A study of the management of group B streptococcal colonisation in pregnant women: Benefits and risks of preventative modalities

A thesis presented in fulfilment of the requirements for the degree of

Doctor of Philosophy, Midwifery

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Centre for Midwifery, Child and Family Health

Faculty of Health

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Certificate of original authorship

I, Kathryn Tina Braye, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, Midwifery, in the Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution. This research is supported by the Australian Government Research Training Program.

Signature:

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Acknowledgements

It is unbelievable to me that I am sitting here, very close to my 60th birthday and just after my 36th wedding anniversary writing a dedication in a PhD thesis. My PhD thesis no less. I left school at 16, barely understanding the significance of a university (although knowing I wanted to continue my education). Well I've done that!

I am dedicating this PhD thesis to myself, as well as my parents. It has been a long haul and I have finally made it. I feel very proud. I would like to honour all mothers and babies whose birth journeys have been part of this work. I would like to honour my parents too, Joyce and Raymond Perry. My mother, Joyce died way too young, the same age as I am now. My babies were small, and she never knew I would still be studying when they were all grown. My dad, Raymond, died just before I started PhD studies, in the days before he died, I told him I was going to be a doctor and complete a PhD. I'm not sure he completely understood but actually it wouldn't matter if I had told him I was going to support a woman to birth her baby, walk 720km to Santiago de Compostela, or fly to the moon and back, he was always so proud of his little girl.

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One of my core values (thank you Carolyn and Ilze) is making a positive difference. Mothers want the best for their babies, no matter what their age. A long-standing vision throughout the period of my candidature was that the work in this thesis would add to the body of knowledge around the complex issue of Group B streptococcus (GBS) risk in pregnancy and enable and empower women to make (sometimes difficult) decisions and decide on the level of risk they are prepared to embrace.

Dedication

To my parents, Joyce and Raymond Perry

Scholarships and awards during candidature

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Presentations at conferences/meetings/reviews/activities associated with this thesis

- 2015: **Braye, K**., Catling, C., Ferguson, J., Foureur, M. Group B streptococcus: Are we doing more harm than good? *19th Biennial ACM Conference, Gold Coast, Queensland*. Poster presentation
- 2015: **Braye, K.,** Catling, C., Ferguson, J., Foureur, M. To douche or not to douche? Chlorhexidine for group B streptococcus (GBS) in otherwise well, healthy pregnant women. *Research Student Forum. University Technology Sydney.* Oral presentation
- 2015: **Braye, K.,** Group B streptococcus: Are we doing more harm than good? Multi- disciplinary meeting. Department of Maternity & Gynaecology John Hunter Hospital, Newcastle, New South Wales. Oral presentation
- 2015: **Braye, K**. Group B streptococcus: Are we doing more harm than good? *Research Students Forum. University of Technology Sydney.* Oral presentation
- 2015: **Braye, K**. Are current guidelines for group B streptococcus causing iatrogenic microbial and epigenetic harm for short term gain? *Australian College of Midwives*, *NSW Branch annual conference, Leura, New South Wales.* Oral presentation
- 2015: **Braye, K.** Group B streptococcus: Are we doing more harm than good? *Belmont Midwifery Group Practice midwives*. *Belmont. New South Wales* Oral presentation. Invited speaker
- 2016: **Braye, K**. Group B streptococcus: Are we doing more harm than good? *Hunter New England infectious diseases physicians and microbiologists. Newcastle. New South Wales* Oral presentation. Invited speaker
- 2016: **Braye, K**. Insights of a 3rd year PhD candidate. *Research Students Forum. University of Technology Sydney.* Oral presentation

- 2016: **Braye, K.** Group B streptococcus, are we doing more harm than good? Informing the narrative on intrapartum prophylaxis. *Australian College of Midwives. Webinar production.* Initial research findings**.** Invited speaker
- 2016: **Braye, K.**, Are current guidelines for Group B streptococcus causing iatrogenic microbial and epigenetic harm for short term gain? *11th International normal labour and birth conference, Sydney.* Oral presentation
- 2016: **Braye, K**. Stage one assessment and presentation in fulfilment of the requirements for the degree of Doctor of Philosophy, Midwifery. *University of Technology Sydney.* Written and oral presentation
- 2017: **Braye, K**. Why increase the dose of intrapartum antibiotic prophylaxis for maternal GBS colonisation: Are we doing more harm than good? *Virtual international day of the midwife conference, Sydney.* On-line presentation
- 2017: **Braye, K**. Group B streptococcus, are we doing more harm than good? Informing the narrative on intrapartum prophylaxis. Initial research findings. *31st ICM triennial congress, Toronto, Canada.* Oral presentation
- 2017: **Braye, K**. Group B streptococcus, are we doing more harm than good? Informing the narrative on intrapartum prophylaxis. Initial research findings. *Meeting of Hunter New England Neonatology clinicians*. *Newcastle, New South Wales*. Oral presentation. Invited speaker
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- 2017: **Braye, K.** Group B streptococcus, are we doing more harm than good? Informing the narrative on intrapartum prophylaxis. Initial research findings. *The third Australian nurses and midwives conference. Newcastle, New South Wales.* Oral presentation

- 2017: **Braye, K**. The truth is out there! Informing the narrative on intrapartum prophylaxis for GBS management. *The 20th Australian college of midwives national conference. Adelaide, South Australia.* Oral presentation
- 2017: **Braye, K**. What are the maternal Group B streptococcal colonisation rates and GBS management experience of a cohort of pregnant women and their babies 2006- 2013? *Research Students Forum*, *University of Technology Sydney.* Oral presentation
- 2018: **Braye, K.** Review of *Microbirth online GBS course*. Invited reviewer
- 2018: **Braye, K**. Optimising maternal wellbeing. *Australian College of Midwives Victoria Branch. Annual update*. Oral presentation. Invited speaker
- 2018: **Braye, K.** Group B streptococcus (GBS) prophylaxis: Does it cause iatrogenic microbial harm for minimal short term gain? *Update for clinicians. Alice Springs.* On-line presentation. Invited speaker
- 2018: **Braye, K.** The Group B Strep dilemma: Are we doing more harm than good? 3 minute thesis (3MT) finalist. *Research Students Conference. University of Technology Sydney*
- 2018: **Braye, K.** Case study discussion New Zealand College of Midwives. Rotorua, New Zealand
- 2018: **Braye, K.** Stage two assessment and presentation in fulfilment of the requirements for the degree of Doctor of Philosophy, Midwifery. *University of Technology Sydney.* Written presentation and discussion
- 2018: **Braye, K.** Epidemiology of early-onset sepsis in a local health district 2006- 2016. *Annual update for Sydney Midwifery Educators*. *University of Technology Sydney*
- 2018: **Braye, K.** Epidemiology of early-onset sepsis in a local health district 2006- 2016. *University of Technology Sydney. Research Students Conference*

- 2019: **Braye, K.** Group B streptococcal screening, intrapartum antibiotic prophylaxis and neonatal early-onset infection rates in the Hunter New England local health district: 2006-2016. *The fourth Australian nurses and midwives conference, Newcastle, New South Wales*. Oral presentation
- 2019: **Braye, K.** Presented by Scarf, V. Antibiotic prophylaxis for women who are screened positive for GBS colonisation: compliance with guidelines. *The International Normal Labour and Birth Conference, Grange over Sands, Cumbria, UK*. Oral presentation

Publications in peer reviewed journals during candidature

This thesis contains four manuscripts outlined below, three published and one under peer review. The manuscripts have individual statements of authors' contributions to each manuscript. The CRediT Taxonomy as used by the journal, PLoS ONE, has been modified and used as a template to describe each author's individual contributions (PLoS ONE).

Area of contribution	Role Definition
Conceptualisation	Ideas; formulation or evolution of overarching research goals and aims
Data curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesize study data
Funding acquisition	Acquisition of the financial support for the project leading to this publication
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection
Methodology	Development or design of methodology; creation of models
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs

Visualisation	Preparation, creation and/or presentation of the published work, specifically visualisation/data presentation
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation)
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages

Author's contributions to published manuscripts

Publication 1

Braye, K., Ferguson, J., Davis, D., Catling, C., Monk, A., Foureur, M. 2019. 'Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B streptococcal infection: An integrative review'. *Women and Birth* vol.31 no.4 pp. 244-253

Area of contribution	Estimated percentage of contribution
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Data Curation	KB 80%, EP 20%
Formal Analysis	KB 60% MF 40%
Methodology	KB 70%, MF 20%, AM 10%
Supervision	MF 70%, CC 20%, DD 10%, JF 10%, AM 10%
Validation	KB 50%, MF 40%, AM 5%, JF 5%
Visualisation	KB 50%, MF 30%, CC 10%, DD 5%, JF 5%
Writing – Original Draft Preparation	KB 100%
Writing – Review & Editing	KB 50%, MF 30%, CC 10%, JF 10%

Publication 2

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Area of contribution	Estimated percentage of contribution
Conceptualisation	KB 60%, JF 40%
Data Curation	KB 50%, EP 30%, MJ 10%, JF 10%
Formal Analysis	KB 60%, MJ 40%
Methodology	KB 40%, JF 30%, MF 15%, MJ 5%,
Supervision	JF 50%, MF 40%, KD 10%,
Validation	KB 30%, MF 30%, KD 5%, EP 5%, JF 30%
Visualisation	KB 60%, EP 20%, MF 20%
Writing – Original Draft Preparation	KB 100%
Writing – Review & Editing	KB, 40%, JF 30%, MF 20%, KD 5%, MJ 5%,

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Braye, K., Foureur, M., de Waal, K., Jones, M., Putt, E., Ferguson, J. 2019, 'Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-onset infection rates in an Australian local health district. *PLoS ONE* vol.14 no.4

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Conceptualisation	KB 70%, MF 30%
Data Curation	KB 50%, MJ 10%, EP 30%, JF 10%
Formal Analysis	KB 60%, MJ 40%
Methodology	KB 50%, MF 30%, MJ 10%, JF10%
Supervision	JF 50%, KW, 10%, MF 40%
Validation	KB 50%, MF,10%, KD 5%, MJ 10%, EP 5%, JF 20%
Visualisation	KB 70%, MJ 30%, MF 10%
Writing – Original Draft Preparation	KB 100%
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Formal Analysis	KB 60%, JB 40%
Methodology	KB 50%, MF 20%, JB 30%
Supervision	MF 100%
Validation	MF 70%, JB 30%
Visualisation	KB 50%, MF 30%, JB 20%
Writing – Original Draft Preparation	KB 100%
Writing – Review & Editing	KB 50%, MF 30%, JB 20%

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Abbreviations

Abbreviation	Term
3MT	Three minute thesis
ACM	Australian College of Midwives
ACOG	American College of Obstetricians and Gynaecologists
EOGBS	Early-onset group B streptococcal infection
EOS	Early-onset sepsis
g	Grams
GBS	Group B streptococcus
HMO	Human milk oligosaccharides
HNE	Hunter New England
HNELHD	Hunter New England Local Health District
HREC	Human Research Ethics Committee
IAP	Intrapartum Antibiotic Prophylaxis
IV	Intravenous
JHH	John Hunter Hospital
LHD	Local Health District
LMC	Lead Maternity Carer
LOGBS	Late-onset group B streptococcus
NICE	National Institute of Health Care and Excellence
NZCOM	New Zealand College of Midwives
PCR	Polymerase chain reaction
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists

RCOG	Royal College of Obstetricians and Gynaecologists
ROM	Release or rupture of membranes (the term release is preferred by the author of this work as it aligns with my preference for woman friendly terminology)
RSF	Research student forum
SROM	Spontaneous release or rupture of membranes
UK	United Kingdom
USA	United States of America
UTS	University of Technology Sydney

Definitions

Term	Definition
Adequate IAP	Common definition: ≥4 hours of IAP before birth of the baby
Bacteria	Microscopic living organisms, usually one-celled, that can be found everywhere. They can be beneficial or pathogenic
Blood culture	A blood test to detect and identify bacteria in the blood
Cerebrospinal fluid	A normally sterile body fluid found within and surrounding the brain and spinal cord
Colonisation	The presence of bacteria on a body surface, mucous membrane or body niche without causing disease in the person
Commensal	Living in a relationship in which one organism derives food or other benefits from another organism without hurting or helping it
Dysbiosis	An imbalance between the types of organism present in the microbiome
Early-onset	Within 72 hours of birth
Early-onset GBS sepsis	Sepsis arising within 72 hours caused by the GBS bacteria as shown by a positive blood or cerebrospinal fluid culture
Early-onset sepsis	Sepsis arising within 72 hours of birth. Generally microbiological culture-confirmed events are included
Eligible pregnancy	A woman's pregnancy that reaches ≥35 weeks gestation and therefore eligible for universal GBS screening. The term pregnancy rather than woman was used as many women had more than one pregnancy over the study period
Eligible preterm	A baby ≥35 weeks, but <37 weeks gestation, whose mother is therefore eligible for universal GBS screening
Eligible term baby	A baby ≥37 weeks, whose mother is therefore eligible for universal GBS screening

GBS management	The medical intervention for the prevention or reduction of the likelihood of having a baby with EOGBS. The management involves selecting women who are deemed most at risk and then offering IAP. After birth women may be asked to remain in hospital so the baby can be observed for signs of infection
Group B streptococcus (GBS)	Group B streptococcus GBS also known as *Streptococcus agalactiae* is a commensal bacterium forming part of the human microbiota or microbiome colonising the gastrointestinal and genitourinary tract
High-income country	The World Bank defines a high-income country as one that has a gross national income per capita exceeding $12,056 (2018 numbers)
IAP in accordance with Hunter New England (HNE) guidelines 2003-2018	IAP for at least 4 hours, repeated 4-hourly until birth
Iatrogenic	A state of ill health or adverse effect caused by medical treatment
Immunoglobulin IgG	Immunoglobulin G (IgG) is a type of antibody. It is the most common antibody found in blood circulation
Intrapartum	Occurring or provided during the process of labour and birth
Intrapartum Antibiotic Prophylaxis	Aims to reduce the likelihood of vertical transmission of maternal Group B Streptococcus and therefore prevent EOGBS in the neonate

Maternal GBS colonisation	GBS bacteria form part of the human microbiota or microbiome colonising the gastrointestinal and genitourinary tract of up to 30% of healthy human adults (asymptomatic carriers), including pregnant women
Microbiome	The genetic make-up of the whole of the microbiota: i.e. the genes from bacteria, eukaryotes, archaea and viruses
Microbiota	Microorganisms that are found within a specific environment
Neonatal	A newborn infant, or neonate under 28 days of age
Neonatal GBS colonisation	GBS bacteria may be passed from mother to her baby in utero prior to or during birth as part of a baby's founding microbiome, this leads to neonatal GBS colonisation which is usually asymptomatic and harmless
Pathogenic bacteria	Bacteria that cause disease
Prophylaxis	Measures designed to preserve health and prevent disease
Screening	The systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action
Screening for maternal GBS colonisation	Selection of women whose babies may benefit from IAP; screening can be universal or based on certain risk factors
Sepsis	A potentially life-threatening condition caused by the body's response to an infection. The body normally releases chemicals into the bloodstream to fight an infection. Sepsis occurs when the body's response to these chemicals is out of balance, triggering changes that can damage multiple organ systems
Symbiosis	Interaction between two different organisms living in close physical association, typically to the advantage of both

Therapeutic	Treats, prevents or alleviates symptoms of disease
Treatment	Medical care given to a patient for an illness or injury

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Thesis Abstract

Background

In high-income countries ~ 30% of women and their babies are exposed to intrapartum antibiotic prophylaxis (IAP), for the prevention of neonatal early-onset group B streptococcal infection (EOGBS). This intervention aims to lower the risk of EOGBS but IAP is not without its own risks. Emerging evidence of the potential impact of antibiotics on the maternal/baby's microbiome is concerning. Evidence of the effectiveness of IAP and its application was needed to establish if current management was the optimum strategy for the reduction of EOGBS.

Purpose

To establish the impact of the normally commensal bacteria, group B streptococcus (GBS), on rates of neonatal early-onset sepsis (EOS) in one large health district; to describe local management of maternal GBS colonisation; and assess clinicians' adherence to GBS guidelines.

Methods

An integrative literature review was undertaken to examine the effectiveness and implications of IAP. Subsequently, two retrospective observational studies explored temporal trends in EOS, GBS management, and EOGBS, in one large health service over 11 years, using logistic regression and covariates for potential modifiers. A third study analysed a subset of women using ordered logistic regression. A 5% margin of error and a 95% confidence interval was used throughout.

Results

This research found management of GBS risk was sub-optimal. Clinical trials reported high effectiveness, but they had major methodological flaws. Observational studies showed poor adherence to GBS management. Whilst scant consideration was given to short-term risks; long-term consequences were not addressed.

In this work, group B streptococcus was the most common cause of EOS in term babies.

All cause EOS reduced significantly over time; EOGBS reduced but this did not reach statistical significance. Analysis of blood culture utilisation revealed intensity of surveillance did not change. Eighteen babies were diagnosed with EOGBS (0.19/1000 live births), ten of these were term. Seven were born to mothers screened negative for GBS. No evidence of difference in rates of EOGBS between screened and unscreened pregnancies was found. Prophylaxis in accord with local guidelines was received by one third of eligible women. Most missed opportunities for IAP were unavoidable, and mainly due to lack of time between admission for labour and birth. Despite this, rates of EOGBS were extremely low at 0.19/1000 live births.

Conclusion

Evidence for screening and IAP is poor. Current management has serious limitations, and risks may outweigh benefit. Overall, management of GBS risk warrants urgent reconsideration. Research is needed to understand factors, other than IAP, that may be contributing to protection from EOGBS.