EFFECTS ON INFANT GROWTH AND NEURODEVELOPMENT OF REPEAT DOSE PRENATAL CORTICOSTEROIDS TO WOMEN AT RISK OF PRETERM BIRTH: A RANDOMISED CONTROLLED TRIAL.

KRISTIN JANE M^{C}LAUGHLIN

Thesis submitted in fulfillment of the requirements for

the degree of Doctor of Philosophy

January 2003

DEPARTMENT OF OBSTETRICS & GYNAECOLOGY

FACULTY OF HEALTH SCIENCES

THE UNIVERSITY OF ADELAIDE

TABLE OF CONTENTS

Table of Contents i

List of Tables iii

List of Figures vii

Abstract x

Declaration xii

Acknowledgements xiii

Author's Contribution xv

1. Literature Review 1

1.1 Purpose and scope 1

1.2 Preterm birth 1

1.3 Single course prenatal corticosteroids 4

1.4 Repeat prenatal corticosteroids 18

1.5 The ACTORDS Trial 51

1.6 The aims and hypotheses of the studies in this thesis 53

2. Methods **56**

2.1 Eligibility and trial entry 57

2.2 Anthropometric assessments 58

2.3 Neurodevelopmental assessments 62

2.4 Primary study endpoints 67

2.5 Sample size 67

2.6 Data collection and management 67

2.7 Data analysis 69

3. Results of Repeat Prenatal Corticosteroids and Infant Growth..... 78

3.1 Introduction..... 78

3.2 Aims and hypotheses..... 78

3.3 Summary of methods..... 79

3.4 Results.....80

3.5 Discussion.....154

4. Results of Repeat Prenatal Corticosteroids and Early Infant Neurodevelopment..... 173

4.1 Introduction..... 173

4.2 Aims and hypotheses..... 173

4.3 Summary of methods..... 174

4.4 Results..... 175

4.5 Discussion..... 195

5. Overall Conclusions..... 203

6. Appendices..... 206

6.1 Patient information sheet and consent form..... 206

6.2 Growth data forms..... 210

6.3 Four and eight month Ages and Stages Questionnaires..... 212

7. References 222

LIST OF TABLES

1.4.2.1	Designation of levels of evidence	20
1.4.4.1	Methodology of randomised controlled trials of repeat prenatal corticosteroids	29
1.4.4.2	Methods of systematic review and meta-analysis of observational studies reporting size at birth	38
2.3.1.1	Validation of ASQ	63
3.4.1.1	Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry	82
3.4.1.2	Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received	84
3.4.1.3	Birth and infant clinical outcomes	85
3.4.2.1	Weight by treatment group	87
3.4.2.2.	Estimated mean weight at the nominal measurement time points	88
3.4.2.3	Weight z-scores by treatment group	95
3.4.2.4	Estimated mean weight z-scores by the nominal measurement time points	96
3.4.2.5	Weight percentiles by treatment group	103
3.4.3.1	Total body length by treatment group	105
3.4.3.2	Estimated mean total body length at the nominal measurement time points	106
3.4.3.3	Total body length z-scores by treatment group	113

3.4.3.4 Estimated total body length z-scores by the nominal measurement time points..... 114
3.4.3.5 Total body length percentiles by treatment group..... 121
3.4.4.1 Head circumference by treatment group..... 123
3.4.4.2 Estimated mean head circumference at the nominal measurement time points..... 124
3.4.4.3 Head circumference z-scores by treatment group..... 131
3.4.4.4 Estimated mean head circumference z-score for nominal measurement time points..... 132
3.4.4.5 Head circumference percentiles by treatment group..... 139
3.4.5.1 Knee-ankle length by treatment group..... 141
3.4.5.2 Estimated mean knee-ankle length at the nominal measurement time points..... 142
3.4.6.1 Ponderal index by treatment group..... 149
3.4.7.1 Gestational age at birth and the number of ACTORDS treatment doses received..... 151
3.4.7.2 Gestational age at birth and the latency between the last ACTORDS treatment dose and birth..... 151
3.4.7.3 The number of ACTORDS treatment doses received and the latency from the last ACTORDS treatment dose to birth..... 152
3.4.8.1 Summary of the main effects of repeat prenatal corticosteroids on size at birth and early infant growth..... 153

4.4.2.1 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry by ASQ receipt..... 178
4.4.2.2 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received by ASQ receipt..... 179
4.4.2.3 Birth and infant clinical outcomes by ASQ receipt..... 179
4.4.2.4 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry for women with infants for whom ASQ were received..... 181
4.4.2.5 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received for women with infants for whom ASQ were received..... 182
4.4.2.6 Birth and infant clinical outcomes for women and their infants for whom ASQ were received..... 183
4.4.2.7 Four month median ASQ scores..... 184
4.4.2.8 Eight month median ASQ scores..... 184
4.4.2.9 Four month ASQ general questions..... 185
4.4.2.10 Eight month ASQ general questions..... 185
4.4.2.11 Estimated means for mixed model analysis of variance of ASQ scores.. 186
4.4.2.12 Four and eight month ASQ developmental domain cut-off scores and adjusted relative risks..... 187
4.4.3.1 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry by FTII completion..... 189
4.4.3.2 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received by FTII completion..... 190

4.4.3.3 Birth and infant clinical outcomes by FTII completion..... 190

4.4.3.4 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry for women whose infants were tested using the FTII... 192

4.4.3.5 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received for women whose infants were tested with the FTII..... 193

4.4.3.6 Birth and infant clinical outcomes for women and their infants who were tested using the FTII..... 193

4.4.3.7 Fagan Test of Infant Intelligence..... 194

LIST OF FIGURES

1.3.4.1	Birth weight (grams) after single course prenatal corticosteroids compared with placebo/control/no treatment	10
1.4.4.1	Meta-analysis of observational studies: birth weight (grams)	40
1.4.4.2	Meta-analysis of observational studies: birth weight less than the 10^{th} percentile for gestation at birth	40
2.0.1.1	Infant growth measurement time points	56
2.2.1.1	Measuring knee-ankle length with the neonatal knemometer	61
2.3.1.1	Developmental domains of the Ages and Stages Questionnaires	62
2.3.2.1	The Fagan Test of Infant Intelligence	66
3.4.1.1	In-depth Growth and Neurodevelopment Trial Profile	80
3.4.2.1	Weight growth curves by corrected age	86
3.4.2.2	Estimated mean weight and 95% CI	89
3.4.2.3	Estimated mean weight and 95% CI by gestational age at birth	91
3.4.2.4	Estimated mean weight and 95% CI by the number of ACTORDS treatment doses received	92
3.4.2.5	Estimated mean weight and 95% CI by the latency from last ACTORDS dose to birth	93
3.4.2.6	Estimated mean weight z-score and 95% CI	97
3.4.2.7	Estimated mean weight z-score and 95% CI by gestational age at birth	99
3.4.2.8	Estimated mean weight z-score and 95% CI by the number of ACTORDS treatment doses received	100

3.4.2.9 Estimated mean weight z-score and 95% CI by the latency from last ACTORDS dose to birth..... 101
3.4.3.1 Total body length growth curves by corrected age..... 104
3.4.3.2 Estimated mean total body length and 95% CI..... 107
3.4.3.3 Estimated mean total body length and 95% CI by gestational age at birth..... 109
3.4.3.4 Estimated mean total body length and 95% CI by the number of ACTORDS treatment doses received..... 110
3.4.3.5 Estimated mean total body length and 95% CI by the latency from last ACTORDS dose to birth..... 111
3.4.3.6 Estimated mean total body length z-score and 95% CI 115
3.4.3.7 Estimated mean total body length z-score and 95% CI by gestational age at birth..... 117
3.4.3.8 Estimated mean total body length z-score and 95% CI by the number of ACTORDS treatment doses received..... 118
3.4.3.9 Estimated mean total body length z-score and 95% CI by the latency from the last ACTORDS dose to birth..... 119
3.4.4.1 Head circumference growth curves by corrected age..... 122
3.4.4.2 Estimated mean head circumference and 95% CI..... 125
3.4.4.3 Estimated mean head circumference and 95% CI by gestational age at birth..... 127
3.4.4.4 Estimated mean head circumference and 95% CI by the number of ACTORDS treatment doses received..... 128

3.4.4.5 Estimated mean head circumference and 95% CI by the latency from last ACTORDS dose to birth..... 129

3.4.4.6 Estimated mean head circumference z-score and 95% CI..... 133

3.4.4.7 Estimated mean head circumference z-score and 95% CI by gestational age at birth..... 135

3.4.4.8 Estimated mean head circumference z-score and 95% CI by the number of ACTORDS doses received 136

3.4.4.9 Estimated mean head circumference z-score and 95% CI by the latency from last ACTORDS dose to birth..... 137

3.4.5.1 Knee-ankle length growth curves by corrected age..... 140

3.4.5.2 Estimated mean knee-ankle length and 95% CI..... 143

3.4.5.3 Estimated mean knee-ankle length and 95% CI by gestational age at birth..... 145

3.4.5.4 Estimated mean knee-ankle length and 95% CI by the number of ACTORDS treatment doses received..... 146

3.4.5.5. Estimated mean knee-ankle length and 95% CI by the latency from last ACTORDS dose to birth..... 147

3.4.6.1 Estimated mean ponderal index (g/cm^3) and 95% CI..... 150

4.4.1.1 In-depth Growth and Neurodevelopment Trial Profile 175

ABSTRACT

Introduction

A single course of prenatal corticosteroids offers no benefits for infants born seven days after treatment. Repeat corticosteroid treatment may improve health outcomes, but with possible adverse effects. This thesis aimed to examine the effects of repeat prenatal corticosteroids on infant growth and neurodevelopment.

Methods

Women at risk of preterm birth more than seven days after a single course of prenatal corticosteroids, who gave informed written consent, were randomised to receive weekly repeat dose corticosteroids or placebo, if still at risk, until 32 weeks gestation. Infant growth was assessed at birth, day three, weekly to four weeks, monthly to four months of age and at 7¼ months corrected age (CA). Neurodevelopmental milestones were assessed at four and eight months CA and novelty preference at 7 ¼ months CA.

Results

One hundred and forty seven infants were randomised. Repeat corticosteroid treatment reduced the weight z-score at birth, four months following birth and at 7¼ months CA, compared with placebo. Total body length z-score and knee-ankle length were reduced at birth for repeat corticosteroid infants, compared with placebo. Total body length z-score was unaffected by repeat corticosteroid treatment from day three to 7¼ months CA. Knee-ankle length was reduced with repeat corticosteroid exposure up to three months following birth, compared with placebo. Head circumference z-scores were unaffected by repeat

corticosteroid treatment from birth to 7¼ months CA. Repeat corticosteroids reduced personal-social development at eight, but not four months CA, compared with placebo. Repeat corticosteroids did not reduce communication, gross motor, fine motor and problem solving scores at four or eight months CA, did not increase the number of infants screened at risk of developmental delay and did not reduce novelty preference, compared with placebo.

Conclusions

Repeat prenatal corticosteroids reduce weight, length and knee-ankle length at birth, although only infant weight remained reduced at 7¼ months CA. No adverse effects on infant neurodevelopment were seen for repeat corticosteroid treated infants, apart from a reduction in personal-social development at eight months CA. Confirmation of and further assessment as to the long-term consequences of these observed effects is required.

DECLARATION

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 a copy of my thesis, when deposited in the University Library, being available for loan and photocopy.

Kristin McLaughlin

January 2003

ACKNOWLEDGEMENTS

It is a pleasure to thank the many people who have supported me in the production of this thesis. I would like to thank my supervisor, Associate Professor Caroline Crowther, for her guidance, support and inspiration throughout the course of this work. I am most grateful to all the women, their infants and families who have participated in this trial.

I would like to thank the ACTORDS Trial steering committee for allowing me to work as part of the ACTORDS team. Thank you to the staff of the Women's and Children's Hospital, Adelaide, for their assistance with this project. Thank you to Pat Ashwood, ACTORDS Trial Coordinator, for her help in recruiting women to this trial and in the collection of trial entry, birth and clinical neonatal data. I thank Professor Jeffrey Robinson and Associate Professor Ross Haslam for their helpful discussions on infant growth and neurodevelopment.

Special thanks to the staff of the Maternal and Perinatal Clinical Trials Unit, for their support, for their confidence in me, and for their continuous supply of cake! Thank you to Sarah Russell for her construction of the database used for data entry and data management and to Kristyn Willson for her patience and good humour in guiding me through the statistical analyses.

I would like to thank Meaghan Coyle, Dr Jodie Dodd, Alice Rumbold and Dr Caroline Smith for the support and encouragement only fellow PhD students can provide. I would like to thank Pam Carroll and Aaron McLaughlin for just being there. To my family, friends and partner for their support and patience in the completion of this project.

Financial support for these studies came from a variety of sources that included the National Health and Medical Research Council, the Channel 7 Research Foundation, the Women's and Children's Hospital Research Foundation and the Ramaciotti Foundation. Thank you to the Perinatal Society of Australia and New Zealand for financial support to attend the Perinatal Society conferences. Finally, I am indebted to the Department of Obstetrics and Gynaecology at The University of Adelaide, for their support throughout my candidature.

AUTHOR'S CONTRIBUTION

I was responsible for the conceptualisation, design and development of the protocols and coordination of The In-depth Growth and Neurodevelopment Trial. I sought ethics approval from the Women's and Children's Hospital Ethics Committee for the trial, developed the data collection forms and obtained the required equipment (excepting the neonatal knemometer). I was responsible for arranging all appointments for the growth and neurodevelopmental assessments and pursuing missed appointments. All growth and neurodevelopmental data were collected by myself, at the Women's and Children's Hospital, at other local and regional hospitals or by home visit as required. I was responsible for sending all four and eight month neurodevelopment questionnaires and pursuing overdue developmental questionnaires by post and telephone and traced 'lost' participants in the trial by telephone when required.

The ACTORDS Trial (Australasian Collaborative Trial of Repeat Doses of Corticosteroids for the Prevention of Neonatal Respiratory Disease) coordinator, Ms Pat Ashwood, primarily conducted recruitment to the ACTORDS Trial and the completion of the ACTORDS Trial data forms, though I assisted in these tasks when required.

I was responsible for the entry and cleaning of all the data presented in this thesis. I undertook all statistical analyses, with guidance from Ms Kristyn Willson, our statistician.

1. LITERATURE REVIEW

1.1. PURPOSE AND SCOPE

The purpose of this review is to provide the background and justification for the current study of the effect of the administration of repeat prenatal corticosteroids, to women at risk of preterm birth, on infant growth and neurodevelopment. This review will initially address the public health issue of preterm birth and its short and long-term sequelae. The benefits of single course prenatal corticosteroid therapy and the time frame over which these benefits persist will be identified. Current clinical practice, recommendations for practice and the available evidence on the safety and efficacy of repeat prenatal corticosteroids will be examined. The primary focus of this review will be the effects of prenatal corticosteroids on size at birth, infant growth and neurodevelopment, in both animal models and in humans. The rationale for and the methodology of the Australasian Collaborative Trial of Repeat Doses of Corticosteroids for the Prevention of Neonatal Respiratory Disease (ACTORDS) will be presented. Finally, the aims and hypotheses of this thesis, which arise from this literature review, will be outlined.

1.2. PRETERM BIRTH

Preterm birth (birth prior to 37 weeks gestation) is a major cause of perinatal morbidity and mortality. In Australia, over 17,000 women give birth preterm each year, of which around ten percent give birth extremely preterm (20-27 weeks gestation) and a further ten percent give birth very preterm (28-31 weeks gestation) (Nassar & Sullivan 2001). Respiratory distress syndrome, which arises as a result of pulmonary immaturity, is one of the most common causes of morbidity and mortality in infants born preterm and affects more than half of all

infants admitted to Australian and New Zealand neonatal intensive care units (Donoghue 2002). Respiratory distress syndrome is gestational age dependent, increasing in incidence with decreasing gestational age. Infants born preterm are at high risk of other morbidities including peri/intraventricular haemorrhage, retinopathy of prematurity, patent ductus arteriosus, necrotising enterocolitis and sepsis.

1.2.1. SEQUELAE OF PRETERM BIRTH

Survivors of preterm birth are at increased risk of long-term neurological sequelae. A neonatal trial examining the efficacy of indomethacin prophylaxis in extremely low birth weight infants reported 46 percent of the placebo group infants were either deceased or had a significant neurosensory impairment at 18 months of age, corrected for gestation (Schmidt *et al.* 2001). Meta-analysis of case-control studies on the cognitive and behavioural outcomes for school age children born preterm indicates ex-preterm infants have lower cognitive scores, are more likely to display externalising or internalising behaviour and are at increased risk of developing attention deficit/hyperactivity disorder, when compared with children born at term (Bhutta *et al.* 2002). This reduction in cognitive scores at school age is directly proportional to the gestational age and weight at birth.

Preterm birth and its sequelae place significant economic pressure on the health care system and considerable social and economic burdens on families. Neonatal intensive care costs of very low birth weight infants are substantial, particularly for those born extremely preterm (Rogowshi 1999). Infants born preterm are more likely to require long-term medication, supportive services (including physiotherapy and orthoptic treatment) and readmission to hospital in their first year, compared with infants born at term (Bucher *et al.* 2002). Families

of infants born preterm, in both the short and long term experience significant psychological and economic stress. Interventions to reduce the incidence of preterm birth and its short and long-term health, social and economic consequences remain major challenges (Goldenberg & Jobe 2001).

1.2.2. FETAL AND INFANT GROWTH AND ITS LONG TERM CONSEQUENCES

Birth weight is a strong marker of perinatal morbidity and mortality (Wilcox *et al.* 1995) and is positively associated with cognition and educational attainment in adulthood (Richards *et al.* 2002). Small body length and low ponderal index at birth has been associated with developmental delay in infancy, increased infant hospitalisations and increased infant mortality (Morris *et al.* 1998). In the early 1990s, Professor David Barker proposed that poor growth *in utero* and during infancy, programs physiological systems, resulting in an increased risk of diseases in adulthood; including cardiovascular disease and non-insulin dependent diabetes mellitus (Barker 1992; Barker 1995a; Barker 1995b). This proposition is commonly known as the Fetal Origins of Adult Disease hypothesis.

During infancy, the rate of growth varies, with some infants exhibiting rapid "catch-up" growth, which may compensate for small size at birth. Rapid childhood growth in infants born small at birth has been associated with an increased risk of raised blood pressure (Huxley *et al.* 2000), childhood obesity (Ong *et al.* 2000), psychological distress in adulthood (Cheung *et al.* 2002) and increased mortality from coronary heart disease (Eriksson *et al.* 1999). Given these findings, it is clear that size at birth, and growth during infancy is of great importance in terms of later health outcomes.

1.3. SINGLE COURSE PRENATAL CORTICOSTEROIDS

In 1969, Sir Professor Mont Liggins reported that prenatal infusion of dexamethasone to fetal lambs accelerated their lung functional maturation (Liggins 1969). A subsequent randomised controlled trial of 1068 women at risk of preterm birth (<37 weeks gestation) examined the effect of the administration of intramuscular betamethasone on the incidence of neonatal respiratory distress syndrome (Liggins & Howie 1972; Howie & Liggins 1977; Howie & Liggins 1982). Infants exposed to prenatal corticosteroids were less likely to develop respiratory distress syndrome (odds ratio (OR) 0.56, 95% confidence intervals (CI) 0.39, 0.80) and had a significantly reduced risk of neonatal death (OR 0.58, 95% CI 0.38, 0.89), compared with placebo group infants.

The Cochrane systematic review on prophylactic corticosteroids for preterm birth, that included 18 randomised controlled trials, evaluated the efficacy of a single course of prenatal corticosteroids in reducing neonatal morbidity and mortality (Crowley 2003). Administration of a single course of prenatal corticosteroids significantly reduced the risk of respiratory distress syndrome (OR 0.53, 95% CI 0.44, 0.63; 18 trials including 3,735 infants). No statistically significant reduction in the risk of respiratory distress syndrome was reported for infants born less than 24 hours after corticosteroid administration (OR 0.70, 95% CI 0.43, 1.16; 6 trials including 349 infants), though infants born more than 24 hours and less than seven days after corticosteroid treatment had a significantly reduced risk of respiratory distress syndrome (OR 0.38, 95% CI 0.25, 0.57; 4 trials including 728 infants).

Exposure to prenatal corticosteroids was associated with a reduction in neonatal mortality (OR 0.60, 95% CI 0.48, 0.75; 14 trials including 3,517 infants) and intraventricular

haemorrhage diagnosed by ultrasound (OR 0.48, 95% CI 0.32, 0.72; 4 trials including 596 infants) (Crowley 2003). There was no statistically significant reduction in the risk of necrotising enterocolitis (OR 0.59, 95% CI 0.32, 1.09; 4 trials including 1,154 infants), chronic lung disease (OR 1.57, 95% CI 0.87, 2.84; 3 trials including 411 infants), fetal/neonatal infection (OR 0.82, 95% CI 0.57, 1.19; 15 trials including 2,675 infants), maternal infection (OR 1.31, 95% CI 0.99, 1.73; 11 trials including 2,109 infants) or long-term neurological abnormalities (OR 0.62, 95% CI 0.36, 1.08; 3 trials including 778 infants) between corticosteroid treated women and their infants and control/placebo women and their infants.

Respiratory distress syndrome is a significant contributor to the high cost of care for infants born preterm. In 1992, the average hospital charges for the care of a preterm infant with respiratory distress syndrome was US$48,686, compared with an average of US$10,056 for a preterm infant without respiratory distress syndrome (Simpson & Lynch 1995). The administration of a single course of prenatal corticosteroids prior to preterm birth confers significant economic benefit. Modelling of the estimated cost effectiveness of single-course prenatal corticosteroid treatment in infants weighing less than 2kg at birth using the Crowley systematic review estimates (Crowley 2003) reported a US$326,200 saving for each 100 infants treated (Simpson & Lynch 1995). A similar economic evaluation in the United Kingdom reported a cost reduction of 10 percent with the administration of a single course of prenatal corticosteroids to women giving birth at less than 35 weeks gestation (Mugford *et al.* 1991).

In 1995, the National Institutes of Health (NIH) convened a Consensus Development

Conference to evaluate the scientific evidence for the use of a single course of prenatal corticosteroids (National Institutes of Health Consensus Development Panel 1995). This conference examined the evidence for the short and long-term benefits and adverse effects of single-course prenatal corticosteroid treatment, to develop recommendations for their use in clinical practice. The panel concluded that the benefits of a single course of prenatal corticosteroids administered prior to preterm birth greatly outweighed any potential risks and should be administered to women at risk of preterm birth from 24-34 weeks gestation, with optimal benefits for infants born more than 24 hours and less than seven days following treatment.

A single course of prenatal corticosteroids given prior to preterm birth has become routine clinical practice in Australia and New Zealand. Just over 80 percent of infants born at less than 34 weeks gestation who are admitted to level three nurseries in Australia and New Zealand receive prenatal corticosteroid therapy, with two-thirds receiving a complete course (two doses 24 hours apart of 11.4mg betamethasone intramuscularly, or four doses 12 hours apart of 6mg dexamethasone intramuscularly) (Donoghue 2002).

1.3.1. HOW DO PRENATAL CORTICOSTEROIDS WORK?

The administration of prenatal corticosteroids prior to preterm birth has several effects on the developing lung. Corticosteroid treatment increases tissue and alveolar surfactant, increases lung compliance, decreases vascular permeability, matures parenchymal structure, improves the clearance of lung water and enhances the response to surfactant treatment, thereby improving neonatal respiratory function, reducing morbidity and mortality (Ballard & Ballard 1995).

1.3.2. HOW MAY PRENATAL CORTICOSTEROIDS ALTER GROWTH?

Increased fetal plasma cortisol modifies the cell cycle, from proliferation to differentiation, resulting in the maturation of fetal tissues close to birth, including the liver, lung and gut, to prepare for extra-uterine life. These maturational changes occur at the expense of fetal growth. Fetal growth is regulated by maternal, placental and fetal factors and involves a tight balance between the accretion of tissue and its differentiation. Corticosteroids are potent inhibitors of cell growth and DNA replication and induce cell differentiation and maturation in fetal tissues (Fowden 1995). Glucocorticoids readily cross the placenta, as they are highly lipophilic. Throughout gestation, the fetus is exposed to low levels of glucocorticoids, as maternal cortisol is inactivated in the placenta. In the sheep during late gestation, the fetal plasma cortisol concentration rises, and is associated with a reduction in the rate of fetal growth (Fowden *et al.* 1996). There is no reduction in the rate of fetal growth in adrenalectomised lambs at term, suggesting that the fetal hypothalamic-pituitary-adrenal (HPA) axis is the source of this cortisol surge (Fowden *et al.* 1996). Fetal lambs, infused with exogenous cortisol for five days prior to preterm birth exhibit plasma cortisol concentrations similar to fetal sheep at term (Fowden *et al.* 1996). The administration of exogenous cortisol is associated with a reduction in the rate of fetal growth.

The maternal administration of exogenous corticosteroids in preparation for preterm birth induces maturation in fetal tissues, including the lung. However the increased concentrations of glucocorticoids in the fetal circulation would be expected to reduce fetal growth.

1.3.3. HOW MAY PRENATAL CORTICOSTEROIDS ALTER NEURODEVELOPMENT?

Although prenatal corticosteroid treatment confers significant benefit (Crowley 2003), there is concern that exposure to corticosteroids may impair neurodevelopment. In particular, concern has been raised following the report that the administration of postnatal corticosteroids to preterm infants for chronic lung disease is associated with an increased risk of motor dysfunction (Doyle & Davis 2000).

Several studies in the animal model have raised concern as to the adverse effects of prenatal corticosteroids on neurodevelopment. Prenatal dexamethasone treatment of pregnant Rhesus monkeys has been demonstrated to induce a dose-dependent degeneration of hippocampal pyramidal neurons in the *cornu ammonis* (CA) regions in the fetal brain, both preterm and at term (Uno *et al.* 1994). Neurons in the hippocampus contain high concentrations of glucocorticoid receptors and neuronal damage may occur through the binding of the glucocorticoids to type II receptors, which inhibits cellular glucose uptake and induces interneuronal accumulation of calcium (Horner *et al.* 1990). These studies suggest the administration of prenatal corticosteroids prior to preterm birth may adversely affect neurodevelopment.

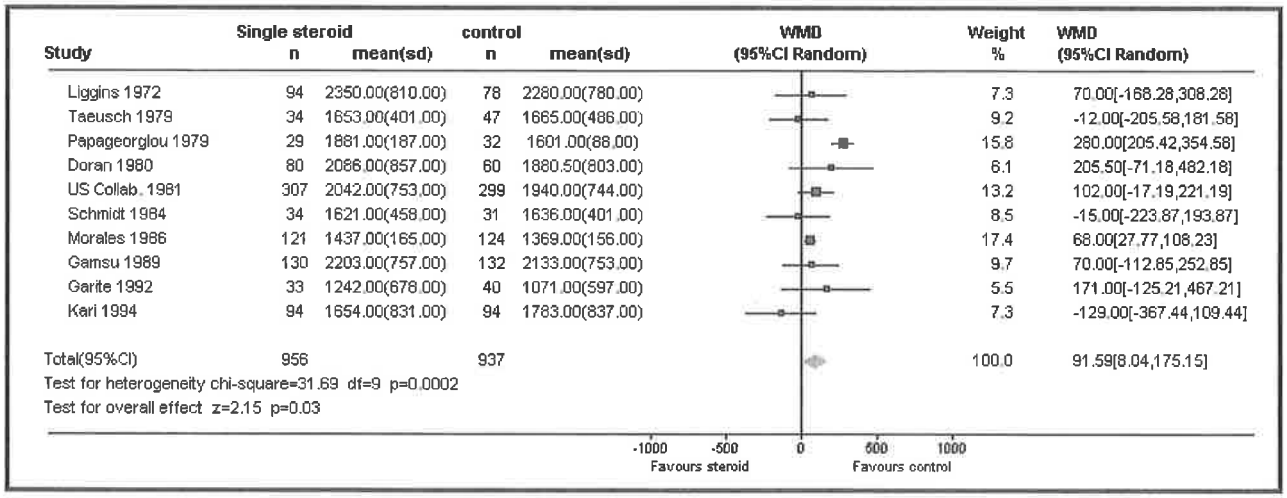
1.3.4. SINGLE COURSE PRENATAL CORTICOSTEROIDS AND SIZE AT BIRTH

The Cochrane systematic review (Crowley 2003) on prophylactic corticosteroids prior to preterm birth provides the best evidence to evaluate the effects of a single course of prenatal corticosteroids on size at birth. However, this review does not report any outcomes of size at birth; neither have previous versions of this review (Crowley 1995a; Crowley 1995b). To

examine the effect of a single course of prenatal corticosteroids on size at birth, I extracted growth measures from the reports of the 18 randomised controlled trials included in the Cochrane systematic review on prophylactic corticosteroids for preterm birth (Crowley 2003). Ten of the randomised controlled trials reported the outcome of birth weight for infants exposed to a single course of prenatal corticosteroids, compared with placebo/control/no treatment (Liggins & Howie 1972; Papageorgiou *et al.* 1979; Taeusch *et al.* 1979; Doran *et al.* 1980; Collaborative Group on Antenatal Steroid Therapy 1981; Schmidt *et al.* 1984; Morales *et al.* 1986; Gamsu *et al.* 1989; Garite *et al.* 1992; Kari *et al.* 1994).

Exposure to a single course of prenatal corticosteroids was associated with an average 91.59 gram increase in weight at birth (weighted mean difference (WMD) 91.59 grams, 95% CI 8.04, 175.15), compared with infants not exposed (Figure 1.3.4.1). In the meta-analysis of birth weight, there was significant heterogeneity (variation in the treatment effect between the included trials, beyond that expected by chance). This may reflect the different populations of infants involved in each of the included trials, or the reporting of outcomes for specific subgroups of infants within the trials. Gestational age at birth was not significantly different when infants exposed to single course corticosteroids and placebo/control/no treatment were compared (WMD 5.69 days 95% CI -5.53, 16.91), suggesting the increased birth weight associated with single course corticosteroid treatment was not a result of differing gestational ages between the two groups. One of the included trials reported the outcome of length at birth (Papageorgiou *et al.* 1979), which showed that infants exposed to a single course of prenatal corticosteroids were born on average 0.78 cm longer (95% CI 0.40, 1.16, $p<0.01$) than infants not exposed.

Figure 1.3.4.1 Birth weight (grams) after single course prenatal corticosteroids compared with placebo/control/no treatment



1.3.5. SINGLE COURSE PRENATAL CORTICOSTEROIDS AND LONG-TERM GROWTH

The best available evidence on the long-term growth effects of exposure to a single course of prenatal corticosteroids comes from the follow-up reports of infants involved in three of the randomised controlled trials of single course prenatal corticosteroid therapy; the New Zealand Trial (MacArthur *et al.* 1982), the US Collaborative Trial (Collaborative Group on Antenatal Steroid Therapy 1984) and the Netherlands Trial (Smolders-de Haas *et al.* 1990; Dessens *et al.* 2000).

Assessment of the growth of surviving children involved in the first randomised controlled trial of single prenatal corticosteroid treatment, the New Zealand Trial (Liggins & Howie 1972; Howie & Liggins 1977; Howie & Liggins 1982), was conducted at six years of age (MacArthur *et al.* 1982), by researchers blinded to the original treatment allocation. There were no statistically significant differences in overall weight or height at six years of age

between corticosteroid and placebo group infants. Similarly, there were no differences in weight or height between the two treatment groups when male children were compared. However, female children exposed to a single course of prenatal corticosteroids were significantly taller and heavier than those female survivors who were allocated to the placebo group. There were no statistically significant differences in head circumference between the two treatment groups, when all children, male and female survivors were compared. The loss of participants between trial entry and this study at six years of age was moderate, with 18 percent of surviving infants not assessed.

Infants randomised to the US Collaborative Trial (Collaborative Group on Antenatal Steroid Therapy 1981) were assessed over the first three years after birth; at term (40 weeks), nine, 18 and 36 months of age (Collaborative Group on Antenatal Steroid Therapy 1984). No significant differences were found between infants exposed to a single course of prenatal corticosteroids or placebo in weight or length measured at term and at nine months of age. At 18 and 36 months however, corticosteroid treated infants were three percent heavier in weight and three percent longer in length compared with placebo infants. There were no differences in head circumference between corticosteroid treated infants and control infants at term, nine, 18 and 36 months of age. Although observer bias was limited by blinding study personnel and participants to the original treatment allocation, bias may be introduced by the high loss to follow-up, with 37 percent of surviving infants not assessed at 36 months.

Assessment of children involved in the Netherlands Trial (Schutte *et al.* 1980) at 10-12 years of age by investigators blinded to treatment allocation reported no statistically significant differences in childhood growth, measured by height, weight and head circumference between

corticosteroid and placebo group infants (Smolders-de Haas *et al.* 1990). The sample size of this study was small (n=78), with one-quarter of surviving infants unable to be assessed. Further follow-up of these children to 20 years of age, again by researchers blinded to the treatment allocation, revealed no statistically significant differences in growth as measured by height, weight and head circumference after exposure to a single course of prenatal corticosteroids, compared with placebo (Dessens *et al.* 2000).

In summary, the randomised clinical trials that examined growth following corticosteroid treatment show that exposure to a single course of prenatal corticosteroids, compared with placebo, does not reduce size at birth or childhood growth. Indeed birth weight is actually increased with exposure to a single course of prenatal corticosteroids.

1.3.6. SINGLE COURSE PRENATAL CORTICOSTEROIDS AND NEURODEVELOPMENT

Follow-up studies of infants involved in three of the randomised controlled trials of single prenatal corticosteroid therapy provides the best evidence with which to assess the neurodevelopmental effects of exposure to a single course of prenatal corticosteroids, the New Zealand Trial (MacArthur *et al.* 1981; MacArthur *et al.* 1982), the US Collaborative Trial (Collaborative Group on Antenatal Steroid Therapy 1984) and the Netherlands Trial (Schmand *et al.* 1990; Dessens *et al.* 2000).

Cognitive and psychosocial development of infants involved in the randomised controlled trial of single course corticosteroid treatment from New Zealand (Liggins & Howie 1972; Howie

& Liggins 1977; Howie & Liggins 1982) were examined at four (MacArthur *et al.* 1981) and six years of age (MacArthur *et al.* 1982). All study investigators and participants were blinded to the original treatment group allocation. Assessment of psychometrics (using Stanford-Binet IQ Test, Peabody Picture Vocabulary Test and Frostig Developmental Test of Visual Perception), speech, social maturity and developmental milestones at four years of age revealed no statistically significant differences between corticosteroid treated and placebo group infants (MacArthur *et al.* 1981). Completeness of follow-up was good, with 85 percent of surviving children assessed at four years of age. At six years of age, assessment of school progress, speech, language and cognitive development showed no statistically significant differences in performance for corticosteroid treated infants, compared with placebo (MacArthur *et al.* 1982). Eighty-two percent of surviving infants were assessed at six years of age.

Follow-up of infants involved in the US Collaborative Trial (Collaborative Group on Antenatal Steroid Therapy 1981), by investigators blinded to treatment group allocation, involved neurologic assessment at term, nine, 18 and 36 months, completion of the Bayley Scales of Infant Development at nine and 18 months and the McCarthy General Cognitive Index at 36 months (Collaborative Group on Antenatal Steroid Therapy 1984). No statistically significant differences were reported between corticosteroid and placebo group infants for each of these assessments, at term, nine, 18 and 36 months of age. These results must be interpreted with caution given the high loss to follow-up, with 37 percent of surviving infants not assessed at 36 months.

Assessment of intelligence and reasoning, memory, visual perception, motor development,

scholastic achievement and social and emotional functioning were conducted on children involved in the Netherlands Trial of single course prenatal corticosteroid treatment at 10-12 years of age (Schmand *et al.* 1990). There were no statistically significant differences between the two treatment groups for these psychological assessments. Further assessment of this group of children at 20 years of age revealed no differences in the level of secondary education attained, level of professional training and intellectual functioning between those exposed to corticosteroids and those in the placebo group (Dessens *et al.* 2000). The follow-up rates for these assessments varied, with 88 percent of survivors assessed at 10-12 years, and 80 percent at 20 years. Comparisons at 20 years suggested non-responders were similar to those who participated, in terms of treatment group allocation, sex, gestational age at birth and birth weight (Dessens *et al.* 2000).

In summary, these follow-up studies of infants exposed to a single course of prenatal corticosteroids compared with placebo show no long-term adverse neurological effects of a single course of prenatal corticosteroids.

1.3.7. DO PRENATAL CORTICOSTEROIDS CONFER BENEFITS MORE THAN SEVEN DAYS AFTER THEIR ADMINISTRATION?

It is widely accepted that there is no reduction in the risk of respiratory distress syndrome for infants who remain undelivered more than seven days following a single course of prenatal corticosteroids. This stemmed from the reports of the first randomised controlled trial on this topic, which stated "Effectiveness does not persist for more than one week... If very premature delivery ... remains imminent, therapy should be repeated at intervals of not less than seven days...." (Howie & Liggins 1977). This view was reinforced by the Cochrane

meta-analysis of seven randomised controlled trials in which no reduction in respiratory distress syndrome was observed for infants treated with a single course of prenatal corticosteroids more than seven days prior to birth, compared with infants not exposed (OR 0.63, 95% CI 0.32, 1.26) (Crowley 1995a). However, this is inconsistent with an updated Cochrane meta-analysis, which included data from only three of these trials, which reported a significant reduction in respiratory distress syndrome for infants born more than seven days following treatment (OR 0.41, 95% CI 0.18, 0.98) (Crowley 2003). This discrepancy has been resolved by a recent systematic review (McLaughlin *et al.* 2003a), which clarified the currently available evidence from published (Liggins & Howie 1972; Howie & Liggins 1977; Doran *et al.* 1980; Schutte *et al.* 1980; Teramo *et al.* 1980; Collaborative Group on Antenatal Steroid Therapy 1981; Howie & Liggins 1982; Morales *et al.* 1986; Garite *et al.* 1992), and previously unpublished data now available from the New Zealand Trial. Meta-analysis of the seven included trials, involving 862 infants who remained undelivered more than seven days after trial entry, revealed no reduction in the risk of respiratory distress syndrome (relative risk (RR) 0.72, 95% CI 0.49, 1.07; 7 trials including 862 infants), or stillbirth (RR 1.67, 95% CI 0.86, 3.25; 3 trials including 732 infants) for corticosteroid treated infants compared with placebo/control infants (McLaughlin *et al.* 2003a). Corticosteroid exposed infants were found to have triple the risk of neonatal death (RR 3.24, 95% CI 1.32, 7.96; 1 trial including 437 infants, p=0.01), and a doubling of perinatal mortality (RR 2.13, 95% CI 1.27, 3.57; 3 trials including 732 infants, p<0.01) compared with placebo/control infants. Corticosteroid treated infants were born on average five days earlier than control infants (95% CI -9.15, -0.85 days; 1 trial including 437 infants, p=0.02) and their mothers were more likely to have chorioamnionitis (RR 2.91, 95% CI 1.25, 6.74; 1 trial including 448 women, p=0.01) (McLaughlin *et al.* 2003a).

In summary, treatment with a single course of prenatal corticosteroids within 24 hours and seven days of birth confers significant benefit to infants born preterm (Crowley 2003). However, for infants who remain undelivered more than seven days after corticosteroid treatment, there is no reduction in the risk of respiratory distress syndrome and an increase in the risk of neonatal death and perinatal mortality (McLaughlin *et al.* 2003a).

1.3.8. WHO GIVES BIRTH MORE THAN SEVEN DAYS AFTER INITIAL CORTICOSTEROID TREATMENT?

Given the brief time frame of effectiveness of a single course of corticosteroids, the substantial benefits for infants born within seven days of treatment (Crowley 2003), and the potential for increased mortality for infants born more than seven days after treatment (McLaughlin *et al.* 2003a), the timing of the administration of prenatal corticosteroids to women at risk of preterm birth is crucial. In a systematic review (McLaughlin *et al.* 2003a), almost 40 percent of infants remained undelivered more than seven days after a single course of corticosteroids. A cohort study, examining the timing of prenatal corticosteroid administration in relation to birth, reported around three-quarters of women received their initial corticosteroid course more than a week prior to birth (Skoll *et al.* 2002). These reports highlight the limited ability of clinicians to predict which women at risk of preterm birth will give birth within the seven days of benefit provided by a single course of prenatal corticosteroids. Additionally, these studies reinforce the large number of women who give birth outside the time frame of benefit provided by a single course of prenatal corticosteroids.

Women who remain undelivered more than seven days following a single course of prenatal corticosteroids and who give birth very preterm (<34 weeks), differ significantly in terms of their demographics, previous and current pregnancy history when compared with those women who give birth within seven days (McLaughlin *et al.* 2002b). Women with a history of infertility treatment, who have had a previous early or late miscarriage or perinatal loss and have pregnancy complications requiring hospital admission including oligohydramnios, antepartum haemorrhage, hypertension and amnionitis are more likely to remain undelivered more than seven days following initial corticosteroid treatment, compared with women without these previous adverse outcomes or pregnancy complications.

The risks of immaturity increase with decreasing gestational age at birth. Initial corticosteroid treatment was given in this cohort study, on average, 1.6 weeks earlier to women who remained undelivered more than seven days following corticosteroid therapy (McLaughlin *et al.* 2002b). Women who received initial prenatal corticosteroid treatment before 28 weeks gestation were 50 percent more likely to give birth more than seven days following treatment, compared with those women treated at later gestational ages. The adverse event leading to the administration of a course of prenatal corticosteroids occurred at an earlier gestational age in women who remained undelivered more than seven days later, compared with women who gave birth within seven days.

This cohort study demonstrates that women who remain undelivered more than seven days following a single course of prenatal corticosteroids, in whom repeat prenatal corticosteroid therapy may be considered, are a higher risk group compared with women who give birth within seven days of treatment.

1.4. REPEAT PRENATAL CORTICOSTEROIDS

It is unclear whether health outcomes for women and their babies, who remain undelivered and at risk of preterm birth more than seven days following an initial course of corticosteroids, may be improved without significant fetal, neonatal or maternal risk with the administration of repeat doses of prenatal corticosteroids.

1.4.1. CURRENT CLINICAL PRACTICE

Much of the evidence on the potential benefits and risks of repeat prenatal corticosteroid therapy is based on research conducted in both small and large animal models, where results may reflect species-specific effects. The existing evidence in humans is mainly in the form of retrospective and prospective cohorts, which report variable outcomes. These study designs have potential for bias. More recently, four randomised controlled trials, involving a total of 740 women have reported outcomes for women and their infants exposed to repeat corticosteroids compared with a single course (Guinn *et al.* 2001; Mercer *et al.* 2001b; Aghajafari *et al.* 2002b; McEvoy *et al.* 2002). There are five randomised controlled trials currently underway in Australia, Canada, the United States, the United Kingdom and Norway to determine the safety and efficacy of the administration of repeat dose prenatal corticosteroids to women who remain at risk of preterm birth following an initial course.

Despite the lack of good quality evidence as to the short and long term effects of repeat prenatal corticosteroids on infant and maternal outcomes, repeat prenatal corticosteroids are currently being used in clinical practice worldwide. Surveys of obstetricians in clinical practice in South Australia (Crowther *et al.* 1998), Australia (Quinlivan *et al.* 1998b) and the

United States (Erickson *et al.* 2001) have reported the use of repeat prenatal corticosteroids by up to 85 percent of respondents; in the United Kingdom they are used in 98 percent of delivery units (Brocklehurst *et al.* 1999). A recent survey reported a more limited use with 44 percent of obstetricians (n=332) and 21 percent of neonatologists (n=19) who practice in Australia and New Zealand recommending repeat prenatal corticosteroids be administered to women who remain at risk of preterm birth following a single course (McLaughlin & Crowther 2003b).

1.4.2. QUALITY OF THE EVIDENCE

When reviewing and interpreting the literature assessing the safety and efficacy of repeat prenatal corticosteroids, the 'quality' and 'level' of the evidence must be considered. The strength of evidence provided in the literature may be graded, using a system such as that used by the National Health and Medical Research Council (NHMRC 1999). Grading of research evidence in terms of its 'level', which reflects the study design and likelihood of bias is described in Table 1.4.2.1. Grading of 'quality' of research evidence assesses the methods used by the researchers to limit bias in their chosen study design and may include the quality of the methods used to minimise bias, the relevance of the study to the clinical question being examined and the precision and reproducibility of the results. Throughout this literature review, the evidence as to the potential benefits and risks of the administration of repeat prenatal corticosteroids will be critically appraised, applying these criteria.

Table 1.4.2.1 Designation of levels of evidence, adapted from (NHMRC 1999)

Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
Level II	Evidence obtained from at least one properly designed randomised controlled trial.
Level III – 1	Evidence obtained from well-designed pseudo-randomised controlled trials.
Level III – 2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group.
Level III – 3	Evidence obtained from comparative studies with historic control, two or more single-arm studies, or interrupted time series without a parallel control group.
Level IV	Evidence obtained from case series, either post-test or pre-test and post-test.

1.4.3. REPEAT PRENATAL CORTICOSTEROIDS – REVIEW OF THE ANIMAL STUDIES

Clinical outcomes

There is a considerable body of animal research evidence that examines the safety and efficacy of the administration of repeat doses of prenatal corticosteroids. A recent systematic review of these studies reported an improvement in measures of respiratory function with repeat corticosteroid treatment, compared with a single course (Aghajafari *et al.* 2002a).

Size at birth

The effect of repeat prenatal corticosteroids on size at birth has been assessed by several research groups in various animal models, including the rat (Welberg *et al.* 2001), mouse (Stewart *et al.* 1997; Stewart *et al.* 1998), guinea pig (McCabe *et al.* 2001), rabbit (Pratt *et al.* 1999a), sheep (Ikegami *et al.* 1997; Jobe *et al.* 1998a; Jobe *et al.* 1998b; Newnham *et al.* 1999; Sloboda *et al.* 2000; Willet *et al.* 2001; Moss *et al.* 2002) and Rhesus macaque (Novy &

Walsh 1983).

Increasing doses of maternally administered prenatal corticosteroids have been demonstrated to reduce weight at birth in mice (Stewart *et al.* 1997; Stewart *et al.* 1998), rats (Welberg *et al.* 2001) and rabbits (Pratt *et al.* 1999a). Repeated doses of maternally administered dexamethasone (total dose 10 mg/kg) reduce birth weight in guinea pigs compared with control, though this is statistically significant only in female offspring (McCabe *et al.* 2001).

Studies in the sheep model have consistently demonstrated a dose-responsive reduction in birth weight with increasing doses of prenatal corticosteroids to the mother (Ikegami *et al.* 1997; Jobe *et al.* 1998b), but not by direct injection to the fetus (Jobe *et al.* 1998a; Newnham *et al.* 1999). Reduction in birth weight, with maternally administered repeat prenatal corticosteroids, occurs in lambs born preterm (Ikegami *et al.* 1997; Jobe *et al.* 1998b; Quinlivan *et al.* 1998a; Newnham *et al.* 1999; Sloboda *et al.* 2000; Willet *et al.* 2001), and persists in lambs born at term (Jobe *et al.* 1998b; Quinlivan *et al.* 1998a; Sloboda *et al.* 2000; Willet *et al.* 2001; Moss *et al.* 2002). Similarly, reductions in fetal biometry measurements (occipital-snout diameter, biparietal diameter, femur length, abdominal circumference) (Jobe *et al.* 1998b; Quinlivan *et al.* 1998a; Newnham *et al.* 1999) and fetal organ size (spleen, liver, kidney, thymus, lung, heart and adrenal gland) (Quinlivan *et al.* 1998a; Newnham *et al.* 1999) have been reported with maternal administration of repeat prenatal corticosteroids. Exposure of Rhesus macaques to repeated doses of maternally administered dexamethasone significantly reduces weight at birth, brain, thymus, adrenal and spleen size, biparietal diameter, occipitofrontal diameter and head circumference, compared with controls (Novy & Walsh 1983).

Long-term growth

There is limited evidence with which to assess the effects of repeat prenatal corticosteroids on long-term growth in the animal model, with one study examining the effect in the mouse (Stewart *et al.* 1998), one in the rat (Welberg *et al.* 2001) and one in the sheep (Moss *et al.* 2002).

In the mouse, Stewart and colleagues' study reported no statistically significant difference in body weights of female offspring exposed to repeat prenatal corticosteroids compared with a single course, on postnatal days one, three, five and 120 (Stewart *et al.* 1998). When body weights of male offspring were compared, exposure to repeat prenatal corticosteroids was associated with significantly lower body weights on postnatal days one and three compared with single course. However, there were no differences in body weight between repeat and single course groups at day five or 120.

In the rat, maternal administration of dexamethasone throughout pregnancy reduces weight up to at least five months after birth compared with control (Welberg *et al.* 2001). Administration of dexamethasone in the last third of gestation reduces weight at birth, but there is no difference in weight at one month of age.

In sheep, Moss and colleagues assessed body weight gain during the first postnatal month, in 23 lambs who were randomised to receive either no treatment (n=5), saline treatment (day 104, 111 and 118; n=6), single prenatal corticosteroid treatment (0.5 mg/kg maternal body weight on day 104 and saline day 111 and 118; n=6) or repeat prenatal corticosteroid

treatment (0.5 mg/kg maternal body weight on day 104, 111 and 118; n=6) (Moss *et al.* 2002). There were no statistically significant differences in the rate of postnatal weight gain in the first month after birth, when lambs exposed to repeat or single course corticosteroids were compared. Similarly, there were no statistically significant differences in body weight in the first month after birth, when repeat corticosteroid lambs were compared with single course or untreated lambs.

Neurodevelopment

Much of the concern surrounding repeat prenatal corticosteroid treatment has arisen from studies on their effect on neurodevelopment and myelination in animal models. Several research groups have examined the effect of maternal repeat corticosteroid administration on neuroanatomy and function in mice (Stewart *et al.* 1997), rats (Welberg *et al.* 2001), sheep (Dunlop *et al.* 1997; Huang *et al.* 1999a; Quinlivan *et al.* 2000; Huang *et al.* 2001) and monkeys (Uno *et al.* 1990).

Assessment of the functional development of mice prenatally exposed to none, two, four or eight doses of 0.1mg betamethasone (with saline placebo) revealed no differences in geotaxis (an early neonatal vestibular and postural reflex), locomotor activity, developmental milestones (incisor eruptions, eye opening and genital development) or the development of the second generation of offspring by prenatal corticosteroid exposure (Stewart *et al.* 1997). Exposure of pregnant rats to prenatal dexamethasone, either throughout pregnancy (100µg/kg/day) or in the last third of gestation reduced exploratory behaviour in the adult offspring (Welberg *et al.* 2001). Exposure during the last third of gestation reduced exploration, behavioural responses and learning, in several developmental tests, at five to

eight months of age.

All of the published studies that have evaluated the effects of repeat prenatal corticosteroid exposure in the sheep model have arisen from a research group of international members, whose work is conducted in Western Australia. This group has examined the effect of repeated administration of prenatal corticosteroids on brain size and the myelination of several nerve tracts in the sheep.

The effect of maternal administration of prenatal betamethasone on fetal brain growth has been examined by comparing lambs born to ewes randomised to control (n=12, four weekly saline injections), single dose betamethasone (n=12, 0.5mg/kg betamethasone on day 104 and three weekly saline injections) or repeated betamethasone treatment (n=12, 0.5mg/kg betamethasone on days 104, 111, 118 and 124) (Huang *et al.* 1999a). Comparisons between repeat-corticosteroid lambs born preterm (n=6) and control lambs, revealed a reduction in the whole-brain weight (35.5±1.65 grams versus 42.5±1.65 grams) (mean ± standard error) and volume (31.6±1.56 ml versus 37.7±1.56 ml), cerebral weight (31.6±1.44 grams versus 37.8±1.53 grams) and volume (28.7±1.32 ml versus 34.3±1.32 ml), and reduced maximum cerebral anterior-posterior length (4.8±0.08 cm versus 5.3±0.08 cm), width (4.7±0.07 cm versus 4.9±0.07 cm) and depth (2.6±0.06 cm versus 2.9±0.06 cm). All these measures of brain size remained significantly reduced for repeat corticosteroid treated lambs born at term, compared with controls. A similar study however, of three lambs exposed to maternally administered repeat prenatal corticosteroids and three control lambs, delivered preterm, reported no differences in brain weight or volume between repeat-corticosteroid treated animals and controls (Dunlop *et al.* 1997).

Several studies have explored the effects of maternally administered repeat corticosteroids on myelination of the ovine central nervous system (Dunlop *et al.* 1997; Huang *et al.* 1999a; Quinlivan *et al.* 2000; Huang *et al.* 2001). Four doses of 0.5mg/kg of maternally administered prenatal corticosteroids have been demonstrated to impair optic nerve myelination in lambs born preterm (Dunlop *et al.* 1997). Repeat corticosteroid treated lambs had significantly more unmyelinated optic nerve axons, compared with control. The myelination of the fetal sciatic nerve is impaired in lambs exposed to four doses of maternally administered prenatal corticosteroids (0.5mg/kg betamethasone) delivered at term, compared with control (Quinlivan *et al.* 2000). However, no differences in the morphometry of the sciatic nerve were detected in lambs born preterm and the proportion of fully myelinated axons in the sciatic nerve did not differ by corticosteroid treatment in lambs born preterm or at term. Exposure to four doses of maternally administered 0.5mg/kg betamethasone did not reduce the number of axons in the corpus callosum in lambs born at term, compared with control (Huang *et al* 2001). The proportion of unmyelinated axons was significantly reduced for repeat corticosteroid treated lambs, as was the myelinated axon diameter and thickness of the myelin sheath, compared with control.

Prenatal maternal intramuscular administration of dexamethasone to Rhesus macaques at 132 days gestation (term 165 days) results in abnormal development of the hippocampal region of the brain (Uno *et al.* 1990). Within a few days of corticosteroid administration, degenerative changes were evident and fetuses born at term exhibited hippocampal pyramidal neurones with retarded cell differentiation and abnormal architecture.

Methodological issues

There are several factors that may introduce bias, and limit the translation of these results in the animal model, to humans. Studies in the sheep model typically use 0.5 mg/kg betamethasone for each corticosteroid course, as compared with the typical course of 0.35 mg/kg administered to women at risk of preterm birth (22.8 mg betamethasone with average maternal weight of 65kg). Furthermore, many of the studies compare a single course of corticosteroids with three or four doses of corticosteroids, in clinical practice, not all infants would be exposed to this number of repeat doses. Additionally, none of the studies in the sheep model reported sample size calculations, with some studies not reporting measures of variability in their data, such as a standard deviation, or standard error, making quality assessment difficult.

Much of the available evidence on the effect of maternally administered repeat corticosteroids on neurodevelopment is based on the sheep model, and interpretation of the results are limited by the different time frame of neural development in the fetal lamb, compared with the human. A report by Dobbing and Sands (1979) suggests that there is a spurt of brain growth, the timing of which is different in various species. This is a period of increased vulnerability of the brain to nutritional and other growth restriction. The spurt in brain growth in fetal lambs, the main animal model used to examine the effect of repeat prenatal corticosteroids, occurs prenatally. In contrast, the period of rapid growth in the human brain takes place at term. This suggests that the observed adverse effects of repeat prenatal corticosteroids on myelination and brain size in fetal sheep may be due to the increased susceptibility of the brain during the prenatal period, which occurs at term in the human.

A review by Huang and colleagues (Huang *et al.* 1999b) described the development of the central nervous system relative to birth in the rat, sheep, monkey and human. The interval from conception to eye opening (cecal period) relative to gestational period was compared between the species; 61 percent for the rat, 120 percent for the sheep, 134 percent for the monkey and 146 percent for the human (length of gestation as a percentage of the cecal period). Thus, at birth, the neonatal rat central nervous system is immature compared with the other species.

In the animal model, repeat prenatal corticosteroid treatment confers significant benefit in terms of respiratory function, though this is associated with a reduction in size at birth. The adverse effects of repeat prenatal corticosteroid treatment on myelination and brain size in the animal model are of great concern. However, given the differences in the time-course of brain maturation between species, caution should be exercised in the extrapolation of these data from the animal model to humans.

1.4.4. REPEAT PRENATAL CORTICOSTEROIDS – REVIEW OF THE HUMAN STUDIES

The current evidence as to the potential benefits and risks of repeat prenatal corticosteroid treatment is based on four randomised controlled trials, and many observational studies. This section of the review will examine the clinical outcomes following repeat prenatal corticosteroid treatment in humans, but will focus primarily on the effect of repeat prenatal corticosteroid exposure on size at birth, infant growth and neurodevelopment.

Randomised controlled trials

Methodologies of the four published randomised controlled trials that have evaluated the safety and efficacy of repeat prenatal corticosteroids are described in Table 1.4.4.1 (Guinn *et al.* 2001; Mercer *et al.* 2001b; Aghajafari *et al.* 2002b; McEvoy *et al.* 2002).

Table 1.4.4.1 Methodology of randomised controlled trials of repeat prenatal corticosteroids

Trial	Publication format	Treatment regimen	Trial population	Sample size
(Guinn *et al.* 2001)	Full paper	Repeat: 12mg betamethasone twice weekly to 34 weeks gestation Single: placebo	At risk of preterm birth 24-32^{+6} weeks who remained undelivered more than seven days after an initial course.	502 women -256 repeat -246 single
(Mercer *et al.* 2001b)	Abstract	Repeat: 12mg betamethasone twice weekly to 34 weeks Single: initial course of corticosteroids administered when pregnancy anticipated to last less than one week, prior to 35 weeks gestation; ie. single 'rescue dose'	Women at risk of preterm birth 23-32 weeks.	189 women (Unclear how many women randomised to each group)
(Aghajafari *et al.* 2002b)	Full paper	Repeat: 12 mg betamethasone twice weekly to 33 weeks Single: placebo	Women 24-30 weeks at continued risk of preterm birth >7 days after initial course.	12 women - 6 repeat - 6 single
(McEvoy *et al.* 2002)	Full paper	Repeat: 12mg betamethasone twice weekly to 34 weeks Single: placebo	Women 25-33 weeks gestation who remained undelivered and at risk of preterm birth more than seven days after an initial course.	37 women -19 single -18 repeat

Guinn et al (2001)

The largest randomised controlled trial of 502 women by Guinn and colleagues, whose methods are summarised in Table 1.4.4.1, reported no statistically significant difference in composite morbidity between infants exposed to repeat or single course prenatal corticosteroids (RR 0.80, 95% CI 0.59, 1.10) (Guinn *et al.* 2001). Composite morbidity was defined as the presence of either: severe respiratory distress syndrome, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising

enterocolitis proven sepsis or death between trial entry and hospital discharge. When composite morbidity was stratified by gestational age at birth, infants born from 24 to 27 weeks gestation who were exposed to repeat prenatal corticosteroids had significantly reduced composite morbidity when compared with single course infants (RR 0.80, 95% CI 0.65, 0.98). There were no statistically significant differences between repeat and single course infants when the risk of perinatal mortality, respiratory distress syndrome, bronchopulmonary dysplasia, any intraventricular haemorrhage, severe intraventricular haemorrhage, periventricular leukomalacia, proven sepsis or proven necrotising enterocolitis were examined. Of potential importance, a significant reduction in the risk of severe respiratory distress syndrome (defined as infants requiring mechanical ventilation for a minimum of 24 hours and surfactant therapy) was reported for infants exposed to repeat prenatal corticosteroids, compared with a single course (RR 0.63, 95% CI 0.44, 0.91).

The measures of growth reported provide some reassurance as no statistically significant difference was detected between the two treatment groups in terms of weight at birth, mean birth weight 2009.1 grams (standard deviation 858.7) for repeat corticosteroid infants and 2138.8 grams (standard deviation 875.8) for single course infants (p=0.10) (Guinn *et al.* 2001). This trial reported no statistically significant difference in mean head circumference at birth by corticosteroid exposure, 29.1 (4.0) cm for repeat course infants versus 29.4 (3.4) cm for single course infants (p=0.45). Similarly, there were no statistically significant differences in the distribution of birth weight by categories between repeat and single course corticosteroid infants.

There are several methodological concerns with this trial by Guinn and colleagues that may

limit the validity of these findings. The anticipated sample size of the trial was 1,000 women, to enable a 90 percent power to detect a one-third reduction in composite morbidity, from 25 percent to 16.5 percent, α=0.05 (Guinn *et al.* 2001). Trial recruitment was prematurely stopped at 502 women, as the investigators reported safety concerns (possibly due to the trend for increased risk of severe intraventricular haemorrhage) and their belief that there was little chance in detecting a significant difference in their composite morbidity primary endpoint between the two treatment groups. The early stopping of recruitment to this trial was highly criticised (Jenkins *et al.* 2002; Murphy *et al.* 2002), particularly for their calculations suggesting little chance of showing a significant difference with their anticipated sample size. Letters to the editor of the Journal of the American Medical Association (JAMA) emphasised the need for the completion of the ongoing trials, particularly given the optimistic findings of this trial for extremely preterm infants and the overall reduction in the risk severe respiratory distress syndrome.

Comparison of the groups of women randomised to repeat or single course prenatal corticosteroids in the Guinn trial reveals an imbalance between the treatment groups for multiple gestations, with 9.4 percent of the study population twins in the repeat corticosteroid group, compared with 14.2 percent in the single corticosteroid group. It is widely known that infants of multiple gestations have worse perinatal outcomes than singleton gestations, and an imbalance between the treatment groups for multiple gestations may introduce bias into the study.

Mercer et al (2001b)

The randomised controlled trial of 189 women by Mercer and colleagues, whose methods are

described in Table 1.4.4.1, reported no statistically significant reduction in the risk of respiratory distress syndrome, bronchopulmonary dysplasia or retinopathy of prematurity with exposure to repeat prenatal corticosteroids compared with a single course (Mercer *et al.* 2001b). The number of infants needed to treat with repeat prenatal corticosteroids to prevent one case of respiratory distress syndrome was calculated to be 14 (no confidence intervals given), with 22 infants needing to be treated to prevent one case of bronchopulmonary dysplasia. Repeat prenatal corticosteroid exposure did not increase the risk of amnionitis or neonatal sepsis. This study however, being only reported as an abstract, limits rigorous methodological assessment. The authors calculated the number of infants required in a study to evaluate each outcome (33 percent difference between groups, β=0.20, α=0.05), which ranged from 964 infants for the outcome of respiratory distress syndrome to 1608 to assess the outcome of bronchopulmonary dysplasia, clearly emphasising that the current trial was underpowered to detect clinically significant differences in neonatal outcomes.

No difference was reported in weight at birth (2260 grams repeat versus 2318 grams single), birth weight percentile (33rd repeat versus 36th single) or head circumference at birth (31cm repeat versus 32 cm single) between infants exposed to repeat or single course prenatal corticosteroids (Mercer *et al.* 2001b). The abstract publication of this trial did not report measures of variability of the growth measurements, such as the standard deviation or confidence intervals. A further abstract published from this trial examined the impact of the total corticosteroid dose on measures of growth including birth weight, percentile birth weight, length and head circumference at birth, when controlling for confounders (Mercer *et al.* 2001a). Prenatal corticosteroids were reported to exert a dose-dependent reduction in weight and length at birth. Each milligram increase in prenatal corticosteroid dose reduced

birth weight by 1.24 grams and head circumference by 0.008 cm. Prenatal corticosteroid dose was not associated with birth weight percentile, head circumference or latency.

McEvoy et al (2002)

The randomised controlled trial of 37 women by McEvoy and colleagues, whose methods are summarised in Table 1.4.4.1, reported no statistically significant difference in functional residual capacity or passive respiratory compliance within 24 hours of birth in infants exposed to repeat prenatal corticosteroids compared with a single course (McEvoy *et al.* 2002). No statistically significant difference in birth weight was found between repeat and single course corticosteroid treated infants, mean (standard deviation) 1767 grams (659) versus 1975 (740) grams (p=0.38) (McEvoy *et al.* 2001). There were no statistically significant differences between the groups in gestation at randomisation or at gestation birth. The sample size of this trial was very small, and had a power of only 0.40 to detect a difference in weight at birth between the two treatment groups, α=0.05.

Aghajafari et al (2002b)

Aghajafari and colleagues reported outcomes from participants in their pilot study of repeat versus single courses of prenatal corticosteroids, whose methods are summarised in Table 1.4.4.1 (Aghajafari *et al.* 2002b). Over the study period, 12 women were randomised to the trial, six women and their nine infants allocated to receive repeat corticosteroids and six women and their seven infants to receive placebo. The number and percentage of infants with each of the clinical outcomes was reported, but no statistical comparisons were made between the two treatment groups. Two infants in each of the treatment groups developed respiratory distress syndrome. The median (interquartile range) weight at birth for infants in the repeat

corticosteroid group was 1840 grams (735, 2360) and 2420 grams (1005, 3914) for single course infants. It is difficult to interpret the results of this study, given the extremely small sample size. This trial, with an anticipated sample size of 1900 women is currently underway in Canada.

To date, no randomised controlled trials have examined the effect of repeat prenatal corticosteroid treatment on infant growth or neurodevelopment.

Systematic reviews of the observational studies – clinical outcomes

Much of the human literature with which to assess the safety and efficacy of the administration of repeat prenatal corticosteroids is derived from observational studies, where any differences reported may reflect differences between the groups of women compared rather than the effect of repeat prenatal corticosteroids. Several research groups have systematically reviewed and meta-analysed these observational studies, in order to assess the effects of repeat prenatal corticosteroid exposure on maternal and neonatal outcomes (Aghajafari *et al.* 2001; Joy *et al.* 2001; McLaughlin & Crowther 2002a).

Aghajafari et al (2001)

The systematic review and meta-analysis by Aghajafari and colleagues included all observational studies published in English which compared repeat versus single prenatal corticosteroid therapy, given to women at increased risk of preterm birth, which reported clinical outcomes (Aghajafari *et al.* 2001). Studies that did not control for differences in gestational age at birth, and those published as abstracts were excluded. Eight studies were included in the systematic review (Ghidini *et al.* 1997; Banks *et al.* 1999; French *et al.* 1999;

Pratt *et al.* 1999b; Abbasi *et al.* 2000; Elimian *et al.* 2000; Smith *et al.* 2000b; Vermillion *et al.* 2000a). The quality of the studies was examined in terms of their data collection (prospective or retrospective), differences between treatment groups in terms of confounders and whether repeat corticosteroid use was part of hospital policy. Repeat prenatal corticosteroid treatment was associated with a significant reduction in the risk of respiratory distress syndrome, compared with a single course (OR 0.79, 95% CI 0.64, 0.98; 10 studies including 2,304 infants). There were no statistically significant differences in mortality, intraventricular haemorrhage, bronchopulmonary dysplasia or sepsis between infants exposed to repeat prenatal corticosteroids and those exposed to a single course. Women exposed to repeat prenatal corticosteroids were more likely however, to develop endometritis compared with single course women (OR 3.42, 95% CI 1.92, 6.11; 2 studies including 822 women), though there were no statistically significant differences between the groups for the outcomes of chorioamnionitis or maternal infection.

Joy et al (2001)

The meta-analysis conducted by Joy and colleagues, published as an abstract only, reviewed all published studies between 1970 and March 2001 on the efficacy of repeat versus single prenatal corticosteroids (Joy *et al.* 2001). Eight observational studies published as full papers and three observational studies reported as abstracts were included in the review, their quality was not assessed. They too report that respiratory distress syndrome was reduced for infants exposed to repeat prenatal corticosteroids, compared with a single course (OR 0.73, 95% CI 0.57, 0.95; 3,068 infants). No statistically significant differences were reported between the repeat and single course corticosteroid treated infants in terms of bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, patent ductus arteriosus,

neonatal sepsis or mortality. However, women exposed to repeat prenatal corticosteroids were more likely to develop endometritis, compared with single course women (OR 2.23, 95% CI 1.60, 3.12; 1,232 women), though there were no statistically significant differences between the groups when the incidence of maternal chorioamnionitis was compared.

McLaughlin & Crowther (2002a)

The systematic review and meta-analysis by McLaughlin and Crowther included all observational studies in which outcomes for women and their infants exposed to repeat prenatal corticosteroids were compared with women and their infants exposed to a single course, with data presented in a form able to be included in the review (McLaughlin & Crowther 2002a). Systematic review of 16 included observational studies revealed no statistically significant reduction in the risk of respiratory distress syndrome (RR 0.76, 95% CI 0.54, 1.07; 15 studies including 3,741 infants), any peri/intraventricular haemorrhage (RR 0.94, 95% CI 0.72, 1.22; 9 studies including 2,066 infants) or fetal/neonatal death (RR 0.84, 95% CI 0.42, 1.67; 12 studies including 3,301 infants) for infants exposed to repeat prenatal corticosteroids, when compared with those exposed to a single course (McLaughlin & Crowther 2002a). There was significant heterogeneity in the meta-analyses of respiratory distress syndrome and fetal/neonatal death, and a random effects model was used. There was no statistically significant increase in the risk of neonatal infection (RR 1.17, 95% CI 0.70, 1.96; 12 studies including 2,717 infants) or maternal chorioamnionitis (RR 1.59, 95% 0.98, 2.58; 8 studies including 1,891 women) with exposure to repeat prenatal corticosteroids, compared with a single course. The risk of respiratory distress syndrome was found to vary significantly by publication type, with a relative risk of 0.18 (95% CI 0.70, 0.48) for abstracts versus RR 0.89 (95% CI 0.78, 1.02) for full papers. The relative risk for respiratory distress

syndrome was lower for retrospective cohorts (RR 0.68, 95% CI 0.57, 0.82) compared with prospective cohorts (RR 1.10, 95% CI 0.90, 1.34).

Systematic review of the observational studies – size at birth

Much of the current evidence evaluating the safety and efficacy of repeat prenatal corticosteroids arises from observational studies, most of which are retrospective in design, which have compared women and their infants exposed to repeat corticosteroids with those exposed to a single course or no corticosteroids. The effect of repeat prenatal corticosteroids on size at birth reported by these observational studies are difficult to interpret, as a result of the potential biases of observational study methodologies. These factors include the potential differences between women who receive single or repeat prenatal corticosteroids, the aetiology of risk for preterm birth and the time frame between initial corticosteroid treatment and birth. In addition, it is difficult to obtain an overall summary of the effects of repeat prenatal corticosteroids on size at birth, with the many studies reporting conflicting results. Currently, The Cochrane Non-Randomised Studies Method Group is preparing recommendations for including non-randomised studies into systematic reviews. For the purposes of this literature review, I have used the Cochrane systematic review methodology to assess the effect of repeat prenatal corticosteroids on size at birth, as reported by the observational studies in humans. The methods of the systematic review and meta-analysis reported in this literature review are outlined in Table 1.4.4.2.

Table 1.4.4.2 Methods of systematic review and meta-analysis of observational studies reporting size at birth

Criteria for considering studies in the review	All observational studies in humans which compared size at birth of infants exposed to repeat prenatal corticosteroids (betamethasone or dexamethasone) compared with a single course, to promote fetal lung maturation, with data presented in a form that was able to be incorporated into the meta-analysis were eligible for inclusion in the review.
Types of participants	Infants of women at risk of preterm birth.
Types of interventions	Maternal administration of repeat prenatal corticosteroids (betamethasone or dexamethasone) compared with a single course, to promote fetal lung maturation.
Types of outcome measures	Size and gestational age at birth.
Search strategy	Medline [online via PubMed, 1960's+], The Web of Science Citation Database [electronic resource: Institute for Scientific Information; including Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, 1995+], Current Contents [online, 1993+] and conference proceedings. Search terms: 'repeat or multiple' and 'prenatal or antenatal' and 'steroids or corticosteroids or betamethasone or dexamethasone' To ensure all relevant studies were identified, reference lists of identified studies were searched manually.
Methods	Unlike quality assessment of trials included in systematic reviews of randomised controlled trials, there is currently little evidence as to the best methods of quality assessment in systematic reviews of observational studies, and the ways that these characteristics may introduce bias into reviews. Study characteristics including the study design, selection of the study population and the publication type (abstract or full paper) were assessed. Two reviewers independently screened identified studies for eligibility. Where possible, the complete publication was obtained for all of the eligible abstracts and for those whose eligibility was unclear from the abstract. For included studies, the two reviewers extracted data independently and any discrepancies were resolved by discussion and consensus. Data were checked and double entered into Review Manager 4.1 software (RevMan 2000) for analysis. Relative risks (RR) and 95% confidence intervals (CI) were reported for dichotomous outcomes and continuous data were expressed as weighted mean differences (WMD) and 95% CI. Data were pooled using a fixed-effects model, unless heterogeneity was present, when a random effects model was used.

Sixteen of the observational studies able to be included in the meta-analysis reported birth weight (Ghidini *et al.* 1997; Terrone *et al.* 1997; Hirsch *et al.* 1998; Mirabile *et al.* 1998; Parilla *et al.* 1999; Pratt *et al.* 1999; Vermillion *et al.* 1999; Abbasi *et al.* 2000; Elimian *et al.* 2000; McEvoy *et al.* 2000; Smith *et al.* 2000; Vermillion *et al.* 2000a; Ogunyemi *et al.* 2001;

Shelton *et al.* 2001; Vermillion *et al.* 2001; Wright *et al.* 2001). This meta-analysis revealed no statistically significant reduction in birth weight with exposure to repeat prenatal corticosteroids, WMD 58.00 grams (95% CI -2.89, 118.89) (Figure 1.4.4.1). There was significant heterogeneity between the included studies, possibly a result of different populations of women and babies in each trial, or differing inclusion and exclusion criteria. However, when the gestational age at birth was examined, infants exposed to repeat prenatal corticosteroids were born on average 0.39 weeks later than those infants exposed to a single course alone (WMD 0.39, 95% CI 0.01, 0.78). Birth weight increases with increasing gestational age and this difference in gestational age at birth between repeat and single corticosteroid treated infants may affect the ability to compare weight at birth between repeat and single corticosteroid exposed infants.

Comparing the proportion of repeat and single corticosteroid exposed infants with weight at birth less than the 10^{th} percentile for gestation allows correction for these differences in gestation at birth between the study groups. Four of the identified observational studies reported the outcome of birth weight less than the 10^{th} percentile (Ghidini *et al.* 1997; Bloom *et al.* 1999; French *et al.* 1999; Ogunyemi *et al.* 2001). The overall relative risk indicated no statistically significant differences in the proportion of infants with birth weight less than the 10^{th} percentile for gestational age when comparing infants exposed to single or repeated courses of prenatal corticosteroids (RR 1.25, 95% CI 0.74, 2.11, p=0.40; 3 studies including 1,039 infants), Figure 1.4.4.2.

Figure 1.4.4.1 Meta-analysis of observational studies: birth weight (grams)

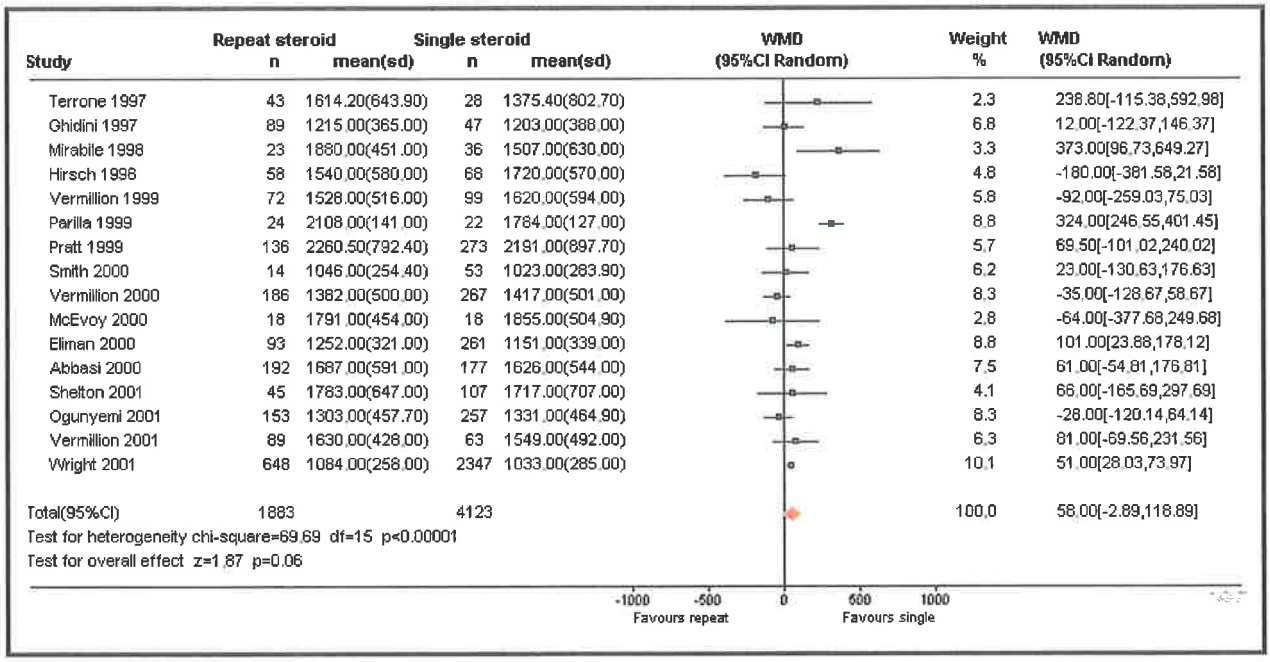
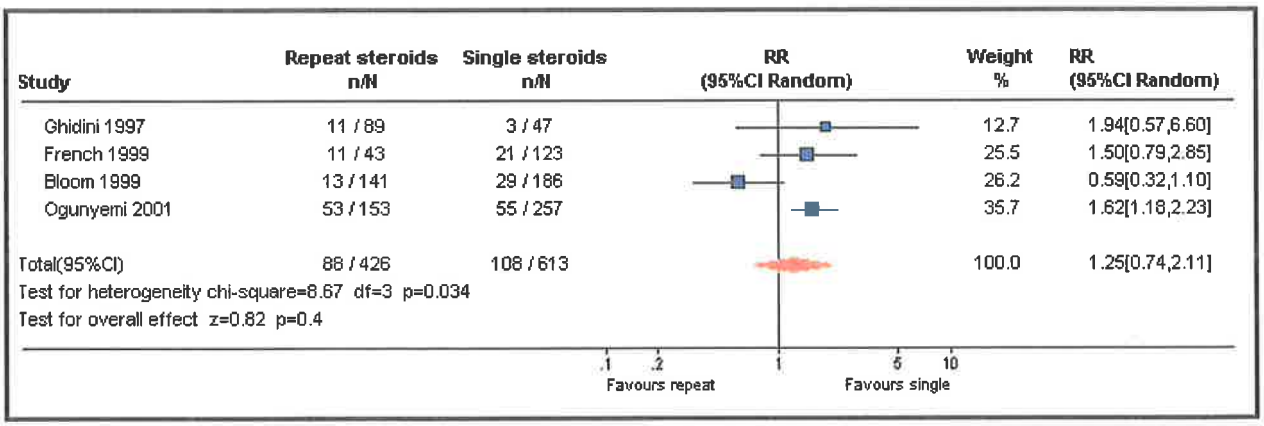


Figure 1.4.4.2 Meta-analysis of observational studies: birth weight less than the 10th percentile for gestation at birth



The effect of repeat prenatal corticosteroids on birth weight has been assessed by several other observational studies, which were unable to be included in the above meta-analysis. Most of these studies reported no difference in birth weight with exposure to repeat prenatal

corticosteroids (Karna 1997; Anderson *et al.* 1998; Espilin *et al.* 2000; Hasbargen *et al.* 2001; Karna *et al.* 2001), two reported increased birth weight with repeat corticosteroid exposure (Bhandari & Brodsky 1999; Thorp *et al.* 2001b) and four reported a reduction in birth weight with exposure to repeat prenatal corticosteroids (Bloom *et al.* 1998; Esters *et al.* 2000; Sinervo & Lange 2000; Mercer *et al.* 2001a).

Several researchers have examined the effect of repeat prenatal corticosteroids on other measures of size at birth, most of which reported no difference in fetal growth after repeat prenatal corticosteroids, compared with a single course, in terms of head circumference percentile (Elimian *et al.* 2000), head circumference (Hasbargen *et al.* 2001; Shelton *et al.* 2001), birth weight percentile (Elimian *et al.* 2000), birth weight ratio (Lam *et al.* 2001), ponderal index (Elimian *et al.* 2000), length percentile (Elimian *et al.* 2000) and length (Hasbargen *et al.* 2001). Two studies have reported reduced length (Mercer *et al.* 2001a) and head circumference (Abbasi *et al.* 2000) at birth.

As previously identified, there is the potential for confounding and bias in observational studies, which may limit the validity of the results. Size at birth is related to gestational age, and differences between repeat and single course corticosteroid groups in terms of gestation at initial corticosteroid treatment, gestational age at birth, latency from initial corticosteroid exposure to birth and proportion of multiple gestations may introduce bias.

There is potential for selection bias in these observational studies assessing the effects of repeat prenatal corticosteroids. Most of the included studies compared women and their infants exposed to single and repeat course prenatal corticosteroids, rather than first selecting

women who remained undelivered and at risk of preterm birth after an initial course of corticosteroids and then comparing women who received single and repeat prenatal corticosteroids. Women who give birth more than seven days following initial corticosteroid treatment are different to those who give birth within seven days, in terms of their previous and current obstetric history, gestation at initial corticosteroid treatment and their aetiology for risk of preterm birth (McLaughlin *et al.* 2002b). Differences reported in the observational studies assessing repeat prenatal corticosteroids compared with a single course may reflect differences between the groups of women compared rather than the effect of repeat prenatal corticosteroids.

Other confounders may include differences between the groups of women compared in terms of risk of preterm birth, the inclusion of multiple gestations and the presence of preterm prelabour rupture of membranes. Given the potential for confounding in the observational studies included in the systematic review, the safety and efficacy of repeat prenatal corticosteroids needs to be assessed by well-designed randomised controlled trials, sufficiently powered to detect clinically significant differences in fetal, maternal and infant outcomes.

Observational studies – long-term growth

To date, no randomised controlled trials have reported long-term growth in humans following treatment with repeat prenatal corticosteroids, compared with a single course. There is little available evidence with which to evaluate the effects of repeat prenatal corticosteroid exposure on long-term childhood growth (French *et al.* 1999; Rotmensch *et al.* 1999; Hasbargen *et al.* 2001), all of which are retrospective studies of infants born preterm. The retrospective review of consecutive survivors of preterm birth by Rotmensch and colleagues

assessed weight, height and head circumference standard deviation scores for gender and age at 2.2 to 6.4 years (median 3.5 years), by prenatal corticosteroid exposure (Rotmensch *et al.* 1999). No statistically significant difference was reported in weight, height or head circumference standard deviation scores between singletons exposed to no corticosteroids, a single or repeat course. Children of multiple gestations exposed to repeat prenatal corticosteroids however, had higher weight standard deviation scores at follow-up when compared with children who were not exposed to prenatal corticosteroids. This study was reported in abstract form only, with no description of the entry criteria or gestational ages at birth for each of the groups of children compared, limiting assessment of the validity of the reported findings. This study did not report the number of infants who were unable to be located for follow-up, and differential losses to follow-up by corticosteroid exposure may introduce bias. Similarly, only a relatively small number of infants were assessed, even fewer who were exposed to two (n=26) or more (n=26) courses of prenatal corticosteroids, limiting the power of the study to assess small differences in growth by corticosteroid exposure.

Follow-up at three years of age of a cohort of singleton infants born in Western Australia at less than 33 weeks gestation assessed the effect of prenatal corticosteroid exposure on childhood growth (French *et al.* 1999). Of the 477 infants in the cohort at birth, 385 (81 percent) were alive at three years and follow-up information was obtained from 354 (92 percent). No difference was reported in weight, height or head circumference ratios (for age and sex) at follow-up, by prenatal corticosteroid exposure, even when dosage and latency to birth were taken into account. However, several methodological aspects of this study may limit the interpretation of these results. This study involved few infants exposed to repeat prenatal corticosteroids; only a third of the cohort were exposed to any prenatal

corticosteroids, and less than ten percent of the cohort received repeat prenatal corticosteroids. There was disproportional loss to follow-up by corticosteroid exposure, with 91 percent of surviving infants not exposed to corticosteroids assessed, 79 percent of surviving single course infants assessed and 88 percent of repeat corticosteroid survivors assessed. This may introduce bias, particularly given the small proportion of infants in the repeat corticosteroid group. There is evidence that the preterm infants who are the most difficult to follow-up may be the most severely affected and by not assessing all children in a cohort, estimates of disability may be gross underestimations of the true rate (Tin *et al.* 1998).

A retrospective matched cohort of German children compared childhood growth at four years between singleton infants exposed to more than five courses of prenatal corticosteroids and matched (for date of birth, gestation at birth and sex) control infants exposed to one or no courses of prenatal corticosteroids (Hasbargen *et al.* 2001). Thirty-five repeat corticosteroid-exposed infants were identified, of whom 28 (80 percent) were located and available for follow-up assessment. There were no statistically significant differences reported in body weight, length or head circumference at four years when the repeat corticosteroid exposed children were compared with their matched controls. This study involved a small and very select group of infants, exposed to high doses of corticosteroids, which limits the application of these results to the typical population of infants exposed to repeat prenatal corticosteroids. Few infants receive more than five courses of prenatal corticosteroids in clinical practice, with less than 20 percent of women exposed to repeat prenatal corticosteroids in the randomised controlled trial by Guinn and colleagues receiving more than five courses (one course is two doses of 12mg betamethasone administered weekly), with a mean of 2.8 courses (standard deviation 2.3) (Guinn *et al.* 2001).

Observational studies – neurodevelopment

No randomised controlled data are available that address the long-term neurodevelopmental consequences of exposure to repeat prenatal corticosteroids. Five research groups have reported long-term neurodevelopment following repeat corticosteroid treatment; a cohort of liveborn survivors born from 20-32 weeks in Western Australia examined at three years of age (French *et al.* 1999), infants born at 1,500 grams or less in Utah, USA examined at 21.5 months corrected age (Esplin *et al.* 2000), a matched cohort of infants born in Germany assessed at four years of age (Hasbargen *et al.* 2001), a secondary analysis of the follow-up of children enrolled in a randomised controlled trial of phenobarbital at seven years (Thorp *et al.* 2001a) and a retrospective cohort of infants born at Northwestern Memorial Hospital, Illinois, USA (Kumar & Grobman 2002).

The follow-up study of survivor infants born from 20 to 32 weeks gestation in Western Australia from January 1990 to June 1992 involved the assessment of 404 of the 497 (81%) infants in the cohort, comprising 186 infants not exposed to prenatal corticosteroids, 164 exposed to a single course, 24 to two courses and 30 to three or more courses of prenatal corticosteroids (French *et al.* 1999). Infants were assessed at three years using the Stanford Binet IQ Test, Child Behaviour Checklist, Parental Stress Index and a full neurologic examination. More infants exposed to repeat prenatal corticosteroids scored high on the externalising subscale of the Child Behaviour Checklist (>90th percentile), 9/30 (30 percent) compared with 22/186 (12 percent) of those not exposed to corticosteroids. Infants in the three or more dose corticosteroid group scored higher on the distractibility scale of the Parental Stress Index, 11/30 (36 percent) of the three or more dose group compared with

26/186 (14 percent) in the no corticosteroid group. The adjusted relative risk for problem scores for infants exposed to three or more doses of corticosteroids was determined to be RR 4.05 (95% CI 2.45, 6.68) for the externalising subscale of the Child Behaviour Checklist and RR 4.26 (95% CI 2.69, 6.73) for the distractibility scale of the Parenting Stress Index. There was no statistically significant difference reported in the total scores of the child behaviour checklist and internalising scales between the exposure groups.

There are some methodological aspects of this follow-up study by French and colleagues however, which may affect the interpretation of these results. Almost half of the infants in this cohort were never exposed to prenatal corticosteroids. Only 13 percent of this cohort received repeat prenatal corticosteroid treatment, which limits the power of this study to detect clinically significant differences in childhood outcome. Infants who received repeat prenatal corticosteroids were administered their initial course at significantly earlier gestations, but there were no differences in gestational age at birth by prenatal corticosteroid exposure, indicating a longer administration to birth interval. Thus, the adverse event that led to the use of prenatal corticosteroids in those infants administered repeat doses occurred at a significantly earlier gestational age, perhaps increasing the risk of adverse long-term outcome.

This study reported that infants exposed to repeat prenatal corticosteroids were more likely to have adverse behaviour outcomes, compared with those not exposed to prenatal corticosteroids, but there were no differences in child behaviour between infants exposed to a single or repeat courses of prenatal corticosteroids (French *et al.* 1999). These differences may reflect differential survival by corticosteroid exposure, with the death of almost one-quarter of infants not exposed to corticosteroids, compared with 11 percent of single course

infants and seven percent of infants in the repeat corticosteroid group, which may affect the ability to attribute the findings of adverse behaviour outcomes observed to the prenatal corticosteroid exposure.

A retrospective cohort of infants born from 1993 to 1998 at ≤1,500g by Esplin and colleagues were assessed for neurodevelopment, using the Bayley Scales of Infant Development, at an average of 21.5 months corrected age (Esplin *et al.* 2000). Four hundred and twenty nine infants were identified; 157 were unexposed to prenatal corticosteroids, 201 received a single course and 71 received repeat courses of prenatal corticosteroids. No statistically significant difference was reported between the unexposed, single and repeat course corticosteroid groups on the Mental Developmental Index (MDI) scores. Similarly, there were no differences reported in the mean Psychomotor Developmental Index (PDI) scores between the unexposed, single and repeat course of corticosteroid groups. When the developmental scores were adjusted for gestational age at birth, birth weight, multiple gestation, preterm prelabour rupture of membranes, pre-eclampsia, mode of birth and cerebral palsy, repeat courses of corticosteroids were reported to be independently associated with abnormal PDI scores (<85), p=0.02. Several aspects of this study however, may introduce bias. This study has been published in abstract form only, limiting assessment of the methods and there is no indication of the number of infants in the cohort who were lost to follow-up. Only a relatively small sample of preterm infants were included, who were very low birth weight and may reflect only a small proportion of the population of infants who would be exposed to prenatal corticosteroids in clinical practice.

A retrospective matched cohort of German children compared indices of neurological and

cognitive development at four years between singleton infants exposed to more than five courses of prenatal corticosteroids and matched (for date of birth, gestation at birth and sex) control infants exposed to one or no courses of prenatal corticosteroids (Hasbargen *et al.* 2001). There were no differences in the mean age at which infants attained the developmental milestones of sitting without assistance, walking without assistance and using two-word phrases, when infants exposed to repeat prenatal corticosteroids and their matched controls were compared. This study however, only assessed a small number of infants exposed to high doses of prenatal corticosteroids, which does not reflect the population of infants who remain undelivered more than seven days after initial corticosteroid treatment. The small number of infants assessed provides little power for the study to detect small differences in neurodevelopmental outcome.

The secondary analysis of infants enrolled in a randomised controlled trial of phenobarbital-vitamin K versus placebo aimed to assess the effects of repeat prenatal corticosteroids on intelligence scores (measures using the Wechsler Intelligence Scale for Children and the Wide Range Achievement Test) at seven years of age (Thorp *et al.* 2001a). This study reported that the duration of prenatal corticosteroid exposure did not affect intelligence or achievement scores, when controlling for potential confounders including obstetric complications, gestational age at birth, severe intraventricular haemorrhage, postnatal steroid exposure and maternal education. There are several methodological aspects of this study however, which may introduce bias and limit the validity of these results; the study was reported in abstract form only which limits the ability to assess its methodological quality and there was significant loss to follow-up (22 percent).

A retrospective review of infants born at less than 1,500 grams at birth from 1995-1998 at Northwestern Memorial Hospital in Illinois USA, assessed neurological outcome using the Bayley Scales of Infant Development between infants exposed to repeat prenatal cortcosteroids, compared with a single course (Kumar & Grobman 2002). One hundred and sixty six infants were followed up at an average of 24 months (interquartile range 18-36 months). Repeat prenatal corticosteroid treatment was not associated with abnormal neurologic outcomes (15 percent of repeat dose infants versus 10 percent of single course infants) or abnormal developmental outcomes (MDI ≥85) (23 percent of repeat infants versus 18 percent of single course infants. The sample size of this study was small, with only 20 percent of infants exposed to repeat prenatal corticosteroids. As this study was reported as an abstract only, it is difficult to assess the methodological quality, and completeness of follow-up.

1.4.5. NATIONAL INSTITUTES OF HEALTH (NIH) RECOMMENDATIONS

In August 2000, The National Institutes of Health held a consensus conference where the available evidence on the safety and efficacy of repeat prenatal corticosteroids was presented and discussed (National Institutes of Health Consensus Development Panel 2001). The independent consensus development panel released a statement, reporting that "Until data establish a favourable benefit-to-risk ratio, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials". Others have recommended similar caution (Kay *et al.* 2000; Smith *et al.* 2000a; Spencer & Pakarian 2000; Walfisch *et al.* 2001).

1.4.6. CONCLUSIONS ON THE SAFETY AND EFFICACY OF REPEAT PRENATAL CORTICOSTEROIDS

Whether the administration of repeat prenatal corticosteroids to women who remain at risk of preterm birth confers benefit to infants, without significant maternal or fetal morbidity remains unclear. The evidence from the observational studies and randomised controlled trials suggests there may indeed be benefits of administering repeat prenatal corticosteroids in terms of neonatal respiratory outcomes, but whether these potential benefits are outweighed by potential adverse effects is uncertain. Methodological concerns with the observational and randomised controlled data emphasise the need for the completion of the ongoing randomised controlled trials currently underway worldwide to determine the safety and efficacy of repeat prenatal corticosteroids.

Any benefits of repeat prenatal corticosteroid administration will need to be balanced against the possibility of adverse effects, both for women and their infants. A major concern with the administration of repeat prenatal corticosteroids is their potential effects on infant growth and neurodevelopment. Studies in the animal model have reported reduced size at birth, and delays in myelination with exposure to repeat prenatal corticosteroids. There are currently no randomised controlled data reporting long-term infant growth and neurodevelopment following repeat corticosteroid treatment. It is unclear whether the suppression of growth observed in the animal models is a true effect, and if so, for how long a reduction in growth may operate. Additionally, the long-term consequences of altered fetal and infant growth are unknown. The delays in myelination with exposure to repeat prenatal corticosteroids in the animal model may be species-specific effects, given the differences in brain growth and development between sheep and humans. Whether there are adverse neurodevelopmental

outcomes following exposure to repeat prenatal corticosteroids in humans is unknown, as are any long-term consequences. The best evidence with which to assess these potential adverse effects on infant growth and neurodevelopment is from randomised controlled trials, such as the ongoing ACTORDS trial (Australasian Collaborative Trial of Repeat Doses of Corticosteroids for the Prevention of Neonatal Respiratory Disease), nested in which are the studies that make up this thesis, The In-depth Growth and Neurodevelopment Trial.

1.5. THE ACTORDS TRIAL

The ACTORDS trial aims to assess the safety and efficacy of repeat prenatal corticosteroids, administered to women at risk of preterm birth following a single course of prenatal corticosteroids. The ACTORDS trial is a multicentred, double-blind, placebo controlled randomised trial, recruiting women from 24 hospitals in Australia and New Zealand. The ACTORDS trial's primary aims are to examine the effects of repeat prenatal corticosteroids in terms of lung maturation, adverse effects on fetus, neonatal and infant, adverse effects on mother, the impact on mother's emotional wellbeing and quality of life, cost effectiveness. The ACTORDS trial collects measures of growth at birth, transfer, hospital discharge, 12 and 24 months corrected age, including weight, length and head circumference. These data however, will provide limited assessment on the short-term effects of repeat prenatal corticosteroids on fetal and infant growth. Infants involved in the ACTORDS Trial will be assessed, at two years corrected age, by a paediatrician and developmental psychologist using the Bayley Scales of Infant Development (Bayley 1993).

1.5.1. THE ACTORDS TRIAL METHODOLOGY

All women who give informed, written consent for the ACTORDS trial, with a singleton, twin

or triplet pregnancy at less than 32 weeks gestation who had received initial treatment with prenatal corticosteroids more than seven days ago, and are considered at risk of very preterm birth by their responsible clinician are eligible for entry into the ACTORDS Trial. Women who have no contraindications for further corticosteroid treatment (chorioamnionitis requiring urgent delivery, a lecithin/sphingomyelin ratio (or equivalent test) judged to be mature, in the second stage of labour or if corticosteroids therapy is considered essential) are eligible for randomisation to the trial.

All women eligible for the ACTORDS trial are given a patient information sheet that contains information on the ACTORDS trial. All women are counselled by a member of the research team and are given the opportunity to have a member of their family, or a friend present, and time to consult with their family before informed, written consent is sought.

Women who give their informed, written consent to the trial are randomised to the treatment groups of the ACTORDS trial by central computer randomisation, accessed by phone at the time of trial entry. Eligibility is confirmed during the call and information to enable stratification is entered via the telephone keypad. Computer generated lists of randomised treatments are allocated sequentially. The treatment allocations are stratified by gestational age at trial entry (≤28 weeks and >28 weeks gestation), the number of fetuses in utero (singleton, twin or higher order) and by collaborating centre. Randomisation schedules are produced using balanced variable blocks. At randomisation, a study number and treatment pack number are allocated.

Following randomisation, the correctly numbered treatment pack is selected, containing either

11.4mg Celestone Chronodose (Schering-Plough Pty Ltd), as 7.8mg betamethasone sodium phosphate in solution and 6mg betamethasone acetate in suspension, or saline placebo. Each syringe is identical, with labelling to conceal the contents of the syringe. Treatment is administered by intramuscular injection, and details of the date and time of administration are recorded.

At weekly intervals, if women remain undelivered and are considered at risk of very preterm birth by their responsible clinician, and are less than 32 weeks gestation, repeat treatment packs are allocated consistent with the treatment group previously allocated, by using the telephone randomisation service. Details of repeat treatment packs and their administration are recorded.

The women randomised to the trial are not informed of their treatment allocation and their healthcare team and ACTORDS study personnel are blinded to their treatment allocation. The study research assistant, blinded to treatment allocation, abstracts data on the pregnancy, birth and neonatal course from their medical records.

1.6. THE AIMS AND HYPOTHESES OF THE STUDIES IN THIS THESIS

1.6.1. AIMS

The aims of this thesis were to examine the effects of repeat prenatal corticosteroids on fetal, neonatal and infant growth and infant neurodevelopment. Parameters of growth over the first eight months after birth were measured to enable the detection of precise changes in growth rate and the duration of any effect of repeat prenatal corticosteroids on fetal and infant growth.

This thesis addresses the following research questions in relation to the effects of repeat prenatal corticosteroids on fetal and infant growth and neurodevelopment:

1. To determine the degree of inhibition, if any, due to repeat doses of maternally administered prenatal corticosteroids on linear and somatic infant growth.
2. To determine the time frame of any inhibition of linear or somatic infant growth as a result of repeat doses of maternally administered prenatal corticosteroids.
3. To assess the effect of repeat doses of maternally administered prenatal corticosteroids on infant developmental milestones as measured by the Ages and Stages Questionnaires (ASQ) at four and eight months corrected age and infant intelligence measured by the Fagan Test of Infant Intelligence (FTII) at 7¼ months postnatal corrected age.

1.6.2. HYPOTHESES

These study aims lead to the following hypotheses;

1. **Repeat doses of prenatal corticosteroids, given at weekly intervals to women who remain at risk of preterm birth at less than 32 weeks gestation will:**
   a) **inhibit size at birth as measured by weight, total body length, head circumference, and knee-ankle length, within 24 hours of birth;**
   b) **inhibit infant growth as measured by weight, total body length, head circumference and knee-ankle length up to 7¼ months corrected age.**
2. **Infant growth inhibition will:**
   a) **be independent of gestational age;**
   b) **increase with the number of doses of weekly prenatal corticosteroids**

administered;

c) **decrease with increased latency from the last injection of prenatal corticosteroids.**

3. **Repeat doses of prenatal corticosteroids, given at weekly intervals to women who remain at risk of preterm birth at less than 32 weeks gestation will:**

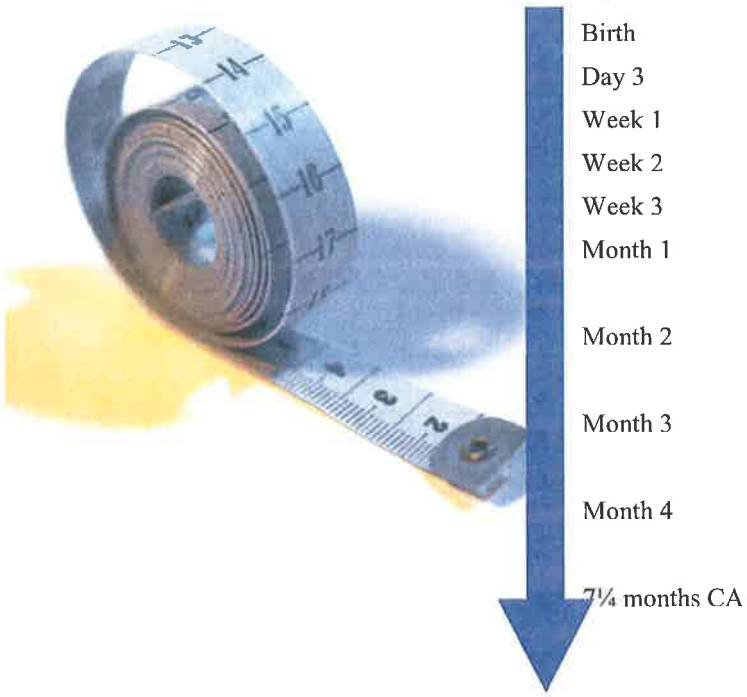
a) **reduce neurodevelopmental milestones at four and eight months corrected age as measured by Ages and Stages Questionnaire (ASQ) scores;**

b) **reduce infant intelligence as measured by the Fagan Test of Infant Intelligence at 7¼ months postnatal corrected age (FTII).**

2. METHODS

Women and their infants were recruited to The In-depth Growth and Neurodevelopment Trial at the Women's and Children's Hospital, Adelaide, from April 6th 1998 to June 11th 2002. The In-depth Growth and Neurodevelopment Trial was approved by the Women's and Children's Hospital Research and Ethics Committee. Following birth, regular measurements of weight, total body length, head circumference and knee-ankle length were collected on infants enrolled in the trial, up to 7¼ months corrected age (Figure 2.0.1.1).

Figure 2.0.1.1 Infant growth measurement time points



Prospective growth measurements were collected from October 15th 1999 to September 13th 2002. At four and eight months corrected age, infant developmental milestones were assessed by postal questionnaire, using the Ages and Stages Questionnaires (Squires *et al.* 1995), from August 18th 1999 to September 13th 2002. At 7¼ months corrected age, the Fagan Test of Infant Intelligence (Fagan & Shepherd 1991) was performed on each infant, to assess infant

intelligence, from April 9th 2000 until September 13th 2002.

2.1. ELIGIBILITY AND TRIAL ENTRY

All women who had given their informed, written consent to the ACTORDS Trial were eligible for inclusion in The In-depth Growth and Neurodevelopment Trial. Women were considered eligible for entry to the ACTORDS Trial if;

- They had a singleton, twin or triplet pregnancy
- Gestational age less than 32 weeks
- Had received initial treatment with corticosteroids more than seven days previously
- Were considered at risk of preterm birth by the clinician responsible for her care
- Had no contraindications to further corticosteroid treatment
- Had given their informed, written consent.

Women with chorioamnionitis requiring urgent delivery, women in whom a lecithin/sphingomyelin ratio (or equivalent test) was judged to be mature, women in the second stage or labour or women for whom corticosteroid therapy was considered essential were excluded from the ACTORDS Trial.

Women eligible for the ACTORDS Trial were given a patient information sheet that contained information on the potential benefits and risks of the administration of repeat prenatal corticosteroids, and the consequences of their involvement in the ACTORDS Trial and The In-depth Growth and Neurodevelopment Trial. This information sheet outlined the assessment of early infant growth and neurodevelopment (Appendix 6.1). All women were counselled by a member of the research team and were given the opportunity to have a member of their family, or a friend present, and time to consult with their family before

informed, written consent for the ACTORDS trial and The In-depth Growth and Neurodevelopment Trial was sought (Appendix 6.1).

All women who gave consent to The In-depth Growth and Neurodevelopment Trial were enrolled in the ACTORDS Trial, where they were randomised by central computer randomisation to receive either 11.4 mg Celestone Chronodose (Schering-Plough Pty Ltd), as 7.8 mg betamethasone sodium phosphate in solution and 6mg betamethasone acetate in suspension, or saline placebo, administered by intramuscular injection. At weekly intervals, women less than 32 weeks gestation who remained undelivered and were considered at risk of very preterm birth by the clinician responsible for their care, were allocated to receive a further ACTORDS treatment dose, in the same treatment group as previously assigned.

Following birth, detailed longitudinal growth and neurodevelopmental assessments were made on the infants enrolled in The In-depth Growth and Neurodevelopment Trial.

2.2. ANTHROPOMETRIC ASSESMENTS

Weight, total body length, head circumference and knee-ankle length were measured within 24 hours of birth (day 1). Weight, total body length, head circumference and knee-ankle length were measured on day three following birth, weekly until four weeks of age and then monthly to four months. These growth measures were collected on one additional occasion, at 7¼ months postnatal corrected age at the time of a neurodevelopmental assessment. Growth measurements were collected by myself, either at the Women's and Children's Hospital (Adelaide), transfer hospital, or by home visit. Growth measurements were collected and recorded on the growth measurement data sheet (Appendix 6.2).

Where infants were too unwell to be measured by myself, growth measurements were abstracted from their medical case records. Although women were recruited to the ACTORDS Trial from March 1998, ethics approval for The In-depth Growth and Neurodevelopment Trial was not obtained until October 1999. Growth data for infants born prior to this date and data for infants born in remote rural country hospitals were abstracted from their medical case records or from Maternal and Child Health record books held by their parents.

Weight

Infant weight was measured with infants unclothed, using an electronic balance (Soehnle Multina Plus, Germany) with graduations to 10 grams, dedicated for use for the trial.

Total body length

Total body length was measured using a neonatal length board (Ellard Instrumentation Pty Ltd, Seattle, USA) with graduations to 0.1 cm. Infants were measured in the supine position, with the head held in the supinated Frankfurt plane (eyes looking directly upwards and lower orbit of the eyes in the same vertical plane as the upper margin of the external auditory meatus) (Cameron 1986). The infant's head was held in this position, while the body and legs were held straight. The foot-piece of the length board was gently brought into contact with the feet and the length measurement recorded.

Head circumference

Head circumference was measured to the nearest 0.1 cm, using a disposable paper tape (Nestle

Pty Ltd, Australia) placed around the most prominent portion of the infant's forehead and occiput, just above the ears, with the infant's head in the supinated Frankfurt plane.

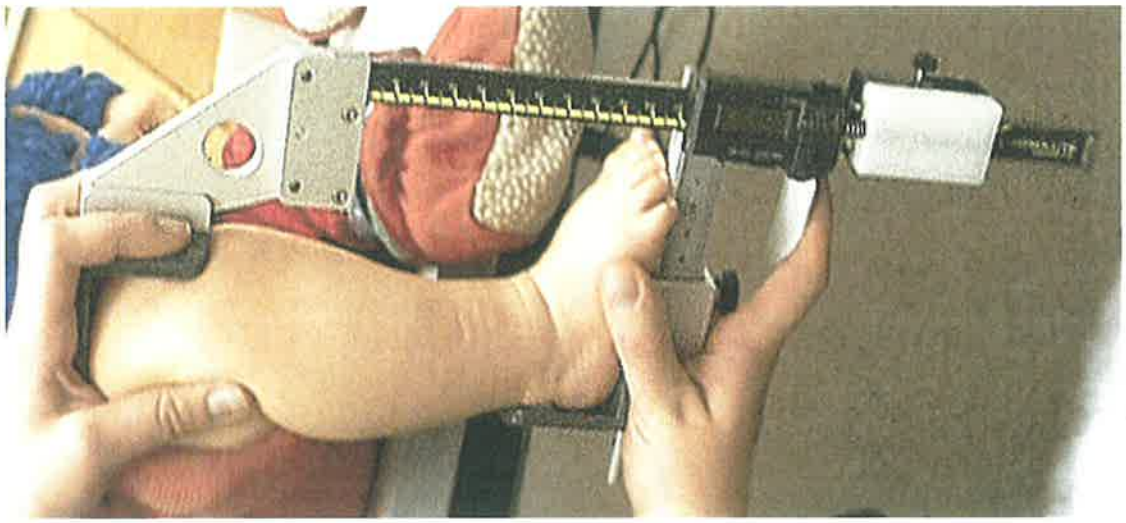
Knee-ankle length

Knemometry enables accurate measurement of longitudinal growth of the lower leg, and was first developed as a hand-held device for use in infants born preterm, at term or toddlers in the 1990's (Michaelsen *et al.* 1991). Knemometry is non-invasive and enables accurate measurement of linear growth, over short periods of time, even in ventilated, preterm infants. Unlike weight, knee-ankle length measured by knemometry is not affected by fat or fluid deposition in the infant. Neonatal knemometry has been used by several research groups to investigate the effect of postnatal dexamethasone (Gibson *et al.* 1993a; Skinner *et al.* 1997; Bloomfield *et al.* 1998), erythrocyte transfusion (Keller *et al.* 1999) and the fortification of breast milk on the growth of infants born preterm (Nicholl & Gamsu 1999). Knee-ankle length however is not a proxy for total body length, with knee-ankle length representing 24 percent of total body length in preterm infants at 30 weeks gestation, 26 percent of total body length at one year and 31 percent of total body length in adults (Michaelsen 1994). Validation of the neonatal knemometer has reported a technical error of 0.31 mm with a mean lower leg length of 98.49 mm, representing a coefficient of variation of 0.31 percent (Gibson *et al.* 1993b).

Knee-ankle length was measured to the nearest 0.01 mm using the infant knemometer (FORCE Institutes, Copenhagen, Denmark). To measure knee-ankle length, infants were placed in the supine position, their lower limbs were exposed and their hip flexed to 90 degrees. Their knee was then fixed into the left-hand cup, the foot was then placed in the

right-hand cup, ensuring that the knee and ankle lay at 90 degrees and the lower leg was parallel to the sliding arm of the knemometer (Figure 2.2.1.1).

Figure 2.2.1.1 Measuring knee-ankle length with the neonatal knemometer



The sliding arm was then gently brought into contact with the sole of the infant's foot and pressure applied until the spring-loaded arm triggered the electronic micrometer and a reading was recorded and printed on the microprocessor. A total of 10 readings were taken from both the left and right leg, where possible. Each of the knemometer measurements were conducted by myself, to reduce inter-observer variation, as recommended by Kaempf and colleagues (Kaempf 1999), excepting 15 measurements collected by Ms Pat Ashwood during a one-month period of sick-leave.

The measurement of knee-ankle length using the knemometer has a 'learning period', where the technical error of the observer reduces over time, as their measurement technique improves (Kaempf 1999). To limit the effect of this 'learning period' on the current trial, ethics approval was obtained for a study measuring the knee-ankle lengths of a cohort of term

infants. Knee-ankle length was measured on these infants using the neonatal Knemometer, prior to the measurement of infants in the In-depth Growth and Neurodevelopment Trial.

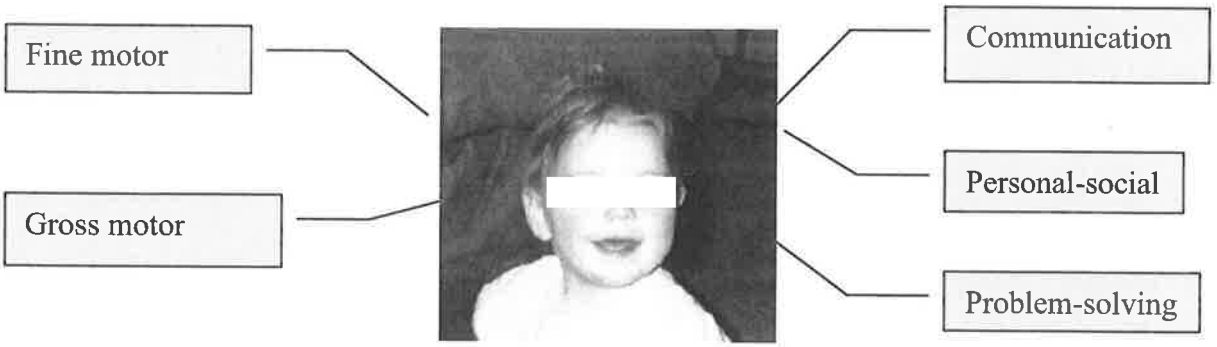
2.3. NEURODEVELOPMENTAL ASSESSMENTS

Neurodevelopment was assessed using two tools; the Ages and Stages Questionnaire (ASQ) (Paul H Brookes Publishing Co., Baltimore, USA), which assesses infant developmental milestones, and the Fagan Test of Infant Intelligence (FTII) (Infantest Corporation, Cleveland Heights, USA), which assesses infant intelligence.

2.3.1. THE FOUR AND EIGHT MONTH AGES AND STAGES QUESTIONNAIRES

The Ages and Stages Questionnaires (ASQ) are parentally completed 30-item screening questionaries (Squires *et al.* 1995), which assess five domains of infant development: communication, gross motor, fine motor, problem solving and personal-social (Figure 2.3.1.1), for infants from four to 48 months of age, corrected for gestation.

Figure 2.3.1.1 Developmental domains of the Ages and Stages Questionnaires



These recently revised questionnaires are simple in their design, are written at a primary-school level of English, and take 10-15 minutes to complete (Squires *et al.* 1997). Each item

in the questionnaire is answered by either "yes"; indicating that the child performs the task, "sometimes"; indicating that the child occasionally performs the task and "not yet"; indicating that the child does not yet perform the task. Scores for each domain are totalled and can be compared with reference ranges, with cut-off scores determined by the authors of the ASQ at two standard deviations below the mean (Squires *et al.* 1995). These questionnaires were chosen for this trial as they enable the assessment of developmental milestones prior to one year (required due to the time frame of this study), they are cost-effective, simply-designed and are quick for parents to complete.

The ASQ were developed as an economical tool to identify infants at risk of developmental delay, with the use of parents as "....first-level screeners..." (Squires *et al.* 1995). The ASQ were developed using various sources of information on developmental milestones, to include questions about skills that could be easily observed by parents in the home, which corresponded to the developmental quotient range of 75-100. This cut-off was chosen by the designers to identify children at the lower end of the scale, to ensure appropriate referral. The four and eight month ASQ validation using the Bayley Scales of Infant Development and the Revised Gessel Developmental Schedules are shown in Table 2.3.1.1.

Table 2.3.1.1 Validation of ASQ (Squires *et al.* 1995)

ASQ time point	Sensitivity %	Specificity %	Under-referred %	Over-referred %	PPV %
4 month	51.02	83.92	12.50	11.98	52.08
8 month	77.78	88.30	3.46	9.66	58.33

PPV = positive predictive value; Validated against the Bayley Scales of Infant Development and the Revised Gessel Developmental Schedules, n=192 infants at four months and n=207 infants at eight months.

The ASQ's test characteristics have recently been established in an Australian, ex-premature population of infants (Skellern *et al.* 2001). In this study, the 12 and 48 month Ages and

Stages Questionnaires were administered to 167 infants born at less than 31 weeks gestation at 12 to 48 months corrected age, and compared with a formal psychometric assessment (Griffith Mental Development Scales for 12 and 24 months, Bayley Mental Development Intelligence Scale for 18 months and McCarthy General Cognitive Intelligence Scale for 48 months). Children were considered to have developmental delay if their score fell below one standard deviation from the mean in the psychometric assessment and two standard deviations from the mean for the ASQ (means and standard deviations derived from a cohort of infants from the United States). The ASQ were compared with the "gold standard" psychometrics to determine their validity and predictive values as a screening tool. The ASQ had a 90 percent sensitivity, 77 percent specificity, 40 percent positive predictive value, 98 percent negative predictive value, 20 percent over-referral rate, one percent under-referral rate and had a 79 percent agreement with the "gold standard" psychometric assessment in this Australian population. These comparisons indicate that the ASQ are an appropriate screening tool for developmental delay in preterm infants, particularly with their high negative predictive value of 98 percent, indicating if a child scores above the cut-off, there is a 98 percent chance that the child does not have developmental a delay. It should be noted however, that the four and eight month ASQ used in this study have not been validated in an Australian, ex-preterm population.

The four and eight month ASQ were mailed to the home address of each child at four and eight months of age, corrected for gestation, with a reply paid envelope for its return (Appendix 6.3). If the questionnaire was not returned within two weeks, a reminder phone call was made to the parents. A further questionnaire was mailed if the first was not received or had been misplaced. Where it was not possible to achieve a response by mail, the parents

were telephoned to make a time to complete the questionnaire over the phone. For infants who had not been discharged from hospital at four or eight months corrected age, contact was made with hospital staff to discuss whether it was appropriate for the questionnaire to be completed by the parents or staff caring for the child. Questionnaires had to be completed within two months of the corrected age time point to be included in the dataset, as recommended by the ASQ authors (Squires *et al.* 1995).

2.3.2. THE FAGAN TEST OF INFANT INTELLIGENCE

The Fagan Test of Infant Intelligence (FTII) assesses novelty preference, which is the preference an infant demonstrates towards a novel, rather than previously seen (familiar) stimulus (Fagan & Shepherd 1991). Novelty preference in early infancy has been shown to be predictive of later intelligence (Thompson *et al.* 1991; Colombo 1997). The FTII also measures look duration, which is the duration of a single look at a stimulus. Look duration has been shown to negatively correlate with performance in intelligence tests performed in childhood (Cohen & Parmelee 1983) and has been hypothesised to represent the speed of information processing (Colombo *et al.* 1991). The FTII has been used to examine the effects on infant intelligence of prenatal cocaine (Bayer *et al.* 1996), ethanol (Jacobson 1998) and polychlorinated biphenyl exposure (Darvill *et al.* 2000) and in small for gestational age infants (Andersson *et al.* 1997). The results of these studies suggest that novelty preference and look duration, measured using the FTII, may be appropriate measures of infant cognition, which are sensitive enough to examine the effects of environmental exposures on infant cognition. The FTII was chosen to assess cognitive development in this study as it could be used at an early postnatal age (7¼ months).

The 7¼ month postnatal corrected age the FTII was used as an index of infant intelligence. The test was performed either at the Women's and Children's Hospital, Adelaide or in the family home (whichever was most convenient for the parents). The child was seated on the parent's lap or in a high chair, facing the stage (Figure 2.3.2.1).

Figure 2.3.2.1 The Fagan Test of Infant Intelligence

Each child was shown a series of 10 novelty problems, with one novel and one familiar picture. The pictures shown were people's faces; infants, women and men. The length of time the infant looked at each picture was measured by corneal reflections over the pupils of the infant's eyes, viewed through the viewing hole of the stage, which were recorded using a laptop computer. The length of time spent looking at each novel and familiar face, and the total score of the FTII was measured. Each of the FTII tests were conducted by myself. The results of the FTII tests were recorded as a text file on a laptop computer. The technique was learned from an instructional video provided with the test and discussion with colleagues who had previously used the FTII in a research capacity. Prior to the assessment of infants enrolled in the In-depth Growth and Neurodevelopment Trial, 'practice' FTII were completed on 10

infants, with parental consent.

2.4. PRIMARY STUDY ENDPOINTS

The primary study endpoints for The In-depth Growth and Neurodevelopment trial were:

1. Weight
2. Total body length
3. Head circumference
4. Knee-ankle length

at birth, day three, weeks one, two and three, months one, two, three and four and at one occasion at 7¼ months postnatal corrected age.

5. Ages and Stages Questionnaire score at four and eight months corrected age.
6. Fagan Test of Infant Intelligence score at 7¼ months postnatal corrected age.

2.5. SAMPLE SIZE

Sufficient women were randomised to provide reliable evidence as to the effects of repeat prenatal corticosteroid administration on infant growth. To detect a five percent difference in knee-ankle length growth rate from 0.36 cm/week to 0.34 cm/week (standard deviation 0.04 cm/week) a total of 140 infants were required (β=0.20, α=0.05) (Skinner *et al.* 1997). A sample size of 140 infants would enable the detection of a 23 percent difference in weight, based on the ACTOBAT Trial (ACTOBAT 1995), and a three percent difference in total body length and head circumference at birth (Kitchen *et al.* 1983).

2.6. DATA COLLECTION AND MANAGEMENT

Information on trial entry, ACTORDS treatment allocation and the receipt of treatment

injections, data on the birth and infants clinical outcomes on women and their infants who were recruited to the In-depth Growth and Neurodevelopment Trial were available from the main ACTORDS Trial data forms. All research staff and healthcare professionals involved in the care of the women and their infants were blinded to the ACTORDS treatment group allocation. Collected data and subject information was stored in a locked filing cabinet and indexed only through allocated study numbers.

Demographic and clinical information collected for the ACTORDS trial was required to describe the population recruited to The In-depth Growth and Neurodevelopment Trial, allow adjustment for potential confounders and the exploration of infant clinical outcomes that may be related to infant growth or neurodevelopment. The variables made available for use in this thesis included maternal demographics, details of obstetric history, current pregnancy plurality, reasons for risk of preterm birth, gestation at trial entry, the number of ACTORDS treatment doses received, gestation at birth, chorioamnionitis requiring antibiotics during labour, mode of birth, infant gender, low Apgar scores, admission to the neonatal intensive care unit, infant length of stay, the need for oxygen supplementation, proven systemic infection, postnatal corticosteroid treatment, any intraventricular haemorrhage and death prior to hospital discharge. The required variables from the main ACTORDS Trial database and data collected from The In-depth Growth and Neurodevelopment Trial were entered into the In-depth Growth and Neurodevelopment Trial Microsoft Access database (Microsoft Corporation 1989-1996). All growth measurements and neurodevelopmental data were double entered to minimise data entry errors. Data entered into the In-depth Growth and Neurodevelopment Trial database was cleaned using Stata 6.0 (Stata 1999).

2.7. DATA ANALYSIS

Following the cleaning of the datasets, all variables that required generation from dates were constructed by the statistician, Ms Kristyn Willson. SEIFA scores (Index of relative socio-economic disadvantage) were generated by Ms Kristyn Willson from the postcode of residence at trial entry using the Australian Bureau of Statistics reference (ABS 1998). All identifying information including study identifiers, names, addresses and all dates were then removed from the dataset by a database manager not involved with recruitment or data collection for the ACTORDS trial, Ms Sarah Russell. New study identifiers, not related to original study ID's were generated by the database manager to enable linkage of the datasets. All analyses were by intention to treat and were conducted blind to treatment group allocation. I conducted all of the data analyses, with guidance from Ms Kristyn Willson (statistician) as required. Analyses were performed using Stata 6.0 (Stata 1999), unless otherwise specified.

2.7.1. TRIAL ENTRY, BIRTH AND INFANT CLINICAL OUTCOMES

Initial analyses tabulated the trial entry characteristics of women recruited to The In-depth Growth and Neurodevelopment Trial, by the two treatment groups (repeat doses and placebo). Normally distributed continuous variables were reported as means and standard deviations. Continuous variables, which were not normally distributed, were expressed as medians and interquartile ranges. Categorical variables were reported as the number and percentage of women or infants in each category.

Post-randomisation characteristics, including the number of ACTORDS treatment doses received, birth outcomes (gestation at birth and chorioamnionitis requiring antibiotics in labour) and infant clinical outcomes (mode of birth, gender, low Apgar scores, admission to a

neonatal intensive care unit, infant length of stay, need for oxygen supplementation, proven systemic infection, postnatal corticosteroid treatment, any intraventricular haemorrhage and death prior to hospital discharge) were compared between the treatment groups. Normally distributed continuous variables were reported as means and standard deviations, and were compared between the two treatment groups using unpaired t-tests. Continuous variables, which were not normally distributed, were expressed as medians and interquartile ranges and were compared between the two treatment groups using Wilcoxon Rank-Sum Tests (Mann-Whitney Two-Sample Test). Categorical variables were reported as the number and percentage of women or infants in each category, and were compared between the two treatment groups using chi-squared analysis, with Fisher's Exact where appropriate (cell value <5), and were reported as relative risks (RR) and 95 percent confidence intervals (95% CI).

2.7.2. INFANT GROWTH

Initial examination of the growth measurements (weight, total body length, head circumference and knee-ankle length), which were normally distributed, involved the descriptive comparison of means and standard deviations at each of the time-points, between the two treatment groups. Knee-ankle length was defined as the mean of the last five measurements recorded on both the left and right leg (Gibson *et al.* 1993b). Where measurements were taken on only one leg, the mean of the last five measurements on that limb was taken to be the knee-ankle length. Ponderal index, a measure of 'thinness', was calculated from the weight and total body length at each of the measurement time-points (ponderal index = [weight (grams) / length^3 (cm)]*1000). Means and standard deviations of the ponderal index at each time-point were descriptively compared between the two treatment groups.

Z-scores enable the comparison of measures of growth between groups independent of gestational age and gender. Z-scores follow a standard normal distribution and an infant whose weight at birth lies two standard deviations below the population mean, for example, would have a z-score of minus two. Z-scores were calculated for each infant for weight, head circumference and total body length, at each of the measurement time-points, using The 1990 British Growth Reference (Freeman *et al.* 1995; Cole *et al.* 1998). Z-scores were calculated by the statistician, Ms Kristyn Willson, for each infant's growth measurements by subtracting the population mean for the same gestational age and gender from the infant's growth measure and dividing this by the standard deviation of the population mean. Means and standard deviations for the weight, total body length and head circumference z-scores at each of the time-points were calculated, and were descriptively compared between the two treatment groups.

The number of infants with weight, total body length or head circumference below the 3rd or 10th percentile was calculated from the z-score data. Infants with z-scores below -1.9 were identified as being less than the 3rd percentile, and z-scores less than -1.3 corresponded to infants less than the 10th percentile. The numbers of infants whose weight, total body length or head circumference fell below the 3rd or 10th percentile at each of the data collection time-points were descriptively compared between the two treatment groups.

The proportion of missing data and whether data was missing completely at random, missing at random or not missing at random was explored to determine the most valid multivariate analysis technique. The number of missing weight measurements was categorised, none or

one, two-five or more than five missing measurements (out of a possible total of ten measurements). Fifty five percent of the infants had none or one weight measurements missing, 25 percent had two to five weight measurements missing and 20 percent had more than five weight measurements missing. These categories were compared with birth weight, using a maximum likelihood random effects model, with adjustment for clustering of infants within the same mother (ie. multiple gestations and women enrolled in the trial for more than one pregnancy). There was no statistically significant difference in the estimated birth weight between the infants missing one or less measurements and those missing two to five weight measurements. Infants with more than five missing measurements were on average 551 grams heavier at birth than those infants missing one or less weight measurements. This relationship may be explained by the fact that a large proportion of infants in the study lived outside the metropolitan area (approximately one-third) and if they were born at later gestations, they may have been more likely to have more missing weight measurements due to the impracticality of prospective collection of regular growth measurements by myself following hospital discharge. To account for infants with more missing measurements being more likely to have higher birth weights mixed model analysis of variance was employed, which is a maximum likelihood technique, suitable for ignorable missingness of data, for the modelling of the growth measurements.

Mixed model analysis of variance was used to fit longitudinal models for weight, total body length, head circumference, knee-ankle length, ponderal index, weight z-scores, total body length z-scores and head circumference z-scores; to allow adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother, using SAS (SAS Institute Inc 1999-2001). Linear, quadratic and cubic models were fitted for each of the

growth measures and the model with the best fit, using the Akaike Information Criterion (AIC), was used for the analysis (Akaike 1974). Graphs of the fitted models were constructed using Sigmaplot (SigmaPlot 2001). The fitted curves were compared against graphs of the raw growth data, to ensure the model approximated the raw data. For the measures of weight, weight z-score and ponderal index, a piecewise quadratic model was used. A piecewise quadratic model incorporates more than one equation to describe different parts of the model and was chosen for these variables because, after birth, weight usually initially drops below birth weight then rises above birth weight within the first week after birth. A sensitivity analysis was used to decide the 'cut-off' between weight loss and weight gain, with a seven-day cut-off providing the best fit.

The models expressing the growth measures were tested to see if adjustment for confounding was required. The potential for confounding was explored for trial entry characteristics that may affect growth, where there was more than a ten percent difference between the two treatment groups. Exploration of trial entry characteristics by gestation at birth revealed further potential confounders that were explored in these analyses. The potential confounders were examined as categorical variables and included parity (nulliparous/multiparous), non-caucasian ethnicity, insurance status (private/public), maternal smoking at booking, plurality of current pregnancy (singleton/multiple) and reasons for risk of preterm birth (preterm prelabour rupture of membranes, preterm labour, indeterminate antepartum haemorrhage, placenta praevia, cervical incompetence, pre-eclampsia and severe intrauterine growth restriction requiring delivery).

To determine the time frame of any inhibition in linear or somatic fetal, neonatal or infant

growth due to repeat doses of maternally administered prenatal corticosteroids, mixed model analysis of variance was used to compare weight, total body length, head circumference, knee-ankle length, weight z-scores, total body length z-scores and head circumference z-scores between the two treatment groups, at each of the nominal measurement time points, using SAS (SAS Institute Inc 1999-2001), with adjustment for confounding as required. These data were presented as estimated means and standard error of the means, mean difference, 95% CI and p-values. These nominal comparisons were not adjusted for repeated measures, and growth measurements were categorised into the nominal time points rather than taken at the actual time they were measured. Therefore, the estimated mean differences reported between the two groups for the nominal comparisons vary slightly from the longitudinal fitted models and statistical significance was considered if $p<0.01$.

Effect modification was examined by the *a-priori* factors; gestational age at birth, the number of ACTORDS treatment doses received and the latency from last ACTORDS dose to birth. Gestational age was examined as two categories; less than 34 weeks and 34 or more weeks gestation, chosen to ensure approximately half the trial population were in each gestational age group. ACTORDS treatment dose categories were determined by constructing tertiles, with dose categorised into zero-one, two-three and four or more. Similarly, categories were constructed with latency categorised into five or less days, six to 25 days and 26 or more days. Differences between the treatment groups for the subgroups of these analyses were compared.

There was an imbalance between the two treatment groups in terms of postnatal corticosteroid exposure and the incidence of postnatal systemic infection. Both infection and exposure to postnatal corticosteroids have been shown to affect infant growth (Schwarzenberg & Kovaks

2002). To explore whether these outcomes may have affected the measures of growth, sensitivity analyses were performed using mixed model analysis of variance (SAS Institute Inc 1999-2001). There was a significant relationship between systemic postnatal infection and postnatal corticosteroid exposure, with half (n=10) of the 20 infants who received postnatal corticosteroids also developing a systemic infection prior to hospital discharge.

2.7.3. INFANT NEURODEVELOPMENT

Initial examination of the Ages and Stages Questionnaires (ASQ) involved the descriptive comparison of the median (interquartile ranges) corrected age at questionnaire completion, median total scores and median scores for each of the five developmental domains (communication, gross motor, fine motor, problem-solving and personal-social), between the treatment groups at four and eight months corrected age. To examine the possible effect of non-response bias, trial entry, birth and infant clinical outcomes were compared between the infants with at least one ASQ received and those infants without ASQ data. Trial entry, birth and infant clinical outcomes were descriptively compared between the two treatment groups for infants with ASQ data. Normally distributed continuous variables were reported as means and standard deviations, and compared between the groups using an unpaired t-test. Continuous variables which were not normally distributed were reported as medians and interquartile ranges, and were compared using Wilcoxon Rank-Sum Tests (Stata 1999). Categorical variables were reported at the number and percentage of women or infants in each category, and were compared between the two groups using chi-squared analysis.

Mixed model analysis of variance (using SAS (SAS Institute Inc 1999-2001)) was used to examine the ASQ scores by treatment group, with adjustment for confounding, repeated

measures, missing data and the inclusion of infants with the same mother. As with the growth data, confounding was explored by including the variables parity (nulliparous/multiparous), non-caucasian ethnicity, insurance status (private/public), maternal smoking at booking, the index of relative socio-economic disadvantage (SEIFA) (low, low-mid, mid, high), plurality of current pregnancy (singleton/multiple), reasons for risk of preterm birth (preterm prelabour rupture of membranes, preterm labour, indeterminate antepartum haemorrhage, placenta praevia, cervical incompetence, pre-eclampsia and severe intrauterine growth restriction requiring delivery) and corrected age at questionnaire completion.

The number of infants scoring below the ASQ cut-offs for each of the developmental domains was descriptively compared between the two treatment groups. Cox proportional hazards regression was used to construct adjusted relative risks for the four and eight month questionnaire cut-offs, with adjustment for clustering within the same mother, repeated measures and confounding (explored using the variables listed for ASQ scores) using SAS (SAS Institute Inc 1999-2001).

Analysis of the Fagan Test of Infant Intelligence (FTII) data involved comparing the median (interquartile ranges) corrected age at testing and FTII results between the two treatment groups. To examine the possible effect of non-response bias, trial entry, birth and clinical neonatal outcomes were compared between the infants for whom a FTII was conducted and for those infants without FTII assessments. Trial entry, birth and infant clinical outcomes were descriptively compared between the two treatment groups for infants tested with the FTII. Normally distributed continuous variables were reported as means and standard deviations, and compared between the groups using unpaired t-tests. Continuous variables,

which were not normally distributed, were reported as medians and interquartile range and were compared using Wilcoxon Rank-Sum Tests. Categorical variables were reported at the number and percentage of women or infants in each category, and were compared between the two groups using chi-squared analysis.

The look duration during the familiarization periods was defined as the mean length of each time the infant looked at the left and the right picture. The familiarization look duration was normally distributed and expressed as a mean, standard deviation and range, and was compared between the two treatment groups using an unpaired t-test. The look duration during the novelty periods was divided into three categories; look duration at the novel stimulus, look duration at the familiar stimulus and the look duration during the period in which the infant was not looking at the stimulus. These normally distributed variables were expressed as means, standard deviations and ranges, and were compared between the two treatment groups using an unpaired t-test. The novelty preference (a percentage) was calculated by the FTII program, was normally distributed and was reported as a mean, standard deviation and range. The novelty preference was compared between the two treatment groups using an unpaired t-test. The FTII defines infants 'at risk' if they have a novelty preference score less than 54.5 percent (Fagan & Shepherd 1991). The number and percentage of infants with novelty preference scores below this cut-off were compared between the two treatment groups using chi-squared analysis.

Statistical significance for primary outcomes and *a-priori* subgroup analyses was indicated by $p<0.05$ and, for all other groups, by $p<0.01$.

3. RESULTS OF REPEAT PRENATAL CORTICOSTEROIDS AND INFANT GROWTH

3.1. INTRODUCTION

Few studies have examined the consequences of exposure to repeat prenatal corticosteroids on infant growth, all of which are retrospective cohorts involving small numbers of infants. To date, there are no randomised controlled trials in humans that have reported longitudinal infant growth measures following repeat prenatal corticosteroid exposure. Given the potential long-term consequences of altered patterns of infant growth, well-designed randomised controlled trials are needed to examine the effects of repeat prenatal corticosteroids on infant growth to determine whether indeed there is an adverse effect and if so, to determine how long this effect persists.

3.2. AIMS AND HYPOTHESES

3.2.1. AIMS

1. To determine the degree of growth inhibition, if any, due to repeat doses of maternally administered prenatal corticosteroids on linear and somatic infant growth.
2. To determine the time frame of any inhibition of linear or somatic infant growth as a result of repeat doses of maternally administered prenatal corticosteroids.

3.2.2. HYPOTHESES

1. Repeat doses of prenatal corticosteroids, given at weekly intervals to women who remain at risk of preterm birth at less than 32 weeks gestation will:
   a) inhibit size at birth as measured by weight, total body length, head circumference and knee-ankle length, within 24 hours of birth;
   b) inhibit infant growth as measured by weight, total body length, head circumference and knee-ankle length up to 7¼ months corrected age.
2. Infant growth inhibition will:
   a) be independent of gestational age;
   b) increase with the number of doses of weekly prenatal corticosteroids administered;
   c) decrease with increased latency from the last injection of prenatal corticosteroids.

3.3. SUMMARY OF METHODS

Data on growth were collected to assess the effect of repeat prenatal corticosteroids on fetal, neonatal and infant growth. Birth weight, total body length, head circumference and knee-ankle length were measured within 24 hours of birth (day one). Weight, total body length, head circumference and knee-ankle length were measured on day three following birth, weeks one, two and three, then months one, two, three and four. These measurements were then collected monthly, until four months after birth, and at one occasion at 7¼ months corrected age.

3.3.1. OUTCOME MEASURES

Weight, total body length, head circumference and knee-ankle length.

3.4. RESULTS

3.4.1. IN-DEPTH GROWTH & NEURODEVELOPMENT TRIAL PARTICIPANTS

Over the study period, 128 women were recruited into The In-depth Growth and Neurodevelopment Trial, 63 women were randomised to receive repeat prenatal corticosteroids and 65 women were randomised to receive the placebo (Figure 3.4.1.1).

Figure 3.4.1.1 In-depth Growth and Neurodevelopment Trial Profile

128 women randomised to the ACTORDS Trial

128 women (147 infants) consented to The In-depth Growth and Neurodevelopment Trial

63 women (72 infants) allocated repeat corticosteroids		65 women (75 infants) allocated placebo	
INFANT GROWTH MEASURES COLLECTED ▽			
Birth	71 (99%)	Birth	72 (96%)
Day 3	64 (89%)	Day 3	69 (92%)
Week 1	58 (81%)	Week 1	66 (88%)
Week 2	52 (72%)	Week 2	61 (81%)
Week 3	53 (74%)	Week 3	59 (79%)
Month 1	52 (72%)	Month 1	52 (69%)
Month 2	50 (69%)	Month 2	55 (73%)
Month 3	48 (67%)	Month 3	47 (63%)
Month 4	44 (61%)	Month 4	48 (64%)
7¼ months CA	39 (54%)	7¼ months CA	44 (59%)

▽Figures give number and percentage of infants with at least one growth measurement (weight, total body length, head circumference or knee-ankle length). CA- corrected age.

The number of growth measures at each of the measurement time points varied, with fewer infants measured at the later time points.

The two groups of women were similar in terms of their age, parity, index of socio-economic disadvantage (SEIFA Index), insurance status, smoking status, area of residence, weight, height and body mass index at booking (Table 3.4.1.1). More women in the repeat corticosteroid group were of non-caucasian ethnicity compared with those in the placebo group (12.7 percent versus 4.6 percent). Women in the repeat corticosteroid group were more likely to have a previous history of preterm labour at less than 37 weeks, previous preterm birth at less than 32 weeks or previous perinatal death at 20 or more weeks gestation, compared with the women in the placebo group. It is important to note that almost one-third of the participants lived outside the metropolitan area of Adelaide, having been referred for tertiary obstetric care, a significant issue when conducting longitudinal growth assessments.

Similar numbers of singleton, twin and triplet pregnancies were allocated to the two treatment groups (Table 3.4.1.1). The most frequent reasons for risk of preterm birth were preterm labour, indeterminate antepartum haemorrhage, placenta praevia and preterm prelabour rupture of membranes. There were similar frequencies of preterm labour and indeterminate antepartum haemorrhage as the reason for risk of preterm birth between the two treatment groups. Women allocated repeat corticosteroids were more likely to be at risk for preterm birth as a result of placenta praevia, pre-eclampsia and severe intrauterine growth restriction requiring delivery but less likely to have been at risk due to preterm prelabour of membranes, cervical incompetence and isoimmunization, compared with women allocated placebo. All of the infants were alive *in utero* at trial entry.

Table 3.4.1.1 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry

	Repeat corticosteroids		Placebo	
	n= 63	%	n =65	%
Maternal age (years)*	30	(26, 34)	31	(27, 34)
Primiparous	23	36.5	21	32.3
Non-Caucasian ethnicity	8	12.7	3	4.6
SEIFA Index				
Low (≤ 950)	28	44.4	29	45.3
Low-mid (951-1010)	16	25.4	19	29.7
Mid-high (1011-1067)	13	20.6	9	14.1
High (>1067)	6	9.5	7	10.9
Private Patient	7	11.1	9	13.9
Maternal weight at booking (kg)*	64.7	(59.5, 80)	66	(56.3, 77)
Maternal height at booking (cm)*	160	(155, 167.6)	164	(159, 168)
BMI at booking (kg/m^2)$^{\#}$	26.6	6.0	25.8	5.3
Smoking at booking	17	27.0	21	32.3
Live outside metropolitan area	22	30.6	23	31.1
Previous obstetric history				
Preterm labour <37 weeks	4	10.0	9	20.5
Preterm birth <32 weeks	3	7.5	7	15.9
Perinatal death ≥ 20 weeks	2	5.0	6	13.6
Plurality of current pregnancy				
Singleton	55	87.3	56	86.2
Twin	7	11.1	8	12.3
Triplet	1	1.6	1	1.5
Reasons for risk of preterm birth$^{\phi}$				
Preterm labour	19	30.2	16	24.6
Indeterminate APH	16	25.4	15	23.1
Placenta praevia	16	25.4	8	12.3
PPROM	15	23.8	25	38.5
Pre-eclampsia	8	12.5	4	6.2
Severe IUGR requiring delivery	6	9.5	1	1.5
Placental abruption	3	4.8	0	0
Cervical incompetence	2	3.2	5	7.8
Twin-twin transfusion syndrome	2	3.2	1	1.5
Isoimmunisation	1	1.6	5	7.8
Congenital anomaly	0	0	2	3.0

Figures mean and standard deviation$^{\#}$; Figures median (interquartile range)*; $^{\phi}$More than one may apply; SEIFA - Index of relative socio-economic disadvantage (ABS 1998); BMI - body mass index; APH – antepartum haemorrhage; PPROM – preterm prelabour rupture of membranes; IUGR – intrauterine growth restriction.

Eligibility for The In-depth Growth and Neurodevelopment Trial required women to have received initial prenatal corticosteroids, more than seven days prior to trial entry. The gestational age at which the first dose of the initial corticosteroids was administered was

similar between the two treatment groups, with a median gestational age (interquartile range) of 26^{+6} weeks (25^{+0}, 28^{+4}) for women allocated repeat corticosteroids, compared with 26^{+4} weeks (24^{+6}, 28^{+4}) for women in the placebo group. Similar numbers of women received their initial prenatal corticosteroids prior to 28 weeks gestation, 44 (69.8 percent) repeat corticosteroid women compared with 42 (64.6 percent) placebo group women. All women received 22.8 mg of Celestone Chronodose (Schering-Plough Pty Ltd) as their initial course of prenatal corticosteroids.

The median gestational age at trial entry was similar between the two treatment groups, 28^{+3} weeks (interquartile range 26^{+3}, 30^{+2}) for repeat corticosteroid women, compared with 28^{+2} weeks (interquartile range 26^{+2}, 30^{+0}) for placebo group women (Table 3.4.1.2). Similar numbers of women in the two treatment groups were randomised to the ACTORDS Trial at less than 28 weeks gestation. Over half of the women in the In-depth Growth and Neurodevelopment Trial received less than three ACTORDS treatment injections, 41 (65.1 percent) repeat dose women compared with 35 (53.8 percent) placebo group women. There was no statistically significant difference between the two treatment groups in the median latency between the first dose of initial corticosteroids and trial entry, with a median of 8 days (interquartile range 7, 10) for both groups (p=0.56). Similarly, there was no difference in the latency from the last ACTORDS dose administered to birth between the two treatment groups, with a median of 7 days (interquartile range 4, 36) for repeat corticosteroid women and 11 days (interquartile range 3, 35) for women in the placebo group (p=0.77). The number of days between randomisation and birth were similar, with a median of 36 days (interquartile range 16, 59) for women in the repeat corticosteroid group compared with 40 days (interquartile range 21, 71) for those in the placebo group (p=0.32). One woman in the repeat corticosteroid

group and three women in the placebo group received additional prenatal corticosteroids outside the ACTORDS trial.

Table 3.4.1.2 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received

	Repeat corticosteroids		Placebo	
	n =63	%	n =65	%
Gestation at ACTORDS trial entry (weeks+days) *	28^{+3}	(26^{+3}, 30^{+2})	28^{+2}	(26^{+2}, 30^{+0})
<28 weeks	29	46.0	29	44.6
≥28 weeks	34	54.0	36	55.4
ACTORDS treatment doses given				
None	1	1.6	1	1.5
One	28	44.4	19	29.2
Two	12	19.1	15	23.1
Three	6	9.5	10	15.4
Four	4	6.4	6	9.2
Five	6	9.5	6	9.2
Six	4	6.4	4	6.2
Seven	0	0	4	6.2
Eight	0	0	0	0
Nine	2	3.2	0	0

Figures median (interquartile range)*

There were no statistically significant differences in the median gestational age at birth between the two treatment groups, with a median gestational age at birth of 33 weeks for both repeat corticosteroid treated and placebo group women (Table 3.4.1.3). Similarly, there was no statistically significant difference in the distribution of categories of gestational age at birth between women exposed to repeat prenatal corticosteroids, compared with those allocated to placebo. Three women required treatment with antibiotics as a result of chorioamnionitis during labour, one in the repeat corticosteroid group and two in the placebo group.

Table 3.4.1.3 Birth and infant clinical outcomes

	Repeat corticosteroids		Placebo		RR	95% CI		Significance p-value
	n= 63	%	n= 65	%				
Gestation at birth (weeks+days)*	33^{+0} (29^{+4}, 36^{+4})		33^{+0} (30^{+3}, 36^{+3})			-		0.55
≤ 28 weeks	11	17.5	6	9.2	1.89	0.74	4.81	0.17
28^{+1}-31^{+6} weeks	18	28.6	21	32.3	0.88	0.52	1.50	0.65
32 –36^{+6} weeks	19	30.2	26	40.0	0.75	0.47	1.22	0.24
≥ 37 weeks	15	23.8	12	18.5	1.29	0.66	2.53	0.46
Chorioamnionitis^	1	1.6	2	3.1	0.52	0.05	5.55	1.00
	n= 72	**%**	**n= 75**	**%**				
Mode of birth								
normal vaginal	16	22.2	25	33.3	0.67	0.39	1.14	0.13
operative vaginal	3	4.2	4	5.3	0.78	0.18	3.37	1.00
caesarean section	53	73.6	46	61.3	1.20	0.96	1.51	0.11
Male infant	45	62.5	40	53.3	1.17	0.89	1.55	0.26
Apgar <7 at 5 minutes	1	1.4	4	5.3	0.26	0.03	2.27	0.37
Admission to NICU	48	66.7	46	61.3	1.09	0.85	1.39	0.50
O_2 supplementation	45	62.5	40	53.3	1.17	0.89	1.55	0.26
Proven systemic infection	15	20.8	4	5.3	3.91	1.36	11.21	**0.005**
Postnatal corticosteroids	16	22.2	4	5.3	4.17	1.46	11.87	**0.003**
Any IVH on cranial U/S closest to 6 weeks	3	4.2	4	5.3	0.78	0.18	3.37	1.00
Death prior to discharge	4	5.6	2	2.7	2.08	0.39	11.03	0.44
Length of stay (days)*	41.5	(8.5, 67.	31	(8.5, 5		-		0.14

Figures are median (interquartile range)*. ^Requiring antibiotics during labour; NICU – neonatal intensive care unit; O_2 – oxygen; IVH – intraventricular haemorrhage; U/S – ultrasound.

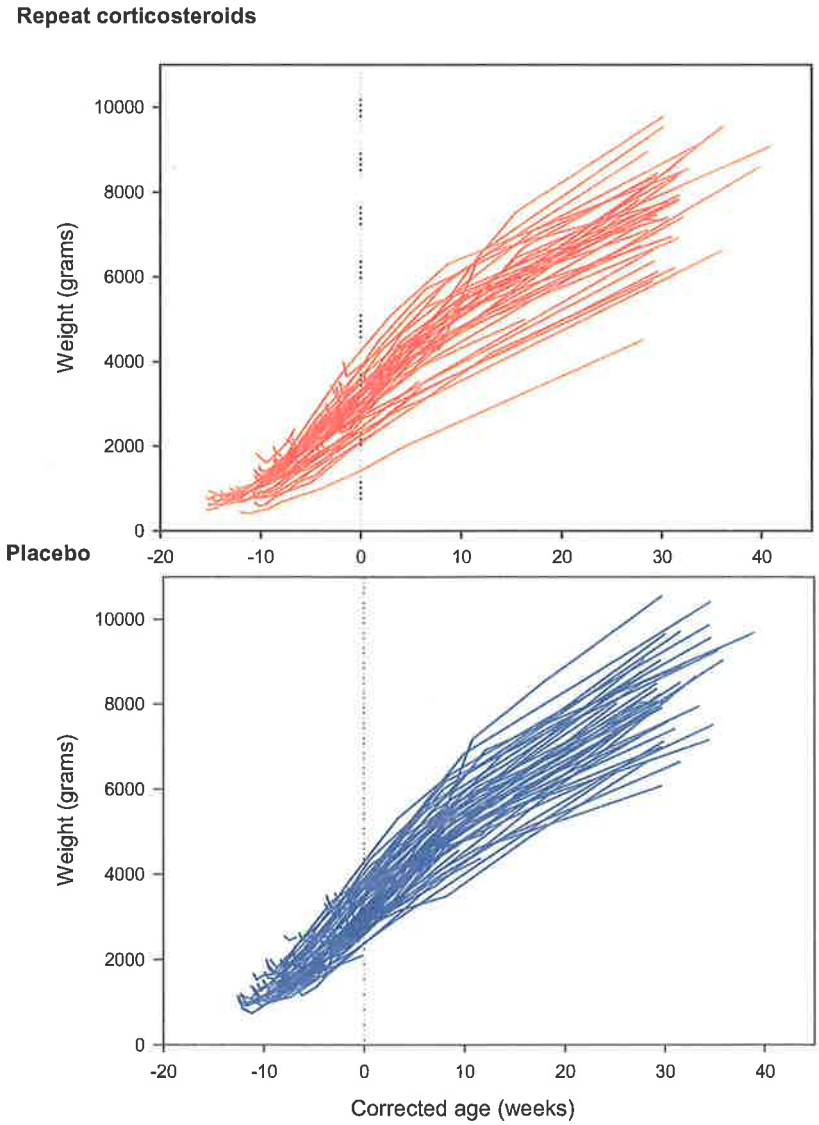
There were no statistically significant differences between the two treatment groups in terms of their mode of birth, gender of the infant, low Apgar scores, admission to the neonatal intensive care unit, need for oxygen supplementation, any intraventricular haemorrhage on cranial ultrasound closest to six weeks, death prior to hospital discharge or infant length of stay (Table 3.4.1.3). Infants exposed to repeat prenatal corticosteroids had almost a four-fold increase in the risk of proven systemic infection (RR 3.91, 95% CI 1.36, 11.21, p<0.01) and were more than four times as likely to have received postnatal corticosteroids (RR 4.17, 95% CI 1.46, 11.87, p<0.01), when compared with infants in the placebo group.

3.4.2. WEIGHT

Descriptive comparisons of weight

The weight growth curves by treatment group, for each infant by their corrected age, are described in Figure 3.4.2.1. Infant weight increased with corrected age.

Figure 3.4.2.1 Weight growth curves by corrected age



At birth, the mean infant weight in the repeat corticosteroid group was 1871 grams (SD 932) and 2019 grams (SD 705) in the placebo group Table 3.4.2.1. The weight of infants in both treatment groups dropped after birth, with repeat corticosteroid infants exceeding the mean weight at birth by day 28, and placebo group infants exceeding the mean weight at birth by day 21. At each of the time points, the mean weight for infants in the repeat corticosteroid group was less than the mean weight for infants in the placebo group. Statistical comparisons were not made between the two treatment groups for mean weight, as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.2.1 Weight by treatment group

Weight (grams)	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	71	1871	932	72	2019	705
Day 3	64	1760	832	69	1906	673
Week 1	58	1677	818	66	1858	675
Week 2	52	1674	778	61	2001	716
Week 3	53	1847	839	59	2205	756
Month 1	52	2120	960	52	2513	873
Month 2	50	3024	1161	55	3455	1016
Month 3	48	3876	1259	47	4538	1018
Month 4	44	4909	1344	48	5437	1105
7¼ months CA	39	7686	1118	44	8245	1030

SD - standard deviation; CA - corrected age.

Mixed model analysis of variance analysis of weight

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on infant weight over time, with adjustment for confounding, repeated measures, missing data and including infants with the same mother. Comparisons at each of the nominal measurement time points revealed that there were no statistically significant differences between the two treatment groups in terms of the estimated mean weight from birth to four months of age (Table 3.4.2.2). However, at 7¼ months postnatal corrected age, infants exposed to repeat prenatal corticosteroids had significantly lower estimated mean weights compared with those in the placebo group (p=0.01).

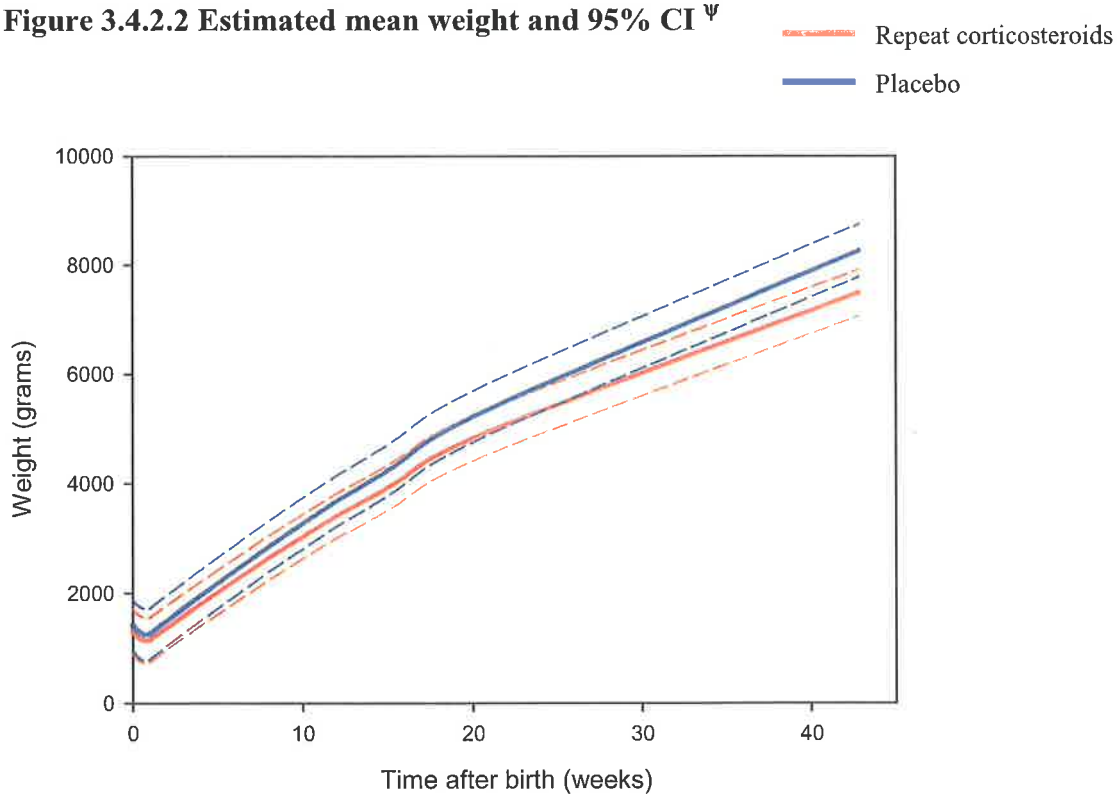
Table 3.4.2.2 Estimated mean weight at the nominal measurement time points[Ψ]

Weight (grams)	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Birth	1326	209	1433	239	108	-198	413	0.49
Day 3	1190	210	1301	239	111	-197	419	0.48
Week 1	1214	211	1311	239	97	-215	409	0.54
Week 2	1381	212	1482	240	100	-215	416	0.53
Week 3	1562	212	1708	240	146	-170	462	0.36
Month 1	1797	212	1976	241	178	-141	497	0.27
Month 2	2629	212	2874	240	245	-74	564	0.13
Month 3	3542	213	3920	242	378	55	701	0.02
Month 4	4400	213	4801	242	402	77	726	0.02
7¼ months CA	7087	217	7540	245	453	110	796	**0.01**

[Ψ]Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth, and multiple gestations. Est. mean - estimated mean; SEM - standard error of mean; CA - corrected age.

A piecewise quadratic model, with adjustment for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth, and multiple gestations provided the best fit for weight (Figure 3.4.2.2). There was no statistically significant difference in the estimated mean weight between infants in the repeat and placebo groups at birth (estimated mean difference -113.3 grams, p=0.46). From birth to day seven, there was no statistically significant difference in the amount of weight gained per day between the treatment groups (estimated mean difference 6.29 grams per day, p=0.89). From day seven, infants in the repeat corticosteroid group gained 2.02 grams less per day than those in the placebo group (p=0.04).

Figure 3.4.2.2 Estimated mean weight and 95% CI [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Gestational age at birth and weight (Figure 3.4.2.3)

There was significant effect modification on weight by gestational age at birth (estimated mean difference in treatment group difference 0.18 grams per day, p=0.05). For infants born at less than 34 weeks gestation, repeat corticosteroid treated infants gained 4.33 grams less per day than those in the placebo group (95% CI 2.00, 6.65, p=0.0003). There was no statistically significant difference in the rate of weight gain between infants in the two treatment groups when infants born at 34 or more weeks gestation were compared (estimated mean difference -0.18 grams per day, 95% CI -3.64, 3.28, p=0.92).

ACTORDS treatment dose and weight (Figure 3.4.2.4)

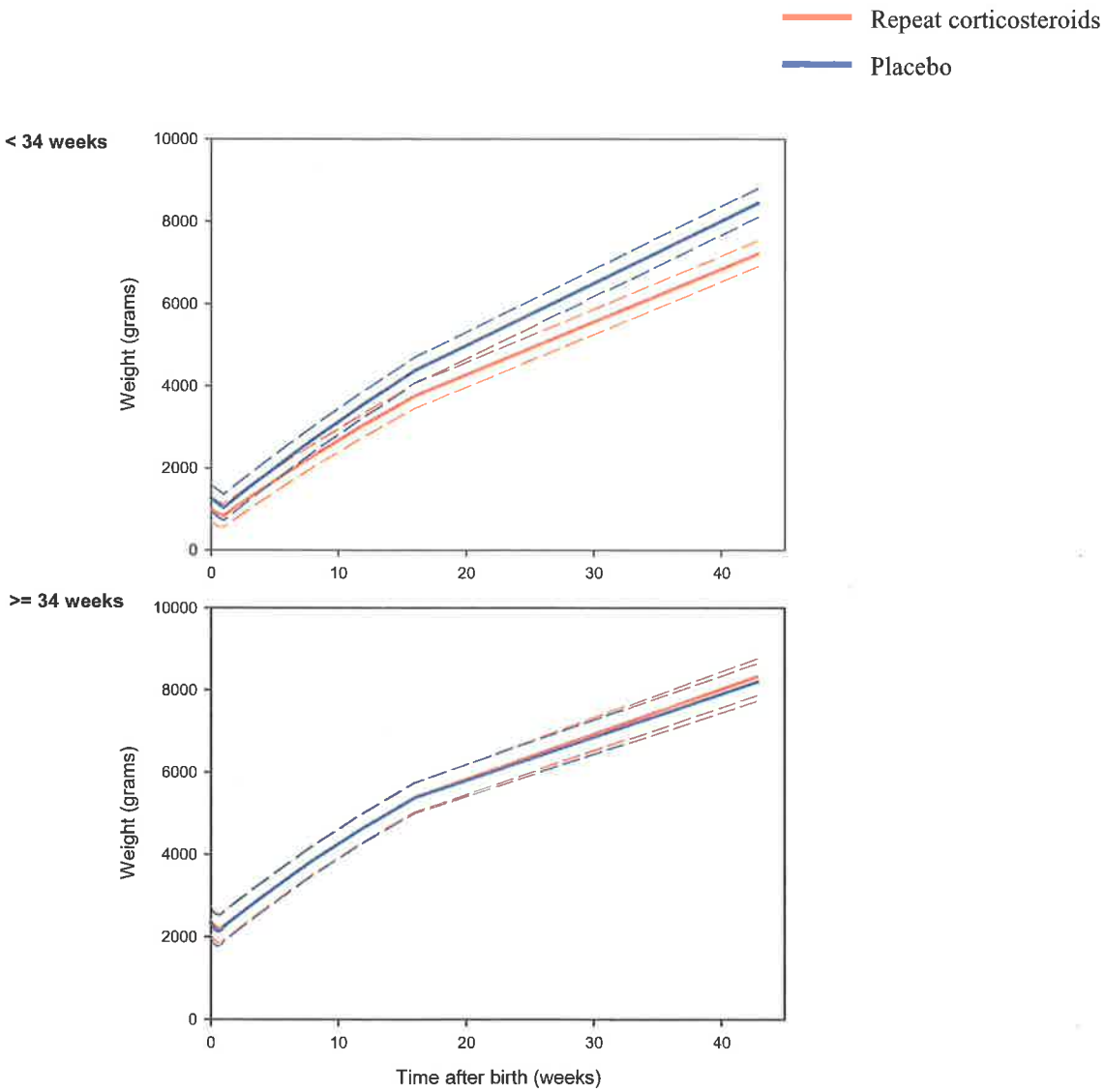
Dose was not a statistically significant effect modifier for weight. For infants exposed to one or less ACTORDS treatment doses, those in the repeat corticosteroid group gained 3.89 grams less per day in weight than placebo-group infants (95% CI 0.66, 7.13, p=0.02). There was no difference in the rate of weight gain between infants in the two treatment groups when infants exposed to two or three ACTORDS treatment doses (estimated mean difference -1.44 grams per day, 95% CI -4.84, 1.95, p=0.40) or four or more ACTORDS treatment doses (estimated mean difference -0.21 grams per day, 95% CI -4.19, 3.78, p=0.92) were examined.

Latency from last ACTORDS treatment dose to birth and weight (Figure 3.4.2.5)

Overall, there was no statistically significant effect modification on weight by the latency from the last ACTORDS dose to birth. When infants with a latency of five or less days were examined, infants exposed to repeat corticosteroids gained 4.37 grams less per day in weight than those exposed to placebo (95% CI 1.24, 7.49, p=0.006). There was no difference in the rate of weight gain between infants in the two treatment groups with a latency of six to 25

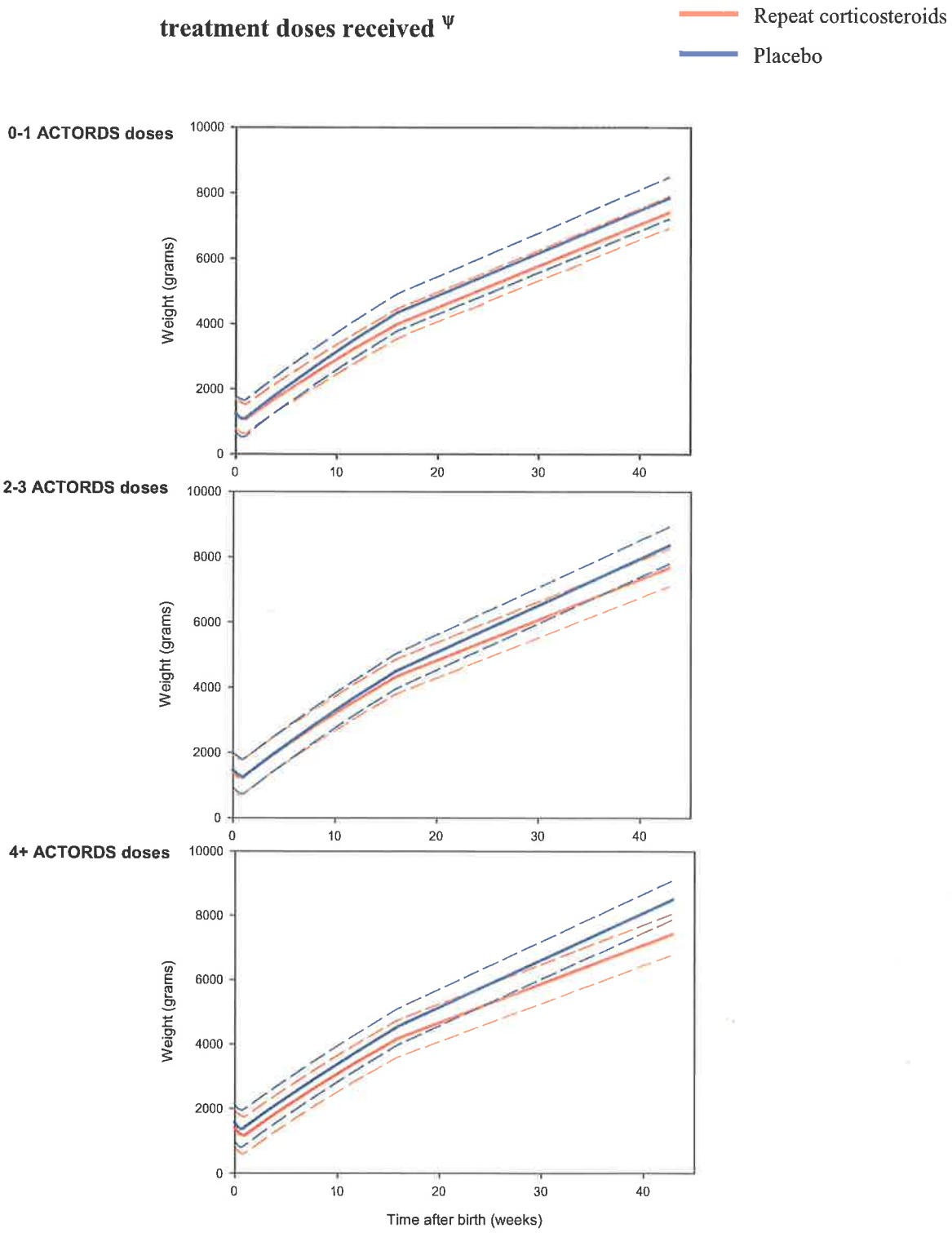
days (estimated mean difference 2.55 grams per day, 95% CI -0.92, 6.03, p=0.15) or 26 or more days (estimated mean difference 1.34 grams per day, 95% CI -2.33, 5.01, p=0.47).

Figure 3.4.2.3 Estimated mean weight and 95% CI by gestational age at birth [Ψ]



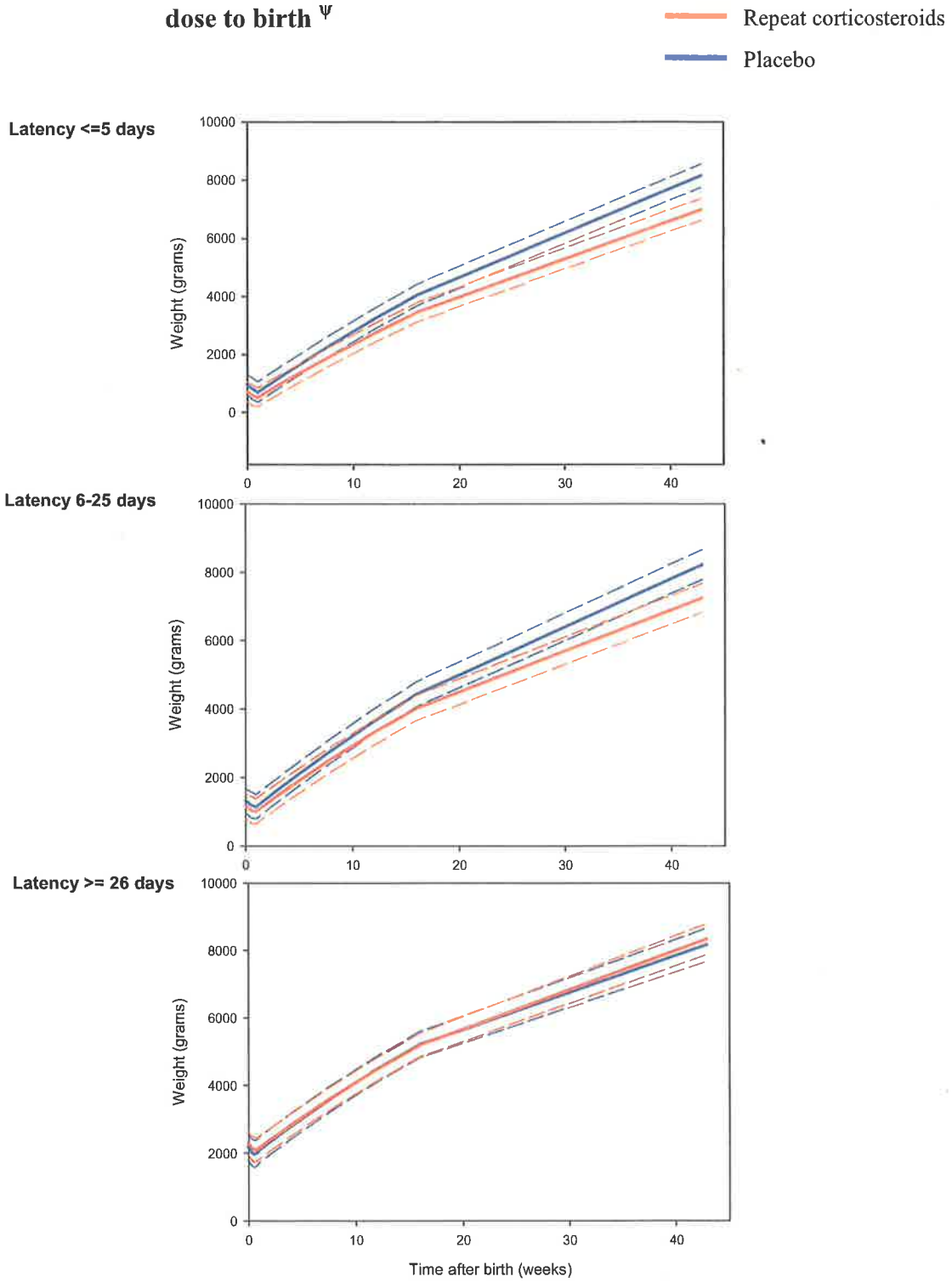
[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Figure 3.4.2.4 Estimated mean weight and 95% CI by the number of ACTORDS treatment doses received [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Figure 3.4.2.5 Estimated mean weight and 95% CI by the latency from last ACTORDS dose to birth [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Postnatal systemic infection and postnatal corticosteroid subgroup analysis

There was an imbalance between the two treatment groups in terms of the incidence of postnatal systemic infection and postnatal corticosteroid treatment, both of which may affect infant growth. To explore the effect of these outcomes on infant growth, analyses comparing growth between the two treatment groups for infants who developed a postnatal infection and those who did not, and by exposure to postnatal corticosteroids were conducted. There was no statistically significant effect modification on weight gain by systemic postnatal infection (estimated mean difference in treatment group difference 1.37 grams per day, p=0.71). There was no statistically significant difference in weight gain between the two treatment groups for infants who did not develop a postnatal systemic infection (estimated mean difference 0.31 grams per day, 95% CI -1.80, 2.42). Similarly, there were no differences in the rate of weight gain between the two treatment groups when infants who developed a systemic infection prior to hospital discharge were compared (estimated mean difference -1.06 grams per day, 95% -7.98, 5.85).

There was significant effect modification on weight gain by postnatal corticosteroid exposure (estimated mean difference in treatment group difference -8.87 grams per day, p=0.004). No statistically significant difference in weight was found between the two treatment groups in weight gain when infants who did not receive postnatal corticosteroids were compared (estimated mean difference -0.01 grams per day, 95% CI -2.16, 2.14). For infants exposed to postnatal corticosteroids, those allocated to repeat corticosteroids gained 8.86 grams less in weight per day (95% CI 3.16, 14.57) than placebo infants.

Descriptive comparisons of weight z-scores (Table 3.4.2.3)

The mean weight z-score at birth for repeat corticosteroid treated infants was -0.43 (SD 1.10) and -0.08 (SD 1.06) for placebo group infants. The weight z-scores of infants in both treatment groups dropped after birth. At each of the time points, the mean weight z-score in the repeat corticosteroid group was less than the mean weight z-score in the placebo group. Statistical comparisons were not made on the mean weight z-scores between the two treatment groups as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.2.3 Weight z-scores by treatment group

Weight z-score	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	71	-0.43	1.10	72	-0.08	1.06
Day 3	64	-1.03	1.01	69	-0.70	0.96
Week 1	58	-1.34	0.92	66	-1.08	0.94
Week 2	52	-1.38	0.92	61	-1.11	0.91
Week 3	53	-1.35	0.95	59	-1.04	0.94
Month 1	52	-1.21	1.05	52	-0.87	1.03
Month 2	50	-1.08	1.20	55	-0.61	1.19
Month 3	48	-0.93	1.28	47	-0.39	1.15
Month 4	44	-0.81	1.38	48	-0.34	1.13
7¼ months CA	39	-0.87	1.34	44	-0.07	1.06

SD - standard deviation; CA - corrected age.

Mixed model analysis of variance of weight z-scores

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on infant weight z-scores, with adjustment for confounding, repeated measures, missing data and including infants with the same mother. Comparisons at each nominal measurement time point revealed infants exposed to repeat prenatal corticosteroids had significantly lower estimated mean weight z-scores at each of the time points up to 7¼ months postnatal corrected age, compared with infants in the placebo group (Table 3.4.2.4).

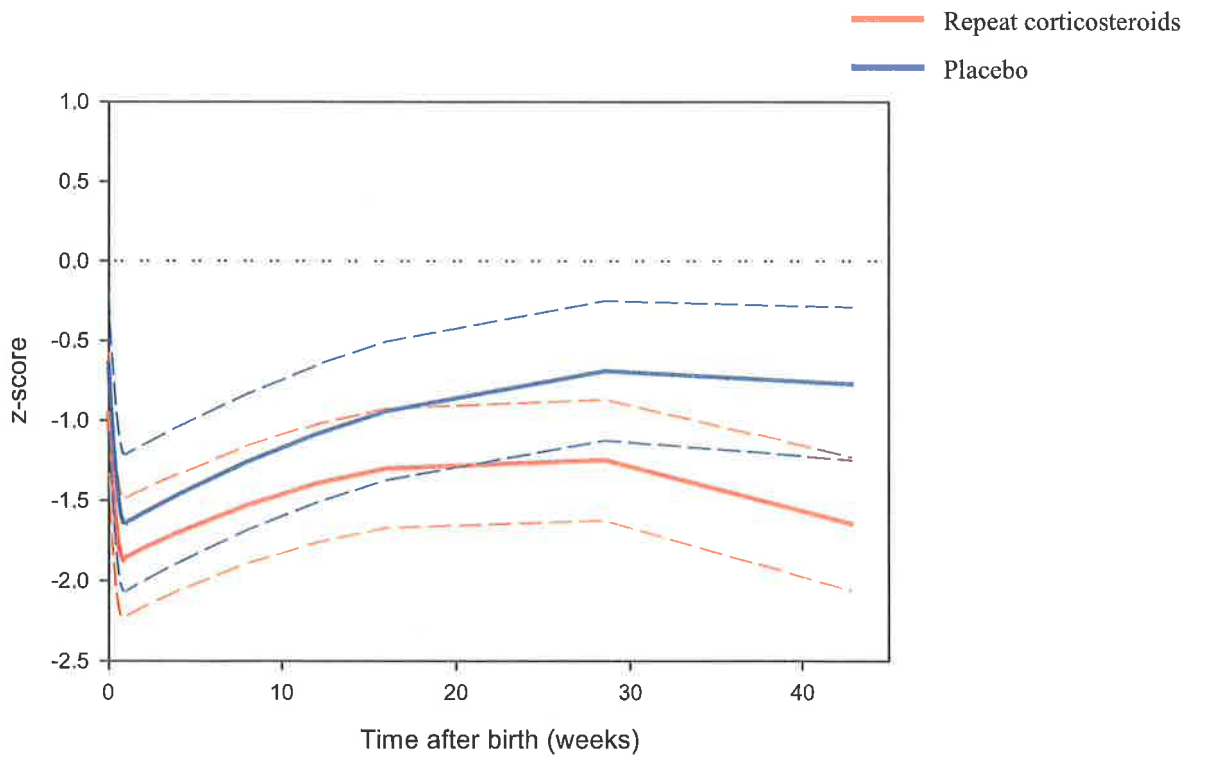
Table 3.4.2.4 Estimated mean weight z-score by the nominal measurement time points[Ψ]

Weight z-score	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Birth	-0.24	0.14	0.22	0.15	0.46	0.10	0.82	**0.01**
Day 3	-0.86	0.14	-0.41	0.15	0.45	0.08	0.81	0.02
Week 1	-1.14	0.14	-0.77	0.15	0.37	0.00	0.74	0.05
Week 2	-1.11	0.15	-0.76	0.15	0.35	-0.03	0.72	0.07
Week 3	-1.07	0.15	-0.67	0.15	0.40	0.03	0.77	0.04
Month 1	-0.94	0.15	-0.54	0.16	0.41	0.03	0.78	0.03
Month 2	-0.80	0.15	-0.33	0.16	0.47	0.09	0.84	0.02
Month 3	-0.62	0.15	-0.16	0.16	0.46	0.07	0.84	0.02
Month 4	-0.63	0.15	-0.08	0.16	0.54	0.16	0.93	**0.005**
7¼ months CA	-0.75	0.16	0.10	0.17	0.84	0.44	1.26	**<0.001**

[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth. Est. mean - estimated mean; SEM - standard error of mean; CA - corrected age.

A piecewise quadratic model, with adjustment for severe intrauterine growth restriction requiring delivery and placenta praevia as the reasons for risk of preterm birth, provided the best fit for weight z-score (Figure 3.4.2.6). There was no statistically significant difference in the estimated mean weight z-score between the two treatment groups at birth (estimated mean difference 0.31, p=0.07). From birth to day seven, and from day seven onwards, there was no significant difference in the gain in weight z-score between the infants in exposed to repeat corticosteroids and those exposed to placebo.

Figure 3.4.2.6 Estimated mean weight z-score and 95% CI [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction and placenta praevia as reasons for risk of preterm birth.

Gestational age at birth and weight z-score (Figure 3.4.2.7)

There was no statistically significant effect modification on weight z-score gain by gestational age at birth. Similarly, there were no statistically significant differences in weight z-score gain between infants two treatment groups when the subgroups born less than 34 weeks gestation, and those born at 34 or more weeks gestation were compared.

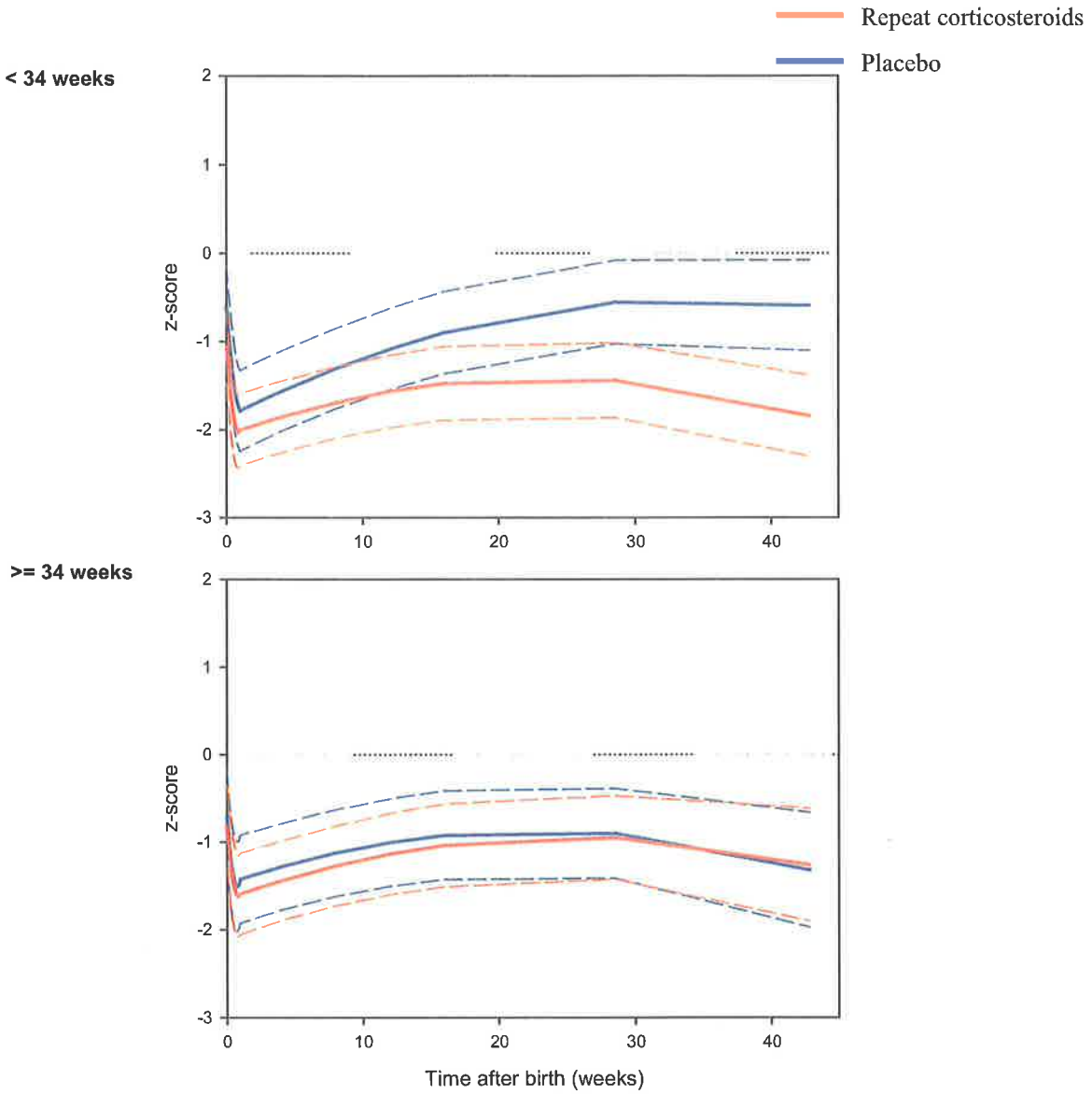
ACTORDS treatment dose and weight z-score (Figure 3.4.2.8)

The number of ACTORDS treatment doses administered was not a statistically significant effect modifier for weight z-score gain. There were no statistically significant differences in weight z-score gain between the infants in the two treatment groups when each of the dose subgroups (0-1, 2-3 and ≥4 doses) were examined.

Latency from last ACTORDS dose to birth and weight z-score (Figure 3.4.2.9)

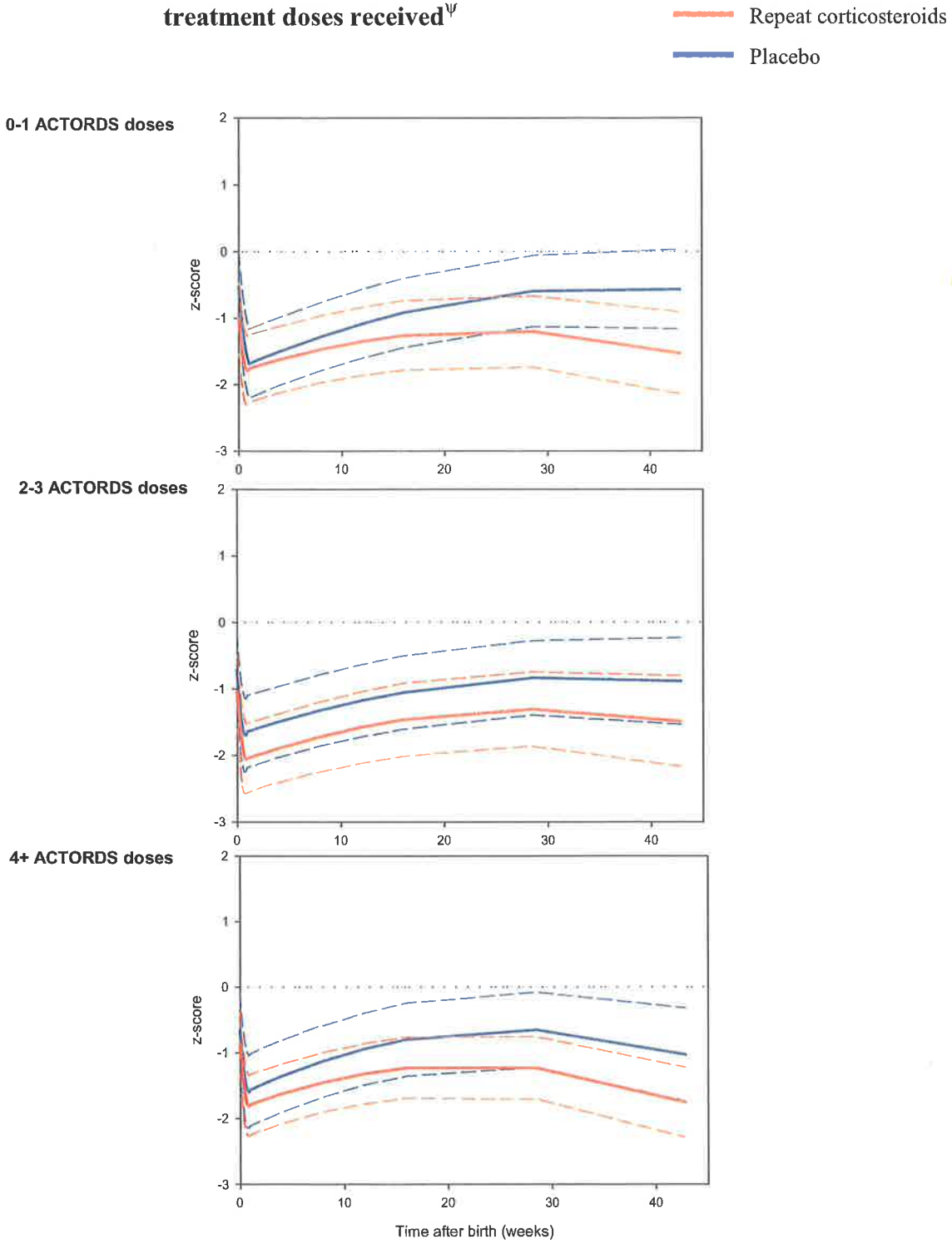
The latency between the last ACTORDS dose and birth was not a statistically significant effect modifier on weight z-score gain, and there were no statistically significant differences in weight z-score gain between the two treatment groups for each of the three latency categories (≤ 5, 6-25 and ≥ 26 days).

Figure 3.4.2.7 Estimated mean weight z-score and 95% CI by gestational age at birth[Ψ]



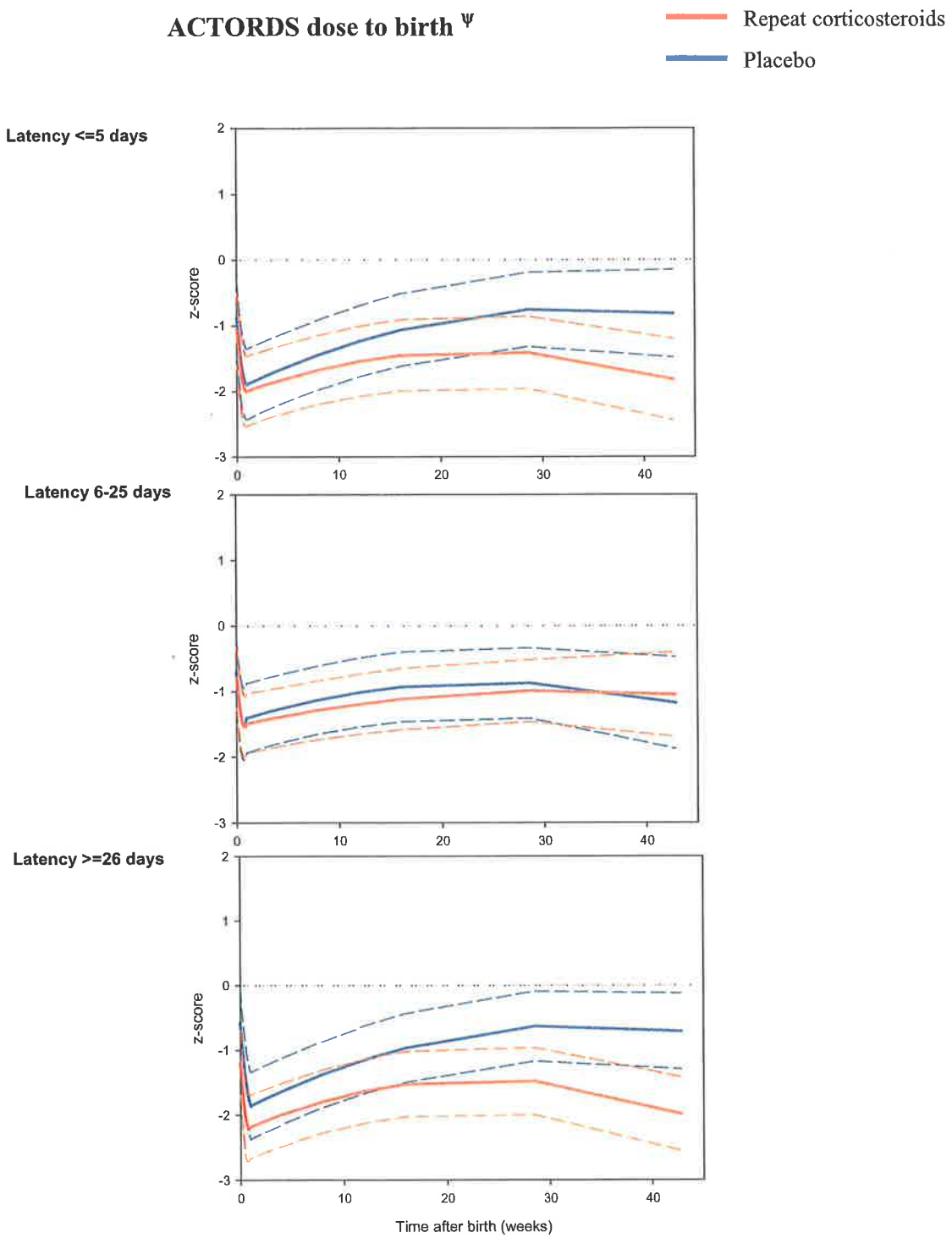
[Ψ] Adjusted for severe intrauterine growth restriction and placenta praevia as reasons for risk of preterm birth.

Figure 3.4.2.8 Estimated mean weight z-score and 95% CI by the number of ACTORDS treatment doses received[Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction and placenta praevia as reasons for risk of preterm birth.

Figure 3.4.2.9 Estimated mean weight z-score and 95% CI by the latency from last ACTORDS dose to birth [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction and placenta praevia as reasons for risk of preterm birth.

Postnatal systemic infection and postnatal corticosteroid subgroup analysis

There was no statistically significant effect modification of systemic postnatal infection on weight z-score gain (estimated mean difference in treatment group difference 0.48 per day, p=0.48). No statistically significant differences between the two treatment groups were identified when infants who did not develop a systemic postnatal infection (estimated mean difference -0.0003 per day, 95% CI -0.004, 0.003) and infants who did develop a systemic postnatal infection (estimated mean difference -0.004 per day, 95% CI -0.01, 0.006) were compared.

Exposure to postnatal corticosteroids however was a significant effect modifier for weight z-score (estimated mean difference in treatment group difference -0.01 per day, p=0.009). Infants in the repeat corticosteroid group gained 0.01 less per day in weight z-score than those similarly exposed in the placebo group (95% CI 0.002, 0.02, p=0.01). There was no statistically significant difference in the weight z-score gain between treatment groups when infants not exposed to postnatal corticosteroids were compared (estimated mean difference -0.002 per day, 95% CI -0.005, 0.001, p=0.24).

Descriptive comparisons of weight percentiles (Table 3.4.2.5)

The proportion of infants with weights below the 3rd and 10th percentile varied and there was significant attrition of participants over time, with losses of over half the infants by 7¼ months corrected age. Statistical comparisons were not made between the two treatment groups for weight percentiles, as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother. Further multivariate analysis of this percentile data was not conducted given it was

not a primary outcome for this trial, that the sample size was small and that the percentiles were derived from the z-score data that has already been explored using multivariate statistics.

Table 3.4.2.5 Weight percentiles by treatment group

	Repeat corticosteroids			Placebo		
	N	n	%	N	n	%
<3rd percentile						
Birth	71	6	9	72	1	1
Day 3	64	9	14	69	7	10
Week 1	60	13	22	66	12	18
Week 2	53	12	23	61	12	20
Week 3	53	12	23	59	11	19
Month 1	52	13	25	52	8	15
Month 2	51	11	22	55	8	15
Month 3	48	10	21	48	5	10
Month 4	44	9	21	48	6	13
7¼ months CA	39	7	18	44	2	5
<10th percentile						
Birth	71	13	18	72	7	10
Day 3	64	21	33	69	16	23
Week 1	60	25	42	66	27	41
Week 2	53	23	43	61	28	46
Week 3	53	24	45	59	29	49
Month 1	52	22	42	52	21	40
Month 2	51	18	35	55	19	35
Month 3	48	14	29	48	12	25
Month 4	44	13	30	48	9	19
7¼ months CA	39	12	31	44	7	16

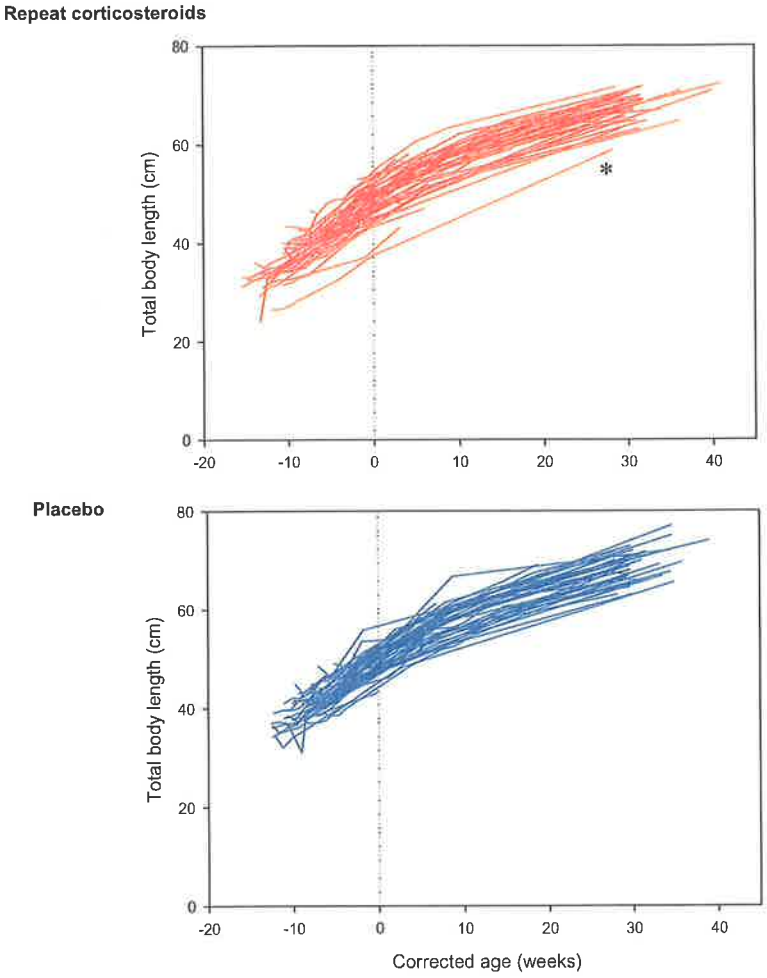
CA - corrected age.

3.4.3. TOTAL BODY LENGTH

Descriptive comparisons of total body length

The total body length growth curves by treatment group, for each infant by their corrected age, are shown in Figure 3.4.3.1. Total body length increased with corrected age.

Figure 3.4.3.1 Total body length growth curves by corrected age



At birth, the mean total body length was 40.7 cm (SD 6.4) in the repeat corticosteroid group and 42.7 cm (SD 4.1) in the placebo group (Table 3.4.3.1). Only five infants had total body length measured on day three, and as a result, the mean total body length at this time point may be misleading. Omitting the mean total body length at day three, total body length increased over time, with the mean total body length of repeat corticosteroid infants always

lower than that of infants in the placebo group.

The total body length measurements recorded on one infant in the repeat corticosteroid group appeared to be an outlier, denoted by * in Figure 3.4.3.1. This infant was a twin, whose mother was at risk of preterm birth due to severe intrauterine growth restriction requiring delivery. This infant was born at 28^{+0} weeks gestation by caesarean section, due twin-twin transfusion syndrome, resulting in severe intrauterine growth restriction and abnormal umbilical artery Doppler in both twins. This infant developed chronic lung disease, was treated with three courses of postnatal corticosteroids and discharged home after 466 days in hospital. Exclusion of this infant from the analyses of total body length made no difference to the results, thus this infant was included in the further comparisons of total body length.

Statistical comparisons were not made between the two groups for mean total body length, as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.3.1 Total body length by treatment group

Total body length (cm)	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	70	40.7	6.4	72	42.7	4.1
Day 3	3	48.7	3.4	2	49.8	1.1
Week 1	51	39.4	5.7	57	42.1	4.0
Week 2	51	40.0	6.1	52	42.9	4.4
Week 3	45	40.9	6.1	52	43.9	4.7
Month 1	51	42.8	6.7	45	46.1	4.9
Month 2	49	48.0	7.0	53	50.6	4.9
Month 3	41	51.5	7.0	45	55.4	4.0
Month 4	42	56.2	6.4	46	58.9	4.2
7¼ months CA	37	67.8	3.0	43	68.8	3.2

SD - standard deviation; CA - corrected age.

Mixed model analysis of variance for total body length

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on total body length over time, with adjustment for confounding, repeated measures, missing data and including infants with the same mother.

Comparisons at each of the nominal measurement time points revealed no statistically significant differences in total body length between repeat corticosteroid and placebo group infants up to 7¼ months postnatal corrected age (Table 3.4.3.2).

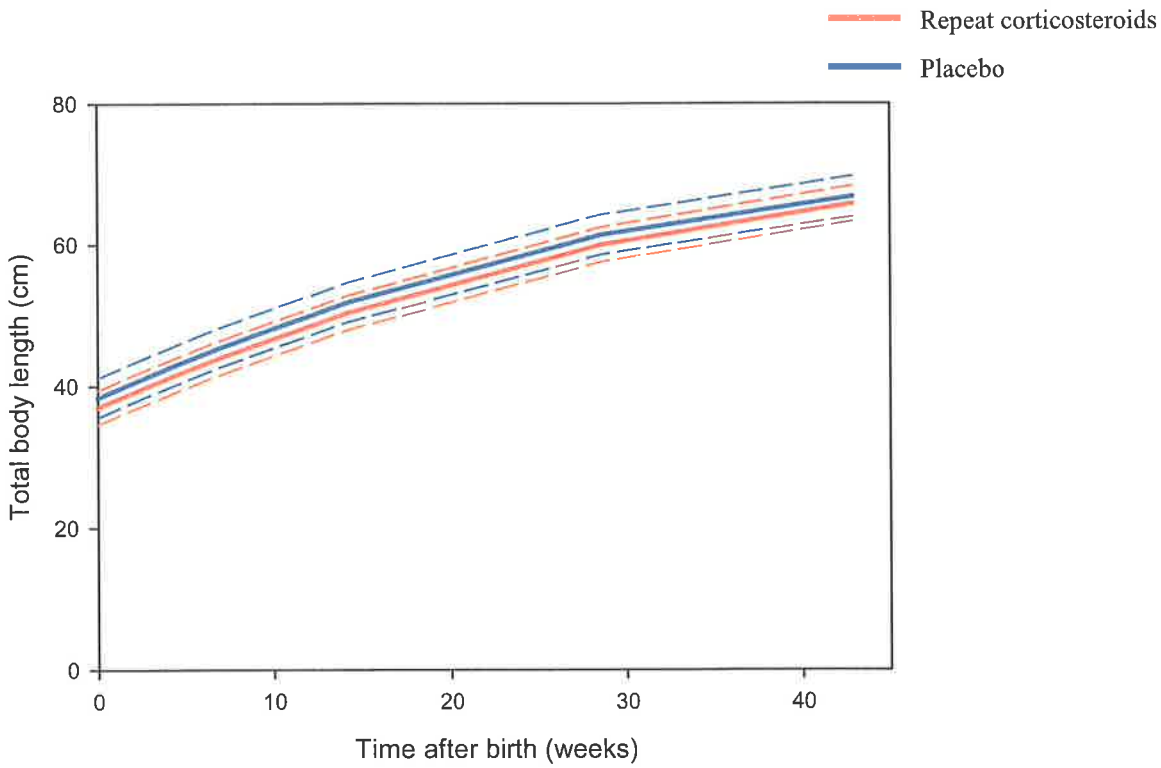
Table 3.4.3.2 Estimated mean total body length at the nominal measurement time points [Ψ]

Total body length (cm)	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Birth	37.5	1.2	39.0	1.4	1.5	-0.2	3.3	0.09
Day 3	39.4	1.7	38.8	2.1	0.6	-4.8	3.5	0.76
Week 1	37.8	1.2	39.1	1.4	1.3	-0.5	3.1	0.17
Week 2	38.5	1.2	40.1	1.4	1.5	-0.3	3.3	0.10
Week 3	39.6	1.3	40.9	1.4	1.2	-0.6	3.1	0.18
Month 1	40.9	1.2	42.5	1.4	1.6	-0.3	3.4	0.09
Month 2	45.4	1.2	47.0	1.4	1.5	-0.3	3.3	0.10
Month 3	49.7	1.3	51.3	1.4	1.6	-0.2	3.5	0.09
Month 4	53.2	1.3	54.8	1.4	1.6	-0.2	3.5	0.09
7¼ months CA	63.1	1.3	64.2	1.4	1.1	-0.8	3.1	0.25

[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth, and multiple gestations. Est. mean - estimated mean; SEM - standard error of mean; CA - corrected age.

A quadratic model, with adjustment for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth, and multiple gestations provided the best fit for total body length (Figure 3.4.3.2). No statistically significant difference was seen in total body length between the two treatment groups at birth (estimated mean difference 1.37 cm, p=0.12), or in the total body length gained per day between infants in the repeat corticosteroid or placebo group (estimated mean difference 0.00001 cm per day, p=0.73).

Figure 3.4.3.2 Estimated mean total body length and 95% CI [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Gestational age at birth and total body length (Figure 3.4.3.3)

There was no statistically significant effect modification on total body length by gestational age at birth (estimated mean difference in treatment group difference 0.002 cm per day, p=0.69). When infants born at less than 34 weeks gestation were examined, there was no difference in the total body length gain between repeat corticosteroid and placebo group infants (estimated mean difference -0.002 cm per day, 95% CI -0.009, 0.004, p=0.54). There was no statistically significant difference in the gain of total body length between the two treatment groups when infants born at 34 or more weeks gestation were compared (estimated mean difference 0.0002 cm per day, 95% CI -0.009, 0.009, p=0.97).

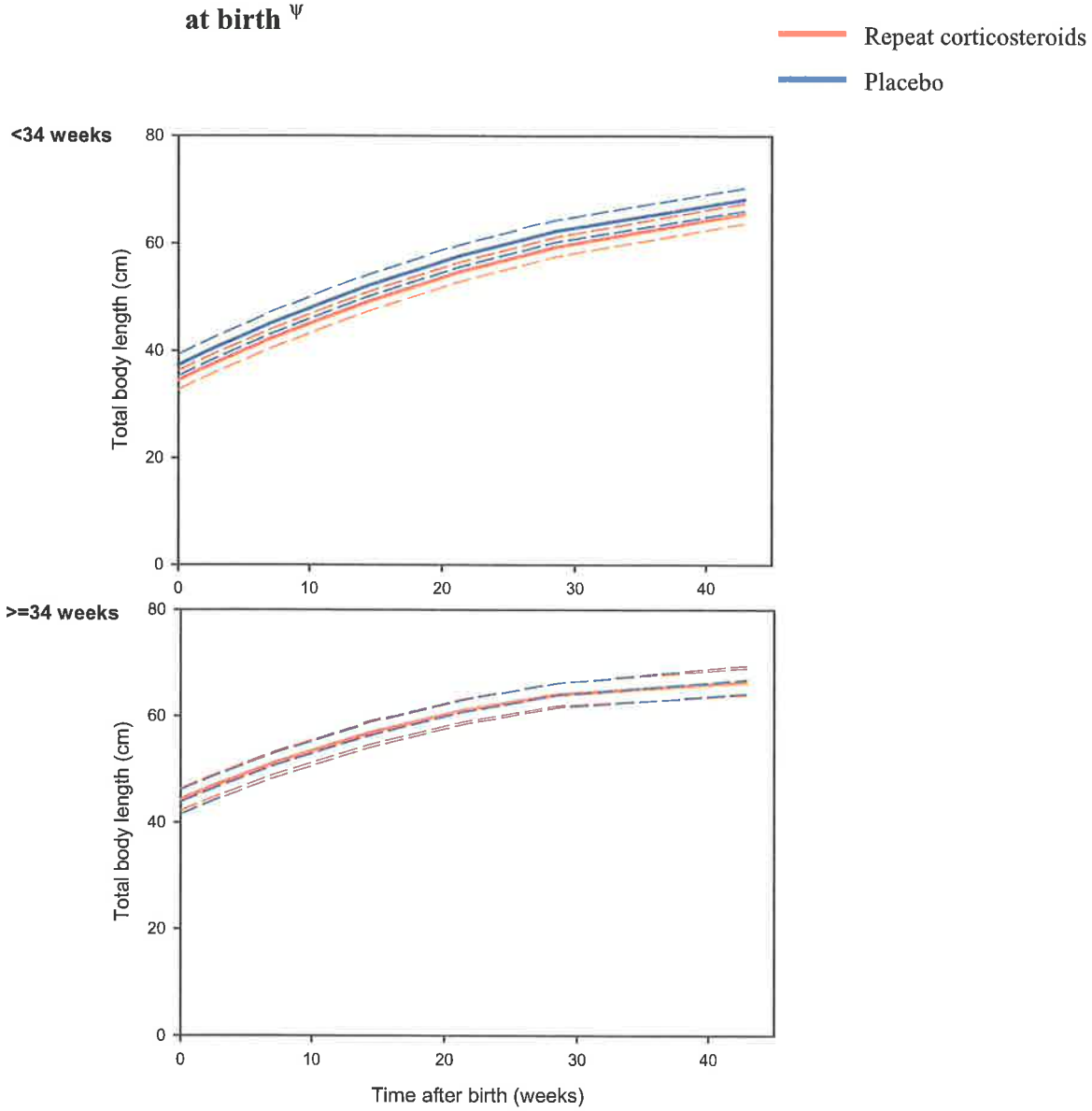
ACTORDS treatment dose and total body length (Figure 3.4.3.4)

Overall, there was statistically significant effect modification on total body length by the number of ACTORDS treatment doses received. When infants exposed to one or less ACTORDS treatment doses or two to three doses were examined, there was no statistically significant difference in the rate of total body length gain between infants in the repeat corticosteroid and placebo groups. For infants exposed to four or more ACTORDS treatment doses, those exposed to repeat corticosteroids gained 0.02 cm less in total body length per day more than placebo group infants (95% CI 0.006, 0.03, p=0.004).

Latency from last ACTORDS dose to birth and total body length (Figure 3.4.3.5)

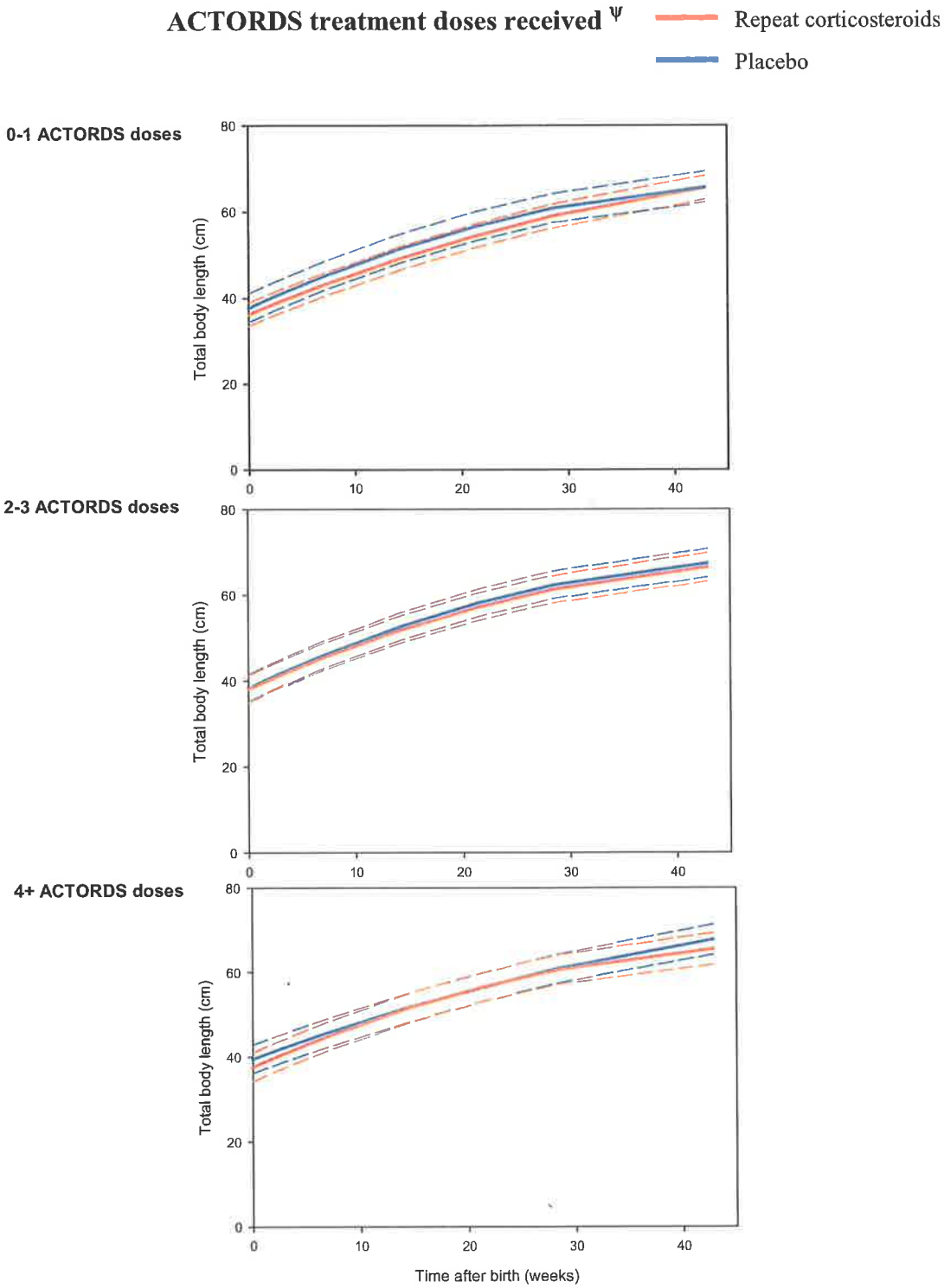
Overall, there was no statistically significant effect modification on total body length by the latency from the last ACTORDS dose to birth. There was no statistically significant difference in the rate of total body length gain between infants in the two treatment groups by each of the latency categories.

Figure 3.4.3.3 Estimated mean total body length and 95% CI by gestational age at birth [Ψ]



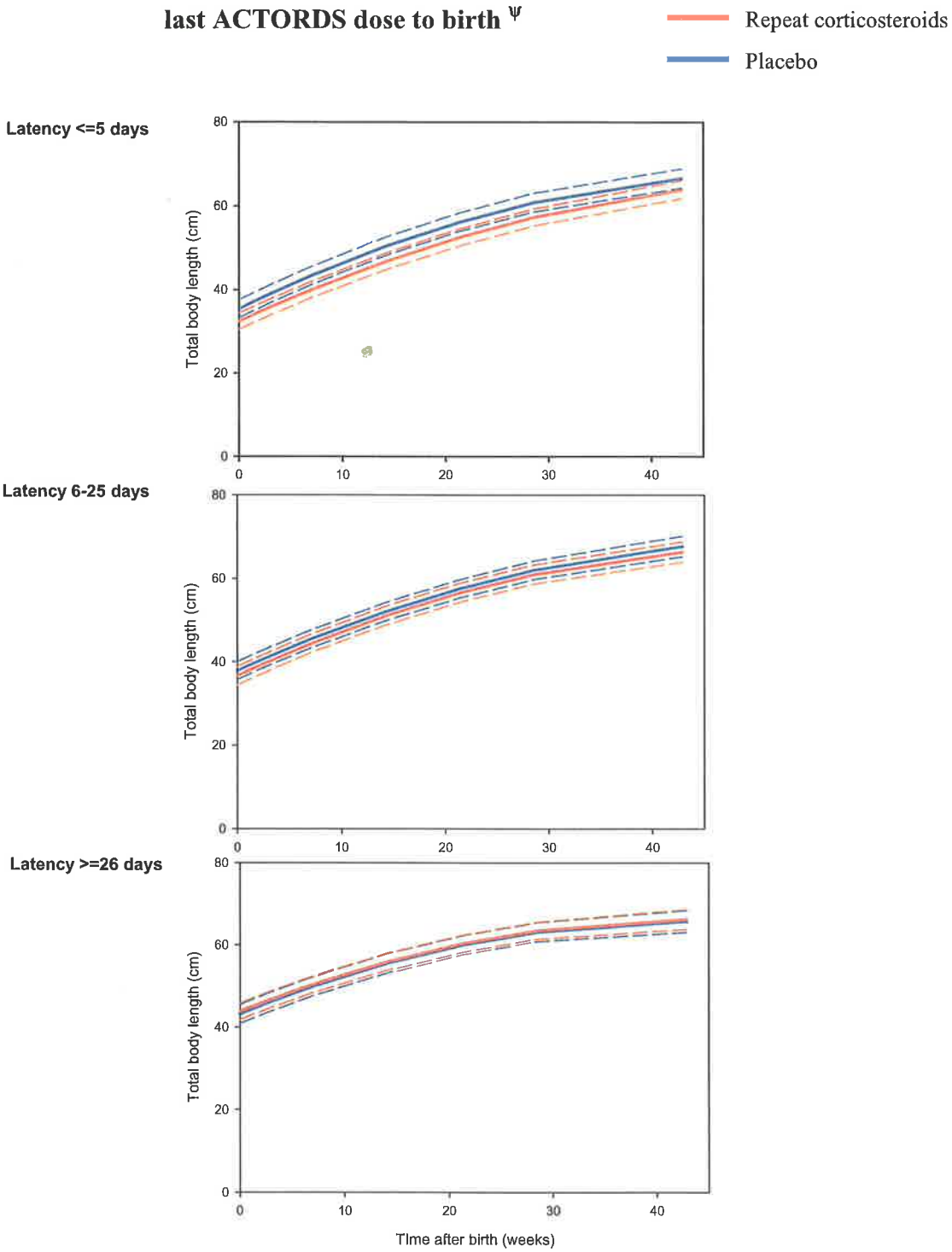
[Ψ] Adjusted for severe intrauterine growth restriction, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Figure 3.4.3.4 Estimated mean total body length and 95% CI by the number of ACTORDS treatment doses received [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Figure 3.4.3.5 Estimated mean total body length and 95% CI by the latency from last ACTORDS dose to birth [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Postnatal systemic infection and postnatal corticosteroid subgroup analysis

There was no statistically significant effect modification on total body length gain by systemic postnatal infection (estimated mean difference in treatment group difference -0.00006 cm per day, p=0.21). No statistically significant difference in total body length gain between the two treatment groups was seen when those without postnatal systemic infection (estimated mean difference 0.001 cm per day, 95% CI -0.006, 0.008) and those who developed a postnatal systemic infection (estimated mean difference -0.01 cm per day, 95% -0.037, 0.009) were compared.

There was no statistically significant effect modification on total body length gain by postnatal corticosteroid exposure (estimated mean difference in treatment group difference 0.007 cm per day, p=0.48). No statistically significant difference in the total body length gain was seen when repeat corticosteroid and placebo group infants who did not receive postnatal corticosteroids (estimated mean difference -0.001 cm per day, 95% CI -0.008, 0.006) and those who were exposed to postnatal corticosteroids (estimated mean difference -0.01 cm per day, 95% CI -0.03, 0.01) were compared.

Descriptive comparisons of total body length z-scores (Table 3.4.3.3)

The mean total body length z-score at birth was -0.88 (SD 1.39) for repeat corticosteroid infants and -0.83 (SD 1.25) for placebo-group infants. Only five infants had total body length measured on day three, and as a result, the mean total body length z-scores at this time point may be misleading. Omitting the mean total body length z-score at day three, total body length z-scores increased over time, with the mean total body length z-score of infants in the repeat corticosteroid group always lower than those in the placebo group. Of importance is

that the reference used to generate z-scores did not allow total body length z-scores to be calculated for infants less than 33 weeks gestation, thus the number of total body length z-scores in each group during the first month after birth are lower than the actual number of measurements collected.

Statistical comparisons were not made between the two treatment groups for the mean total body length z-scores as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.3.3 Total body length z-scores by treatment group

Total body length z-score	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	31	-0.88	1.39	37	-0.83	1.25
Day 3	3	0.05	2.73	2	0.74	0.11
Week 1	18	-1.33	1.22	29	-1.28	1.23
Week 2	23	-1.44	1.35	34	-1.29	1.34
Week 3	21	-1.25	1.20	41	-1.20	1.31
Month 1	38	-1.42	1.62	38	-0.79	1.28
Month 2	44	-1.32	2.07	53	-0.51	1.57
Month 3	41	-1.29	1.96	45	-0.14	1.35
Month 4	42	-0.90	1.85	46	-0.32	1.37
7¼ months CA	37	-0.41	1.24	43	0.17	1.24

SD - standard deviation; CA - corrected age.

Mixed model analysis of variance for total body length z-scores

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on total body length z-scores, with adjustment for confounding, repeated measures, missing data and including infants with the same mother. Comparisons at each of the nominal measurement time points revealed that infants exposed to repeat prenatal corticosteroids had lower estimated mean total body length z-scores, though not statistically significant at the $p<0.01$ level (Figure 3.4.3.4).

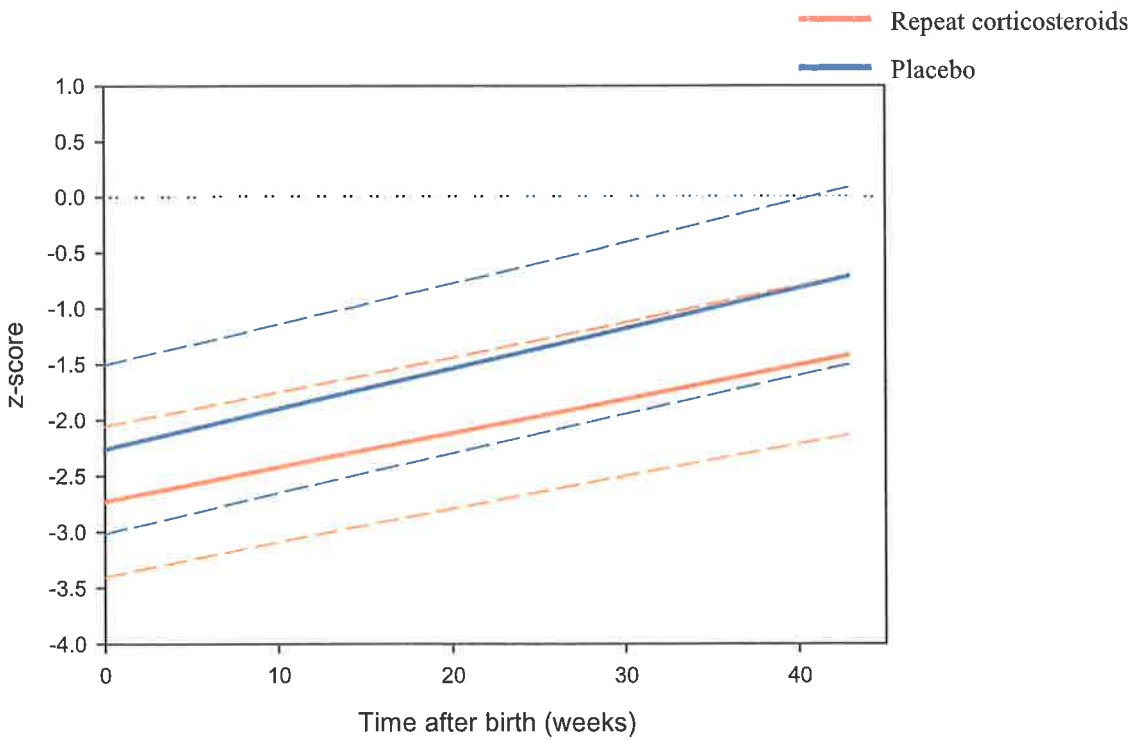
Table 3.4.3.4 Estimated total body length z-score by the nominal measurement time points [Ψ]

Total body length z-score	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Birth	-2.86	0.38	-2.28	0.41	0.58	-0.01	1.16	0.05
Day 3	-2.16	0.57	-2.61	0.69	0.45	-1.93	1.04	0.56
Week 1	-3.15	0.39	-2.67	0.42	0.48	-0.16	1.12	0.14
Week 2	-3.05	0.38	-2.47	0.41	0.59	-0.02	1.19	0.06
Week 3	-2.79	0.39	-2.44	0.41	0.35	-0.26	0.96	0.26
Month 1	-2.82	0.37	-2.20	0.41	0.62	0.05	1.19	0.03
Month 2	-2.31	0.37	-1.73	0.41	0.58	0.03	1.13	0.04
Month 3	-2.06	0.37	-1.53	0.41	0.53	-0.03	1.09	0.06
Month 4	-1.95	0.37	-1.35	0.41	0.59	0.04	1.15	0.04
7¼ months CA	-1.96	0.38	-1.31	0.42	0.64	0.05	1.24	0.03

[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth and multiple gestations. Est. mean - estimated mean; SEM - standard error of mean; CA - corrected age.

A linear model, with adjustment for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reason for risk of preterm birth, and multiple gestations provided the best fit for total body length z-score (Figure 3.4.3.6). At birth, infants in the repeat corticosteroid group had a estimated mean total body length z-score 0.47 smaller than those infants in the placebo group, p=0.05. There was no statistically significant difference in the gain in total body length z-score between the infants in the two treatment groups over time.

Figure 3.4.3.6 Estimated mean total body length z-score and 95% CI [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Gestational age at birth and total body length z-score (Figure 3.4.3.7)

There was no statistically significant effect modification by gestational age at birth on total body length z-score gain. Similarly, there were no statistically significant differences in total body length z-score gain between infants in the two treatment groups when the subgroups born less than 34 weeks gestation, and those born at 34 or more weeks gestation were compared.

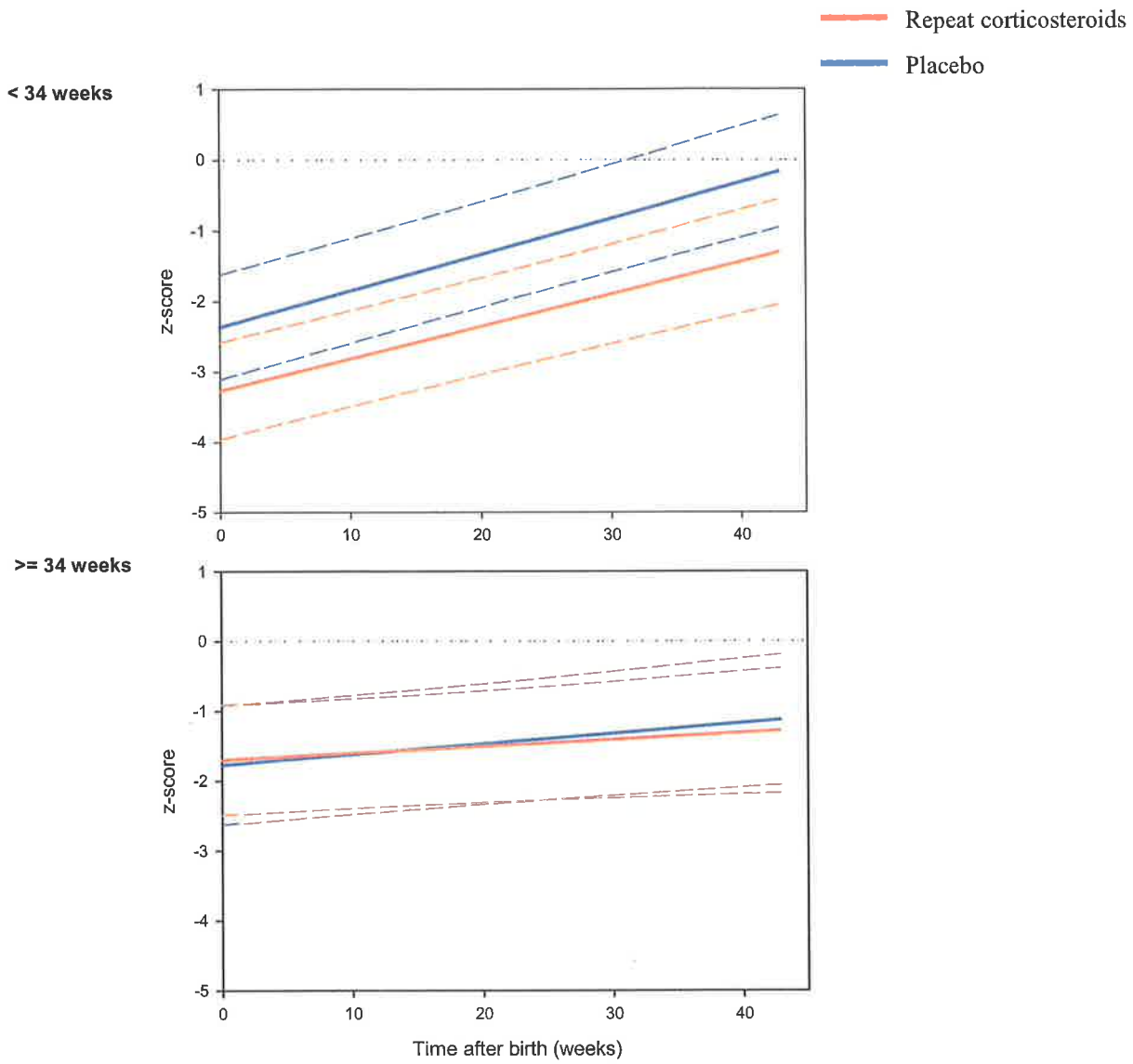
ACTORDS treatment dose and total body length z-score (Figure 3.4.3.8)

The number of ACTORDS treatment doses administered was not a statistically significant effect modifier for total body length z-score gain. There were no statistically significant differences in total body length z-score gain between the infants in the two treatment groups when each of the dose subgroups were examined (0-1, 2-3 and ≥ 4 doses).

Latency from last ACTORDS dose to birth and total body length z-score (Figure 3.4.3.9)

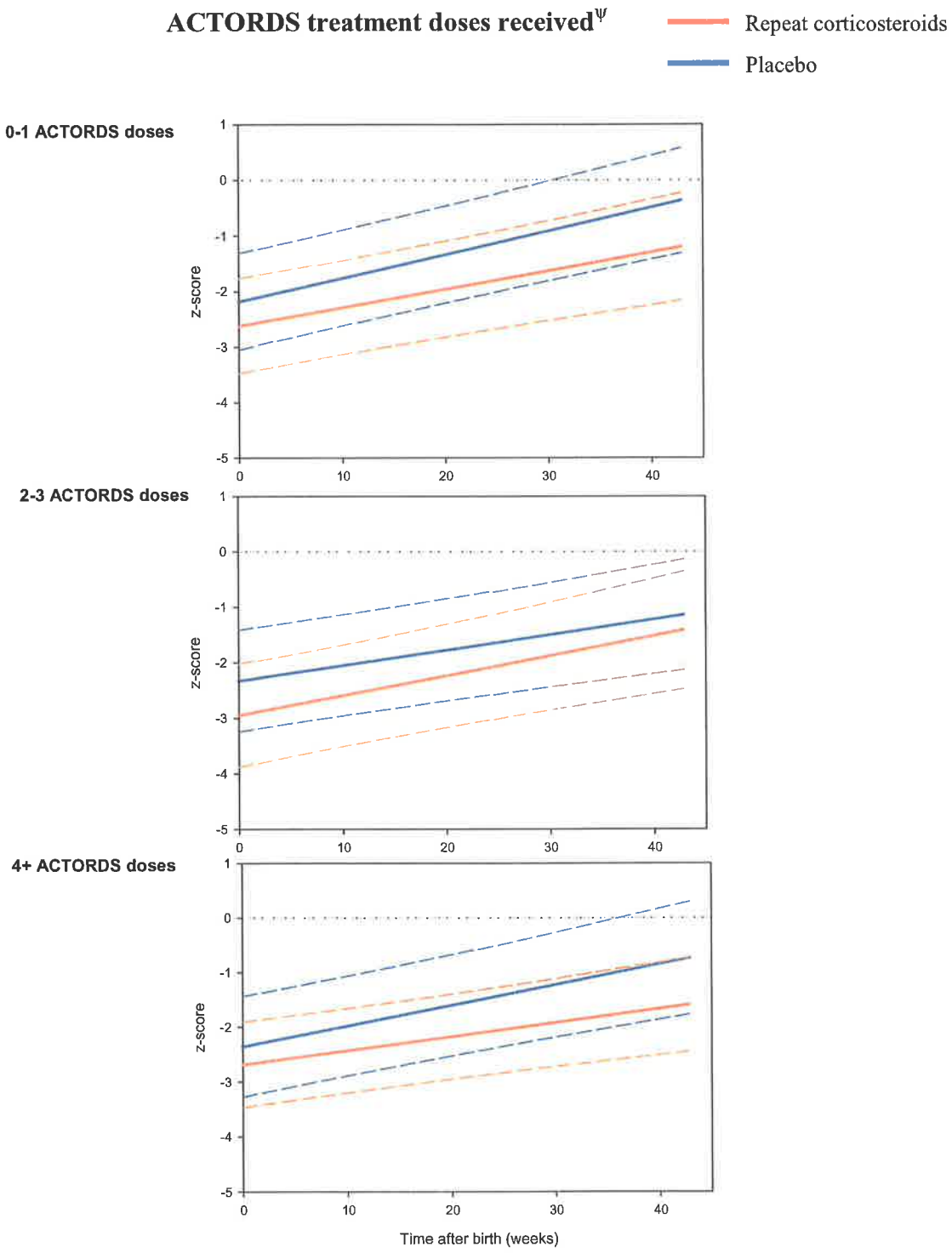
The latency between the last ACTORDS dose and birth was not a statistically significant effect modifier on total body length z-score gain, and there were no statistically significant differences in total body length z-score gain between the treatment groups for each of the three latency categories (≤ 5, 6-25 and ≥26 days).

Figure 3.4.3.7 Estimated mean total body length z-score by gestational age at birth[Ψ]



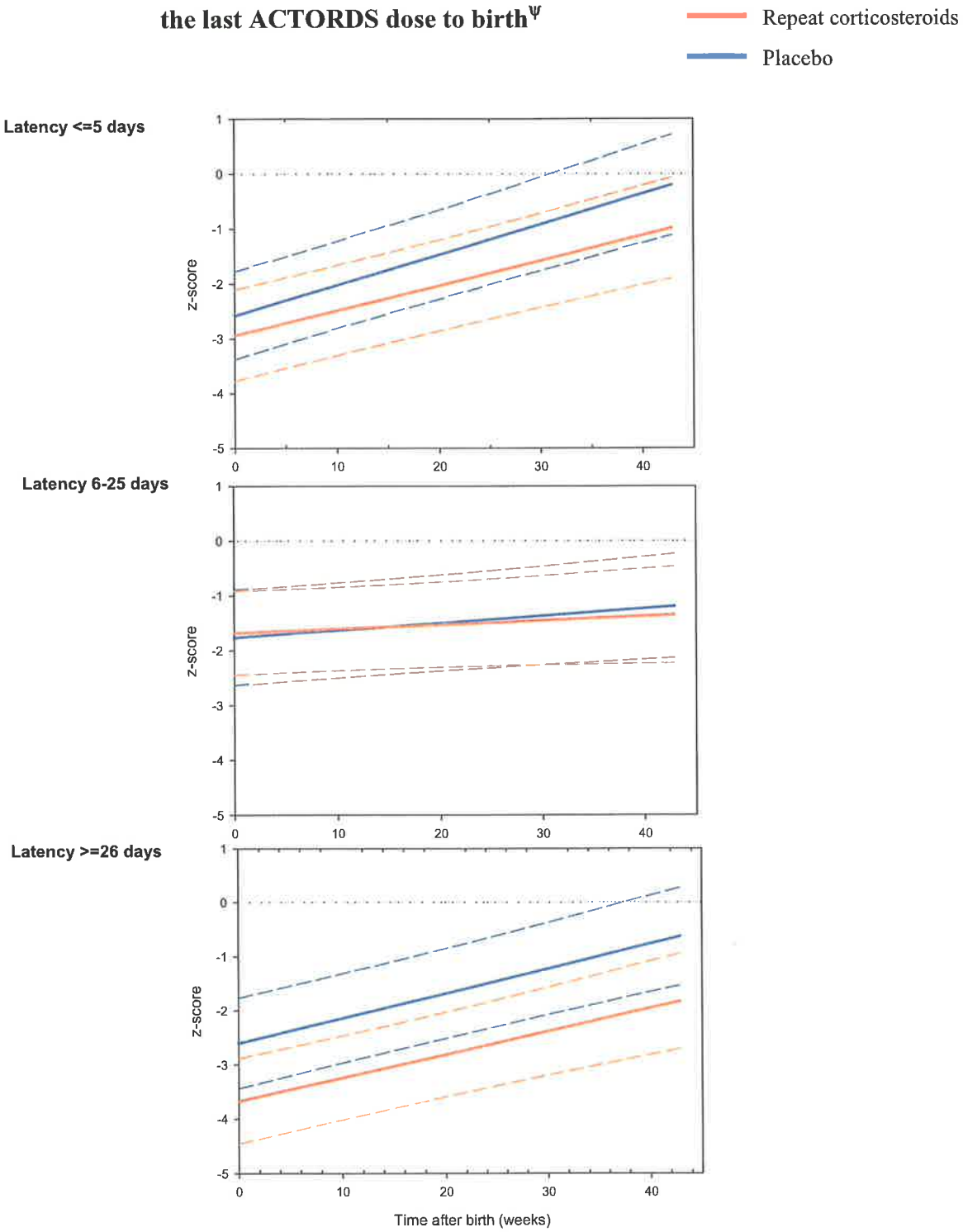
[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Figure 3.4.3.8 Estimated mean total body length z-score and 95% CI by the number of ACTORDS treatment doses received[Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Figure 3.4.3.9 Estimated mean total body length z-score and 95% CI by the latency from the last ACTORDS dose to birth[Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as the reasons for risk of preterm birth and multiple gestations.

Postnatal systemic infection and postnatal corticosteroid subgroup analysis

There was no statistically significant effect modification of systemic postnatal infection on total body length z-score gain (estimated mean difference in treatment group difference 0.006 per day, p=0.15). No statistically significant differences were identified between the two treatment groups in total body length z-score gain when infants who did not develop a systemic postnatal infection (estimated mean difference 0.0008 per day, 95% CI -0.0008, 0.002) and those who did develop a systemic postnatal infection (estimated mean difference -0.005 per day, 95% CI -0.01, 0.002) were compared.

There was no statistically significant effect modification of postnatal corticosteroid exposure of total body length z-score gain (estimated mean difference in treatment group difference -0.0007 per day, p=0.78). There were no statistically significant differences in total body length z-score gain between the repeat corticosteroid and placebo group infants when infants exposed to postnatal corticosteroids, and those unexposed to postnatal corticosteroids, were compared.

Descriptive comparisons of total body length percentiles (Table 3.4.3.5)

The proportion of infants below the 3rd and 10th percentile varied over time. There was significant attrition of participants over time, with losses of over half the infants by 7¼ months corrected age. Statistical comparisons were not made between the two treatment groups for total body length percentiles, as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother. Further multivariate analysis of this percentile data was not conducted given it was not a primary outcome for this trial, that the sample size was small and that the

percentiles were derived from the z-score data that has already been explored using multivariate statistics.

Table 3.4.3.5 Total body length percentiles by treatment group

	Repeat corticosteroids			Placebo		
	N	n	%	N	n	%
<3rd percentile						
Birth	71	7	10	72	1	1
Week 1	60	10	17	66	6	9
Week 2	53	11	21	61	8	13
Week 3	53	10	19	59	7	12
Month 1	52	8	16	52	1	2
Month 2	51	6	12	55	0	0
Month 3	48	5	10	48	3	6
Month 4	44	6	14	48	2	4
7¼ months CA	39	6	15	44	2	5
<10th percentile						
Birth	71	10	14	72	15	21
Week 1	60	8	13	66	15	23
Week 2	53	13	25	61	19	31
Week 3	53	11	21	59	20	34
Month 1	52	21	40	52	13	25
Month 2	51	19	37	55	15	27
Month 3	48	18	38	48	10	21
Month 4	44	13	30	48	11	23
7¼ months CA	39	8	21	44	6	14

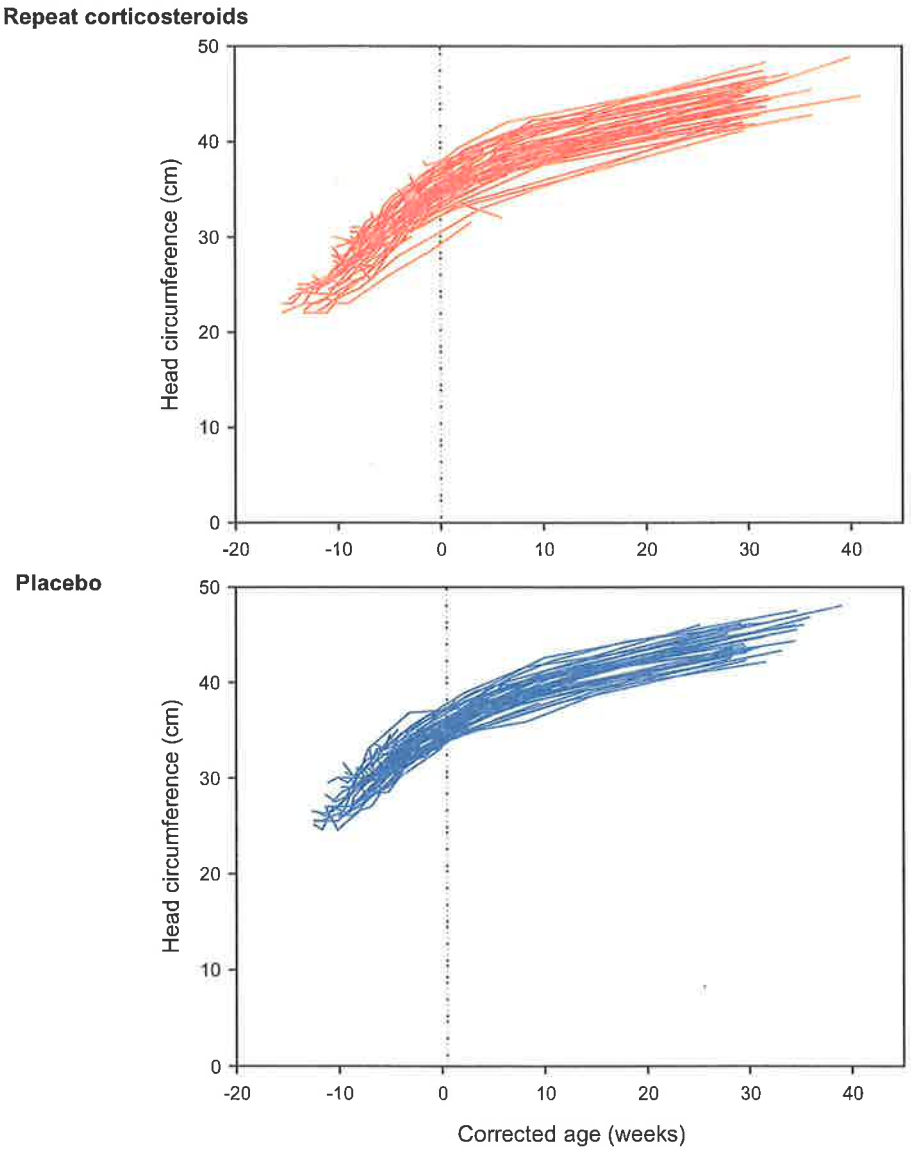
CA - corrected age

3.4.4. HEAD CIRCUMFERENCE

Descriptive comparisons of head circumference

Head circumference growth curves by treatment group, for each infant by their corrected age, are shown in Figure 3.4.4.1. Head circumference increased with corrected age.

Figure 3.4.4.1 Head circumference growth curves by corrected age



At birth, the mean head circumference was 29.5 cm (SD 4.1) in the repeat corticosteroid group and 30.5 cm (SD 2.7) in the placebo group (Table 3.4.4.1). There were few infants for which head circumference was measured on day three and as a result, the mean head circumference on day three appeared larger than at birth, probably as a result of the head circumference only being measured on larger infants. Excluding the measurements at day three, the mean head circumference increased over time. It was lower in repeat corticosteroid treated infants compared with placebo group infants, at each of the time points except at 7¼ months corrected age where the means were identical. Statistical comparisons were not made between the two treatment groups for head circumference, as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.4.1 Head circumference by treatment group

Head circumference (cm)	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	70	29.5	4.1	72	30.5	2.7
Day 3	11	32.2	3.1	16	31.9	2.0
Week 1	52	28.3	3.8	59	29.9	2.7
Week 2	50	28.9	3.5	55	30.5	2.9
Week 3	48	29.7	3.8	54	31.5	2.9
Month 1	51	31.0	4.3	48	32.6	2.6
Month 2	50	34.6	3.9	53	36.0	2.4
Month 3	44	36.7	3.4	46	38.0	1.7
Month 4	42	39.1	3.0	46	39.9	1.5
7¼ months CA	38	44.5	1.9	43	44.5	1.5

SD - standard deviation; CA - corrected age.

Mixed model analysis of variance for head circumference

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on head circumference over time, with adjustment for confounding, repeated measures, missing data and including infants with the same mother. Comparisons at each of the nominal measurement time points revealed no statistically significant differences in the estimated mean head circumference between repeat corticosteroid and placebo group infants from birth to 7¼ months postnatal corrected age (Table 3.4.4.2).

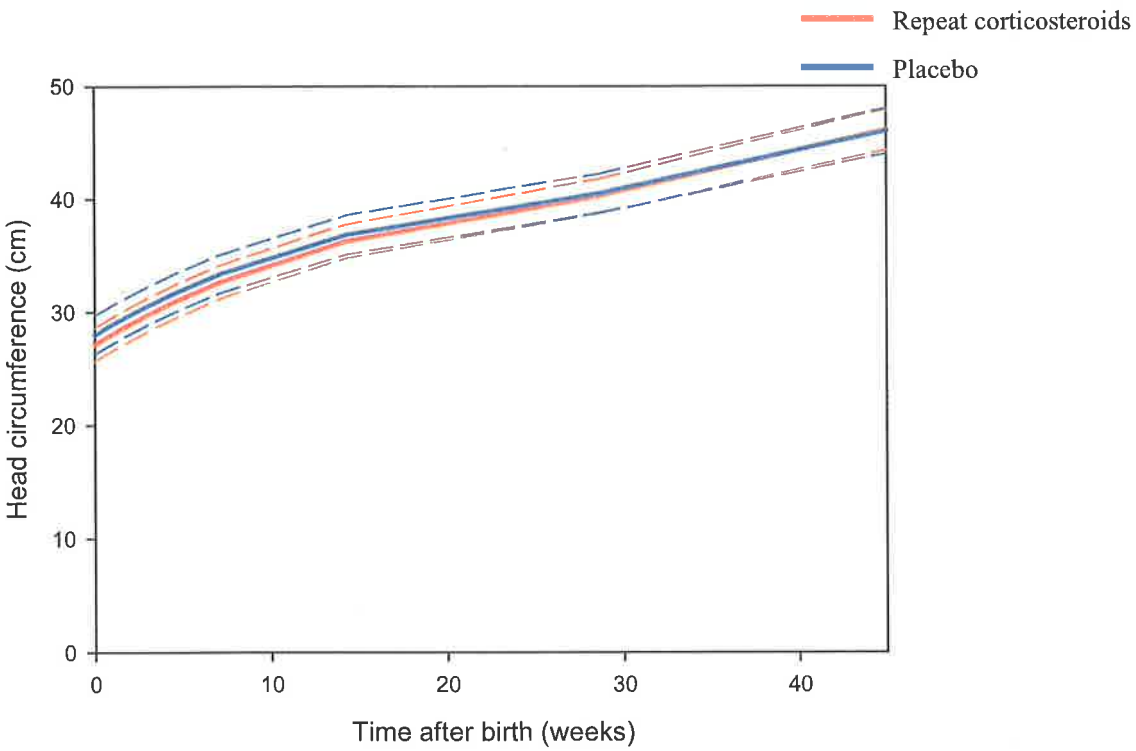
Table 3.4.4.2 Estimated mean head circumference at the nominal measurement time points[Ψ]

Head circumference (cm)	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Birth	28.0	0.7	28.8	0.8	0.9	-0.2	2.0	0.10
Day 3	27.8	0.8	29.0	0.9	1.2	-0.3	2.6	0.11
Week 1	27.6	0.7	28.5	0.8	0.9	-0.2	2.0	0.09
Week 2	28.3	0.7	29.1	0.8	0.8	-0.3	1.9	0.17
Week 3	29.2	0.7	30.1	0.8	0.9	-0.3	2.0	0.13
Month 1	30.2	0.7	31.2	0.8	1.0	-0.1	2.1	0.08
Month 2	33.5	0.7	34.4	0.8	0.9	-0.2	2.0	0.10
Month 3	35.9	0.7	36.2	0.9	0.3	-0.8	1.4	0.62
Month 4	37.6	0.8	38.0	0.9	0.4	-0.7	1.6	0.45
7¼ months CA	42.3	0.8	42.3	0.9	0.0	-1.2	1.2	0.99

[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth, and multiple gestations. Est. mean - estimated mean; SEM - standard error of mean; CA - corrected age.

A cubic model, with adjustment for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth, and multiple gestations provided the best fit for head circumference (Figure 3.4.4.2). There were no statistically significant differences in head circumference between the two treatment groups at birth (estimated mean difference 0.87 cm, p=0.10). Repeat corticosteroid exposed infants gained 0.0031 cm more in head circumference per day compared with those in the placebo group (p=0.006).

Figure 3.4.4.2 Estimated mean head circumference and 95% CI [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth and multiple gestations.

Gestational age at birth and head circumference (Figure 3.4.4.3)

There was significant effect modification on head circumference gain by gestational age at birth (estimated mean difference in treatment group difference -0.0047 cm per day, p=0.02). When infants born at less than 34 weeks gestation were examined, those in the repeat corticosteroid group gained 0.0043 cm more per day in head circumference than infants in the placebo group (95% CI -0.0065, -0.0020, p=0.0002). There was no statistically significant difference in the rate of head circumference gain, between infants in the two treatment groups, when infants born at 34 or more weeks gestation were compared (estimated mean difference 0.0005 cm per day, 95% CI -0.0027, 0.0036, p=0.77).

ACTORDS treatment dose and head circumference (Figure 3.4.4.4)

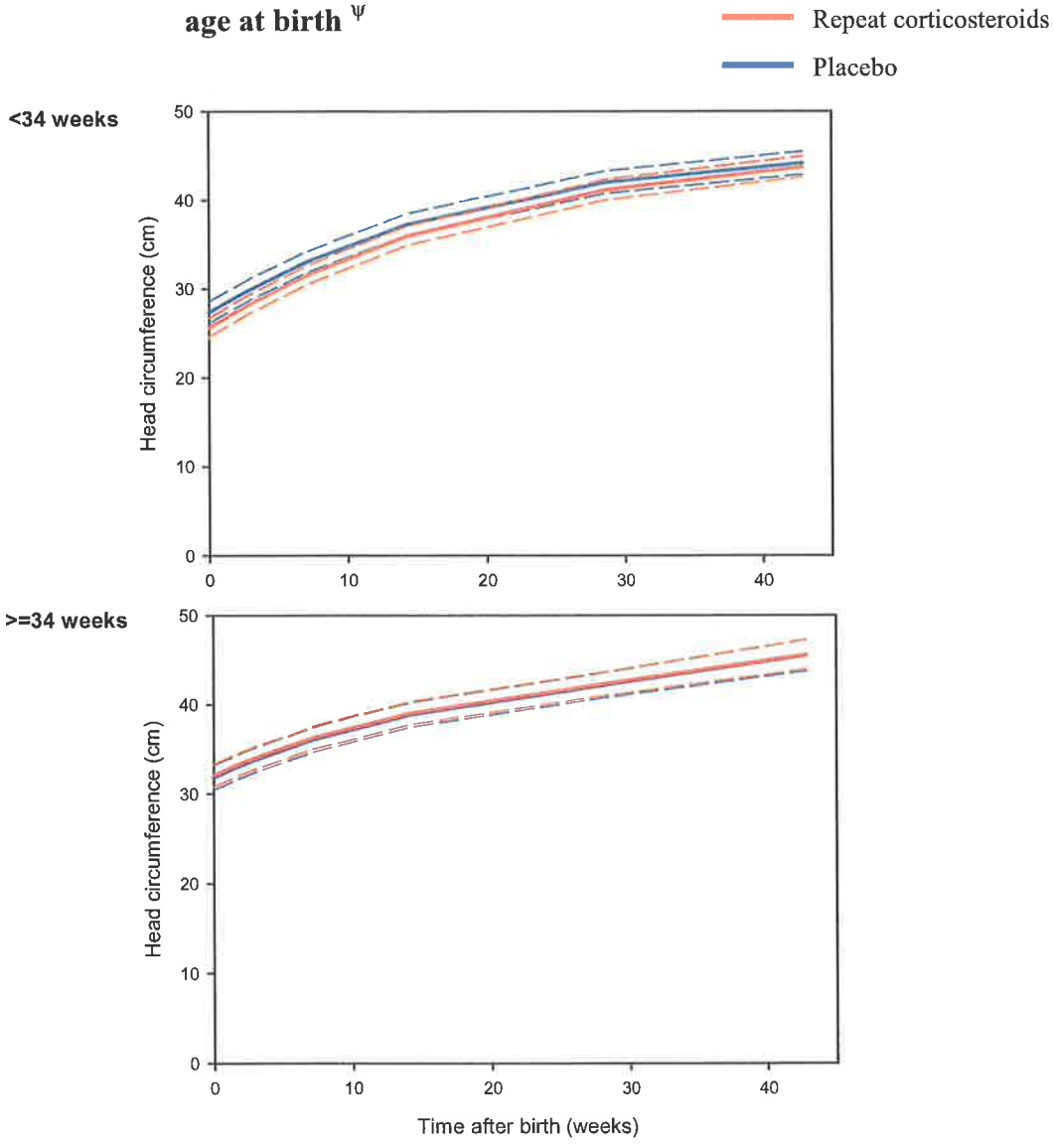
Overall, there was significant effect modification on head circumference gain by the number of ACTORDS treatment doses received. When infants exposed to one or less ACTORDS treatment doses or two to three doses were examined, there was no statistically significant difference in the rate of head circumference gain between infants in the two treatment groups. For infants exposed to four or more ACTORDS treatment doses, those in the repeat corticosteroid group gained 0.0080 cm more per day in head circumference than those in the placebo group (95% CI -0.0123, -0.0039, p=0.0002).

Latency from last ACTORDS dose to birth and head circumference (Figure 3.4.4.5)

There was significant effect modification on head circumference gain by the latency from last ACTORDS dose to birth. For infants with a latency of five or less days, those exposed to repeat corticosteroids gained 0.0042 cm more per day in head circumference than infants in the placebo group (95% CI -0.0073, -0.0012, p=0.007). For infants with a latency of six to 25

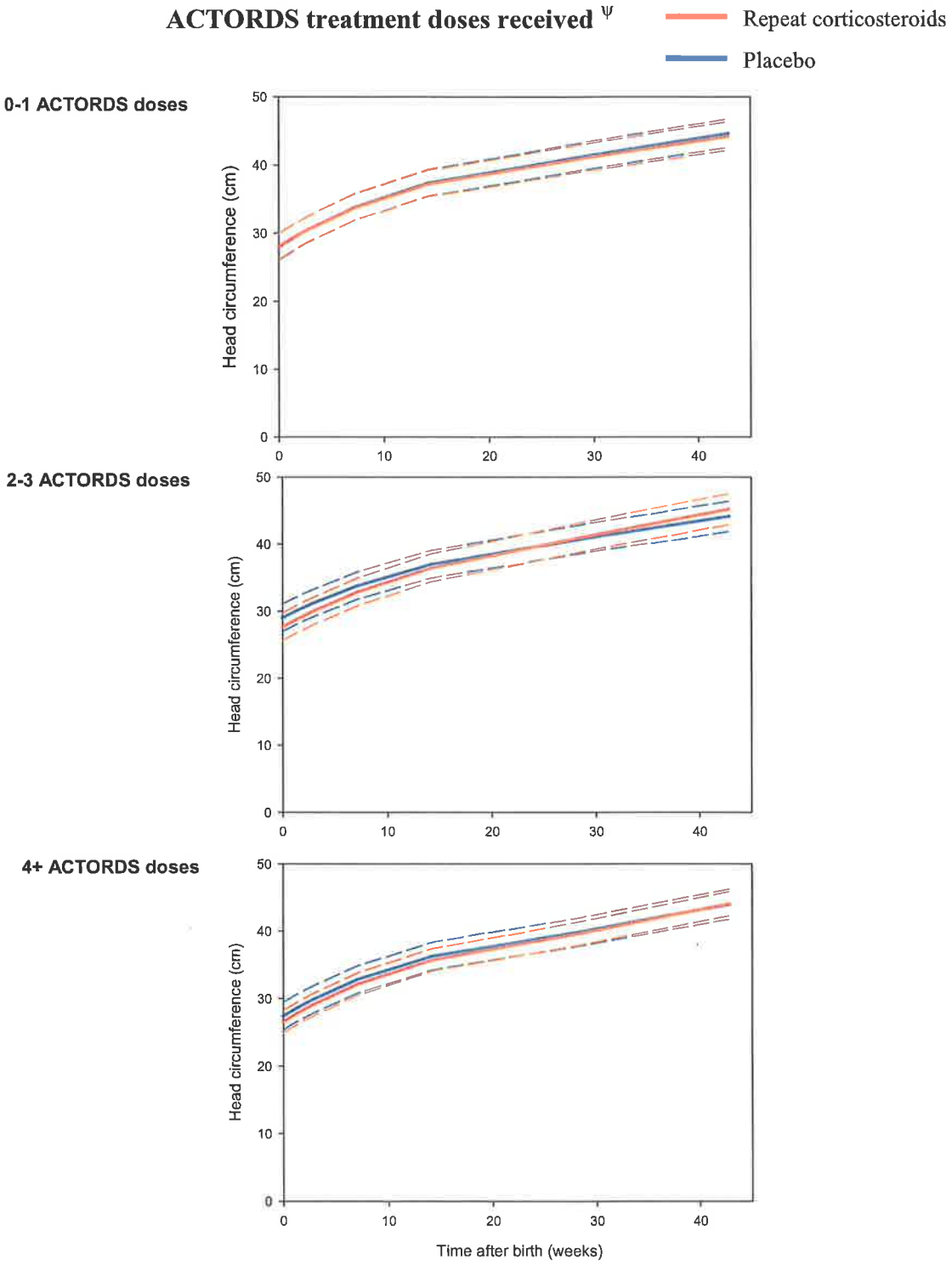
days, those in the repeat corticosteroid group gained 0.0054 cm more per day in head circumference that those in the placebo group (95% CI -0.0088, -0.0021, p=0.002). There were no statistically significant differences in the rate of head circumference gain between the two treatment groups when those infants with a latency of 26 or more days were compared (estimated mean difference 0.0003 cm per day, 95% CI -0.0031, 0.0037, p=0.86).

Figure 3.4.4.3 Estimated mean head circumference and 95% CI by gestational age at birth [Ψ]



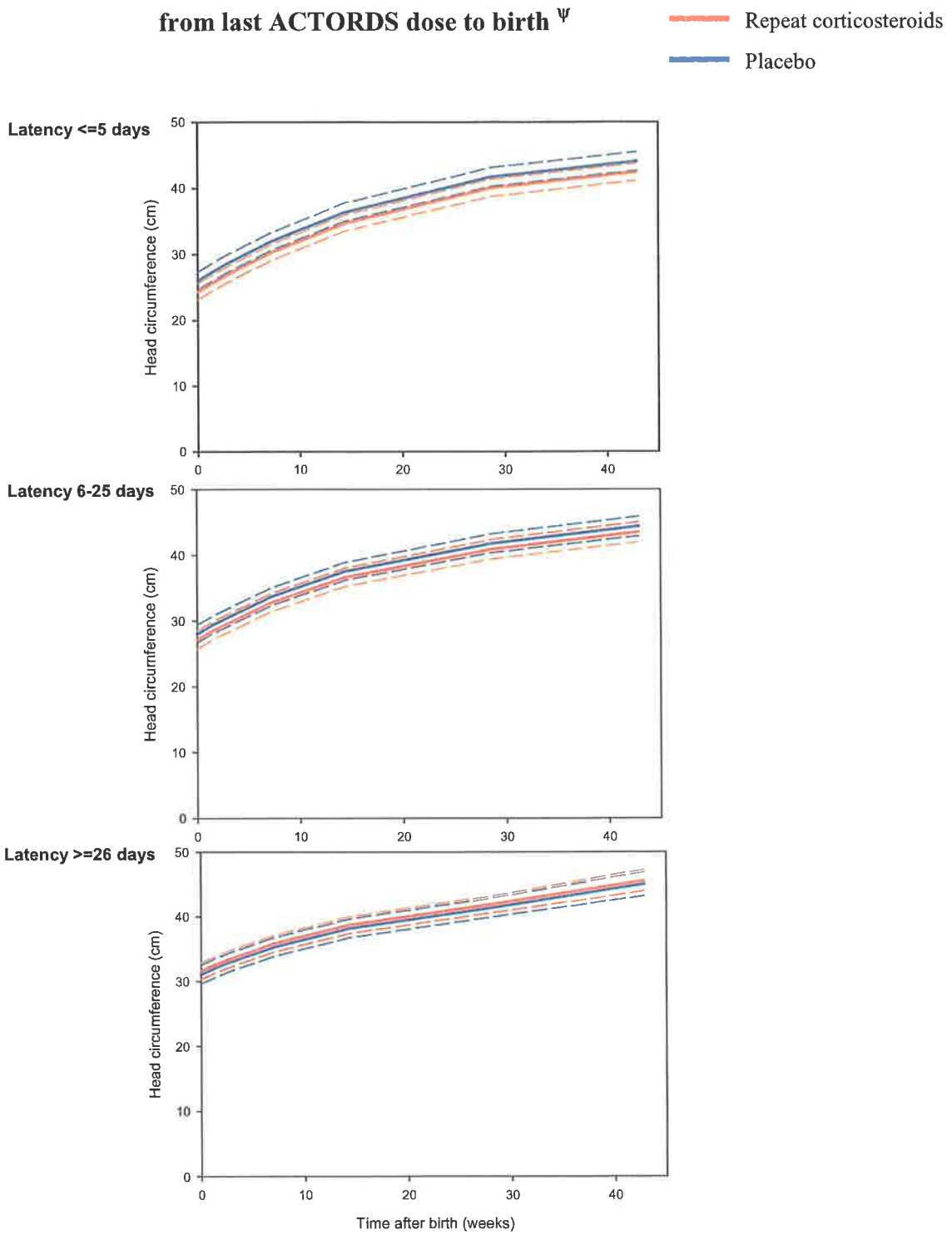
[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth and multiple gestations.

Figure 3.4.4.4 Estimated mean head circumference and 95% CI by the number of ACTORDS treatment doses received [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth and multiple gestations.

Figure 3.4.4.5 Estimated mean head circumference and 95% CI by the latency from last ACTORDS dose to birth [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery, pre-eclampsia and placenta praevia as reasons for risk of preterm birth and multiple gestations.

Postnatal systemic infection and postnatal corticosteroid subgroup analysis

There was no statistically significant effect modification on head circumference gain by systemic postnatal infection (estimated mean difference in treatment group difference -0.0075 cm per day, p=0.70). No statistically significant differences were detected between the treatment groups in head circumference gain when infants who did not develop a postnatal systemic infection (estimated mean difference -0.0022 cm per day, 95% CI -0.0044, 0.0001) and those who did develop a systemic infection prior to hospital discharge (estimated mean difference 0.0053 cm per day, 95% -0.0036, 0.0142) were compared.

There was no statistically significant effect modification on head circumference gain by postnatal corticosteroid exposure (estimated mean difference in treatment group difference 0.0038 cm per day, p=0.023). No statistically significant difference was detected in the head circumference gain between the two treatment groups when infants who did not receive postnatal corticosteroids (estimated mean difference -0.0133 cm per day, 95% CI -0.0037, 0.0010) and infants exposed to postnatal corticosteroids (-0.0052 cm per day (95% CI -0.0110, 0.0006) were compared.

Descriptive comparisons of head circumference z-scores (Table 3.4.4.3)

The mean head circumference z-score at birth was -0.20 (SD 1.20) for repeat corticosteroid treated infants and 0.12 (SD 0.99) for placebo-group infants. Over time, the mean head circumference z-score was lower in the repeat corticosteroid group, compared with the placebo group. Statistical comparisons were not made on the mean head circumference z-scores between the two treatment groups as they may be misleading since there has been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.4.3 Head circumference z-scores by treatment group

Head circumference z-score	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	70	-0.20	1.28	72	0.12	0.99
Day 3	11	-0.28	1.51	16	-0.18	1.03
Week 1	52	-1.07	1.09	59	-0.66	0.99
Week 2	50	-1.05	1.05	55	-0.75	0.98
Week 3	48	-0.93	1.28	54	-0.56	1.06
Month 1	51	-0.73	1.56	48	-0.27	0.92
Month 2	50	-0.16	1.61	53	0.45	1.40
Month 3	44	-0.18	1.53	46	-0.003	1.00
Month 4	42	-0.22	1.71	46	-0.02	1.05
7¼ months CA	38	-0.26	1.47	43	-0.13	1.10

SD - standard deviation; CA - corrected age.

Mixed model analysis of variance for head circumference z-scores

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on head circumference z-scores, with adjustment for confounding, repeated measures, missing data and including infants with the same mother. There were no statistically significant differences between the two treatment groups in estimated mean head circumference z-scores from birth to 7¼ months corrected age, at the $p<0.01$ significance level (Table 3.4.4.4).

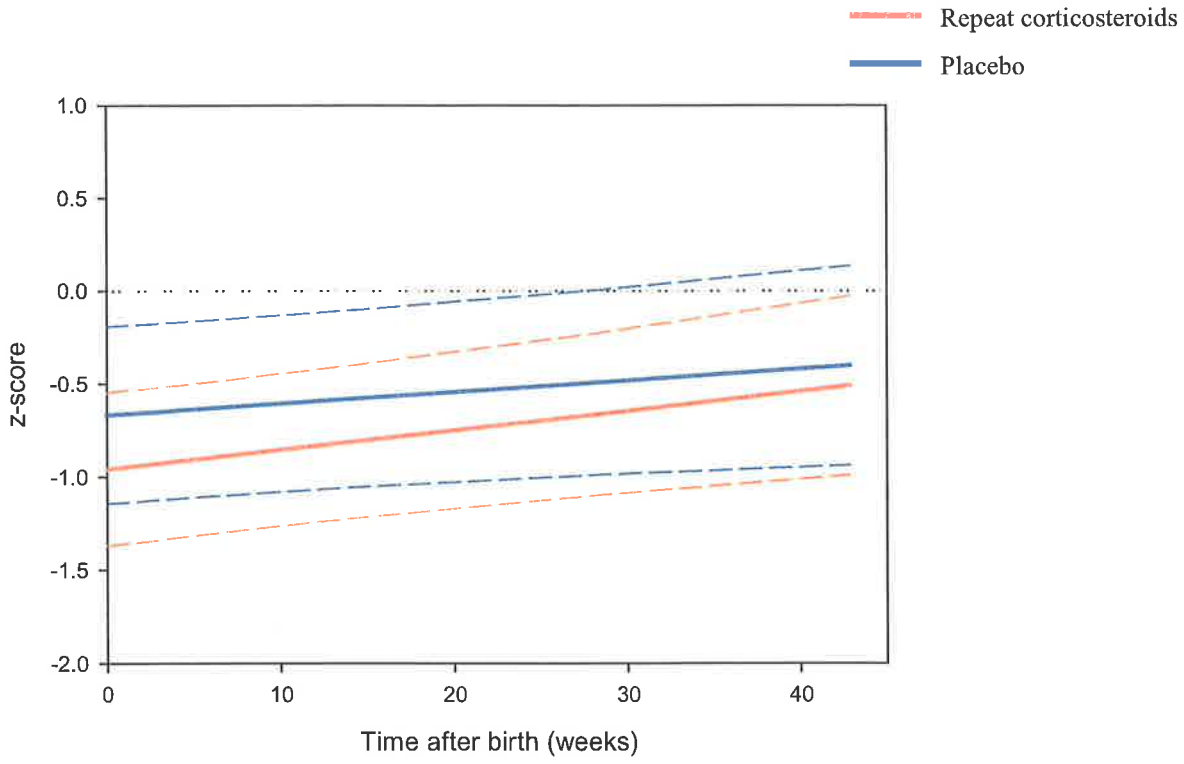
Table 3.4.4.4 Estimated mean head circumference z-score for nominal measurement time points [Ψ]

Head circumference z-score	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Birth	-0.61	0.22	-0.34	0.25	0.27	-0.13	0.67	0.18
Day 3	-1.32	0.31	-0.70	0.30	0.62	-0.05	1.29	0.70
Week 1	-1.37	0.23	-1.09	0.26	0.28	-0.14	0.71	0.19
Week 2	-1.34	0.23	-1.16	0.26	0.19	-0.24	0.62	0.39
Week 3	-1.23	0.23	-0.95	0.26	0.28	-0.16	0.71	0.21
Month 1	-1.06	0.23	-0.68	0.26	0.38	-0.05	0.82	0.08
Month 2	-0.48	0.23	0.00	0.26	0.48	0.04	0.91	0.03
Month 3	-0.48	0.23	-0.45	0.26	0.03	-0.41	0.48	0.88
Month 4	-0.64	0.23	-0.45	0.26	0.19	-0.26	0.64	0.42
7¼ months CA	-0.89	0.24	-0.73	0.27	0.17	-0.32	0.66	0.50

[Ψ]Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth. Est. mean - estimated mean; SEM - standard error of mean; CA - corrected age.

A linear model, with adjustment for severe intrauterine growth restriction requiring delivery and placenta praevia as the reason for risk of preterm birth, provided the best fit for head circumference z-score (Figure 3.4.4.6). There were no statistically significant differences between the estimated mean head circumference z-scores between infants in the repeat corticosteroid and placebo groups at birth (estimated mean difference 0.29, p=0.10). There was no statistically significant difference in the gain in head circumference z-score between the two treatment groups over time (estimated mean difference -0.0006 per day, p=0.41).

Figure 3.4.4.6 Estimated mean head circumference z-score and 95% CI [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Gestational age at birth and head circumference z-score (Figure 3.4.4.7)

There was no statistically significant effect modification by gestational age at birth on head circumference z-score gain. Similarly, there were no statistically significant differences in head circumference z-score gain, between infants in the two treatment groups, when the subgroups born less than 34 weeks gestation and those born at 34 or more weeks gestation were compared.

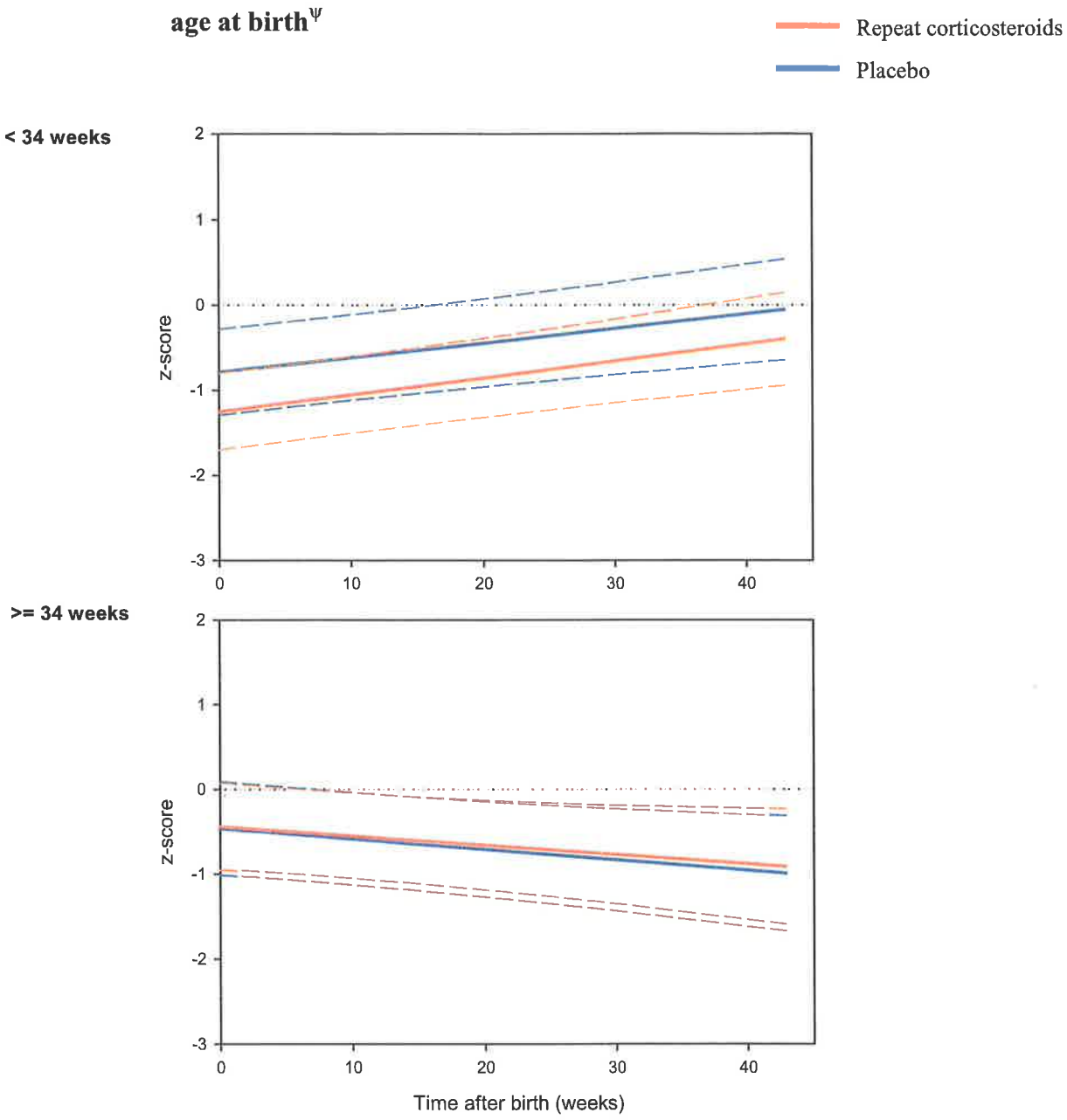
ACTORDS treatment dose and head circumference z-score (Figure 3.4.4.8)

The number of ACTORDS treatment doses administered was an effect modifier for head circumference z-score gain. There were no statistically significant differences in head circumference z-score gain between the two treatment groups when the subgroups having zero to one dose and two to three doses were compared. For infants who received four or more ACTORDS treatment doses however, those in the repeat corticosteroid group gained 0.004 per day in head circumference z-score more than placebo-group infants (95% CI -0.006, -0.0009, p=0.01).

Latency between last ACTORDS dose and birth and head circumference z-score (Figure 3.4.4.9)

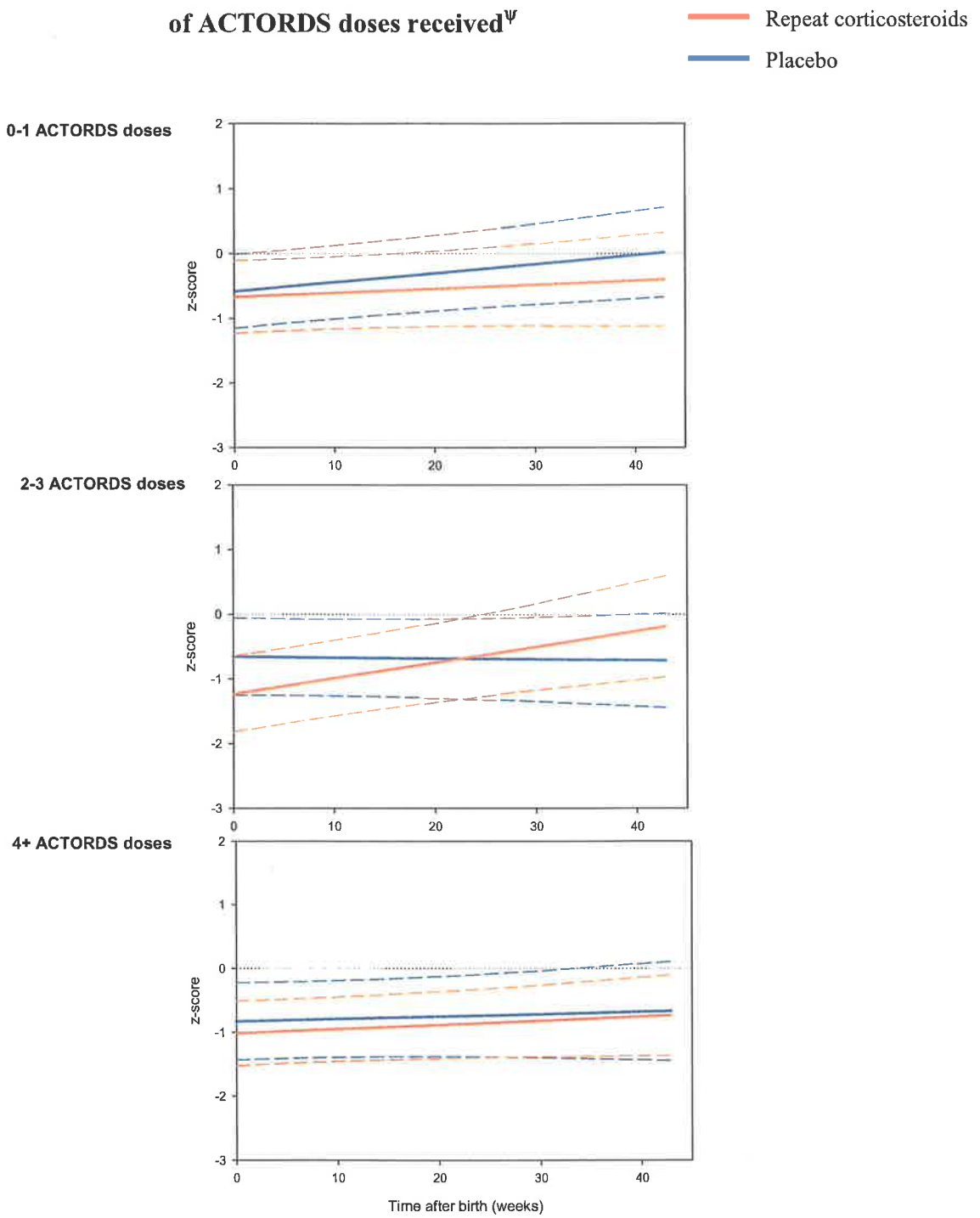
The latency between the last ACTORDS dose and birth was not a statistically significant effect modifier on head circumference z-score gain. There were also no statistically significant differences in head circumference z-score gain between the treatment groups for each of the three latency categories (≤ 5, 6-25 and ≥ 26 days).

Figure 3.4.4.7 Estimated mean head circumference z-score and 95% CI by gestational age at birth[Ψ]



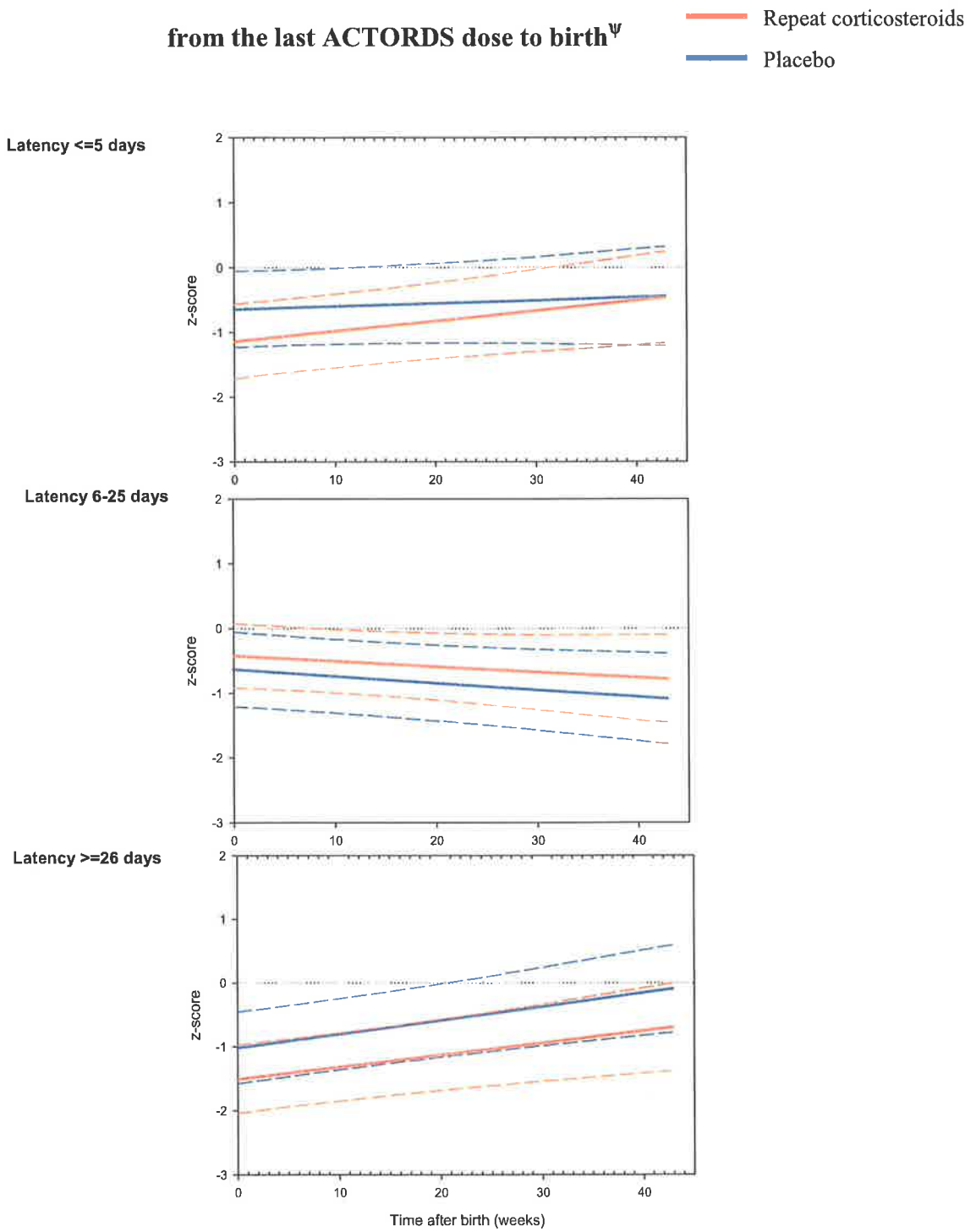
[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Figure 3.4.4.8 Estimated mean head circumference z-score and 95% CI by the number of ACTORDS doses received[Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Figure 3.4.4.9 Estimated mean head circumference z-score and 95% CI by the latency from the last ACTORDS dose to birth[Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Postnatal systemic infection and postnatal corticosteroid subgroup analysis

Systemic postnatal infection was a significant effect modifier for head circumference z-score gain (estimated mean difference in treatment group difference -0.01 per day, p=0.0006). For infants who developed a systemic postnatal infection, those exposed to repeat corticosteroids gained 0.009 per day less in head circumference z-score than those in the placebo group (95% CI 0.004, 0.02, p=0.002). For those infants who did not develop an infection, there was no statistically significant difference in the gain of head circumference z-score between the two treatment groups.

There was no statistically significant effect modification of postnatal corticosteroid exposure on head circumference z-score gain (estimated mean difference in treatment group difference –0.001 per day, p=0.49). No statistically significant differences were found in head circumference z-score gain between the two treatment groups, when comparisons were made by postnatal corticosteroid treatment.

Descriptive comparisons of head circumference percentiles (Table 3.4.4.5)

The proportion of infants below the 3rd and 10th percentile varied over time. There was significant attrition of participants over time, with losses of close to half the infants by 7¼ months corrected age. Statistical comparisons were not made between the two treatment groups for head circumference percentiles, as they may be misleading since there had been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother. Further multivariate analysis of this percentile data was not conducted given it was not a primary outcome for this trial, that the sample size was small and that the percentiles were derived from the z-score data that has already been explored using

multivariate statistics.

Table 3.4.4.5 Head circumference percentiles by treatment group

	Repeat corticosteroids			Placebo		
	N	n	%	N	n	%
<3rd percentile						
Birth	71	7	10	72	1	1
Week 1	60	10	17	66	6	9
Week 2	53	11	21	61	8	13
Week 3	53	10	19	59	7	12
Month 1	52	8	15	52	1	2
Month 2	51	6	12	55	0	0
Month 3	48	5	10	48	3	6
Month 4	44	6	14	48	2	4
7¼ months CA	39	6	15	44	2	5
<10th percentile						
Birth	71	13	18	72	8	11
Week 1	60	20	33	66	15	23
Week 2	53	18	34	61	15	25
Week 3	53	18	34	59	14	24
Month 1	52	19	37	52	7	14
Month 2	51	12	24	55	3	6
Month 3	48	10	21	48	4	8
Month 4	44	10	23	48	6	13
7¼ months CA	39	8	21	44	4	9

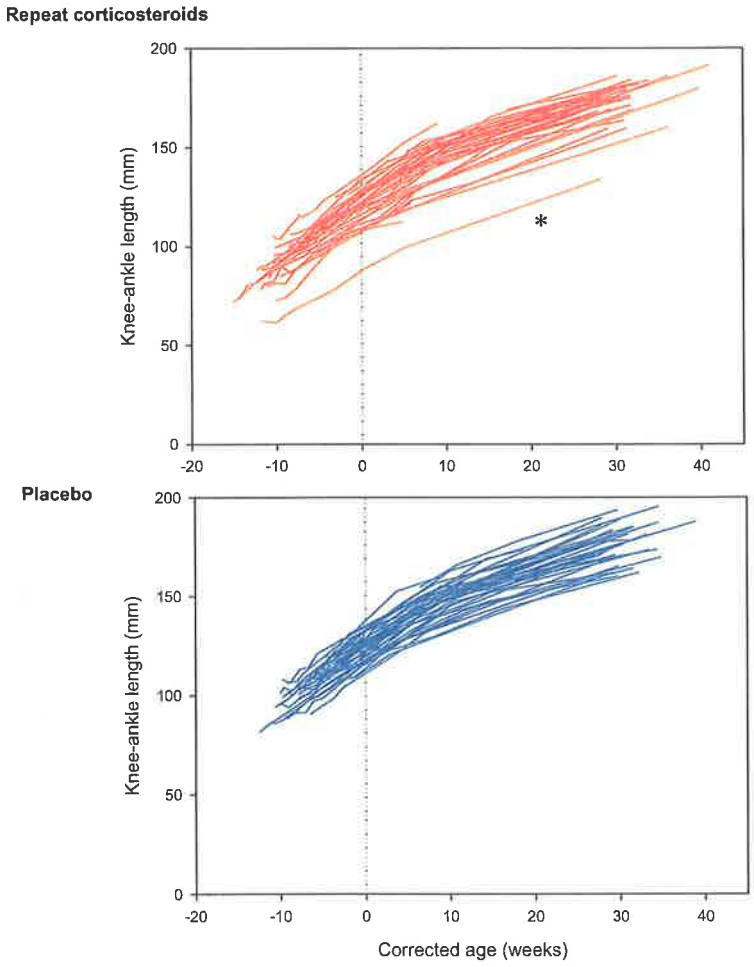
CA - corrected age

3.4.5. KNEE-ANKLE LENGTH

Descriptive comparisons of knee-ankle length

The knee-ankle length growth curves by treatment group, for each infant by their corrected age, are shown in Figure 3.4.5.1. Knee-ankle length increased with corrected age.

Figure 3.4.5.1 Knee-ankle length growth curves by corrected age



At birth, the mean knee-ankle length was 99.1 mm (SD 18.2) for infants in the repeat corticosteroid group, compared with 105.3 mm (SD 13.3) in the placebo group (Table 3.4.5.1). Mean knee-ankle length increased over time and at each of the time points, the mean knee-ankle length of the repeat corticosteroid group was less than the mean knee-ankle length

of the placebo group.

The knee-ankle length measurements recorded on one infant in the repeat corticosteroid group appeared to be an outlier, denoted by * in Figure 3.4.5.1. This infant was a twin, whose trial entry, birth and neonatal characteristics are described on page 105. Exclusion of this infant from the analyses of knee-ankle length made no difference to the results, thus this infant was included in the further comparisons of knee-ankle length.

Statistical comparisons were not made on the mean knee-ankle length between the treatment groups as they may be misleading since there has been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.5.1 Knee-ankle length by treatment group

Knee-ankle length (mm)	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	12	99.1	18.2	15	105.3	13.3
Day 3	21	95.8	16.4	25	106.4	8.6
Week 1	28	98.0	13.0	36	108.3	11.1
Week 2	34	101.2	15.0	33	110.3	11.5
Week 3	34	105.6	15.3	36	114.1	9.5
Month 1	31	109.5	15.6	33	118.1	12.2
Month 2	34	124.4	17.5	39	130.1	12.3
Month 3	34	135.1	16.8	37	142.8	10.8
Month 4	34	146.4	16.2	43	150.5	10.4
7¼ months CA	35	173.4	10.5	40	176.2	10.5

SD - standard deviation; CA - corrected age.

Mixed model analysis of variance for knee-ankle length

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on knee-ankle length over time, with adjustment for confounding, repeated measures, missing data and including infants with the same mother. Comparisons at each of the nominal measurement time points revealed no statistically significant difference in knee-ankle length at birth between the two treatment groups (Table 3.4.5.2). Infants exposed to repeat prenatal corticosteroids had significantly lower estimated mean knee-ankle lengths when compared with placebo group infants, from day three to one month after birth (at $p<0.01$ level of significance). There were no statistically significant differences between the treatment groups in estimated mean knee-ankle length at 7¼ months postnatal corrected age.

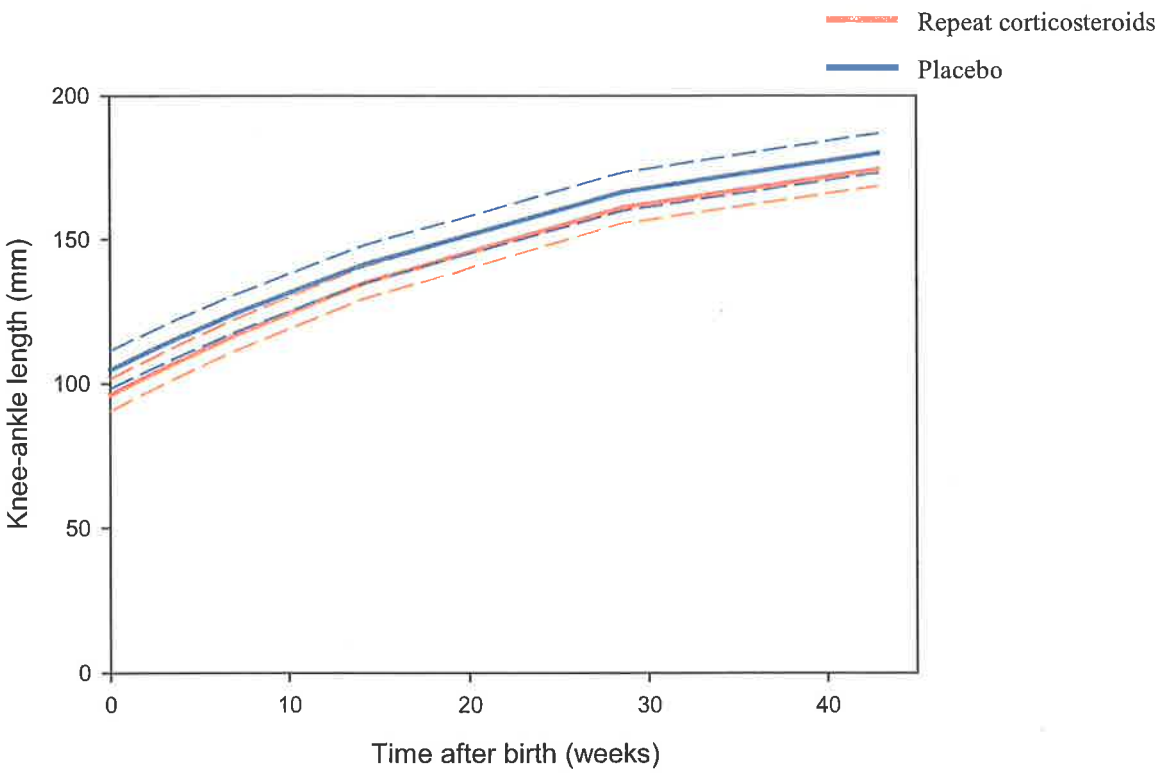
Table 3.4.5.2 Estimated mean knee-ankle length at the nominal measurement time points[Ψ]

Knee-ankle length (mm)	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Birth	98.4	3.2	105.6	3.6	7.1	0.5	13.8	0.03
Day 3	97.7	3.0	105.5	3.4	7.8	1.9	13.7	**0.01**
Week 1	98.3	2.9	106.8	3.4	8.5	2.9	14.1	**0.003**
Week 2	101.3	2.9	109.8	3.4	8.5	2.9	14.1	**0.003**
Week 3	104.9	2.9	112.5	3.4	7.7	2.1	13.2	**0.007**
Month 1	108.2	2.9	117.1	3.4	8.9	3.3	14.5	**0.002**
Month 2	121.8	2.9	127.9	3.4	6.2	0.7	11.7	0.03
Month 3	133.2	2.9	140.3	3.4	7.2	1.6	12.7	**0.01**
Month 4	142.4	2.9	148.7	3.3	6.3	0.8	11.8	0.02
7¼ months CA	168.8	2.9	172.8	3.4	4.1	-1.6	9.7	0.16

[Ψ]Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth. Est. mean - estimated mean; SEM - standard error of mean; CA - corrected age.

A quadratic model, with adjustment for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth, provided the best fit for knee-ankle length (Figure 3.4.5.2). At birth, the estimated mean knee-ankle length was significantly smaller in infants exposed to repeat corticosteroids compared with placebo infants (estimated mean difference -7.44 mm, p=0.004). Infants exposed to repeat corticosteroids, however, gained 0.02 mm more in knee-ankle length per day compared with those in the placebo group (p=0.03).

Figure 3.4.5.2 Estimated mean knee-ankle length and 95% CI [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Gestational age at birth and knee-ankle length (Figure 3.4.5.3)

There was no statistically significant effect modification on knee-ankle length gain by gestational age at birth (estimated mean difference in treatment group difference 0.03 mm per day, p=0.12). When infants born at less than 34 weeks gestation were examined, there was no statistically significant difference in knee-ankle length gain per day between the treatment groups (estimated mean difference –0.0001 mm per day, 95% CI -0.02, 0.02, p=0.99). For infants born at 34 or more weeks gestation, those exposed to repeat corticosteroids gained 0.03 mm per day more than those in the placebo group (95% CI -0.06, 0.0001, p=0.05).

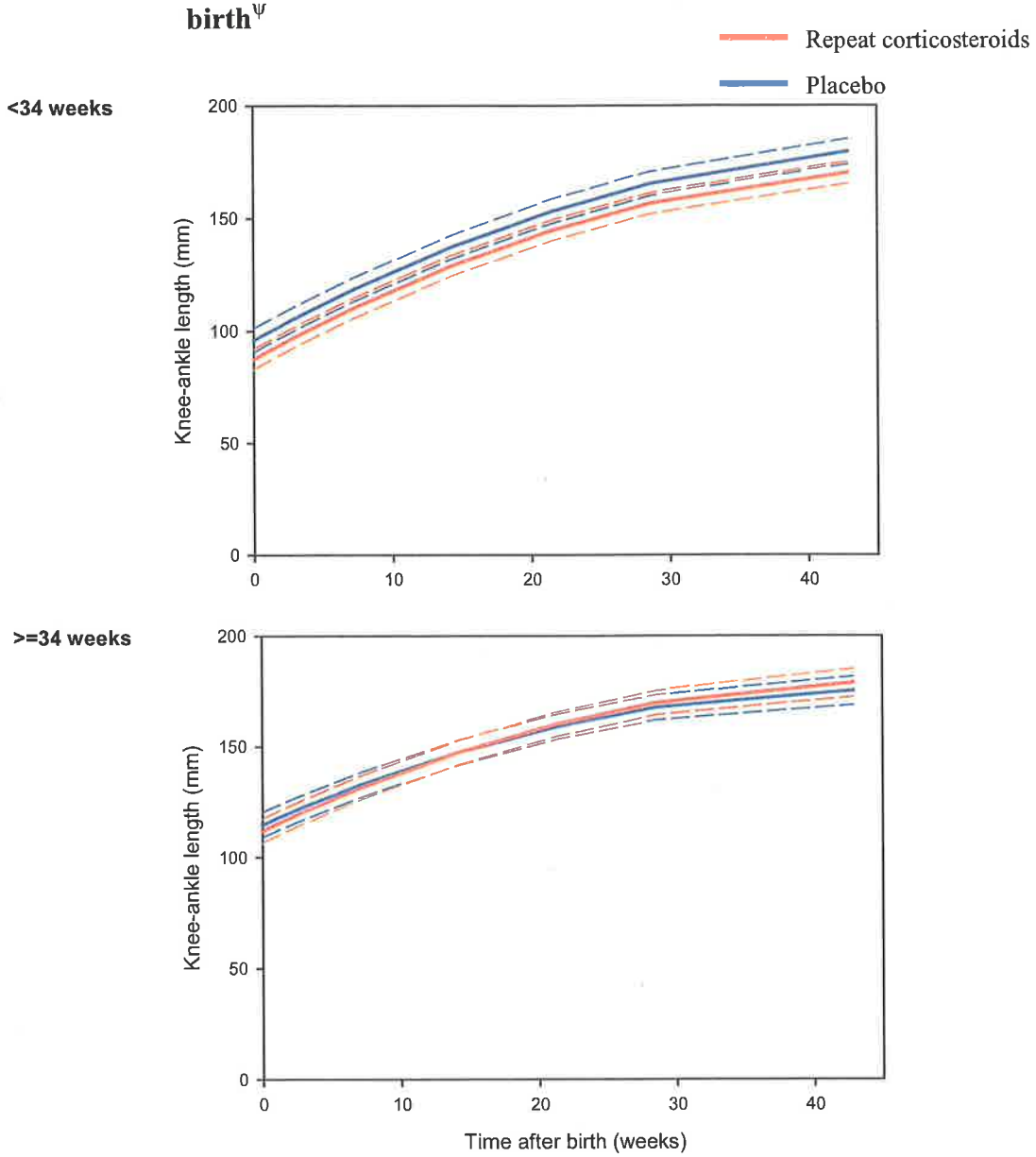
ACTORDS treatment dose and knee-ankle length (Figure 3.4.5.4)

Overall, there was no statistically significant effect modification on knee-ankle length gain by the number of ACTORDS treatment doses received. When infants in each of the dose subgroups were examined, there were no statistically significant differences between the gain of knee-ankle length over time between the treatment groups.

Latency from last ACTORDS to birth and knee-ankle length (Figure 3.4.5.5)

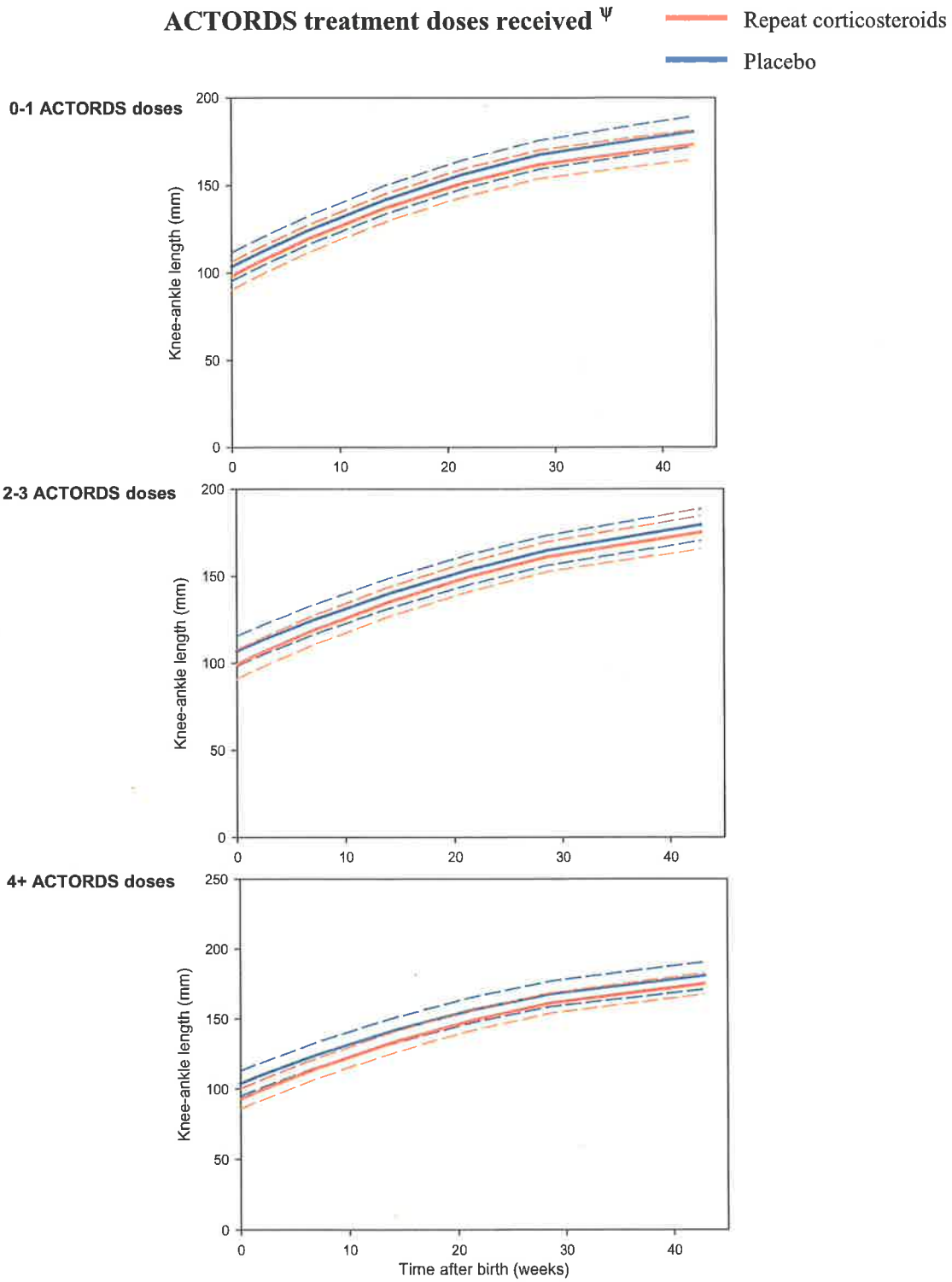
Overall, there was significant effect modification on knee-ankle length gain by the latency between the last ACTORDS dose and birth. When infants with a latency of five or less days, or six to 26 days, were examined there were no statistically significant differences between infants in the two treatment groups. For infants with a latency of 26 or more days, those in the repeat corticosteroid group gained 0.03 mm more per day in knee-ankle length than the infants in the placebo group (95% CI -0.06, -0.001, p=0.04).

Figure 3.4.5.3 Estimated mean knee-ankle length and 95% CI by gestational age at birth[Ψ]



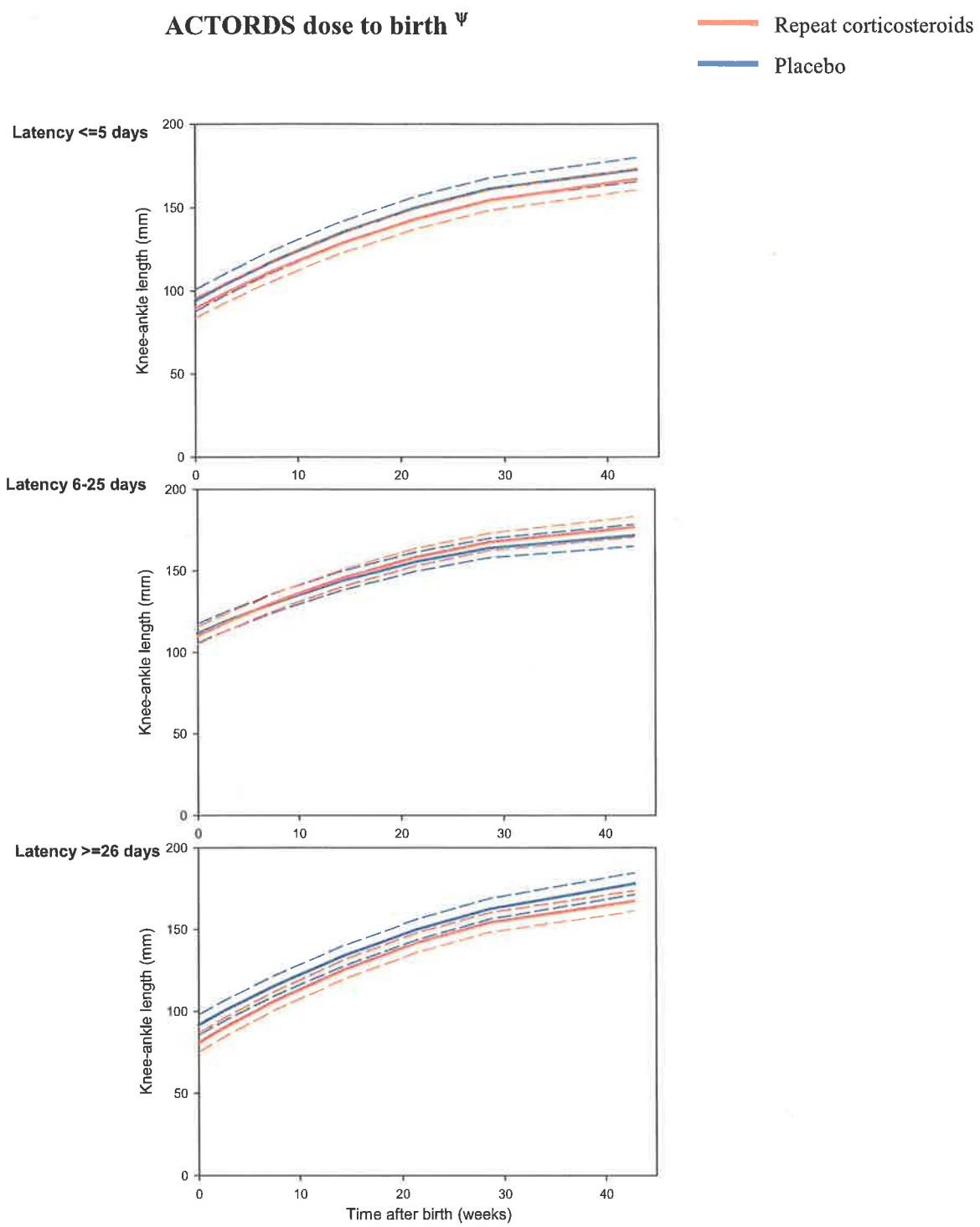
[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Figure 3.4.5.4 Estimated mean knee-ankle length and 95% CI by the number of ACTORDS treatment doses received [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Figure 3.4.5.5 Estimated mean knee-ankle length and 95% CI by the latency from last ACTORDS dose to birth [Ψ]



[Ψ] Adjusted for severe intrauterine growth restriction requiring delivery and placenta praevia as reasons for risk of preterm birth.

Postnatal systemic infection and postnatal corticosteroid subgroup analysis

There was no statistically significant effect modification on knee-ankle length gain by systemic postnatal infection (estimated mean difference in treatment group difference -0.03 mm per day, p=0.69). For infants who did not develop a systemic postnatal infection, those exposed to repeat corticosteroids gained 0.03 mm more per day in knee-ankle length compared with those in the placebo group (95% CI -0.05, -0.004, p=0.02). There was no statistically significant difference in knee-ankle length gain between infants in the two treatment groups when infants who developed a systemic infection were compared (estimated mean difference 0.0004 mm per day, 95% CI -0.13, 0.13).

There was no statistically significant effect modification on knee-ankle length gain by postnatal corticosteroid exposure (estimated mean difference in treatment group difference -0.04 mm per day, p=0.30). When infants who did not receive postnatal corticosteroids were examined, repeat corticosteroid sub-group infants gained 0.10 mm more in knee-ankle length per day compared with the placebo sub-group infants (95% CI -0.05, -0.004). For those exposed to postnatal corticosteroids, however, there was no statistically significant difference in knee-ankle length gain per day (estimated mean difference 0.01 mm per day, 95% CI -0.06, 0.08), between the two treatment groups.

3.4.6. PONDERAL INDEX

Descriptive comparisons of ponderal index (Table 3.4.6.1)

Ponderal index is a measure of thinness, calculated from the weight and total body length. The mean ponderal index at birth was the same for both treatment groups, 2.5 g/cm^3 (SD 0.3). Ponderal index appeared to remain relatively constant over time. Loss of a number of

measurements occurred over time, particularly since measurements for both weight and length needed to be obtained to enable the calculation of the index. Statistical comparisons were not made on the mean ponderal index between the two treatment groups as they may be misleading since there has been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 3.4.6.1 Ponderal index by treatment group

Ponderal index (g/cm^3)	Repeat corticosteroids			Placebo		
	n	mean	SD	n	mean	SD
Birth	70	2.5	0.3	72	2.5	0.3
Day 3	49	2.3	0.3	57	2.2	0.3
Week 1	50	2.4	0.5	52	2.3	0.2
Week 2	45	2.4	0.2	52	2.5	0.3
Week 3	51	2.5	0.3	45	2.5	0.2
Month 1	48	2.6	0.3	53	2.6	0.3
Month 2	41	2.8	0.4	45	2.7	0.3
Month 3	42	2.8	0.4	46	2.7	0.3
Month 4	37	2.5	0.2	43	2.5	0.2

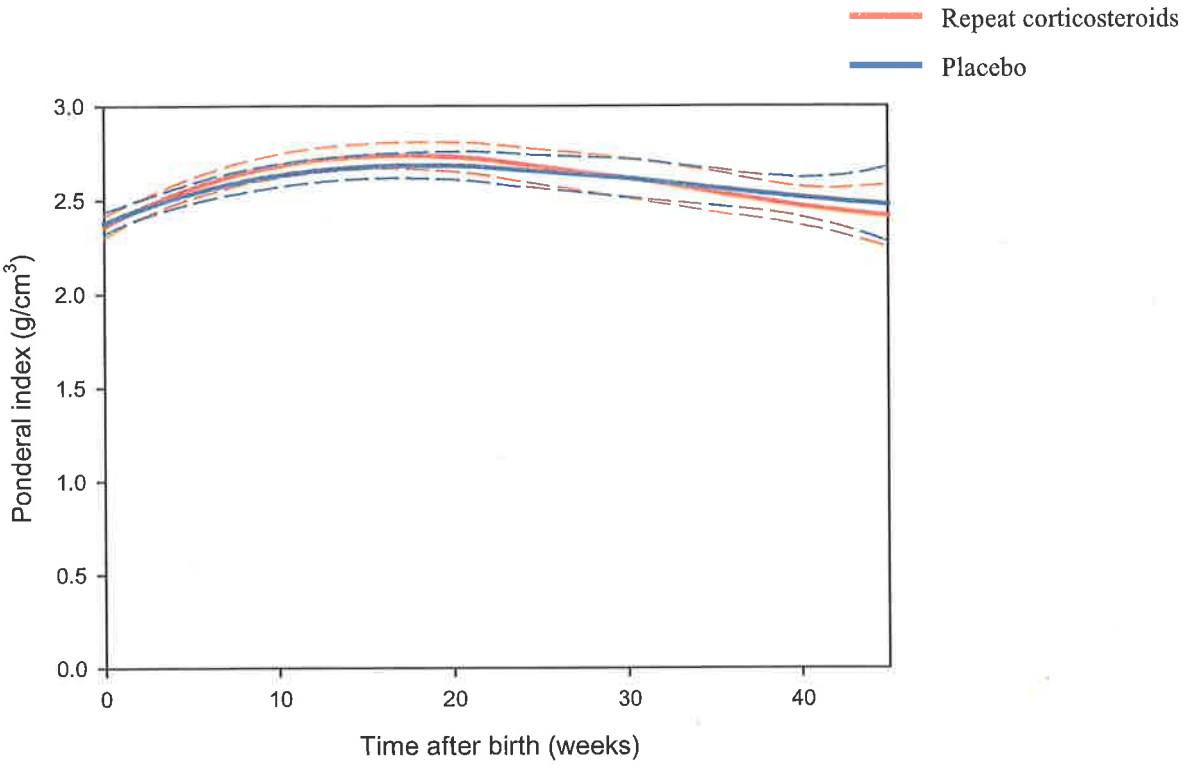
SD - standard deviation; CA - corrected age; ponderal index = [weight (grams) / length^3 (cm)]*1000 (g/cm^3).

Mixed model analysis of variance for ponderal index (Figure 3.4.6.1)

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on ponderal index over time, with adjustment for confounding, repeated measures, missing data and including infants with the same mother. A piecewise quadratic model provided the best fit for ponderal index. There was no statistically significant difference in the ponderal index between the two treatment groups at birth (estimated mean difference -0.002 g/cm^3 per day, p=0.96). Similarly, there was no statistically significant difference in the gain of ponderal index over time between infants in the repeat corticosteroid group, compared with placebo group infants (estimated mean difference -0.001 g/cm^3 per day, p=0.14). Gestational age at birth, the number of ACTORDS treatment doses received and the latency from last ACTORDS dose to birth were not statistically significant effect modifiers

for ponderal index.

Figure 3.4.6.1 Estimated mean ponderal index (g/cm^3) and 95% CI



3.4.7. GESTATIONAL AGE AT BIRTH, DOSE AND LATENCY

A-priori subgroup analyses were completed on all variables by gestational age at birth, the number of ACTORDS treatment doses received and the latency from the last ACTORDS dose to birth. Each variable was constructed to ensure similar numbers of infants were in each category. Comparisons between the categories of gestational age at birth, dose and latency revealed these variables were interrelated. Gestational age at birth was related to the number of ACTORDS doses received, with those infants born at less than 34 weeks gestation more likely to have received fewer ACTORDS treatment doses (Table 3.4.7.1).

Table 3.4.7.1 Gestational age at birth and the number of ACTORDS treatment doses received

		0-1 doses		2-3 doses		4+ doses
Gestational age at birth <34 weeks	n	41	n	29	n	18
	%	46.6	%	33.0	%	20.5
Gestational age at birth ≥34 weeks	n	15	n	21	n	23
	%	25.4	%	35.6	%	39.0
TOTAL	n	56	n	50	n	41
	%	38.1	%	34.0	%	27.9

Pearson chi-squared = 8.57, p=0.01

Gestational age at birth was also related to the latency between the last ACTORDS treatment dose and birth, with infants born at less than 34 weeks gestation more likely to be in a lower latency category (Table 3.4.7.2).

Table 3.4.7.2 Gestational age at birth and the latency between the last ACTORDS treatment dose and birth

		Latency ≤ 5days		Latency 6-25 days		Latency ≥26 days
Gestational age at birth <34 weeks	n	53	n	32	n	2
	%	60.9	%	36.8	%	2.3
Gestational age at birth ≥34 weeks	n	0	n	10	n	48
	%	0	%	17.2	%	82.8
TOTAL	n	53	n	42	n	50
	%	36.6	%	29.0	%	34.5

Pearson chi-squared = 105.25, p<0.001

The latency between the last ACTORDS treatment dose and birth was related to the number of ACTORDS treatment doses administered, with those infants who received fewer ACTORDS treatment doses more likely to have a shorter latency (Table 3.4.7.3).

Table 3.4.7.3 The number of ACTORDS treatment doses received and the latency from the last ACTORDS treatment dose to birth

	Latency ≤ 5days		Latency 6-25 days		Latency ≥26 days	
0-1 doses	n	28	n	16	n	9
	%	52.8	%	30.2	%	17.0
2-3 doses	n	13	n	14	n	15
	%	31.0	%	33.3	%	35.7
4+ doses	n	13	n	20	n	17
	%	26.0	%	40.0	%	34.0
TOTAL	n	54	n	50	n	41
	%	37.2	%	34.5	%	28.3

Pearson chi-squared = 10.13, p=0.04

3.4.8. SUMMARY OF RESULTS

A summary of the main results of this study, in terms of size at birth and infant growth, are described in Table 3.4.8.1.

Table 3.4.8.1 Summary of the main effects of repeat prenatal corticosteroids on size at birth and early infant growth

	Size at birth	Infant growth	Growth rate	*A-priori* subgroups
Weight	Repeat dose steroid infants significantly smaller z-score compared with placebo group infants.	Day 3 – Month 3 No statistically significant difference in z-score between two treatment groups. 4 months - 7¼ months CA Repeat dose steroid infants significantly smaller z-score compared with placebo.	No statistically significant difference in daily z-score gain between the two treatment groups.	Daily z-score gain is independent of GA at birth, the number of ACTORDS treatment doses and the latency from the last ACTORDS dose to birth.
Total body length	Repeat dose steroid infants significantly smaller z-score compared with placebo group infants.	No statistically significant differences between two treatment groups from day three after birth to 7¼ months CA.	No statistically significant difference in daily z-score gain between the two treatment groups.	Daily z-score gain is independent of GA at birth, the number of ACTORDS treatment doses and the latency from the last ACTORDS dose to birth.
Head circumference	No statistically significant difference in z-score between two treatment groups.	No statistically significant difference between repeat dose steroid and placebo group infants in z-score up to 7¼ months CA.	No statistically significant difference in daily z-score gain between repeat dose steroid and placebo group infants.	Daily z-score gain is independent of GA at birth and the latency from the last ACTORDS dose to birth. Repeat dose steroid infants exposed to 4+ ACTORDS treatment doses gained significantly more in z-score per day than placebo group infants.
Knee-ankle length (KAL)	Repeat dose steroid infants significantly lower mean KAL compared with placebo.	Day 3 – Month 1 & Month 3 Repeat dose steroid infants significantly smaller than placebo. 7 ¼ months CA No significant differences between two treatment groups in mean KAL.	Repeat dose steroid infants gained significantly more in mean KAL each day compared with placebo group infants.	Daily KAL gain independent of number of ACTORDS treatment doses. Subgroup differences in daily KAL gain between treatment groups by GA at birth and the latency from last ACTORDS dose to birth.

3.5. DISCUSSION

3.5.1. OVERVIEW OF RESULTS OF REPEAT PRENATAL CORTICOSTEROIDS AND INFANT GROWTH

Weight

Repeat prenatal corticosteroid exposure did not affect the mean infant weight from birth to four months of age. Infants exposed to repeat prenatal corticosteroids however, were 453 grams smaller, on average, at 7¼ months corrected age compared with placebo group infants. Adjustments for gestational age and gender, using z-scores, revealed that repeat corticosteroid treated infants were significantly smaller at birth compared with placebo group infants. However, from day three to three months after birth, there were no statistically significant differences in weight z-scores between the two treatment groups (at $p<0.01$), though at four months after birth, and at 7¼ months corrected age, infants exposed to repeat prenatal corticosteroids again had significantly lower weight z-scores compared with placebo group infants.

Infants exposed to repeat prenatal corticosteroids gained an average 2.02 grams less per day compared with placebo group infants, though when the rate of weight gain was compared using z-scores, there were no statistically significant differences between the two treatment groups.

Gestational age at birth was a significant effect modifier for mean weight gain. Repeat corticosteroid group infants born at less than 34 weeks gestation gained 4.33 grams less per day than placebo group infants. Infant morbidity is gestational age dependent with all infants

who received postnatal corticosteroid treatment, or who developed a postnatal infection, being born at less than 34 weeks gestation. This increased morbidity, particularly in the repeat corticosteroid group, may explain the differences in weight gain by gestational age at birth. The differences between the two treatment groups, in weight at birth and weight gain, may reflect a period of increased susceptibility to the effects of repeat prenatal corticosteroids. Adjustment for gestational age and gender, using z-scores, showed gestational age at birth was not a significant effect modifier for weight z-score gain. This suggests that the differences at birth in mean weight gain by gestational age may be an artefact of differences in the distribution of gestational age and gender between the two treatment groups.

Infants allocated repeat prenatal corticosteroids, and who were exposed to one or none ACTORDS treatment doses, gained 3.89 grams less per day than those in the placebo group. There were no statistically significant differences in daily weight gain between the two treatment groups for the two-three or four or more dose categories. The dose and gestational age categories examined were highly related, with infants born at less than 34 weeks gestation being more likely to have received less ACTORDS treatment doses. Adjustment for gestational age using z-scores revealed no differences in z-score weight gain by dose, suggesting the differences in dose category for mean weight gain most likely result from an imbalance in gestational age between the two treatment groups.

Repeat corticosteroid treated infants, with a latency of five or less days between their last ACTORDS treatment dose and birth, gained 4.37 grams less per day than placebo group infants. There were no statistically significant differences in daily weight gain between the treatment groups for the other latency categories of 6-25 days and 26 or more days.

Gestational age and the latency from the last ACTORDS dose to birth were related, with infants born at less than 34 weeks gestation being most likely to have a lower latency. Adjustment for gestational age using weight z-scores indicated no effect of latency on weight z-score gain, suggesting the difference by mean weight is an artefact of imbalances in gestational age and gender between the two treatment groups.

In this study, infants in the repeat corticosteroid group were more than three times as likely to develop a postnatal systemic infection. Corticosteroids may induce immunosuppression, increasing the risk of neonatal infection. However, no increased risk in neonatal sepsis with repeat prenatal corticosteroid exposure, compared with a single course, has been reported by the two published randomised controlled trials reporting this outcome (Guinn *et al.* 2001; Mercer *et al.* 2001b). Similarly, no statistically significant difference in the risk of neonatal sepsis when comparing repeat and single course corticosteroid therapy, has been reported by the three systematic reviews of the non-randomised studies (Aghajafari *et al.* 2001; Joy *et al.* 2001; McLaughlin & Crowther 2002a). Three small cohort studies have reported an increased risk of neonatal sepsis with repeat corticosteroid exposure (Debbs *et al.* 1997; Vermillion *et al.* 1999; Vermillion *et al.* 2000b), though the methodologies of these studies may introduce bias. Further investigation is required as to whether the increase in the risk of neonatal infection in the current study is a true effect of repeat prenatal corticosteroids, or a result of other factors that differ between the two treatment groups. This will be explored as part of the ongoing ACTORDS trial.

Could the increased incidence of postnatal infection among repeat corticosteroid treated infants, in this trial, be an explanation for the difference in infant weight between the two

treatment groups? There is limited literature examining the effects of systemic neonatal infection on growth in infants born preterm. Studies of the effect of infection on the growth of children in developing countries have shown dramatic reductions in weight gain with episodes of childhood infection (Stephensen 1999). In particular, catch-up growth is limited in children who experience a high frequency of infections in childhood (Stephensen 1999). In the current study, sub-group analysis of weight and weight z-scores by infection revealed no statistically significant difference in the rate of weight gain by postnatal systemic infection between the two treatment groups. Thus, it is possible that the between-group difference in weight gain is a result of the imbalance in incidence of postnatal systemic infection. Further research is required to determine whether prenatal corticosteroid exposure is responsible for this observed increase in postnatal systemic infection that, in turn may be responsible for the altered infant growth pattern. Each of the postnatal systemic infections occurred prior to hospital discharge, with the median (interquartile range) time from birth to discharge being 41.5 days (8.5, 67.5) for repeat corticosteroid treated infants and 31 days (8.5, 51) for placebo infants. Given that the estimated mean difference in infant weight z-score increased over time, with the greatest difference being between the two treatment groups at 7¼ months corrected age, the biological plausibility of these early postnatal systemic infections being responsible for this weight difference between the two treatment groups is questionable.

Infants born preterm have a high rate of hospital readmission after discharge, many for acute respiratory infections (Elder *et al.* 1999). Infants who develop a postnatal systemic infection may be more likely to have poor growth as a result of a factor we have not measured. Possibly, these infants may have long-standing poor-health, with recurrent infections, which may limit infant growth. Further exploration of the incidence of post-discharge infections and

chronic illness in this population of infants is required. Other possible factors related to postnatal systemic infection, which may also explain the significant reduction in weight at 7¼ months corrected age for repeat corticosteroid treated infants compared with placebo, should be explored. These post-discharge health outcome measures are being collected as part of the ongoing ACTORDS trial.

It is widely known that exposure to postnatal corticosteroids reduces infant growth, including weight gain, head circumference and linear growth (Skinner *et al.* 1997). In this study, repeat corticosteroid treated infants were more than four times as likely to have received postnatal corticosteroid treatment. Sub-group analysis by postnatal corticosteroid exposure revealed that treatment with postnatal corticosteroids was a significant effect modifier both for weight and weight z-score gain. No significant differences were identified in the rate of weight, or weight z-score gain for infants unexposed to postnatal corticosteroids. Repeat corticosteroid group infants exposed to postnatal corticosteroids, however, gained 8.87 grams less per day than similarly exposed placebo group infants. When weight z-scores were compared, infants in the repeat corticosteroid group who received postnatal corticosteroid treatment gained 0.01 less in weight z-score compared with similarly exposed placebo group infants. Exposure to repeat prenatal corticosteroids may amplify the known adverse effects of postnatal corticosteroid exposure on infant weight gain. This reduction in weight gain with postnatal corticosteroid exposure, for infants prenatally exposed to repeat corticosteroids, might reflect the dosage and timing of postnatal corticosteroid treatment. Postnatal corticosteroids were administered, on average, at earlier postnatal ages over more courses and with a longer duration to the repeat corticosteroid group infants compared with those in the placebo group. Increasing doses of postnatal corticosteroids have been demonstrated to reduce infant weight

(Skinner *et al.* 1997).

Total body length

Between group comparisons showed that, compared with placebo infants, the administration of repeat doses of prenatal corticosteroids did not reduce total body length but reduced the mean total body length z-score at birth. From day three to 7¼ months corrected age, repeat prenatal corticosteroid treatment did not reduce total body length or total body length z-score, compared with placebo. For the repeat prenatal corticosteroid group, daily gain in total body length up to 7¼ months corrected age did not alter. Further, the rate of total body length and total body length z-score gain were independent of all: gestational age at birth (<34, ≥34weeks), latency from the last ACTORDS treatment dose to birth (≤5, 6-25 and ≥26 days), treatment with postnatal corticosteroids and the incidence of postnatal systemic infections.

The number of ACTORDS treatment doses received was a significant effect modifier for the daily gain in mean total body length. Repeat corticosteroid treated infants, who received four or more ACTORDS treatment doses, gained 0.02 cm less in mean total body length per day than placebo group infants. However, there were no statistically significant differences in total body length gain between the two treatment groups when infants who received one or less, or two-three doses were compared. Adjustment for gestational age and gender using z-scores showed no statistically significant difference in total body length z-score gain by the number of ACTORDS treatment doses received. This suggests that the observed effect of four or more ACTORDS treatment doses on the mean total body length gain was most likely a result of an imbalance in gestational age between the two treatment groups, rather than the 'true' effect of dose.

Head circumference

Repeat prenatal corticosteroid treatment did not affect the mean head circumference or the mean head circumference z-scores from birth to 7¼ months postnatal corrected age, compared with placebo. Further, while infants exposed to repeat prenatal corticosteroids gained 0.0031 cm more per day in head circumference than placebo group infants, there were no statistically significant differences in head circumference z-score gain between the two treatment groups. This suggests the observed difference in head circumference gain is an artefact of an imbalance in gestational age and gender between the two treatment groups.

Gestational age was a significant effect modifier for the mean head circumference, with repeat corticosteroid infants born at less than 34 weeks gestation gaining 0.005 cm more per day in head circumference than placebo group infants. This difference was not observed when head circumference z-scores were compared, suggesting there was no 'true' effect of gestational age at birth on head circumference gain.

The number of ACTORDS treatment doses was related to the mean head circumference gain, with repeat corticosteroid treated infants exposed to four or more ACTORDS treatment doses gaining 0.008 cm more in head circumference per day compared with placebo group infants. There were no statistically significant differences between the two treatment groups when infants exposed to one or none, or two-three doses were compared. This dose effect persisted when head circumference z-scores were compared, with repeat corticosteroid treated infants exposed to four or more ACTORDS treatment doses gaining 0.004 more in z-score per day than placebo infants. Similarly, there were no statistically significant differences between the

two treatment groups for the two lower dose categories. This difference may reflect a 'catch-up' period after repeat prenatal corticosteroid exposure, although there were no statistically significant differences in head circumference at birth.

Latency from the last ACTORDS treatment dose to birth was a significant effect modifier for mean head circumference gain. Repeat corticosteroid infants with latencies of five or less days, or six to 25 days, gained more in head circumference per day than placebo group infants. There were no differences between the two treatment groups and latency of 26 or more days. Comparison of head circumference z-score gains between the two treatment groups for the three latency categories revealed no statistically significant differences. This suggests the differences in mean head circumference gain were most likely due to differences in gestational age between the two treatment groups rather than a 'true' effect of latency.

Systemic postnatal infection was a significant effect modifier for head circumference z-score gain, but not the mean head circumference gain. For infants who developed a postnatal systemic infection, those treated with repeat prenatal corticosteroids gained less in head circumference z-score per day, compared with placebo group infants. The mechanism behind this difference is unclear.

Knee-ankle length

Repeat prenatal corticosteroid treatment significantly reduced the mean knee-ankle length up to four months after birth, compared with placebo. At birth, infants exposed to repeat prenatal corticosteroids had knee-ankle lengths on average 7.44 mm smaller than placebo group infants. However, by 7¼ months corrected age, there was no longer a statistically

significant difference. The infants exposed to repeat prenatal corticosteroids gained 0.02 mm more in knee-ankle length per day, when compared with placebo group infants.

For infants born at less than 34 weeks gestation, there was no statistically significant difference in the daily gain of knee-ankle length between the two treatment groups, but for infants born at 34 or more weeks gestation, those allocated repeat prenatal corticosteroids gained 0.03mm more per day in knee-ankle length than infants in the placebo group infants.

Dose was not an effect modifier for knee-ankle length gain, with no significant differences found between the two treatment groups for any of the dose categories. Latency between the last ACTORDS dose and birth was a significant effect modifier for knee-ankle length gain. Repeat corticosteroid treated infants with a latency of 26 or more days gained on average 0.03 mm more in knee-ankle length per day, compared with placebo group infants. There were no significant differences in knee-ankle length gain between the two treatment groups for the latency categories of five or less days, or six to 26 days.

These *a-priori* subgroup differences by treatment group for knee-ankle length should be interpreted with caution, since using z-scores for weight, total body length and head circumference showed that the subgroup differences may be a result of an imbalance in gestational age and gender between the two treatment groups, rather than a 'true' gestational age, dose or latency effect. Z-scores were unable to be calculated for knee-ankle length, as there are no reference populations of knee-ankle length in infancy. Direct adjustment for gestational age on knee-ankle length could have been performed, though adjustment for post-randomisation characteristics is considered inappropriate in a randomised controlled trial.

Repeat prenatal corticosteroid treated infants who did not develop a postnatal systemic infection gained, on average, 0.03 mm more in knee-ankle length per day than placebo group infants who did not develop an infection. There were no differences between the two treatment groups in daily knee-ankle length gain when infants who did develop a postnatal systemic infection were compared.

Repeat corticosteroid treated infants who did not receive postnatal corticosteroids gained on average 0.10 mm more per day in knee-ankle length, when compared with placebo group infants. No significant differences in daily knee-ankle length gain were found between the two treatment groups when infants exposed to postnatal corticosteroids were compared.

Ponderal index

There were no statistically significant differences between repeat corticosteroid and placebo group infants in ponderal index, from birth to 7¼ months corrected age. Ponderal index is a measure of thinness, and these findings suggest that repeat prenatal corticosteroid exposure does not affect, adversely or otherwise, the proportionality of weight to total body length. This lack of difference between the two treatment groups is important as disproportional growth, indicated by a low ponderal index, has been associated with childhood mortality, hospitalisations and developmental delay (Morris *et al.* 1998).

3.5.2. LIMITATIONS OF THIS STUDY

There are several methodological aspects of this study that may introduce bias. The planned sample size for this trial (140 infants with knee-ankle length measurements) was not reached.

There was a reduction in the number of women eligible for The In-depth Growth and Neurodevelopment Trial over the four-year study period. The number of women and their infants randomised to this trial may limit the ability to detect clinically relevant differences in infant growth, particularly for sub-group analyses where group sizes are small. The initial sample size calculation for this trial was based on a knee-ankle length velocity of 0.36 cm per week in the placebo group (Skinner *et al.* 1997), but the velocity in the placebo group in current trial was 0.20 cm per week. Post-hoc calculations to determine the sample size required to detect a five percent difference in knee-ankle length velocity using the observed growth rate in the placebo group established 250 infants would be required in each of the two treatment groups. The number of infants randomised to this trial from whom knee-ankle length measurements were collected enabled the detection of a 40 percent difference in knee-ankle length velocity, β=0.2 and α=0.05. Although the current trial had insufficient power to detect a five percent difference in knee-ankle length velocity as intended at the outset, the results showed that repeat corticosteroid treated infants gained significantly more in knee-ankle length per day, compared with placebo group infants.

A major challenge in the analysis of data from this trial was the consideration of, and allowance for, missing data. In our trial population, almost one-third of the participants lived outside the Adelaide metropolitan area, having been transferred to the Women's and Children's Hospital for tertiary prenatal care. Given the frequency of the initial growth measurements collected for this trial, it was deemed impractical and cost-ineffective to collect growth measurements from these infants at their home at weekly intervals. Longer-term growth measurements were prospectively collected from infants living up to six-hours return by car from the Women's and Children's Hospital, Adelaide. For infants who lived further

from the hospital, or where home visits were not possible, growth measures were obtained from transfer hospitals' records, or from their Maternal and Child Health record book. Preliminary analysis, to characterise the nature of this missing data suggested these data were missing at random. This implied that the missing data was unlikely to affect interpretation of the results.

Despite the gestational age at trial entry being similar between the two treatment groups, differences in the distribution of gestational age at birth between repeat corticosteroid and placebo group infants may affect the interpretation of growth measures, as size at birth and infant growth is related to gestational age. More infants in the repeat corticosteroid group were male, compared with placebo group infants. Adjustment for any differences in gestational age and gender, using z-scores of growth, was the most appropriate method to make comparisons between repeat corticosteroid and placebo group infants for the measures of weight, total body length and head circumference. The reference population used to construct these z-scores was derived from a group of infants in the United Kingdom (Freeman *et al.* 1995; Cole *et al.* 1998). Although comparisons between the two treatment groups in this trial using the z-scores derived from this reference cohort are valid, external comparisons of these z-scores may not be. The growth of infants in this UK reference, from which the z-scores are derived, approximates the Australian population, with a male infant born at 32 weeks gestation having a median birth weight of 1822 grams in the United Kingdom reference, compared with a median of 1890 grams in the Australian reference (Roberts & Lancaster 1999). The UK population was used for this analysis as z-scores could be constructed for the measures of weight, total body length and head circumference, from birth to 7¼ months corrected age. However, this UK population did not provide a reference from

which total body length z-scores for infants with a gestational age of less than 33 weeks could be calculated. This loss of infants at lower gestations may limit the interpretation of the total body length z-score comparisons between the two treatment groups.

There are no reference populations for knee-ankle length for use over the time-period we measured. The comparisons between the two treatment groups using 'raw' mean knee-ankle length measures may be biased as any effects of differing gestational age at birth, or differences in the distribution of gender, have not been controlled for.

3.5.3. CONCORDANCE WITH PREVIOUS WORK

Previous randomised controlled trials have reported no reduction in weight at birth (Guinn *et al.* 2001; Mercer *et al.* 2001b; McEvoy *et al.* 2002) or head circumference at birth (Guinn *et al.* 2001; Mercer *et al.* 2001b) following exposure to repeat prenatal corticosteroids, compared with exposure to a single course. The three cohort studies that have explored the effect of repeat prenatal corticosteroids on longer-term growth have measured children from three years of age, and the results have the potential for bias (French *et al.* 1999; Rotmensch *et al.* 1999; Hasbargen *et al.* 2001). To my knowledge, the current study is the first randomised placebo-controlled trial reported in humans that has examined the effect of repeat prenatal corticosteroids on longitudinal infant growth. The three previous randomised controlled trials that have examined infant growth following repeat prenatal corticosteroid treatment are all in the animal model (Stewart *et al.* 1998; Welberg *et al.* 2001; Moss *et al.* 2002). Prenatal treatment of gravid mice with repeat corticosteroids did not reduce the weight of female offspring up to four months after birth, though male offspring had reduced body weights at birth and day three compared with single course animals (Stewart *et al.* 1998). At five days,

and at four months after birth however, there were no differences between repeat and single course groups in the body weight of male offspring. Exposure to repeat prenatal corticosteroids in the last trimester of gestation reduced birth weight in the rat, but did not reduce weight at one month after birth, compared with a single course (Welberg *et al.* 2001). The administration of repeat prenatal corticosteroid treatment to pregnant ewes did not reduce birth weight, or weight up to one month after birth, compared with the administration of a single course (Moss *et al.* 2002). The effect of repeat prenatal corticosteroids on weight in the animal model may not reflect their effect in humans. The extent to which the results of this current study in humans can be compared with these animal studies is restricted, given the differences in the dose and type of prenatal corticosteroids administered, the potential for species-specific effects, the lack of longitudinal growth measures and the small sample sizes of these animal studies. The current study has reported regular measures of both somatic and linear growth, in a larger sample of infants, over a longer time frame than these previous animal studies.

3.5.4. FUTURE DIRECTIONS

The effects of repeat prenatal corticosteroids on early infant growth found in this trial will need to be balanced against any benefits or adverse effects on neonatal morbidities including respiratory distress syndrome, intraventricular haemorrhage, chronic lung disease, neonatal mortality and longer-term outcomes. Results of the ongoing randomised controlled trials examining the safety and efficacy of repeat prenatal corticosteroids will help to answer this question and place the results of the current study in terms of growth into an appropriate clinical context.

Further research should explore the relationships between repeat corticosteroid treatment and neonatal infective morbidity, both in the neonatal period and after discharge home. The study reported here suggests a link between repeat prenatal corticosteroid treatment and postnatal systemic infection. This increased risk of systemic neonatal infection is not supported by the previously published randomised controlled trials (Guinn *et al.* 2001; Mercer *et al.* 2001b) or systematic reviews of the non-randomised studies assessing the safety and efficacy of repeat prenatal corticosteroid treatment (Aghajafari *et al.* 2001; Joy *et al.* 2001; McLaughlin & Crowther 2002a). The risk of postnatal corticosteroid exposure was found to be significantly greater in repeat corticosteroid treated infants, compared with those who received placebo. No randomised controlled trials have reported exposure to postnatal corticosteroids following repeat prenatal corticosteroid treatment and the two cohort studies which reported this outcome found no difference in use between repeat and single course prenatal corticosteroid treated infants (Abbasi *et al.* 2000; Dirnberger *et al.* 2001). Further studies, with larger sample sizes are required to determine whether the increase in risk of postnatal systemic infection and postnatal corticosteroid treatment are due to exposure to repeat prenatal corticosteroids, or have occurred as a result of a chance imbalance between the two treatment groups. Future work may also explore any biological basis for these associations.

Analysis and interpretation of the results of this thesis indicated that z-scores of growth measures, which allow adjustment for gestational age and gender, provided the most reliable comparison of growth between the two treatment groups. I was unable to compared knee-ankle length between the two treatment groups using z-scores, as neonatal kneomometry is a relatively new method of growth assessment, and references of normal knee-ankle length growth have not been derived. Direct adjustment for gestational age at birth was not made, as

adjustment for post-randomisation characteristics is inappropriate. Future researchers may construct a population reference for knee-ankle length over the first year after birth. This would enable calculation of knee-ankle length z-scores. Total body length z-scores were unable to be calculated for infants with gestational ages less than 33 weeks in this study. Further work may focus on extending the UK growth reference to these lower gestational ages.

Further, long-term assessment of the growth of infants in this randomised controlled trial should be continued through to adulthood. Assessment of size at 7¼ months corrected age revealed no statistically significant difference in total body length, head circumference, knee-ankle length or ponderal index between repeat corticosteroid treated and placebo group infants. However, infants exposed to repeat prenatal corticosteroids were significantly smaller in both estimated mean weight, and estimated mean weight z-score at 7¼ months corrected age. The clinical relevance of these observed differences is unknown. Further assessment of these children is required to determine the length of time over which these differences persist and any long term consequences of these differences in infant growth.

3.5.5. CONCLUSIONS

Do repeat prenatal corticosteroids inhibit size at birth as measured by weight, total body length, head circumference, and knee-ankle length, within 24 hours of birth?

Treatment with repeat prenatal corticosteroids significantly reduced the mean weight z-score, mean total body length z-score and the mean knee-ankle length at birth, but not the mean head circumference z-score at birth, compared with placebo.

Do repeat prenatal corticosteroids inhibit infant growth as measured by weight, total body length, head circumference and knee-ankle length up to 7¼ months corrected age?

Repeat prenatal corticosteroid treatment did not significantly reduce the mean weight z-score from day three to the third month following birth, though repeat corticosteroid treated infants had a significantly lower mean weight z-score at four months following birth, and at 7¼ months corrected age. The daily weight z-score gain did not differ significantly between the two treatment groups.

The mean total body length z-score did not differ between repeat corticosteroid and placebo group infants up to 7 ¼ months corrected age. The daily total body length z-score gain did not differ between repeat corticosteroid and placebo group infants. No differences were detected in the mean head circumference z-scores between repeat corticosteroid and placebo group infants up to 7¼ months corrected age. Similarly, daily head circumference z-score gain did not differ between the two treatment groups.

Repeat corticosteroid treatment significantly reduced the mean knee-ankle length from birth to three months of age, compared with placebo. At 7¼ months corrected age, there were no differences in mean knee-ankle length between the two treatment groups. The daily gain in knee-ankle length was significantly greater for repeat corticosteroid treated infants, compared with placebo.

Is infant growth inhibition independent of gestational age?

The daily gain in weight z-score, total body length z-score and head circumference z-score was independent of gestational age at birth. Repeat corticosteroid treated infants born at 34 or

more weeks gestation had a significantly greater daily knee-ankle length gain compared with placebo infants. There were no statistically significant differences in daily knee-ankle length gain between the two treatment groups for infants born at less than 34 weeks gestation.

Does infant growth inhibition increase with the number of doses of weekly prenatal corticosteroids administered?

Weight z-score, total body length z-score and mean knee-ankle length gain were unaffected by the number of ACTORDS treatment doses administered. Repeat corticosteroid treated infants who received four or more ACTORDS treatment doses had a significantly greater daily head circumference z-score gain compared with placebo. There were no differences between the two treatment groups in terms of head circumference z-score gain for those infants who received one or less, or two-three ACTORDS treatment doses.

Does growth inhibition decrease with increasing latency from the last injection of prenatal corticosteroids?

Weight z-score, total body length z-score and head circumference z-score gain was independent of the latency from the last ACTORDS treatment dose to birth. Repeat corticosteroid treated infants with the greatest latency (26 or more days) gained significantly more in mean knee-ankle length per day than placebo group infants. There were no differences between the two treatment groups in knee-ankle length gain for the latency categories of five or less days, and six to 25 days.

4. RESULTS OF REPEAT PRENATAL CORTICOSTEROIDS AND EARLY INFANT NEURODEVELOPMENT

4.1. INTRODUCTION

There is a paucity of good-quality evidence available to assess the neurodevelopmental effects of repeat prenatal corticosteroids. Studies in the animal model have shown reductions in brain size and delays in myelination with repeat prenatal corticosteroid treatment. The current evidence as to the neurodevelopmental consequences of repeat prenatal corticosteroids in humans is sourced from cohort studies, which have the potential for bias. To date, no randomised controlled trials have reported neurological outcome measures following repeat prenatal corticosteroid exposure. Well-designed randomised controlled trials are needed that examine neurodevelopmental outcomes following repeat prenatal corticosteroid exposure.

4.2. AIMS AND HYPOTHESES

4.2.1. AIM

Assess the effect of repeat doses of maternally administered prenatal corticosteroids on infant developmental milestones as measured by the Ages and Stages Questionnaires (ASQ) at four and eight months corrected age and infant intelligence measured by the Fagan Test of Infant Intelligence (FTII) at 7¼ months postnatal corrected age.

4.2.2. HYPOTHESES

Repeat doses of prenatal corticosteroids given at weekly intervals to women who remain at risk of very preterm birth at less than 32 weeks gestation will:

a) reduce neurodevelopmental milestones at four and eight months corrected age as measured by Ages and Stages Questionnaire (ASQ) scores;

b) reduce infant intelligence as measured by the Fagan Test of Infant Intelligence at 7¼ months postnatal corrected age (FTII).

4.3. SUMMARY OF METHODS

Neurodevelopment was assessed using two tools; the Ages and Stages Questionnaire (ASQ), which assesses developmental milestones, and the Fagan Test of Infant Intelligence (FTII), which assesses infant intelligence.

The ASQ was mailed to the home address of each child at four and eight months of age, corrected for gestation. The FTII was performed either at the Women's and Children's Hospital (Adelaide) or in the family home, by appointment at 7¼ months postnatal age, corrected for prematurity.

4.3.1. OUTCOME MEASURES

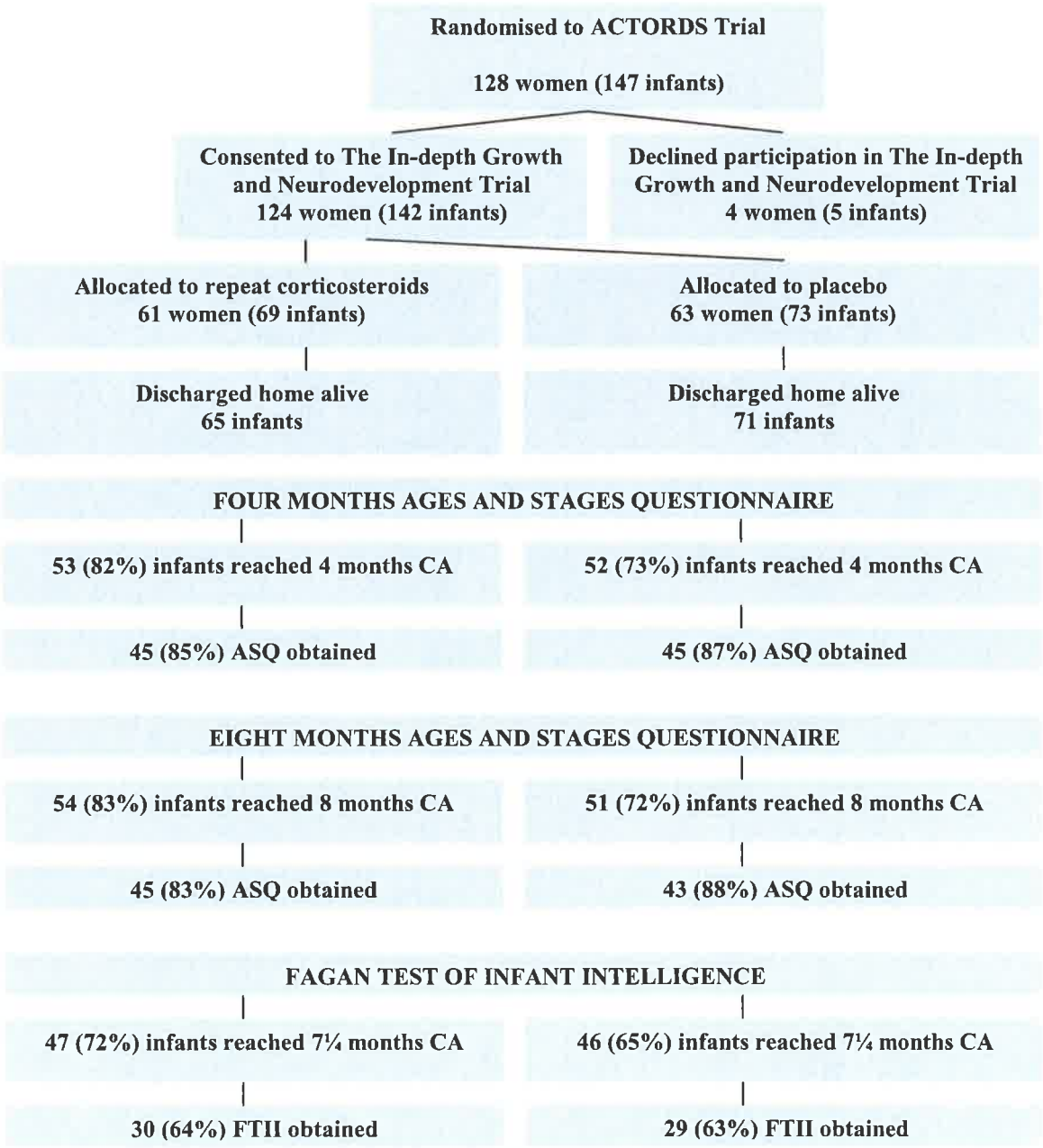
Ages and Stages Questionnaire scores at four and eight months corrected age and Fagan Test of Infant Intelligence score at 7¼ months postnatal corrected age.

4.4. RESULTS

4.4.1. IN-DEPTH GROWTH & NEURODEVELOPMENT TRIAL PARTICIPANTS

Over the study period, 128 women were recruited into the ACTORDS Trial, of which 124 gave consent to The In-depth Growth and Neurodevelopment Trial (Figure 4.4.1.1).

Figure 4.4.1.1 In-depth Growth and Neurodevelopment Trial Profile



CA – corrected age; ASQ - Ages and Stages Questionnaire; FTII - Fagan Test of Infant Intelligence.

Sixty-one women and their 69 infants were randomised to receive repeat corticosteroids and 63 women and their 73 infants were randomised to the placebo group. The proportion of infants enrolled in The In-depth Growth and Neurodevelopment Trial for whom four and eight month Ages and Stages Questionnaires and 7¼ month Fagan Tests of Infant Intelligence are shown in Figure 4.4.1.1. The proportion of infants who reached the corrected age for each of the assessments is shown, below which is the proportion of these infants for whom assessments were obtained.

4.4.2. AGES AND STAGES QUESTIONNAIRES

Description of ASQ study population

Over the time frame of this study (August 18th 1999 – September 13th 2002), 105 infants in The In-depth Growth and Neurodevelopment Trial reached four months corrected age, and 105 infants reached eight months corrected age, and were eligible to complete the Ages and Stages Questionnaires (Figure 4.4.1.1). A total of 90 (86%) four month Ages and Stages Questionnaires (ASQ) were completed on the infants who reached four months corrected age during the data collection period, half from repeat corticosteroid treated infants and half from infants in the placebo group. Eighty-eight (84%) eight month ASQ were collected on infants in The In-depth Growth and Neurodevelopment Trial who reached eight months corrected age during the data collection period, 45 from infants in the repeat corticosteroid group and 43 from infants in the placebo group.

To examine the effect of non-response bias, trial entry, birth and clinical neonatal outcomes were compared between the women and infants for whom at least one Ages and Stages Questionnaire was received (ie. either four or eight months) and those women and infants for

whom there was no ASQ data. ASQ data were collected from 120 infants, and there was no ASQ data on 40 infants. Infants for whom ASQ data were available had mothers who were significantly older, and were more likely to have a high SEIFA index and were less likely to smoke when compared with the mothers of infants for whom no ASQ data were available (Table 4.4.2.1). For all other trial entry characteristics, there were no statistically significant differences between the mothers of infants for whom ASQ data were available and those without ASQ data.

There were no statistically significant differences in the gestation at trial entry or the median number of ACTORDS treatment doses received when the mothers of infants who had ASQ questionnaires completed were compared with the mothers of infants with no ASQ data (Table 4.4.2.2).

For infants for whom ASQ data were available it was less likely that their mother was treated during labour with antibiotics for chorioamnionitis, compared with women with infants without ASQ questionnaires (Table 4.4.2.3). There were no statistically significant differences between infants with ASQ data and those without, when the other birth and clinical neonatal outcomes were compared.

Table 4.4.2.1 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry by ASQ receipt

	ASQ received		No ASQ		Significance
	n= 86	%	n =37	%	p-value
Maternal age (years)*	30.9	5.1	27.9	6.0	**0.01**
Primiparous	32	37.2	11	29.7	0.41
Non-Caucasian ethnicity	5	5.8	6	16.2	0.06
SEIFA Index					
Low (≤ 950)	34	39.5	21	56.8	0.08
Low-mid (951-1010)	24	27.9	10	27.0	0.92
Mid-high (1011-1067)	15	17.4	6	16.2	0.87
High (>1067)	12	14.0	0	0	**0.02**
Private Patient	13	15.1	3	8.1	0.29
Maternal weight at booking (kg)*	67.6	13.5	72.5	20.4	0.15
Maternal height at booking (cm)*	162.7	7.4	162.8	8.4	0.97
BMI at booking (kg/m^2)#	25.8	5.4	27.3	6.6	0.28
Smoking at booking	20	23.3	16	43.2	**0.03**
Live outside metropolitan area	25	29.1	15	40.5	0.21
Previous obstetric history					
Preterm labour <37 weeks	9	16.7	3	11.5	0.69
Preterm birth <32 weeks	7	13.0	2	7.7	0.59
Perinatal death ≥ 20 weeks	7	13.0	1	3.8	0.20
Plurality of current pregnancy					
Singleton	73	84.9	34	91.9	0.29
Twin	11	12.8	3	8.1	0.45
Triplet	2	2.3	0	0	0.35
Reasons for risk of preterm birthϕ					
PPROM	22	25.6	15	40.5	0.10
Preterm labour	26	30.2	8	21.6	0.33
Indeterminate APH	19	22.1	10	27.0	0.55
Placenta praevia	18	20.9	6	16.2	0.55
Cervical Incompetence	6	7.0	0	0	0.10
Isoimmunisation	7	8.1	1	2.7	0.26
Pre-Eclampsia	8	9.3	3	8.1	0.83
Congenital anomaly	1	1.2	1	2.7	0.54
Severe IUGR requiring delivery	3	3.5	3	8.1	0.28
Twin-twin transfusion syndrome	1	1.2	1	2.7	0.54
Placental abruption	2	2.3	1	2.7	0.90

#Figures mean and standard deviation; *Figures median (interquartile range), ϕ More than one may apply; ASQ - Ages and Stages Questionnaire; SEIFA - Index of relative socio-economic disadvantage (ABS 1998); BMI - body mass index; PPROM - preterm prelabour rupture of membranes; APH - antepartum haemorrhage; IUGR - intrauterine growth restriction.

Table 4.4.2.2 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received by ASQ receipt

	ASQ received		No ASQ		Significance
	n =86	%	n =37	%	p-value
Gestation at ACTORDS trial entry (weeks+days) *	28^{+3}	(26^{+2}, 30^{+1})	27^{+3}	(26^{+1}, 29^{+4})	0.41
<28 weeks	37	43.0	19	51.4	0.40
≥28 weeks	49	57.0	18	48.6	0.40
ACTORDS treatment doses given *	2	(1, 4)	2	(1, 4)	0.82

*Figures median (interquartile range)

Table 4.4.2.3 Birth and infant clinical outcomes by ASQ receipt

	Received ASQ		No ASQ		Significance p-value
	n= 86	%	n= 37	%	
Gestation at birth (weeks+days)*	33^{+3}	(30^{+1}, 36^{+6}	31^{+6}	(29^{+0}, 36^{+2}	0.14
≤ 28 weeks	8	9.3	8	21.6	0.06
28^{+1}-31^{+6} weeks	27	31.4	11	29.7	0.85
32 –36^{+6} weeks	30	34.9	13	35.1	0.98
≥ 37 weeks	21	24.4	5	13.5	0.17
Chorioamnionitis ^	0	0	3	8.1	**0.01**
	n= 102	**%**	**n= 40**	**%**	
Mode of birth					
normal vaginal	25	24.5	13	32.5	0.33
operative vaginal	5	4.9	3	7.5	0.55
caesarean section	72	70.6	24	60.0	0.23
Male infant	55	53.9	28	70.0	0.08
Apgar <7 at 5 minutes	3	2.9	2	5.0	0.55
Admission to NICU	64	62.7	26	65.0	0.80
Needed O_2 supplementation	57	55.9	23	57.5	0.86
Proven systemic infection	9	8.8	7	17.5	0.14
Postnatal corticosteroids	13	12.7	5	12.5	0.97
Any IVH on cranial U/S closest to six weeks	2	2.0	1	2.5	0.84
Infant length of stay (days)*	40.1	52.1	40.4	34.9	0.97

*Figures are mean and standard deviation; ^Requiring antibiotics during labour;
NICU - neonatal intensive care unit; O_2 – oxygen; IVH - intraventricular haemorrhage; U/S - ultrasound.

Comparisons between repeat corticosteroid and placebo group women and their infants were made on trial entry characteristics, birth and neonatal outcomes for those infants for whom at least one Ages and Stages Questionnaire (ASQ) were received. Women in the repeat corticosteroid group, with infants for whom ASQ data was received, were similar in terms of age, parity, ethnicity, SEIFA index, insurance status, weight, height and body mass index at booking (Table 4.4.2.4). Repeat corticosteroid treated women were more likely to smoke at booking (26.7 percent versus 19.1 percent), more likely to live outside the metropolitan area (33.3 percent versus 23.8 percent) and less likely to have experienced a previous perinatal death (7.1 percent versus 18.5 percent), compared with placebo group women. Repeat corticosteroid treated women were more likely to be at risk of preterm birth because of preterm labour, indeterminate antepartum haemorrhage, placenta praevia, pre-eclampsia and severe intrauterine growth restriction requiring urgent delivery, compared with women in the placebo group.

Repeat corticosteroid treated women had a similar median gestation at ACTORDS trial entry compared with placebo group women (Table 4.4.2.5). A similar proportion of women in each of the two treatment groups entered the ACTORDS trial at less than 28 weeks gestation. Women in the repeat corticosteroid group received a median of two ACTORDS treatment doses (interquartile range 1, 3) and those women in the placebo group also received a median of two ACTORDS treatment doses (interquartile range 1, 5).

Table 4.4.2.4 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry for women with infants for whom ASQ questionnaires were received

	Repeat corticosteroids		Placebo	
	n= 45	%	n =42	%
Maternal age (years)*	30	(27, 34)	32	(28, 35)
Primiparous	17	37.8	15	35.7
Non-Caucasian ethnicity	3	6.7	2	4.8
SEIFA Index				
Low (≤ 950)	17	37.8	17	40.5
Low-mid (951-1010)	13	28.9	11	26.2
Mid-high (1011-1067)	9	20.0	6	14.3
High (>1067)	6	13.3	7	16.7
Private Patient	5	11.1	8	19.5
Maternal weight at booking (kg)*	65.3	(59.8, 78.5)	62.8	(55, 71.2)
Maternal height at booking (cm)*	160	(155, 168)	164	(159, 168)
BMI at booking (kg/m^2)#	26.8	5.9	24.9	4.7
Smoking at booking	12	26.7	8	19.1
Live outside metropolitan area	15	33.3	10	23.8
Previous obstetric history				
Preterm labour <37 weeks	4	14.3	5	18.5
Preterm birth <32 weeks	3	10.7	4	14.8
Perinatal death ≥ 20 weeks	2	7.1	5	18.5
Plurality of current pregnancy				
Singleton	39	86.7	35	83.3
Twin	5	11.1	6	14.3
Triplet	1	2.2	1	2.4
Reasons for risk of preterm birth$^{\phi}$				
Preterm labour	15	33.3	11	26.2
Indeterminate APH	12	26.7	7	16.7
Placenta praevia	13	28.9	5	11.9
PPROM	8	17.8	14	33.3
Pre-eclampsia	6	13.3	3	7.1
Severe IUGR requiring delivery	3	6.7	0	0
Placental abruption	2	4.4	0	0
Cervical incompetence	2	4.4	4	9.5
Twin-twin transfusion syndrome	0	0	1	2.4
Isoimmunisation	3	6.7	4	9.5
Congenital anomaly	0	0	1	2.4

Figures mean and standard deviation#; Figures median (interquartile range)*; $^{\phi}$More than one may apply; SEIFA - Index of relative socio-economic disadvantage (ABS 1998); BMI - body mass index; APH – antepartum haemorrhage; PPROM – preterm prelabour rupture of membranes; IUGR – intrauterine growth restriction.

Table 4.4.2.5 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received for women with infants for whom ASQ questionnaires were received

	Repeat corticosteroids		Placebo	
	n =45	%	n =42	%
Gestation at ACTORDS trial entry (weeks+days) *	28^{+3}	(26^{+3}, 30^{+1})	28^{+4}	(26^{+2}, 30^{+2})
<28 weeks	19	42.2	18	42.9
≥28 weeks	26	57.8	24	57.1
ACTORDS treatment doses given *	2	(1, 3)	2	(1, 5)

Figures median (interquartile range)*

Comparisons between the mothers of repeat corticosteroid and placebo group infants, for whom ASQ data were available, revealed no statistically significant group differences in the median gestation at birth and the proportion of women who gave birth in each of the gestational age categories (Table 4.4.2.6). The mode of birth, proportion of male infants, number of infants with low Apgar scores, requiring admission to the neonatal intensive care unit or oxygen supplementation, were similar between the two treatment groups. Infants exposed to repeat prenatal corticosteroids for whom ASQ data were available were more than seven times as likely to have developed a proven systemic infection (RR 7.69, 95% CI 1.00, 59.29, p=0.02) and more than three-times as likely to have received postnatal corticosteroid treatment (RR 3.21, 95% CI 0.94, 10.97, p=0.05), compared with placebo group infants.

Table 4.4.2.6 Birth and infant clinical outcomes for women and their infants for whom ASQ questionnaires were received

	Repeat corticosteroids		Placebo		RR	95% CI		Significance p-value
	n= 45	%	n= 42	%				
Gestation at birth (weeks+days)*	33^{+0} (29^{+4}, 37^{+0})		34^{+0} (31^{+1}, 36^{+6})			-		0.28
≤ 28 weeks	6	13.3	2	4.8	2.80	0.60	13.11	0.17
28^{+1}-31^{+6} weeks	14	31.1	13	31.0	1.01	0.54	1.88	0.99
32 –36^{+6} weeks	13	28.9	18	42.9	0.67	0.38	1.20	0.17
≥ 37 weeks	12	26.7	9	21.4	1.24	0.58	2.65	0.57
Chorioamnionitis^	0	0	0	0	-			
	n= 52	**%**	**n= 50**	**%**				
Mode of birth								
normal vaginal	10	19.2	15	30.0	0.64	0.32	1.29	0.21
operative vaginal	2	3.9	3	6.0	0.64	0.11	3.68	0.61
caesarean section	40	76.9	32	64.0	1.20	0.93	1.55	0.15
Male infant	30	57.7	25	50.0	1.15	0.80	1.66	0.44
Apgar <7 at 5 minutes	1	1.9	2	4.0	0.48	0.04	5.14	0.53
Admission to NICU	36	69.2	29	58.0	1.19	0.89	1.61	0.24
O_2 supplementation	32	61.5	26	52.0	1.18	0.84	1.66	0.33
Proven systemic infection	8	15.4	1	2.0	7.69	1.00	59.29	**0.02**
Postnatal corticosteroids	10	19.2	3	6.0	3.21	0.94	10.97	**0.05**
Any IVH on cranial U/S closest to 6 weeks	2	3.9	0	0		-		0.16
Length of stay (days)*	48	(10, 63)	31	(10, 46)		-		**0.05**

Figures are median (interquartile range)*. ^Requiring antibiotics during labour; NICU – neonatal intensive care unit; O_2 – oxygen; IVH – intraventricular haemorrhage; U/S – ultrasound.

Descriptive comparisons of ASQ scores

Four month ASQ questionnaires for repeat corticosteroid treated infants were completed at a significantly earlier corrected age than for infants in the placebo group, p=0.008 (Table 4.4.2.7). For the four-month ASQ, repeat corticosteroid treated infants had lower median total scores, and lower scores for the communication and gross motor domains, compared with infants in the placebo group (Table 4.4.2.7). There was no statistically significant difference in the corrected age at which the eight-month ASQ were completed, between the two treatment groups (Table 4.4.2.8). Infants in the repeat corticosteroid group had raw lower median total scores on the eight month ASQ, and lower median scores for the communication,

gross motor and personal social domains when compared with infants in the placebo group (Table 4.4.2.8). Statistical comparisons were not made between the groups for ASQ scores, as they may be misleading since there has been no adjustment for confounding, repeated measures, missing data and the inclusion of infants with the same mother.

Table 4.4.2.7 Four month median ASQ scores

	Repeat corticosteroids n=45		Placebo n=45	
Corrected age at questionnaire administration (months)$^{\nabla}$	4.2	(4.1, 4.3)	4.4	(4.2, 4.5)
Total Score	250	(200, 260)	265	(240, 285)
Developmental Domains				
Communication	50	(40, 55)	55	(50, 60)
Gross Motor	50	(40, 55)	55	(45, 60)
Fine Motor	50	(30, 55)	50	(45, 60)
Problem Solving	55	(45, 55)	55	(55, 60)
Personal-Social	50	(40, 55)	50	(45, 55)

Figures are median (interquartile range). $^{\nabla}$ Statistically significant difference in corrected age at questionnaire completion, Two sample Wilcoxon Rank-Sum Test, p=0.008.

Table 4.4.2.8 Eight month median ASQ scores

	Repeat corticosteroids n=45		Placebo n=43	
Corrected age at questionnaire administration (months)$^{\nabla}$	8.6	(8.5, 8.7)	8.5	(8.4, 8.8)
Total Score	250	(220, 270)	255	(235, 285)
Developmental Domains				
Communication	50	(40, 60)	55	(50, 60)
Gross Motor	40	(30, 50)	45	(35, 60)
Fine Motor	60	(55, 60)	60	(55, 60)
Problem Solving	55	(45, 60)	55	(45, 60)
Personal-Social	45	(40, 50)	55	(45, 60)

Figures are median (interquartile range). $^{\nabla}$ No statistically significant difference in corrected age at questionnaire completion, Two sample Wilcoxon Rank-Sum Test, p=0.53.

No statistically significant differences were found between the two treatment groups when the progress of the infants, as rated by their parents, was compared at four (Table 4.4.2.9) or eight months corrected age (Table 4.4.2.10).

Table 4.4.2.9 Four month ASQ general questions

	Repeat corticosteroids n=45	%	Placebo n=45	%	RR	95% CI	
Do you think your baby hears well?							
No	0	-	0	-		-	
Does your baby use both hands equally well?							
No	3	6.8	6	13.6	0.05	0.13	1.88
When you help your baby stand, are its feet flat on the surface most of the time?							
No	13	29.5	10	22.7	1.30	0.64	2.65
Does either parent have any family history of childhood deafness or hearing impairment?							
Yes	1	2.3	7	15.6	0.14	0.02	1.11
Has your child had any medical problems in the last several months?							
Yes	16	36.4	22	48.9	0.73	0.44	1.19
Does anything about your child worry you?							
Yes	10	22.7	9	20.0	1.11	0.50	2.47

Table 4.4.2.10 Eight month ASQ general questions

	Repeat corticosteroids n=45	%	Placebo n=43	%	RR	95% CI	
Do you think your baby hears well?							
No	0	-	0	-		-	
Does your baby use both hands equally well?							
No	1	2.2	3	7.0	0.32	0.03	2.95
When you help your baby stand, are its feet flat on the surface most of the time?							
No	11	25.6	7	16.3	1.50	0.64	3.51
Does either parent have any family history of childhood deafness or hearing impairment?							
Yes	5	11.1	8	18.6	0.60	0.21	1.68
Has your child had any medical problems in the last several months?							
Yes	25	55.6	16	37.2	1.49	0.93	2.38
Does anything about your child worry you?							
Yes	9	20.0	6	14.0	1.43	0.56	3.69

Mixed model analysis of variance for ASQ scores (Table 4.4.2.11)

Mixed model analysis of variance was used to explore the effect of repeat prenatal corticosteroids on the mean scores for each of the ASQ domains, with adjustment for confounding, missing data and including infants with the same mother. No statistically significant differences were identified between the two treatment groups for the total ASQ score assessed at four or eight months, or the four developmental domains of communication, gross motor, fine motor and problem solving. No statistically significant differences were found between the two treatment groups for the personal-social domain at four months. However, repeat corticosteroid treated infants had significantly lower personal-social domain scores at eight months when compared with placebo group infants (estimated mean difference 4.5, 95% CI 0.03, 26.1, p=0.05).

Table 4.4.2.11 Estimated means for mixed model analysis of variance of ASQ scores[Ψ]

Domains	Repeat corticosteroids		Placebo		Mean Difference	95% CI		Significance
	Est. mean	SEM	Est. mean	SEM				p-value
Total Score *								
4 month	231.2	15.9	243.4	15.9	12.2	-4.7	29.2	0.15
8 month	167.3	15.6	180.7	15.9	13.4	-3.5	30.2	0.12
Communication[#]								
4 month	39.9	4.1	44.0	4.0	4.2	-0.2	8.6	0.06
8 month	41.5	4.1	45.7	4.1	4.2	-0.2	8.5	0.06
Gross Motor*								
4 month	47.8	5.2	48.2	5.1	0.4	-5.1	5.9	0.89
8 month	22.2	5.1	24.9	5.2	2.7	-2.8	8.1	0.33
Fine Motor								
4 month	48.3	4.8	52.1	4.8	3.8	-1.4	8.9	0.15
8 month	36.7	4.7	38.5	4.8	1.8	-3.4	26.8	0.50
Problem Solving								
4 month	48.6	3.9	52.5	4.0	3.9	-0.3	8.1	0.71
8 month	39.4	3.9	39.8	4.0	2.1	-3.8	4.6	0.86
Personal-Social								
4 month	44.6	4.2	45.4	4.2	0.8	-3.8	5.3	0.74
8 month	32.0	4.1	36.5	4.2	4.5	0.03	26.1	**0.05**

Est. mean - estimated mean; SEM - standard error of the mean; [Ψ] Adjusted for severe intrauterine growth restriction as reason for risk of preterm birth and corrected age at questionnaire completion. * Adjusted also for multiple gestations; [#] Adjusted also for multiple gestations and SEIFA score.

Cox proportional hazards regression for ASQ cut-off scores (Table 4.4.2.12)

Cox proportional hazards regression was used to calculate adjusted relative risks for the proportion of infants scoring below each of the developmental domain cut-offs for the ASQ, with adjustment for confounding, missing data and clustering within the same mother. No statistically significant differences were identified between repeat corticosteroid treated and placebo infants, in the proportion scoring below each of the developmental domain cut-offs, at the four or eight month ASQ assessments.

Table 4.4.2.12 Four and eight month ASQ developmental domain cut-off scores and adjusted relative risks [Ψ]

	Repeat corticosteroids		Placebo		Adjusted RR	95% CI		Significance p-value
FOUR MONTHS	**n=45**	**%**	**n=45**	**%**				
Communication <33.3[#]	5	11.1	3	6.7	1.79	0.30	10.54	0.52
Gross Motor <40.1*	13	28.9	10	22.2	0.95	0.45	2.01	0.89
Fine Motor <27.5	7	15.6	2	4.4	2.66	0.54	13.02	0.23
Problem Solving <35.0	3	6.7	1	2.2	1.17	0.11	12.02	0.89
Personal-Social <33.0	5	11.1	2	4.4	1.59	0.33	7.59	0.56
EIGHT MONTHS	**n=45**	**%**	**n=43**	**%**				
Communication <36.7[#]	10	22.2	4	9.3	2.18	0.51	9.36	0.29
Gross Motor <24.3*	8	17.8	5	11.6	1.34	0.49	3.66	0.57
Fine Motor <36.8	5	11.1	2	4.7	2.28	0.46	11.28	0.31
Problem Solving <32.3	4	8.9	1	2.3	1.93	0.19	19.22	0.58
Personal-Social <30.5	7	15.6	2	4.7	2.89	0.62	13.45	0.18

RR - relative risk; [Ψ] Adjusted for severe intrauterine growth restriction as reason for risk of preterm birth and corrected age at questionnaire completion; * Adjusted also for multiple gestations; [#] Adjusted also for multiple gestations and SEIFA score.

4.4.3. FAGAN TEST OF INFANT INTELLIGENCE

Description of FTII study population

Over the period during which FTII assessments were performed (April 9th 2000 – September 13th 2002), 93 infants reached 7¼ months corrected age (Figure 4.4.4.1). FTII tests were successfully completed on 60 (65%) of these infants. There were several reasons why FTII

tests were not completed on all infants who reached 7¼ months corrected age; 16 (17%) infants were unable to be tested at the organised assessment due to limited attention, 10 (11%) infants lived in the far-country where follow-up was impractical (more than six-hours return by car from the Women's and Children's Hospital) and seven (7.5%) infants were lost to follow-up. To examine the effect of non-response bias, trial entry, birth and clinical neonatal outcomes were compared between the women and infants for whom a FTII was completed and those women and infants for whom there was no FTII data. Of the entire In-depth Growth and Neurodevelopment Trial population, FTII were completed on 60 infants, and 87 infants had no FTII data.

Infants with FTII test results had mothers who were significantly older, were more likely to have a high SEIFA index and were more likely to have been at risk of preterm birth due to isoimmunization, when compared with the mothers of infants for whom no FTII data were available (Table 4.4.3.1). For all other trial entry characteristics, there were no statistically significant differences between the mothers of infants for whom FTII were conducted and those without FTII assessments.

There were no statistically significant differences in the gestational age at trial entry or the median number of ACTORDS treatment doses received when the mothers of infants who had FTII tests completed were compared with the mothers of infants without FTII tests (Table 4.4.3.2). Infants for which no FTII data were available were more likely to have been born at earlier gestational ages (Table 4.4.3.3). There were no statistically significant differences between infants with FTII data and those without, when the other birth and neonatal clinical outcomes were compared.

Table 4.4.3.1 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry by FTII completion

	FTII conducted		No FTII		Significance
	n= 52	%	n =76	%	p-value
Maternal age (years)*	31.4	5.0	28.8	5.8	**0.01**
Primiparous	21	40.4	23	30.3	0.24
Non-Caucasian ethnicity	1	1.9	10	13.2	0.03
SEIFA Index					
Low (≤ 950)	20	38.5	37	48.7	0.25
Low-mid (951-1010)	14	26.9	21	27.6	0.93
Mid-high (1011-1067)	7	13.5	15	19.7	0.36
High (>1067)	10	19.2	3	3.9	**0.005**
Private Patient	8	15.4	8	10.5	0.41
Maternal weight at booking (kg)*	66.8	14.0	70.1	16.6	0.27
Maternal height at booking (cm)*	163.9	7.8	161.9	7.3	0.18
BMI at booking (kg/m^2)#	25.3	5.6	26.8	5.8	0.20
Smoking at booking	11	21.2	27	35.5	0.08
Live outside metropolitan area	15	28.8	26	34.2	0.52
Previous obstetric history					
Preterm labour <37 weeks	4	7.7	9	17.0	0.45
Preterm birth <32 weeks	3	5.8	7	13.2	0.48
Perinatal death ≥ 20 weeks	3	5.8	5	9.4	0.97
Plurality of current pregnancy					
Singleton	45	86.5	66	78.9	0.96
Twin	6	11.5	9	11.8	0.96
Triplet	1	1.9	1	1.3	0.79
Reasons for risk of preterm birthϕ					
PPROM	11	36.5	29	38.2	0.04
Preterm labour	17	32.7	18	23.7	0.26
Indeterminate APH	12	23.1	19	25.0	0.80
Placenta praevia	13	25.0	11	14.5	0.13
Cervical Incompetence	2	3.8	5	6.6	0.50
Isoimmunisation	6	11.5	2	2.6	**0.04**
Pre-Eclampsia	3	5.8	9	17.0	0.25
Congenital anomaly	1	1.9	1	1.3	0.79
Severe IUGR requiring delivery	2	3.8	5	9.4	0.50
Twin-twin transfusion syndrome	0	0	3	3.9	0.15
Placental abruption	2	3.8	1	1.3	0.35

#Figures mean and standard deviation; *Figures median (interquartile range); ϕ More than one may apply;
FTII – Fagan Test of Infant Intelligence; SEIFA - Index of relative socio-economic disadvantage (ABS 1998); BMI - body mass index; PPROM - preterm prelabour rupture of membranes; APH - antepartum haemorrhage; IUGR - intrauterine growth restriction.

Table 4.4.3.2 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received by FTII completion

	FTII conducted		No FTII		Significance
	n =52	%	n =76	%	p-value
Gestation at ACTORDS trial entry (weeks) *	28^{+3} (26^{+2}, 30^{+2})		28^{+1} (26^{+2}, 30^{+0})		0.61
<28 weeks	22	43.2	36	47.4	0.57
≥28 weeks	30	57.7	40	52.6	0.57
ACTORDS treatment doses given *	2	(1, 4)	2	(1, 3)	0.31

*Figures median (interquartile range)

Table 4.4.3.3 Birth and infant clinical outcomes by FTII completion

	FTII conducted		No FTII		Significance
	n= 52	%	n= 76	%	p-value
Gestation at birth (weeks)*	34^{+4}	(31^{+3}, 36^{+6})	31^{+6}	(29^{+4}, 36^{+2})	**0.04**
≤ 28 weeks	4	7.7	13	17.1	0.12
28^{+1}-31^{+6} weeks	13	25.0	26	34.2	0.27
32 –36^{+6} weeks	23	44.2	22	28.9	0.08
≥ 37 weeks	12	23.1	15	19.7	0.65
Chorioamnionitis ^	0	0	3	3.9	0.15
	n=60	**%**	**n=87**	**%**	
Mode of birth					
normal vaginal	16	26.6	25	28.7	0.69
operative vaginal	2	3.3	6	6.9	0.33
caesarean section	42	70.0	56	64.4	0.67
Male infant	32	53.3	53	60.9	0.26
Apgar <7 at 5 minutes	2	3.3	3	3.4	0.94
Admission to NICU	35	58.3	59	67.8	0.24
Needed O_2 supplementation	32	53.3	53	60.9	0.36
Proven systemic infection	5	8.3	13	14.9	0.20
Postnatal corticosteroids	9	24.2	11	12.6	0.68
Any IVH on cranial U/S closest to six weeks	0	0	3	3.4	0.14
Infant length of stay (days)*	40.6	63.7	41.1	32.9	0.95

*Figures are mean and standard deviation; ^ Requiring antibiotics during labour; NICU - neonatal intensive care unit; O_2 – oxygen; IVH - intraventricular haemorrhage; U/S – ultrasound.

Comparisons between repeat corticosteroid and placebo group women and their infants were made on trial entry characteristics, birth and neonatal outcomes for those infants for whom the Fagan Test of Infant Intelligence was performed. Women in the repeat corticosteroid group with infants tested using the FTII were similar in terms of their age, parity, ethnicity, SEIFA index, insurance status, weight, height and body mass index at booking (Table 4.4.3.4). Repeat corticosteroid treated women were more likely to smoke at booking (30.8 percent versus 11.5 percent) and were more likely to live outside the metropolitan area (34.6 percent versus 23.1 percent). Repeat corticosteroid treated women were more likely to be at risk of preterm birth because of indeterminate antepartum haemorrhage and placenta praevia and less likely to be at risk as a result of preterm prelabour rupture of membranes and isoimmunisation, compared with placebo group women.

Repeat corticosteroid treated women with FTII tested infants had a similar median gestation at ACTORDS trial entry compared with placebo group women (Table 4.4.3.5). A similar proportion of women in each of the two treatment groups entered the ACTORDS trial at less than 28 weeks gestation. Women in the repeat corticosteroid group received a median of two ACTORDS treatment doses (interquartile range 1, 4) and those women in the placebo group also received a median of two ACTORDS treatment doses (interquartile range 1, 5).

Comparisons between repeat corticosteroid and placebo group infants for whom FTII data was collected revealed no statistically significant differences between the two groups of women in the median gestational age at birth and the proportion of women who gave birth in each of the gestational age categories (Table 4.4.3.6). No statistically significant differences were determined between the two treatment groups in terms of infant clinical outcomes including

mode of birth, the proportion of male infants, the number of infants with low Apgar scores, infants who required admission to the neonatal intensive care unit or required oxygen supplementation.

Table 4.4.3.4 Maternal demographics, obstetric history and reason for risk of preterm birth at trial entry for women whose infants were tested using the FTII

	Repeat corticosteroids		Placebo	
	n= 26	%	n =26	%
Maternal age (years)*	31.5	(27, 35)	31	(28, 35)
Primiparous	11	42.3	10	38.5
Non-Caucasian ethnicity	1	3.9	0	0
SEIFA Index				
Low (≤ 950)	10	38.5	10	38.5
Low-mid (951-1010)	7	26.9	7	26.9
Mid-high (1011-1067)	3	11.5	4	15.4
High (>1067)	6	23.1	4	15.4
Private Patient	4	15.4	4	15.4
Maternal weight at booking (kg)*	61	(58.5, 75.3)	62.5	(54, 77)
Maternal height at booking (cm)*	164	(157.25, 169.5)	163.5	(159, 167.8)
BMI at booking (kg/m^2)#	25.4	5.8	25.3	5.6
Smoking at booking	8	30.8	3	11.5
Live outside metropolitan area	9	34.6	6	23.1
Previous obstetric history				
Preterm labour <37 weeks	2	13.3	2	12.5
Preterm birth <32 weeks	2	13.3	1	6.3
Perinatal death ≥ 20 weeks	1	6.7	2	12.5
Plurality of current pregnancy				
Singleton	22	84.6	23	88.5
Twin	3	11.5	3	11.5
Triplet	1	3.9	0	0
Reasons for risk of preterm birth$^{\phi}$				
Preterm labour	9	34.6	8	30.8
Indeterminate APH	9	34.6	3	11.5
Placenta praevia	9	34.6	4	15.4
PPROM	3	11.5	8	30.8
Pre-eclampsia	2	7.7	1	3.9
Severe IUGR requiring delivery	2	7.7	0	0
Placental abruption	2	7.7	0	0
Cervical incompetence	0	0	2	7.7
Twin-twin transfusion syndrome	0	0	0	0
Isoimmunisation	2	7.7	4	15.4
Congenital anomaly	0	0	1	3.9

Figures mean and standard deviation#; Figures median (interquartile range)*; $^{\phi}$More than one may apply; SEIFA - Index of relative socio-economic disadvantage (ABS 1998); BMI - body mass index; APH – antepartum haemorrhage; PPROM – preterm prelabour rupture of membranes; IUGR – intrauterine growth restriction.

Table 4.4.3.5 Gestation at ACTORDS trial entry and number of ACTORDS treatment doses received for women whose infants were tested with the FTII

	Repeat corticosteroids		Placebo	
	n =26	%	n =26	%
Gestation at ACTORDS trial entry (weeks) *	28^{+5}	(26^{+4}, 30^{+4})	28^{+3}	(26^{+2}, 29^{+6})
<28 weeks	10	38.5	12	46.2
≥28 weeks	16	61.5	14	53.9
ACTORDS treatment doses given *	2	(1, 4)	2	(1, 5)

Figures median (interquartile range)*

Table 4.4.3.6 Birth and infant clinical outcomes for women and their infants who were tested using the FTII

	Repeat corticosteroids		Placebo		RR	95% CI		Significance p-value
	n= 26	%	n= 26	%				
Gestation at birth (weeks.days)*	34^{+0} (31^{+2}, 37^{+0})		34^{+5} (31^{+3}, 36^{+6})			-		0.96
≤ 28 weeks	3	11.5	1	3.9	3.00	0.33	26.99	0.30
28^{+1}-31^{+6} weeks	5	19.2	8	30.8	0.63	0.24	1.66	0.34
32 –36^{+6} weeks	11	42.3	12	46.2	0.92	0.50	1.69	0.78
≥ 37 weeks	7	26.9	5	19.2	1.40	0.51	3.85	0.51
Chorioamnionitis∝	0	0	0	0		-		-
	n= 31	**%**	**n= 29**	**%**				
Mode of birth								
normal vaginal	6	19.4	10	34.5	0.56	0.23	1.35	0.19
operative vaginal	0	0	2	6.9		-		0.14
caesarean section	25	80.7	17	58.6	1.38	0.97	1.95	0.06
Male infant	18	58.1	14	48.3	1.20	0.74	1.95	0.45
Apgar <7 at 5 minutes	0	0	2	6.9		-		0.14
Admission to NICU	20	64.5	15	51.7	1.25	0.80	1.93	0.32
O_2 supplementation	18	58.1	14	48.3	1.20	0.74	1.95	0.45
Proven systemic infection	4	12.9	1	3.5	3.74	0.44	31.55	0.19
Postnatal corticosteroids	7	22.6	2	6.9	3.27	0.74	14.5	0.09
Any IVH on cranial U/S closest to 6 weeks	0	0	0	0		-		-
Length of stay (days)*	31	(10, 54)	24	(7, 42)		-		0.16

Figures are median (interquartile range)*. ∝Requiring antibiotics during labour; NICU – neonatal intensive care unit; O_2 – oxygen; IVH – intraventricular haemorrhage; U/S – ultrasound.

The Fagan Test of Infant Intelligence scores (Table 4.4.3.7)

A total of 60 (65%) Fagan Tests of Infant Intelligence (FTII) were completed on the infants who reached 7¼ months corrected age during the testing period, 31 on repeat corticosteroid

treated infants and 29 on infants in the placebo group. FTII were completed at a median of 7.8 (interquartile range 7.4, 8.0) months postnatal corrected age for repeat corticosteroid treated infants and 7.5 months (interquartile range 7.4, 8.3) postnatal corrected age for infants in the placebo group. There were no statistically significant differences between the two treatment groups when the look duration during the familiarization period was compared. When the look durations during the novelty tests were compared, there were no statistically significant differences between repeat corticosteroid and placebo infants for the look duration at the novel stimulus, familiar stimulus and the look duration not looking at the stimulus. No statistically significant differences were found between the two treatment groups in the mean novelty preference or the number of infants with 'at risk' novelty preferences (<54.5%).

Table 4.4.3.7 Fagan Test of Infant Intelligence

	Repeat corticosteroids n= 31	Placebo n= 29	Significance p-value
Corrected age at testing (months)	7.8 (7.4, 8.0)	7.5 (7.4, 8.3)	0.39
Familiarization period			
Look duration (seconds)#	1.24 0.63	1.14 0.63	0.55
range	(0.90 - 3.79)	(0.67 - 3.52)	
Novelty Tests			
Look duration novel (s)	1.27 0.44	1.23 0.09	0.93
range	(0.89 - 2.91)	(0.75 - 2.64)	
Look duration familiar (s)	0.98 0.32	0.92 0.42	0.86
range	(0.56 - 1.87)	(0.65 - 2.49)	
Look duration (not looking) (s)	1.37 1.03	1.37 0.60	0.48
range	(0.54 - 4.45)	(0.33 - 2.88)	
Novelty preference (percentage)	59.8 5.8	59.4 6.4	0.80
range	(45.7 - 70.6)	(48.5 - 75.6)	
Novelty preference <54.5% *	5 17.9	7 25.0	0.52

Figures are mean and standard deviation or *number and percentage of infants;
look duration = average of looks to left and right stimulus.

4.5. DISCUSSION

4.5.1. OVERVIEW OF RESULTS OF REPEAT PRENATAL CORTICOSTEROIDS AND EARLY INFANT DEVELOPMENT

Repeat prenatal corticosteroid exposure did not significantly reduce the total score, or the scores in the communication, gross motor, fine motor and problem solving domains of the ASQ at four and eight month assessments, when compared with placebo. There were no significant differences between the two treatment groups in the personal-social domain scores at four months, though repeat corticosteroid treated infants had significantly lower personal-social domain scores at eight months, compared with placebo group infants. The personal-social domain of the ASQ focuses on solitary social play, play with others and with toys (Squires *et al.* 1995).

Comparisons between repeat and placebo group infants, for whom ASQ data were collected, revealed infants in the repeat corticosteroid group were more likely to have mothers who smoked at booking, to have developed a postnatal systemic infection, to have received postnatal corticosteroid treatment and have a significantly longer length of stay in hospital. Each of these factors may influence personal-social development. Differences found in personal-social development at eight months corrected age between the two treatment groups, may be a result of these differences between the two treatment groups in terms of trial entry characteristics and infant clinical outcomes (Bradley & Corwyn 2002).

The ASQ has been designed as a screening tool to identify 'at risk' children who require further developmental assessment. The mean difference in the personal-social domain at eight months, between repeat corticosteroid treated infants and placebo group infants, was 4.5

points. It is unknown whether this difference is clinically important. Comparisons of the proportion of infants scoring 'at risk' on the four or eight month ASQ assessments revealed no statistically significant differences between repeat corticosteroid and placebo group infants. No statistically significant differences were found, between the two treatment groups, in the questions where parents assessed their child's performance and reported any concerns. However, the power of this study to detect small differences in these outcomes between the two treatment groups was low, ranging from 0.05 to 0.60 for each of the questions, α=0.05.

It is important that long-term developmental outcomes be reported for infants involved in perinatal randomised controlled trials. However, the best method by which this can be achieved is unclear. Assessment by health professionals is expensive and time-consuming, and single, short visits may not allow a child's true performance to be established. Parentally completed questionnaires have been developed as simple, low-cost tool with which to identify infants at risk of developmental problems. The validity of assessment of child development by parents using these questionnaires has been examined by several researchers (Glascoe & Dworkin 1995; Heiser *et al.* 1995; Fooks *et al.* 1997; Heiser *et al.* 2000; Bortolus *et al.* 2002; Malhi & Singhi 2002). A study of preterm and term children at 18 months of age reported parental agreement (using a questionnaire developed from the Griffith's Developmental Scales) with health professionals was high on measures of development, hearing, vision, weight and height (Bortolus *et al.* 2002). Although it is shown that agreement of parental and paediatric assessments is high, identification of infants with more subtle impairments, which exist without functional loss, is better done by a paediatrician (Fooks *et al.* 1997). Further research could examine whether assessment of neurodevelopmental milestones at four and eight months corrected age, using the Ages and Stages Questionnaires, is predictive of later

performance with the Bayley Scales of Infant Development. This will be completed on all infants enrolled in the ACTORDS trial at 2 years corrected age.

No statistically significant differences were found between infants exposed to repeat prenatal corticosteroids, and those in the placebo group, when the 7¼ month Fagan Test of Infant Intelligence mean novelty preference and at risk novelty preferences were compared. No significant differences were detected in the look duration during the familiarization period and the look durations at the novel and familiar stimulus during the novelty tests. This finding is guardedly reassuring, given the adverse effects reported of repeat prenatal corticosteroids on myelination of several nerve tracts in the ovine model.

4.5.2. LIMITATIONS OF THIS STUDY

Several aspects of this study must be examined, including the sample size, the completeness of follow-up and the clinical relevance of the assessment tools used. Not all infants enrolled in The In-depth Growth and Neurodevelopment Trial reached four and eight months corrected age for the ASQ, or 7¼ months corrected age to be assessed using the FTII, in the time course available for this study. The sample size of this trial enabled the detection of mean differences in the total score, and each of the developmental domains, ranging from 25 to 35 percent between the two treatment groups, β=0.2 and α=0.05. The number of infants on whom FTII assessments were conducted enabled the detection of a ten percent difference in the novelty preference score between the two treatment groups, β=0.2 and α=0.05.

Completeness of follow-up may introduce bias into a follow-up study. There is evidence to suggest that infants who are the most difficult to follow-up are more likely to have a disability

or low IQ scores (Tin *et al.* 1998; Callanan *et al.* 2001). To address this issue, comparisons were made on trial entry, birth and clinical neonatal outcomes between infants and their mothers for whom ASQ or FTII data were available, and those without follow-up data. These comparisons revealed that infants with ASQ data were more likely to have older mothers, of higher socio-economic status (SEIFA >1067), who were less likely to smoke at booking and less likely to have received antibiotic treatment during labour for chorioamnionitis. Similar differences were detected between women and their infants with FTII test results and those without, with tested infants having older mothers, who were more likely to have high socio-economic status, and more likely to have been at risk for preterm birth due to isoimmunization. Infants without FTII tests were born at significantly lower gestational ages compared with infants who received FTII testing. With reference to the other trial entry and clinical outcome variables, the infants for whom neurodevelopmental data were collected appear similar to those for whom data was unable to be collected. Differences between infants and their mothers with neurodevelopmental follow-up, and those without, particularly in terms of maternal age and socio-economic status, may impact on the interpretation of the results of this study.

The FTII relies on infants concentrating on the pictures involved in the test for up to 20 minutes. Unfortunately, at home visits, some infants had poor behaviour and were not always able to complete the FTII test. These tests were unable to be repeated when these infants lived in regional areas of South Australia, with over one-third of the study population residing outside the Adelaide metropolitan area. Efforts were made to ensure all infants were assessed using the FTII, though for logistical reasons, infants residing more than six hours return from Adelaide were unable to assessed. Difficulties in obtaining complete follow-up are not unique

to this study, and complete follow-up is a major challenge in perinatal research.

The time frame over which the neurodevelopmental assessments were made in this study must be addressed. Assessments were made on infants up to eight months corrected age. It is unclear whether assessments using the ASQ and FTII up to this time frame are predictive of future development.

4.5.3. CONCORDANCE WITH PREVIOUS WORK

The current study is the first randomised controlled trial of infant neurodevelopmental outcomes after repeat prenatal corticosteroid exposure. Evidence of delayed myelination and reduced brain size in the ovine model has raised concern as to the adverse neurodevelopmental consequences of repeat prenatal corticosteroid treatment (Dunlop *et al.* 1997; Huang *et al.* 1999a; Quinlivan *et al.* 2000; Huang *et al.* 2001; Quinlivan *et al.* 2001; Quinlivan *et al.* 2002). Previous non-randomised human studies have reported varied neurodevelopmental outcomes following repeat prenatal corticosteroid therapy. A cohort study of West Australian infants reported increased externalising behaviour and distractibility at three years of age (French *et al.* 1999) and a study of very-low-birth-weight infants at 21.5 months reported abnormal psychomotor development with repeat corticosteroid treatment (Esplin *et al.* 2000). The remaining studies reported no adverse effect of repeat prenatal corticosteroid treatment on neurological and cognitive development at two (Kumar & Grobman 2002) or four years of age (Hasbargen *et al.* 2001) and no impact on intelligence or achievement at seven years of age (Thorp *et al.* 2001). The current study provides no clear evidence of adverse effect of repeat prenatal corticosteroid treatment on early infant neurodevelopment.

4.5.4. FUTURE DIRECTIONS

The current study is the first randomised controlled trial reporting infant neurodevelopment following repeat prenatal corticosteroid treatment, compared with a single course. These data are cautiously reassuring in suggesting no large adverse effect of repeat prenatal corticosteroid exposure on infant neurodevelopment, as measured by the ASQ and FTII. However, the ASQ is a screening tool, whose future predictive validity at four and eight months has not been established in an Australian, ex-preterm population. Further long-term neurodevelopmental assessment, to at least school-age, of infants involved in this trial is essential. These assessments should address developmental milestone attainment, psychomotor and neurodevelopment, including assessment of infant behaviour. Children in this trial will be assessed at two years corrected age as part of the ongoing follow-up of the ACTORDS trial. These assessments include the Bayley Scales of Infant Development (Bayley 1993), paediatric assessment and completion of postal questionnaires including the Child Behaviour Checklist and the Parental Stress Index.

4.5.5. CONCLUSIONS

Does the administration of repeat doses of maternally administered prenatal corticosteroids affect infant developmental milestone attainment?

Repeat prenatal corticosteroid administration was not associated with a reduction in the total score on the Ages and Stages Questionnaires at four and eight months corrected age, compared with placebo. Mean communication, gross motor, fine motor and problem solving domain scores did not differ between the two treatment groups at the four or eight month assessments. Four month mean personal-social domain scores were not significantly different between the two treatment groups, though the mean personal-social domain score at eight

months was significantly reduced for repeat corticosteroid treated infants, compared with placebo. The proportion of infants screening 'at risk' for each of the developmental domains did not differ significantly between the two treatment groups, at four or eight months corrected age.

Does the administration of repeat doses of maternally administered prenatal corticosteroids affect infant intelligence?

Repeat corticosteroid treatment was not associated with a reduction in infant intelligence as measured by the FTII at 7¼ months corrected age. There were no significant differences between the two treatment groups in terms of the look durations or novelty preference on the FTII.

5. OVERALL CONCLUSIONS

This randomised controlled trial aimed to examine the effects of repeat prenatal corticosteroid exposure on infant growth and neurodevelopment. This current study is the first randomised controlled trial evidence evaluating the effects of repeat prenatal corticosteroid treatment on infant growth and early infant neurodevelopment.

Repeat prenatal corticosteroid treatment significantly reduced the mean weight z-score at birth, at four months and at 7¼ months corrected age, compared with placebo. However, mean total body length was unaffected by repeat prenatal corticosteroid treatment from day three to 7¼ months corrected age, while knee-ankle length was reduced with repeat corticosteroid treatment for up to three months following birth, compared with placebo. Head circumference z-score, at birth, was not significantly different between the two treatment groups and was unaffected by repeat corticosteroid treatment up to 7¼ months corrected age.

Exposure to repeat prenatal corticosteroids was associated with a reduction in the mean personal-social domain score of the Ages and Stages Questionnaire at eight, but not four months corrected age, compared with placebo. No significant differences were detected between the two treatment groups in the total score, scores on the developmental domains, or the number of infants scoring 'at risk' at four or eight months corrected age. No statistically significant difference was found in novelty preference or look durations on the Fagan Test of Infant Intelligence with repeat corticosteroid treatment, compared with placebo.

The short and long-term implications of the inhibition in linear and somatic infant growth

following repeat corticosteroid exposure observed in the present study are unclear, and will need to be placed into context with relevant clinical neonatal outcomes. The differences in growth between repeat corticosteroid and placebo group infants were modest, and encouraging, given the considerable reductions in size at birth reported in the ovine model with repeat corticosteroid exposure. Similarly, the lack of clear evidence of adverse effects of repeat prenatal corticosteroid treatment on early infant neurodevelopment in the present study is cautiously reassuring, given the delays in myelination and reduction in brain size reported in the ovine model with repeat corticosteroid exposure.

Future research should continue to explore the relationships between prenatal corticosteroids, infant growth and neurodevelopment. Assessment of the long-term health of the children in this study may provide insight as to any long-term effects of the observed differences in weight at 7¼ months corrected age. This current study identified postnatal systemic infections as a possible explanation for the observed differences in infant weight at 7¼ months corrected age. Further research is required to determine whether the observed increase in infection is a result of repeat prenatal corticosteroids, or due to a chance imbalance between the two treatment groups. The biological mechanism by which postnatal systemic infections might mediate growth also requires further elucidation.

Further, long-term assessment of the growth of children in this randomised controlled trial should be continued through to adulthood. The clinical relevance of the observed differences in size at birth, and weight at 7¼ months corrected age after repeat corticosteroid exposure, and their long-term consequences are unknown. Differences between the two treatment groups in the mean weight z-score continued to 7¼ months corrected age. Further assessment

of these children is required to determine the length of time over which these differences persist and any long term consequences of these differences on childhood or later growth, particularly in terms of the Fetal Origins of Adult Disease hypothesis.

Further long-term assessment of the neurodevelopment of infants in this trial is essential. These assessments should address developmental milestone attainment, psychomotor and neurodevelopment and assessment of infant behaviour. Children in this trial will be assessed at two years corrected age as part of the ongoing follow-up of the ACTORDS trial.

In clinical practice, the effects of repeat prenatal corticosteroids on early infant growth and neurodevelopment found in this trial will need to be balanced against any benefits or adverse effects on neonatal morbidities including respiratory distress syndrome, intraventricular haemorrhage, chronic lung disease, and neonatal mortality. Results from the ongoing randomised controlled trials examining the safety and efficacy of repeat prenatal corticosteroids will help to answer this question and place the results of the current study in terms of infant growth neurodevelopment into an appropriate clinical context.

Until the completion of the ongoing randomised controlled trials, the implications for clinical practice are that corticosteroid use should be limited to a single course and repeat prenatal corticosteroids should be administered only within the context of a randomised controlled trial, as recommended by the National Institutes of Health (National Institutes of Health Consensus Development Panel 2001).

6. APPENDICES

6.1. PATIENT INFORMATION SHEET AND CONSENT FORM

SIDE STUDIES

Women who consent to participate in the ACTORDS Trial at the Women's and Children's Hospital will be asked if they are interested in taking part in these side studies. We aim to assess, in greater detail than in the main trial, fetal wellbeing, the baby's response to stress in the early weeks of life and the growth and nerve maturation of babies in the first 8 months of life.

Shortly before, and within 2 days of each trial injection, a CTG will be performed for 20 minutes to assess your baby's wellbeing. This should cause neither you nor your baby any pain or discomfort.

We will collect a cord blood sample at birth to determine the levels of hormones that influence growth. This routine non-invasive blood collection will not cause your baby any discomfort. On day 3, a saliva sample will be collected from your baby just prior to, and 30 minutes after, a stressful event (eg. the Guthrie test) to assess the level of cortisol in saliva, an indicator of baby's response to stress. Further cortisol measurements will be made on single saliva samples taken on days 7, 14 and 21. Saliva collection is a painless procedure that takes only a few mihutes.

We will be making regular measurements of your baby's growth, initially within the first 24 hours of birth, on Day 3, then weekly until 4 weeks of age, then monthly until 16 weeks of age. If baby has been discharged before this time, we hope to continue the measurements during a visit to baby's home. At 4 and 8 months of corrected age we will send you a questionnaire to complete that assesses your child's development. At 6¾ and 7¼ months (corrected age) we would like to measure your child's growth and blood pressure and during a home visit and carry out a test of your child's development.

COORDINATING COMMITTEE:- ADELAIDE
A/Prof Caroline Crowther

Prof Janet Hiller

Dr Ross Haslam

Prof Jeffrey Robinson

ACTORDS (27)
University Dept. of Obstetrics & Gynaecology
Women's & Children's Hospital
Reply Paid 60836
NORTH ADELAIDE
South Australia 5006
Phone: (08) 8161 7767 Fax: (08) 8161 7652

COLLABORATING CENTRES:-

Canberra Hospital, ACT
Christchurch Women's Hospital, NZ
Dunedin Hospital, NZ
Hervey Bay Hospital, Qld
Kirwan Hospital for Women, Townsville
Mater Mothers' Hospital, Brisbane
Mercy Hospital for Women, Melbourne
Middlemore Hospital, Auckland
Monash Medical Centre, Melbourne
National Women's Hospital, Auckland
St George Hospital, Sydney
Royal Hobart Hospital, Hobart
Royal Hospital for Women, Sydney
Royal North Shore Hospital, Sydney
Royal Women's Hospital, Brisbane
Royal Women's Hospital, Melbourne
Toowoomba Base Hospital, Qld
Waikato Hospital, Hamilton, NZ
Wellington Women's Hospital, NZ
and others.....

ACTORDS

AUSTRALASIAN COLLABORATIVE TRIAL OF REPEAT DOSES OF CORTICOSTEROIDS FOR THE PREVENTION OF NEONATAL RESPIRATORY DISEASE

ACTORDS TRIAL AND SIDE STUDY

WOMEN'S AND CHILDREN'S HOSPITAL

COORDINATING CENTRE
Maternal Perinatal Clinical Trials Unit
Department of Obstetrics & Gynaecology
University of Adelaide
Women's & Children's Hospital
NORTH ADELAIDE
South Australia 5006

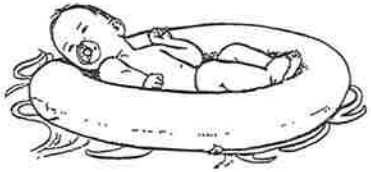
Phone: (08) 8161 7767
Fax: (08) 8161 7652
E-mail: actords@adelaide.edu.au

ACTORDS RESEARCH ASSISTANT
Pat Ashwood x17767
ACTORDS SIDE STUDIES
Kristin McLaughlin x17642

You will be aware that your baby is likely to be born very early or preterm. Very small babies these days, with intensive care support, often survive and progress normally. However, even with support, not all babies born preterm will survive.

Babies who are born too soon have a high chance of developing breathing difficulties, known as Respiratory Distress Syndrome (RDS), in the first few days of life. This can be life threatening.

You have received a course of steroid treatment which is proven to reduce the risk of RDS in babies born early and is helpful in other ways. This steroid course has been well studied and is not known to be harmful to you or your baby in anyway. In particular there is no increased risk of infection for you or your baby, and no effect on baby's growth or development. The beneficial effects of steroid treatment are thought only to last 7 days. Because of this, it has become common practice to repeat the steroid treatment. Whether the beneficial effects can continue by repeating the steroid treatment given to mothers who remain at risk of preterm birth is unknown.



Animal and human studies suggest that repeating the steroid treatment can help the baby by reducing the risk of breathing difficulties and brain haemorrhage. This should increase the chances of survival and improve the long term outlook for babies who are born early. Some human studies also suggest harmful effects. For the mother these include an increased risk of infection, maybe requiring the use of antibiotics. For the baby these include an increased risk of infection, a slightly lower birthweight of the baby, or, in animal studies alone, temporary delay in the development of some nerves. The long term effects of these findings is uncertain. In the studies available to date, babies who had received repeat doses of steroids were not found to be different in their development, at the age of 3, to babies who had not received repeat steroids.

This study seeks to assess whether repeat steroid treatment benefits babies who are born early by reducing the chances of them developing RDS, and examines any potential harmful effects to the mother and baby such as a possible increased susceptibility to infection or an effect on the baby's growth and development. If effective, repeat doses of corticosteroid would be a simple and inexpensive way of improving the health of babies born early.

Everyone in the study will have already received a course of steroid treatment 7 or more days ago.

If you agree to take part in the study, you will be randomly entered into one of two study groups. One group will receive repeat corticosteroids, the other group will be given a placebo. You will have a 50% chance of being entered into the study group that receives corticosteroids but neither you nor staff involved in your care will know which treatment group you belong to. The trial will involve a weekly intramuscular injection until 32 weeks whilst the risk of very preterm delivery remains. In all other respects you will receive the current standard care.

It should be emphasised that you are free to withdraw from this study at any time without prejudice to future treatment. If you enter the study the progress of your baby will be followed whilst in the hospital. For the success of the study we will need to have details about your baby's progress after discharge from hospital (6 and 12 months) and at two years after birth. At 6 and 12 months you will be invited to complete a brief postal questionnaire.

At two years of age a standard assessment of your child's progress would be made by a developmental paediatrician which will include an eye and hearing test and a check on developmental milestones. It would be necessary for you to attend the clinic for this assessment to be made. Most babies who are born early are routinely followed in the paediatric clinic.

The study is due to be completed in the year 2002 and, if you would be interested in receiving details of the results of the trial we will forward these to you.

A member of the study group can be contacted via the Women's and Children's Hospital on 8204 7000, to answer further questions about the study, if required.

If you wish to speak with someone not directly involved with the study, the Secretary of the Women's and Children's Hospital Research and Ethics Committee, can be contacted by telephoning the Hospital on 8204 7000.

Women's and Children's Hospital ADELAIDE

ACTORDS

AUSTRALASIAN COLLABORATIVE TRIAL OF REPEAT DOSES OF CORTICOSTEROIDS FOR THE PREVENTION OF NEONATAL RESPIRATORY DISEASE

CONSENT FORM FOR ACTORDS TRIAL AND SIDE STUDY

I, _____ *(please print full name)*

the undersigned, hereby consent to my involvement in the research project entitled:

Repeat Prenatal Steroids to Women at Risk of Preterm Birth to Reduce Neonatal Morbidity

1. I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me and my baby have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

2. The details of the procedure proposed, as outlined in the Patient Information Sheet, has also been explained to me, including the anticipated length of time it will take, the frequency with which the procedure will be performed, the possible risks and/or side effects and an indication of any discomfort and inconveniences which may be expected.

3. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me or my baby.

4. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.

5. I am informed that no information regarding my or my baby's medical history will be divulged and the results of any tests involving me or my baby will not be published so as to reveal my/his/her identity.

6. I understand that my involvement in the project will not affect any relationship with my medical advisers in their management of my or my baby's health. I also understand that I am free to withdraw from the project at any stage and that this will not affect medical care or any other aspects of my relationship with this hospital.

7. I am aware that I may be invited to take part in side studies investigating the effects of repeat doses of corticosteroids on:
   (a) my baby's growth and development. This will involve the collection of cord blood at the delivery of my baby and the weighing and measuring of my baby shortly after birth and on several occasions thereafter.
   (b) my baby's response to stress. This will involve the collection of five saliva samples in the early weeks of life.
   (c) my baby's fetal heart rate. This will involve taking a CTG for 20 minutes shortly before and within 2 days of each trial injection.

8. I am aware that I will be invited to complete a questionnaire six and 12 months after delivery.

9. I am aware that I will be invited to have my child's progress checked at 2 years of age.

10. I am aware that I should retain a copy of the completed Consent Form and the Information Sheet.

11. I consent to ACTORDS research staff having access to my casenotes and the casenotes of my baby.

SIGNED: _____

ADDRESS: _____

WITNESS: _____

RESEARCH WORKER: _____

DATE: _____

6.2. GROWTH DATA FORMS

ACTORDS Growth Studies

AUSTRALASIAN COLLABORATIVE TRIAL OF REPEAT DOSES OF CORTICOSTEROIDS FOR THE PREVENTION OF NEONATAL RESPIRATORY DISTRESS SYNDROME

INFANT GROWTH DATA FORM

Day ☐☐☐

Study Number: ☐☐☐☐☐☐

UR Number: ☐☐☐☐☐☐

Name: .....

.....

DOB: ☐☐.☐☐.☐☐

Gender: ☐ M ☐ F

Address: .....

.....

.....

Home Phone: (....) .....

***

ATTACH PATIENT ID STICKER HERE

***

Date: ☐☐.☐☐.☐☐ Time: ☐☐☐☐ hours

Knee-ankle Length (mm)

Observer: .....

Knee-heel cap ☐ 1 ☐ 2

Knee cab arm ☐ A (36 mm)
☐ B (84 mm)
☐ C (112 mm)
☐ D (174 mm)

Knee cab height ☐☐ mm

	Left Leg	*Right Leg*
R1	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R2	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R3	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R4	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R5	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R6	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R7	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R8	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R9	☐☐☐☐.☐☐	☐☐☐☐.☐☐
R10	☐☐☐☐.☐☐	☐☐☐☐.☐☐

Weight (to nearest 5g)

Observer: .....

☐☐☐☐ g

Occipital-frontal Circumference

Observer: .....

☐☐☐.☐ cm

Total Body Length

Observer: .....

☐☐☐.☐ cm

Crown-rump Length

Observer: .....

☐☐☐.☐ cm

***** ATTACH KNEMOMETER PRINTOUT HERE *****

6.3. FOUR AND EIGHT MONTH AGES AND STAGES QUESTIONNAIRES

Bricker, D., Squires, J. Mounts, L. with assistance from Potter, L., Nickel, R. & Farrell, J. (1995). *Ages & stages questionnaires: a parent-completed, child-monitoring system,* Paul H. Brooks Publishing Co.

7. REFERENCES

Abbasi S, Hirsch D, Davis J, Tolosa J, Stouffer N, Debbs R, Gerdes JS. Effect of single versus multiple courses of antenatal corticosteroids on maternal and neonatal outcome. Am J Obstet Gynecol. 2000;**182**(5):1243-9.

ABS. 1996 Census of Population and Housing. Socio-economic indexes for areas. Australian Bureau of Statistics, Commonwealth of Australia, 1998.

ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. Lancet. 1995;**345**(8954):877-82.

Aghajafari F, Murphy K, Matthews S, Ohlsson A, Amankwah K, Hannah M. Repeated doses of antenatal corticosteroids in animals: a systematic review. Am J Obstet Gynecol. 2002a;**186**(4):843-9.

Aghajafari F, Murphy K, Ohlsson A, Amankwah K, Matthews S, Hannah ME. Multiple versus single courses of antenatal corticosteroids for preterm birth: a pilot study. J Obstet Gynaecol Can. 2002b;**24**(4):321-9.

Aghajafari F, Murphy K, Willan A, Ohlsson A, Amankwah K, Matthews S, Hannah M. Multiple courses of antenatal corticosteroids: a systematic review and meta-analysis. Am J Obstet Gynecol. 2001;**185**(5):1073-80.

Akaike H. A New Look at the Statistical Model Identification, IEEE Transaction on Automatic Control. AC 1974; **19**:716-723.

Andersson H, Erhart B. Repeated corticosteroid doses have no effect on birth weight. Am J Obstet Gynecol. 1998; **178**(1 part 2): S183.

Andersson HW, Gotlieb SJ, Nelson KG. Home environment and cognitive abilities in infants born small-for-gestational-age. Acta Obstet Gynecol Scand Suppl. 1997;**165**:82-6.

Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. Am J Obstet Gynecol. 1995;**173**(1):254-62.

Banks BA, Cnaan A, Morgan MA, Parer JT, Merrill JD, Ballard PL, Ballard RA. Multiple courses of antenatal corticosteroids and outcome of premature neonates. North American Thyrotropin-Releasing Hormone Study Group. Am J Obstet Gynecol. 1999;**181**(3):709-17.

Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995a;**311**(6998):171-4.

Barker D. Mothers, babies and disease in later life. London: BMJ Publishing Group;1995b.

Barker D. Fetal and infant origins of adult disease. London: BMJ Publishing Group; 1992

Bayer D, Bleichfeld B, Lane S, Volker M, Alif B, Floss B. The relationship between the

movement assessment of infants and the Fagan test of infant intelligence in infants with prenatal cocaine exposure. Phys Occup Ther Pediatr.1996;**16**(1): 145-153.

Bayley N. Bayley Scales of Infant Development. San Antonio: The Psychological Corporation, Harcourt Brace & Co; 1993.

Bhandari V, Brodsky N. Repetitive doses of antenatal steroids (ANS) are associated with increased gastroesophageal reflux (GER). Society of Pediatric Research, 1999; 186A.

Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA. 2002;**288**(6):728-37.

Bloom S, Sheffield J, Cox S, McIntire D, Leveno K. Is Dexamethasone for Fetal Maturation Associated with Diminished Fetal Growth? Am J Obstet Gynecol. 1998; : S104.

Bloomfield FH, Knight DB, Harding JE. Side effects of 2 different dexamethasone courses for preterm infants at risk of chronic lung disease: a randomized trial. J Pediatr. 1998;**133**(3):395-400.

Bortolus R, Parazzini F, Trevisanuto D, Cipriani S, Ferrarese P, Zanardo V. Developmental assessment of preterm and term children at 18 months: reproducibility and validity of a postal questionnaire to parents. Acta Paediatr. 2002;**91**(10):1101-7.

Bradley RH, Corwyn RF. Socioeconomic status and child development. Annu Rev Psychol. 2002;**53**:371-99.

Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain G. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol. 1999;**106**(9):977-9.

Bucher HU, Killer C, Ochsner Y, Vaihinger S, Fauchere JC. Growth, developmental milestones and health problems in the first 2 years in very preterm infants compared with term infants: a population based study. Eur J Pediatr. 2002;**161**(3):151-6.

Callanan C, Doyle L, Rickards A, Kelly E, Ford G, Davis N. Children followed with difficulty: how do they differ? J Paediatr Child Health. 2001;**37**(2):152-6.

Cameron N. The methods of auxological anthropometry. In: Falkner F and Tanner JM, editors. Human growth: a comprehensive treatise. New York: Plenum; 1986. p.3-46.

Cheung YB, Khoo KS, Karlberg J, Machin D. Association between psychological symptoms in adults and growth in early life: longitudinal follow up study. BMJ. 2002;**325**(7367):749.

Cohen SE, Parmelee AH. Prediction of five-year Stanford-Binet scores in preterm infants. Child Dev. 1983;**54**(5):1242-53.

Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height,

body mass index and head circumference fitted by maximum penalized likelihood. Stat Med. 1998;**17**(4):407-29.

Collaborative Group on Antenatal Steroid Therapy. Effects of antenatal dexamethasone administration in the infant: long-term follow-up. J Pediatr. 1984;**104**(2):259-67.

Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome. Am J Obstet Gynecol. 1981;**141**(3):276-87.

Colombo J. Individual differences in infant cognition: methods, measures and models. In: Dobbing J, editor. Developing brain and behaviour: the role of lipids in infant formula. San Diego: Academic Press; 1997. p.339-385.

Colombo J, Mitchell DW, Coldren JT, Freeseman LJ. Individual differences in infant visual attention: are short lookers faster processors or feature processors? Child Dev. 1991;**62**(6):1247-57.

Crowley P. Prophylactic corticosteroids for preterm birth (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

Crowley P. Corticosteroids prior to preterm delivery. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, editors. Pregnancy and Childbirth Module of The Cochrane Database of Systematic Reviews, 1995a [updated 24 February 1995]. Available from the BMJ Publishing

group: London.

Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am J Obstet Gynecol. 1995b;**173**(1):322-35.

Crowther C, Vigneswaran P, Willson K. Prenatal corticosteroid prescribing: Current practice in South Australia. 2nd Annual PSANZ Congress 1998: P12.

Darvill T, Lonky E, Reihman J, Stewart P, Pagano J. Prenatal exposure to PCBs and infant performance on the Fagan test of infant intelligence. Neurotoxicology. 2000;**21**(6):1029-38.

Debbs R, Abassi S, Tolosa J, Weiner S, Wapner R. Does serial versus single course betamethasone therapy increase neonatal morbidity? Am J Obstet Gynecol 1997;**176**(1(2)): S47, A130.

Dessens AB, Haas HS, Koppe JG. Twenty-year follow-up of antenatal corticosteroid treatment. Pediatrics. 2000;**105**(6):E77.

Dirnberger DR, Yoder BA, Gordon MC. Single versus repeated-course antenatal corticosteroids: outcomes in singleton and multiple-gestation pregnancies. Am J Perinatol. 2001;**18**(5):267-7.

Dobbing J, Sands J. Comparative aspects of the brain growth spurt. Early Hum Dev. 1979;**3**(1):79-83.

Donoghue D and the ANZNN. 2002 Report of the Australian & New Zealand Neonatal Network 2000. Sydney: ANZNN.

Doran TA, Swyer P, MacMurray B, Mahon W, Enhorning G, Bernstein A, Falk M, Wood MM. Results of a double-blind controlled study on the use of betamethasone in the prevention of respiratory distress syndrome. Am J Obstet Gynecol. 1980;**136**(3):313-20.

Doyle L, Davis P. Postnatal corticosteroids in preterm infants: systematic review of effects on mortality and motor function. J Paediatr Child Health. 2000 ;**36**(2):101-7.

Dunlop SA, Archer MA, Quinlivan JA, Beazley LD, Newnham JP. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. J Matern Fetal Med. 1997;**6**(6):309-13.

Elder D, Hagan R, Evans S, Benninger H, French N. Hospital admissions in the first year of life in very preterm infants. J Pediatr Child Health 1999; **35**:145-50.

Elimian A, Verma U, Visintainer P, Tejani N. Effectiveness of multidose antenatal steroids. Obstet Gynecol. 2000;**95**(1):34-6.

Erickson K, Schmidt L, Santesso DL, Schulkin J, Gregory K, Hobel C. Obstetrician-gynecologists' knowledge and training about antenatal corticosteroids. Obstet Gynecol. 2001;**97**(1):140-6.

Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. BMJ. 1999;**318**(7181):427-31.

Esplin M, Fausett M, Smith S, Oshiro B, Porter T, Branch D, Varner M. Multiple courses of antenatal steroids are associated with a delay in long-term psychomotor development in children with birth weights <= 1,500 grams. Am J Obstet Gynecol 2000.Miami Beach, Florida.

Esters D, Pass J, Egan J. Serial betamethasone use in a clinic practice: does it affect fetal growth? Society for Maternal-Fetal Medicine 2000 20th Annual Meeting, 2000.Miami Beach, Florida.

Fagan J, Shepherd P. The Fagan Test of Infant Intelligence. Manual. Cleveland, Ohio: Infantest Corporation ;1991.

Fooks J, Mutch L, Yudkin P, Johnson A, Elbourne D. Comparing two methods of follow up in a multicentre randomised trial. Arch Dis Child. 1997;**76**(4):369-76.

Fowden AL. Endocrine regulation of fetal growth. Reprod Fertil Dev. 1995;**7**(3):351-63.

Fowden AL, Szemere J, Hughes P, Gilmour RS, Forhead AJ. The effects of cortisol on the growth rate of the sheep fetus during late gestation. J Endocrinol. 1996;**151**(1):97-105.

Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child. 1995;**73**(1):17-24

French NP, Hagan R, Evans SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids: size at birth and subsequent development. Am J Obstet Gynecol. 1999;**180**(1 Pt 1):114-21.

Gamsu HR, Mullinger BM, Donnai P, Dash CH. Antenatal administration of betamethasone to prevent respiratory distress syndrome in preterm infants: report of a UK multicentre trial. Br J Obstet Gynaecol. 1989;**96**(4):401-10.

Garite TJ, Rumney PJ, Briggs GG, Harding JA, Nageotte MP, Towers CV, Freeman RK. A randomized, placebo-controlled trial of betamethasone for the prevention of respiratory distress syndrome at 24 to 28 weeks' gestation. Am J Obstet Gynecol. 1992;**166**(2):646-51.

Ghidini A, Salafia CM, Minior VK. Repeated courses of steroids in preterm membrane rupture do not increase the risk of histologic chorioamnionitis. Am J Perinatol. 1997;**14**(6):309-13.

Gibson AT, Pearse RG, Wales JK. Growth retardation after dexamethasone administration: assessment by knemometry. Arch Dis Child. 1993a;**69**(5 Spec No):505-9.

Gibson AT, Pearse RG, Wales JK. Knemometry and the assessment of growth in premature

babies. Arch Dis Child. 1993b;**69**(5 Spec No):498-504.

Glascoe FP, Dworkin PH. The role of parents in the detection of developmental and behavioral problems. Pediatrics. 1995;**95**(6):829-36.

Goldenberg RL, Jobe AH. Prospects for research in reproductive health and birth outcomes. JAMA. 2001;**285**(5):633-9.

Guinn DA, Atkinson MW, Sullivan L, Lee M, MacGregor S, Parilla BV, Davies J, Hanlon-Lundberg K, Simpson L, Stone J, Wing D, Ogasawara K, Muraskas J. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial. JAMA. 2001;**286**(13):1581-7.

Hasbargen U, Reber D, Versmold H, Schulze A. Growth and development of children to 4 years of age after repeated antenatal steroid administration. Eur J Pediatr. 2001;**160**(9):552-5.

Heiser A, Curcin O, Luhr C, Grimmer I, Metze B, Obladen M. Parental and professional agreement in developmental assessment of very-low-birthweight and term infants. Dev Med Child Neurol. 2000;**42**(1):21-4.

Heiser A, Grimmer I, Metze B, Obladen M. Parents' estimation of psychomotor development in very low birthweight (VLBW) infants. Early Hum Dev. 1995;**42**(2):131-9.

Hirsch D, Bichotte S, Wolkoff L, Sicuranza G, Davis J. Comparison of single vs multiple

courses of antenatal steroids on neonatal outcome. J Invest Med 1998; **46**(1): 187A.

Horner HC, Packan DR, Sapolsky RM. Glucocorticoids inhibit glucose transport in cultured hippocampal neurons and glia. Neuroendocrinology. 1990;**52**(1):57-64.

Howie R, Liggins G. Clinical Trial of Antepartum Betamethasone Therapy for Prevention of Respiratory Distress in Pre-term Infants. In: Anderson ABM, Beard R, Brudenell JM, Dunn P, editors. Preterm Labour: Proceedings of the Fifth Study Group of the Royal College of Obstetricians and Gynaecologists. London: RCOG; 1977. p. 281-9.

Howie R, Liggins G. The New Zealand study of antepartum glucocorticoid treatment. In: Farnell P, editor. Lung Development: Biological and Clinical Perspectives, Volume II. Academic Press;1982. p.255-65.

Huang WL, Beazley LD, Quinlivan JA, Evans SF, Newnham JP, Dunlop SA. Effect of corticosteroids on brain growth in fetal sheep. Obstet Gynecol. 1999a;**94**(2):213-8.

Huang WL, Dunlop SA, Harper CG. Effect of exogenous corticosteroids on the developing central nervous system: a review. Obstet Gynecol Surv. 1999b;**54**(5):336-42.

Huang WL, Harper CG, Evans SF, Newnham JP, Dunlop SA. Repeated prenatal corticosteroid administration delays astrocyte and capillary tight junction maturation in fetal sheep. Int J Dev Neurosci. 2001a;**19**(5):487-93.

Huang WL, Harper CG, Evans SF, Newnham JP, Dunlop SA. Repeated prenatal corticosteroid administration delays myelination of the corpus callosum in fetal sheep. Int J Dev Neurosci. 2001b;**19**(4):415-25.

Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens. 2000;**18**(7):815-31.

Ikegami M, Jobe AH, Newnham J, Polk DH, Willet KE, Sly P. Repetitive prenatal glucocorticoids improve lung function and decrease growth in preterm lambs. Am J Respir Crit Care Med. 1997;**156**(1):178-84.

Jacobson SW. Specificity of neurobehavioral outcomes associated with prenatal alcohol exposure. Alcohol Clin Exp Res. 1998;**22**(2):313-20.

Jenkins TM, Wapner RJ, Thom EA, Das AF, Spong CY. Are weekly courses of antenatal steroids beneficial or dangerous? JAMA. 2002;**287**(2):187-8.

Jobe AH, Newnham J, Willet K, Sly P, Ikegami M. Fetal versus maternal and gestational age effects of repetitive antenatal glucocorticoids. Pediatrics. 1998a;**102**(5):1116-25.

Jobe AH, Wada N, Berry LM, Ikegami M, Ervin MG. Single and repetitive maternal glucocorticoid exposures reduce fetal growth in sheep. Am J Obstet Gynecol. 1998b;**178**(5):880-5.

Joy S, Sanchez-Ramos L, Kaunitz A. Single course versus multiple courses of antenatal corticosteroids: a meta-analysis. Am J Obst Gynecol 2001;**185**(6 part 2): A189.

Kaempf DE, Pfluger MS, Thiele AM, Linderkamp O. Validation of a newly developed mini-knemometer for premature infants. Ann Hum Biol. 1999;**26**(3):259-66.

Kari MA, Hallman M, Eronen M, Teramo K, Virtanen M, Koivisto M, Ikonen RS. Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomized placebo-controlled multicenter study. Pediatrics. 1994;**93**(5):730-6.

Karna P. How many courses of antenatal steroids? 1997;: 157A.

Karna P, Moist D, Angel L, Omar S. Effect of multiple (MANS) courses of antenatal steroids (ANS) on retinopathy of prematurity (ROP). Pediatric Academic Societies Annual Meeting, 2001.Baltimore, Maryland, USA.

Kay HH, Bird IM, Coe CL, Dudley DJ. Antenatal steroid treatment and adverse fetal effects: what is the evidence? J Soc Gynecol Investig. 2000;**7**(5):269-78.

Keller A, Hermanussen M, Vogtmann C, Kiess W, Keller E. Effect of erythrocyte transfusion on longitudinal bone growth of premature infants assessed by mini-knemometry. Eur J Pediatr. 1999;**158**(10):871-2.

Kitchen WH, Robinson HP, Dickinson AJ. Revised intrauterine growth curves for an Australian hospital population. Aust Paediatr J. 1983;**19**(3):157-61.

Kumar P, Grobman W. Neurodevelopmental outcome of very low birth weight infants after multiple courses of antenatal steroids. Am J Obst Gynecol 2002; **187**(6):S119.

Lam PM, Yuen PM, Lau TK, Leung TN. Relationship between birthweight and repeated courses of antenatal corticosteroids. Aust N Z J Obstet Gynaecol. 2001;**41**(3):281-4.

Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. 1972;**50**(4):515-25.

Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol. 1969;**45**(4):515-23.

MacArthur BA, Howie RN, Dezoete JA, Elkins J. School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. Pediatrics. 1982;**70**(1):99-105.

MacArthur BA, Howie RN, Dezoete JA, Elkins J. Cognitive and psychosocial development of 4-year-old children whose mothers were treated antenatally with betamethasone. Pediatrics. 1981;**68**(5):638-43.

Malhi P, Singhi P. Role of parents evaluation of developmental status in detecting developmental delay in young children. Indian Pediatr. 2002;**39**(3):271-5.

McCabe L, Marash D, Li A, Matthews SG. Repeated antenatal glucocorticoid treatment decreases hypothalamic corticotropin releasing hormone mRNA but not corticosteroid receptor mRNA expression in the fetal guinea-pig brain. J Neuroendocrinol. 2001;**13**(5):425-31.

McEvoy C, Bowling S, Williamson K, Collins J, Tolaymat L, Maher J. Timing of antenatal corticosteroids and neonatal pulmonary mechanics. Am J Obstet Gynecol. 2000;**183**(4):895-9.

McEvoy C, Bowling S, Williamson K, Lozano D, Tolymat L, Collins J, Izquierdo L, Maher J, Helfgott A. Effect of single versus weekly courses of antenatal steroids (AS) on functional residual capacity in preterm infants: a randomized trial. Pediatric Academic Societies Annual Meeting, 2001.Baltimore, Maryland, USA.

McEvoy C, Bowling S, Williamson K, Lozano D, Tolaymat L, Izquierdo L, Maher J, Helfgott A. The effect of a single remote course versus weekly courses of antenatal corticosteroids on functional residual capacity in preterm infants: a randomized trial. Pediatrics. 2002;**110**(2 Pt 1):280-4.

McLaughlin K, Crowther C. Repeat prenatal corticosteroids: a systematic review of the observational studies. Perinatal Society of Australia and New Zealand 6th Annual Congress; Christchurch, New Zealand; 2002a. p. A85.

McLaughlin K, Crowther C, Vigneswaran P, Hancock E, Willson K. Who remains undelivered more than 7 days after a single course of prenatal corticosteroids and gives birth very preterm (<34 weeks)? Aust NZ J Obstet Gynecol 2002b; **42**(4): 353-7.

McLaughlin K, Crowther C, Walker N, Harding J. Effects of a single course of corticosteroids given more than seven days before birth: a systematic review. Aust NZ J Obstet Gynaecol 2003a (in press).

McLaughlin K, Crowther C. Repeat prenatal corticosteroids: who still recommends their use and why? Aust NZ J Obstet Gynaecol 2003b (in press).

McLean A, Townsend A, Clark J, Sawyer MG, Baghurst P, Haslam R, Whaites L. Quality of life of mothers and families caring for preterm infants requiring home oxygen therapy: a brief report. J Paediatr Child Health. 2000;**36**(5):440-4.

Mercer B, Egerman R, Beazley D, Sibai B, Carr T, Sepesi J. Steroids reduce fetal growth: analysis of a prospective trial. 2001a.

Mercer B, Egerman R, Beazley D, Sibai B, Carr T, Sepesi J. Weekly antenatal steroids in women at risk for preterm birth: a randomized trial. Society for Maternal-Fetal Medicine 21st Annual Meeting, 2001b., Am J Obstet Gynecol.

Michaelsen KF, Skov L, Badsberg JH, Jorgensen M. Short-term measurement of linear

growth in preterm infants: validation of a hand-held knemometer. Pediatr Res. 1991;**30**(5):464-8.

Michaelsen KF. Short-term measurements of linear growth using knemometry. J Pediatr Endocrinol. 1994;**7**(2):147-54.

Microsoft Access 97 [computer program]. Microsoft Corporation; 1989-1996.

Mirabile C, Draper M, Veille JC, Mueller-Heubach E. Single versus multiple course glucocorticoid administration and effects on fetal growth. Am J Obstet Gynecol. 1998; **178**(1 part 2): S183.

Modi N, Lewis H, Al-Naqeeb N, Ajayi-Obe M, Dore CJ, Rutherford M. The effects of repeated antenatal glucocorticoid therapy on the developing brain. Pediatr Res. 2001;**50**(5):581-5.

Morales WJ, Diebel ND, Lazar AJ, Zadrozny D. The effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome in preterm gestations with premature rupture of membranes. Am J Obstet Gynecol. 1986;**154**(3):591-5.

Morris SS, Victora CG, Barros FC, Halpern R, Menezes AM, Cesar JA, Horta BL, Tomasi E. Length and ponderal index at birth: associations with mortality, hospitalizations, development and post-natal growth in Brazilian infants. Int J Epidemiol. 1998;**27**(2):242-7.

Moss TJ, Harding R, Newnham JP. Lung function, arterial pressure and growth in sheep during early postnatal life following single and repeated prenatal corticosteroid treatments. Early Hum Dev. 2002;**66**(1):11-24.

Mugford M, Piercy J, Chalmers I. Cost implications of different approaches to the prevention of respiratory distress syndrome. Arch Dis Child. 1991;**66**(7 Spec No):757-64.

Murphy KE, Hannah M, Brocklehurst P. Are weekly courses of antenatal steroids beneficial or dangerous? JAMA. 2002;**287**(2):188.

Nassar N, Sullivan EA. 2001 Australia's Mothers and Babies 1999. AIHW Cat. No. PER 19. Sydney: AIHW National Perinatal Statistics Unit (Perinatal Statistics Series no. 11).

National Institutes of Health Consensus Development Panel. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. JAMA. 1995;**273**(5):413-8.

National Institutes of Health Consensus Development Panel. Antenatal corticosteroids revisited: repeat courses - National Institutes of Health Consensus Development Conference Statement, August 17-18, 2000. Obstet Gynecol. 2001;**98**(1):144-50.

Newnham JP, Evans SF, Godfrey M, Huang W, Ikegami M, Jobe A. Maternal, but not fetal, administration of corticosteroids restricts fetal growth. J Matern Fetal Med. 1999;**8**(3):81-7.

NHMRC. A guide to the development, implementation and evaluation of clinical practice guidelines, Commonwealth of Australia; 1999.

Nicholl RM, Gamsu HR. Changes in growth and metabolism in very low birthweight infants fed with fortified breast milk. Acta Paediatr. 1999;**88**(10):1056-61.

Novy MJ, Walsh SW. Dexamethasone and estradiol treatment in pregnant rhesus macaques: effects on gestational length, maternal plasma hormones, and fetal growth. Am J Obstet Gynecol. 1983;**145**(8):920-31.

Ogunyemi D, Alperson B, Berger J. Effectiveness of antenatal steroids: is more bad? Am J Obst Gynecol 2001; **184**.

Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ. 2000;**320**(7240):967-71.

Papageorgiou AN, Desgranges MF, Masson M, Colle E, Shatz R, Gelfand MM. The antenatal use of betamethasone in the prevention of respiratory distress syndrome: a controlled double-blind study. Pediatrics. 1979;**63**(1):73-9.

Parilla B, Logan J. Multiple courses of betamethasone do not appear to decrease fetal adrenal steroidogenesis. Prenat Neonat Med 1999; **4**:312-6.

Pratt L, Magness RR, Phernetton T, Hendricks SK, Abbott DH, Bird IM. Repeated use of betamethasone in rabbits: effects of treatment variation on adrenal suppression, pulmonary maturation, and pregnancy outcome. Am J Obstet Gynecol. 1999a;**180**(4):995-1005.

Pratt L, Waschbusch L, Ladd W, Gangnon R, Hendricks SK. Multiple vs. single betamethasone therapy. Neonatal and maternal effects. J Reprod Med. 1999b;**44**(3):257-64.

Quinlivan JA, Beazley LD, Archer M, Evans SF, Newnham JP, Dunlop SA. Repeated prenatal corticosteroids reduce glial fibrillary acidic protein in the ovine central nervous system. J Perinat Med. 2002;**30**(3):209-19.

Quinlivan J, Archer M, Evans S, Newnham J, Dunlop S. Fetal sciatic nerve growth is delayed following repeated maternal injections of corticosteroid in sheep. J Perinat Med 2000a;**28**: 26-33.

Quinlivan JA, Beazley LD, Evans SF, Newnham JP, Dunlop SA. Retinal maturation is delayed by repeated, but not single, maternal injections of betamethasone in sheep. Eye. 2000b;**14** (Pt 1):93-8.

Quinlivan JA, Archer MA, Dunlop SA, Evans SF, Beazley LD, Newnham JP. Fetal growth retardation, particularly within lymphoid organs, following repeated maternal injections of betamethasone in sheep. J Obstet Gynaecol Res. 1998a;**24**(3):173-82.

Quinlivan JA, Evans SF, Dunlop SA, Beazley LD, Newnham JP. Use of corticosteroids by

Australian obstetricians--a survey of clinical practice. Aust N Z J Obstet Gynaecol. 1998b;**38**(1):1-7.

Review Manager (RevMan) [computer program]. Version 4.1. The Cochrane Collaboration; 2000.

Richards M, Hardy R, Kuh D, Wadsworth ME. Birthweight, postnatal growth and cognitive function in a national UK birth cohort. Int J Epidemiol. 2002;**31**(2):342-8.

Roberts CL, Lancaster PA. Australian national birthweight percentiles by gestational age. Med J Aust. 1999;**170**(3):114-8.

Rogowshi J. Measuring the cost of neonatal and perinatal care. Pediatrics 1999; **103**(1): 329-335.

Rotmensch S, Vishne T, Reece E, Linder N, Celentano C, Glezerman M, Sirotta L. Longterm outcome of infants exposed to multiple courses of betamethasone in-utero. Am J Obstet Gynecol 1999; **180**(1 part 2): S98.

Schmand B, Neuvel J, Smolders-de Haas H, Hoeks J, Treffers PE, Koppe JG. Psychological development of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome. Pediatrics. 1990;**86**(1):58-64.

Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer

M, Wright LL. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med. 2001;**344**(26):1966-72.

Schmidt PL, Sims ME, Strassner HT, Paul RH, Mueller E, McCart D. Effect of antepartum glucocorticoid administration upon neonatal respiratory distress syndrome and perinatal infection. Am J Obstet Gynecol. 1984;**148**(2):178-86.

Schutte MF, Treffers PE, Koppe JG, Breur W. The influence of betamethasone and orciprenaline on the incidence of respiratory distress syndrome in the newborn after preterm labour. Br J Obstet Gynaecol. 1980;**87**(2):127-31.

Schwarzenberg SJ, Kovacs A. Metabolic effects of infection and postnatal steroids. Clin Perinatol. 2002;**29**(2):295-312.

Shelton SD, Boggess KA, Murtha AP, Groff AO, Herbert WN. Repeated fetal betamethasone treatment and birth weight and head circumference. Obstet Gynecol. 2001;**97**(2):301-4.

SigmaPlot 2001 for Windows [computer program]. Version 7.101. SPSS Inc; 2001.

Simpson KN, Lynch SR. Cost savings from the use of antenatal steroids to prevent respiratory distress syndrome and related conditions in premature infants. Am J Obstet Gynecol. 1995;**173**(1):316-21.

Sinervo K, Lange I. Maternal and neonatal outcomes following single versus multiple courses

of corticosteroids. Society for Maternal-Fetal Medicine 2000 20th Annual Meeting, 2000.Miami Beach, Florida.

Skellern CY, Rogers Y, O'Callaghan MJ. A parent-completed developmental questionnaire: follow up of ex-premature infants. J Paediatr Child Health. 2001;**37**(2):125-9.

Skinner AM, Battin M, Solimano A, Daaboul J, Kitson HF. Growth and growth factors in premature infants receiving dexamethasone for bronchopulmonary dysplasia. Am J Perinatol. 1997;**14**(9):539-46.

Skoll A, Ferreira E, Pedneault L, Duchesne M, Letourneau G. Do we use too much antenatal betamethasone? J Obstet Gynaecol Can. 2002;**24**(4):330-4.

Sloboda DM, Newnham JP, Challis JR. Effects of repeated maternal betamethasone administration on growth and hypothalamic-pituitary-adrenal function of the ovine fetus at term. J Endocrinol. 2000;**165**(1):79-91.

Smith GN, Kingdom JC, Penning DH, Matthews SG. Antenatal corticosteroids: is more better? Lancet. 2000a;**355**(9200):251-2.

Smith LM, Qureshi N, Chao CR. Effects of single and multiple courses of antenatal glucocorticoids in preterm newborns less than 30 weeks' gestation. J Matern Fetal Med. 2000b;**9**(2):131-5.

Smolders-de Haas H, Neuvel J, Schmand B, Treffers PE, Koppe JG, Hoeks J. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: a 10- to 12-year follow-up. Pediatrics. 1990;**86**(1):65-70.

Spencer C, Pakarian F. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. BJOG. 2000;**107**(3):434-5.

Squires J, Bricker D, Potter L. Revision of a parent-completed development screening tool: Ages and Stages Questionnaires. J Pediatr Psychol. 1997;**22**(3):313-28.

Squires J, Potter L, Bricker D. The ASQ users guide for the Ages for Stages Questionnaires: a parent-completed, child-monitoring system. Baltimore: Paul H Brookes Publishing Co; 1995.

Stata [computer program]. Release 6.0. College Station (Texas): Stata Corporation; 1999.

Stephensen CB. Burden of infection on growth failure. J Nutr. 1999;**129**(2S Suppl):534S-538S.

Stewart JD, Sienko AE, Gonzalez CL, Christensen HD, Rayburn WF. Placebo-controlled comparison between a single dose and a multidose of betamethasone in accelerating lung maturation of mice offspring. Am J Obstet Gynecol. 1998;**179**(5):1241-7.

Stewart JD, Gonzalez CL, Christensen HD, Rayburn WF. Impact of multiple antenatal doses

of betamethasone on growth and development of mice offspring. Am J Obstet Gynecol. 1997;**177**(5):1138-44.

Taeusch HW Jr, Frigoletto F, Kitzmiller J, Avery ME, Hehre A, Fromm B, Lawson E, Neff RK. Risk of respiratory distress syndrome after prenatal dexamethasone treatment. Pediatrics. 1979;**63**(1):64-72.

Teramo K, Hallman M, Raivio KO. Maternal glucocorticoid in unplanned premature labor. Controlled study on the effects of betamethasone phosphate on the phospholipids of the gastric aspirate and on the adrenal cortical function of the newborn infant. Pediatr Res. 1980;**14**(4 Pt 1):326-9.

Terrone DA, Smith LG Jr, Wolf EJ, Uzbay LA, Sun S, Miller RC. Neonatal effects and serum cortisol levels after multiple courses of maternal corticosteroids. Obstet Gynecol. 1997;**90**(5):819-23.

The SAS System for Windows [computer program]. Release 8.02. Cary (NC, USA): SAS Institute Inc; 1999-2001.

Thompson LA, Fagan JF, Fulker DW. Longitudinal prediction of specific cognitive abilities from infant novelty preference. Child Dev. 1991;**62**(3):530-8.

Thorp J, Etzenhauser J, O'Connor M, Jones A, Jones P, Belden B, Hoffman E. Effects of phenobarbital and multiple-dose antenatal/postnatal steroid on developmental outcome at age

7 years. Am J Obst Gynecol 2001a; **185**(6 part 2): A42.

Thorp JA, Jones AM, Hunt C, Clark R. The effect of multidose antenatal betamethasone on maternal and infant outcomes. Am J Obstet Gynecol. 2001b;**184**(2):196-202.

Tin W, Fritz S, Wariyar U, Hey E. Outcome of very preterm birth: children reviewed with ease at 2 years differ from those followed up with difficulty. Arch Dis Child Fetal Neonatal Ed. 1998;**79**(2):F83-7.

Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O, Holden J. Neurotoxicity of glucocorticoids in the primate brain. Horm Behav. 1994 ;**28**(4):336-48.

Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, Farrell PM. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. I. Hippocampus. Brain Res Dev Brain Res. 1990;**53**(2):157-67.

Vermillion ST, Bland ML, Soper DE. Effectiveness of a rescue dose of antenatal betamethasone after an initial single course. Am J Obstet Gynecol. 2001;**185**(5):1086-9.

Vermillion ST, Soper DE, Newman RB. Neonatal sepsis and death after multiple courses of antenatal betamethasone therapy. Am J Obstet Gynecol. 2000a;**183**(4):810-4.

Vermillion S, Soper D, Newman R. Neonatal sepsis and death after multiple doses of antenatal betamethasone. Society for Maternal-Fetal Medicine 2000 20th Annual Meeting,

2000b.Miami Beach, Florida.

Vermillion ST, Soper DE, Chasedunn-Roark J. Neonatal sepsis after betamethasone administration to patients with preterm premature rupture of membranes. Am J Obstet Gynecol. 1999;**181**(2):320-7.

Walfisch A, Hallak M, Mazor M. Multiple courses of antenatal steroids: risks and benefits. Obstet Gynecol. 2001;**98**(3):491-7.

Welberg LA, Seckl JR, Holmes MC. Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behaviour. Neuroscience. 2001;**104**(1):71-9.

Wilcox A, Skjaerven R, Buekens P, Kiely J. Birth weight and perinatal mortality. A comparison of the United States and Norway. JAMA. 1995;**273**(9):709-11.

Willet KE, Jobe AH, Ikegami M, Kovar J, Sly PD. Lung morphometry after repetitive antenatal glucocorticoid treatment in preterm sheep. Am J Respir Crit Care Med. 2001;**163**(6):1437-43.

Wright L, Fanaroff A, Poole K, Carlo W, Vohr B, Ehrenkranz R, Stoll B, McDonald S. Repeat courses of antenatal steroids (R-ANS): risks and benefits. Pediatric Academic Societies Annual Meeting, 2001.Baltimore, Maryland, USA.