma levels of n6 fatty acids (mg/L) .......................................................... 211
Table 7.31. Temporal analysis of asthma severity on maternal circulating plasma levels of n3 fatty acids (mg/L) .......................................................... 212
Table 7.32. Maternal circulating plasma tocopherol levels (mg/L) as classified by asthma severity .......................................................... 213
Table 7.33. Maternal erythrocyte tocopherol levels (mg/L) as classified by asthma severity .......................................................... 214
Table 7.34. Temporal analysis of maternal circulating plasma tocopherol levels (mg/L) as classified by asthma severity .......................................................... 215
Table 7.35. Temporal analysis of maternal erythrocyte tocopherol levels (mg/L) as classified by asthma severity .......................................................... 216
Table 7.36. Maternal circulating plasma levels of carotenoids (mg/L) as classified by asthma severity .......................................................... 217
Table 7.37. Maternal erythrocyte levels of carotenoids (mg/L) as classified by asthma severity .......................................................... 218
Table 7.38. Temporal analysis of maternal circulating plasma levels of carotenoids (mg/L) as classified by asthma severity...........................................................................................................219
Table 7.39. Temporal analysis of maternal erythrocyte levels of carotenoids (mg/L) as classified by asthma severity ..............................................................................................................................................220
Abbreviations

·OH  Hydroxyl radical
11βHSD2  Eleven beta hydroxysteroid dehydrogenase type 2
18:2n6  Linoleic acid (LA)
18:3n3  α-linolenic acid (αLNA)
20:3n6  Dihomo-gamma-linolenic acid (dGLA)
20:4n6  Arachidonic acid (AA)
20:5n3  Eicosapentaenoic acid (EPA)
22:5n3  Docosapentaenoic acid (DPA)
22:6n3  Docosahexaenoic acid (DHA)
5-LOX  5-Lipoxygenase
8-OH-dG  8-hydroxydeoxyguanosine
AGA  Appropriate for gestational age
AHR  Airway hyperresponsive
ATP  Adenosine triphosphate
BDP  Beclomethasone dipropionate
BALF  Bronchoalveolar lavage fluid
BPD  Biparietal diameter
cAMP  Cyclic adenosine monophosphate
CAPS  Childhood asthma prevention study
CBMC  Cord blood mononuclear cell
COX-  Cyclooxygenase-
CRP  C-reactive protein
DHA  Docosahexaenoic acid
DNA  Deoxyribonucleic acid
EFA  Essential fatty acid
EPA  Eicosapentaenoic acid
FABP  Fatty acid binding protein
FEV1:FVC  Forced expiratory volume in one second-forced vital capacity ratio
FEV1  Forced expiratory volume in one second
FL  Femur length
FVC  Forced vital capacity
G  Gestational week
GR  Glutathione reductase
H2O2  Hydrogen peroxide
HC  Head circumference
HDL  High density lipoprotein
HPLC  High performance liquid chromatography
ICS  Inhaled corticosteroid
IFN-  Interferon-
IgE  Immunoglobulin E
IL-  Interleukin-
IGF-  Insulin-like growth factor-
IUGR  Intrauterine growth restriction
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA</td>
<td>Long acting beta agonist</td>
</tr>
<tr>
<td>LCPUFA</td>
<td>Long chain polyunsaturated fatty acid</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LGA</td>
<td>Large for gestational age</td>
</tr>
<tr>
<td>LT</td>
<td>Leukotriene</td>
</tr>
<tr>
<td>MDA</td>
<td>Malondialdehyde</td>
</tr>
<tr>
<td>MUFA</td>
<td>Monounsaturated fatty acid</td>
</tr>
<tr>
<td>n-</td>
<td>Omega-</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>O$_2$</td>
<td>Oxygen</td>
</tr>
<tr>
<td>O$_2^-$</td>
<td>Superoxide anion</td>
</tr>
<tr>
<td>PE</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>PEFR</td>
<td>Peak expiratory flow rate</td>
</tr>
<tr>
<td>PG</td>
<td>Prostaglandin</td>
</tr>
<tr>
<td>PMA</td>
<td>Phorbol 12-myristate 13-acetate</td>
</tr>
<tr>
<td>PMN</td>
<td>Polymorphonuclear Neutrophil</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acid</td>
</tr>
<tr>
<td>RANTES</td>
<td>Regulated upon activation normal T-cell expressed and secreted</td>
</tr>
<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RNS</td>
<td>Reactive nitrogen species</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>SABA</td>
<td>Short acting beta agonist</td>
</tr>
<tr>
<td>SD</td>
<td>Systolic-diastolic ratio</td>
</tr>
<tr>
<td>SEATON</td>
<td>Study of eczema and asthma to observe the influence of nutrition</td>
</tr>
<tr>
<td>SFA</td>
<td>Saturated fatty acid</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age</td>
</tr>
<tr>
<td>sICAM</td>
<td>Soluble intercellular adhesion molecule</td>
</tr>
<tr>
<td>SOD</td>
<td>Superoxide dismutase</td>
</tr>
<tr>
<td>sVCAM</td>
<td>Soluble vascular adhesion molecule</td>
</tr>
<tr>
<td>TBARS</td>
<td>Thiobarbituric acid reactive substances</td>
</tr>
<tr>
<td>Th</td>
<td>T-helper cell</td>
</tr>
<tr>
<td>TNF-</td>
<td>Tumour necrosis factor-</td>
</tr>
<tr>
<td>TX</td>
<td>Thromboxane</td>
</tr>
<tr>
<td>USBPD</td>
<td>Ultrasound biparietal diameter</td>
</tr>
<tr>
<td>USHC</td>
<td>Ultrasound head circumference</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very low density lipoprotein</td>
</tr>
</tbody>
</table>
Abstract

Asthma is one of the leading respiratory diseases affecting pregnancies today. Its effects on the mother and on fetal growth in particular are of great interest since the development of the fetus is highly plastic at this crucial period of development. Since inflammation and oxidative stress inherent in asthma have been shown to affect maternal and fetal outcomes, it was therefore the primary aim of this thesis to characterise the maternal circulating levels of fatty acids and antioxidants and to investigate the potential relationships with maternal dietary intake and fetal and neonatal growth parameters between groups. As a part of a larger prospective study on asthma, 131 pregnant women; non-asthmatic control subjects (n=47) and asthmatic women (mild [n=31] & moderate/severe [n=53]), were recruited at their first antenatal visit to the John Hunter Hospital in Newcastle, Australia. Women completed a 24 hour dietary food recall questionnaire at each subsequent visit; gestational (G) weeks G18, G30 and G36, at which times blood was collected. Corticosteroid use and smoking were assessed by direct questioning by respiratory nurses. We found no differences in maternal characteristics including gravidity, parity, height, smoking, weight, body mass index (BMI) or weight gain over the course of pregnancy, or in fetal or neonatal growth parameters between non-asthmatic women and women with mild or moderate/severe asthma. Moderate/severe asthmatics were found to have a reduced dietary consumption of energy, total, saturated, polyunsaturated and monounsaturated fats, carbohydrates, thiamine, riboflavin and magnesium.

Maternal circulating fatty acids and antioxidants increased as pregnancy progressed in each group, but unexpectedly, higher maternal circulating levels of omega (n3) fatty acids were found in moderate/severe asthmatics at the end of pregnancy (G36), and were inversely associated with fetal/neonatal head growth. Since there were no growth restricted neonates found in this cohort, it seems that placental transfer of n3 PUFA may be compromised in asthmatic pregnancies. Due to the study protocol, the asthmatic women had well controlled asthma, this is possibly why no growth restricted neonates were found in this cohort. There were no significant differences found in maternal circulating levels of fatty acids or tocopherols in wome who were using ICS or who were cigarette smokers; however, smokers tended to have reduced levels of carotenoids. High levels of n3 fatty acids and antioxidants were found in moderate/severe asthmatics, suggesting there is a
maternally mediated compensatory mechanism to protect the fetus during pregnancy from asthma induced inflammation and oxidative stress during pregnancy. Therefore, the maternal circulating fatty acid and antioxidant profile is altered in women with moderate/severe asthma in response to the increased inflammation and oxidative load. Fatty acid levels were inversely associated with fetal growth in the presence of adequate asthma control, adequate diet and low antioxidant levels, whereas antioxidant levels were generally positively associated with, and may protect fetal growth, suggesting that factors other than asthma severity and diet may influence fetal growth, including inadequate transfer of fatty acids to the fetus. From a clinical perspective, women with moderate/severe asthma should be vigilant in controlling their asthma throughout pregnancy, since controlling the inflammation and subsequent oxidative stress will enable normal fetal growth within an adverse environment. Finally, in order to gain any benefit towards improving fetal growth, pregnant women with moderate/severe asthma should consider supplementation with antioxidants.
Declaration

I hereby declare that the work embodied in this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Penelope McLernon, 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 text.

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Signature:

Date:
Acknowledgements

In the first instance, I would like to thank my principal supervisor, Vicki, who, first and foremost, believed in me, supported me and above all, acknowledged that life happens along the way. Vic, you had faith in me from the start, I appreciate your support, advice and encouragement. To my supervisors Lisa and Vanessa, thank you for your long distance support. Whilst it has been a long and difficult road, we got there in the end. To each of you, for your help and guidance, I am truly grateful. I have been very fortunate to have such a broad array of experience from which I could learn, which has made this period of my life more meaningful as a result. Through your leadership and encouragement, I have found my way, and with your help and guidance, I feel that I am finally able to achieve some of my life goals. To Gus, the silent partner, thank you for being there when we needed you! I am grateful for this opportunity to have learned so much in this field, but also, and most importantly, about myself and about life. The experience I have gained from working towards this PhD will, without a doubt, hold me in good stead for my future career in medicine, and for that I am extremely grateful.

To my dear friend Nic, I am not sure I could ever see this time arrive, but you certainly could! You listened along the way knowing exactly what I was going through, you encouraged me to realise that it wasn’t a train coming the other way, although it sometimes felt like it! I appreciate your support and encouragement more than you can imagine. Without your advice, this may have been too much for such a pedantic mind to bear, thank you for keeping me grounded. I cannot express how grateful I am for your continued support, advice, clarity and friendship. To my dear Annetty, we have come such a long way, and your laid back attitude was also a lesson for me to let go and relax a little, thank you for teaching me a skill with which I am slowly coming to terms. Although I have made many sacrifices, such as being apart from my family, I can never thank you enough for supporting me emotionally and academically through this huge endeavour.

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To my dear friend Jack, who was with me and endured the pain every single step of the way, I am grateful to have been able to lean on you when I needed – which was more often than not. When I was isolated and trying to do this either away from my family, or away from my group, you were my long suffering support, and I will be forever grateful to have been able to burst your eardrums on a regular basis! Thank you for not only listening, but for hearing me - always.
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To my dear ole Mum and Dad; you did whatever you could, whenever you could, unconditionally and without question. Thank you so much for being there when we needed you. If only I did this 20 years ago! Although you might not have always understood the continual pressures, I appreciate the unconditional support that you have both provided. I must say that building a flat for us to live in was exceptionally supportive, and I am grateful that we were able to spend some precious time together with your new Granddaughter, even if it was under the pressured guise of a continually unfinished thesis! I am so glad that you are both well enough to see this come to fruition. Thank you for your continued help, support and encouragement along the way. I couldn't have done it without you. Thank you for always being there, I love you both deeply.

Finally, to the greatest loves of my life:

Keith, you are my rock. Taking life in your stride and being so accepting of what the world has to offer has seen me learn a great deal from you. Without you, such a highly strung and pedantic person would never have made it to the end. You have believed in me all along, prior to and post the PhD, and I am not sure how you managed to put up with me along the way! I am, however, grateful for a busy work/study life, since you talk as much as a fish! Having said that, you are a realist and I can never thank you enough for your support and love, and for the sacrifices we as a family have had to make to enable this to come to fruition. Thank you from the heart of my bottom ;o)

To our dear precious Kate, who talks way more than a fish... you came along half way through the PhD and although you threw a spanner in the works for a brief period, you have taught me more about life and love than I could ever have imagined, and I am so happy and grateful to have you in my life. As a young family, we have already endured a great deal and much time apart. I promise to make it up to you and Daddy. You are our precious little gift and I love you more than I could possibly express. I hope to be a positive role model for you. I want you to live your life for you, to be happy and to do whatever you want in this world. If there is anything I can impart, it is that the world truly is your oyster. I promise to give you the best start I can, and to help you learn and appreciate life such that you squeeze everything substantial out of it in order to make a great life for yourself.

I am grateful for the experience of this PhD, for it has taught me many, many years earlier than I would have otherwise realised that I love you both unconditionally and more than I could have hoped to understand.

‘I am not afraid of storms, for I am learning how to sail my ship.’
~ Louisa May Alcott ~
For the true loves of my life:

Keith
&
Kate
**Published Works Arising From This Thesis**


**Conference Abstracts Arising From This Thesis**

McLernon, P. C., Wood, L. G., Murphy, V. E., Dekker, G. A., & Clifton, V. L (2010). Maternal circulating levels of omega (n) 3 long chain polyunsaturated fatty acids; eicosapenaeoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) during early pregnancy are associated with fetal growth measures in later pregnancy. International Federation of Placenta Associations (IFPA). Santiago, Chile.


