The evidence to inform our practice for the care of the peri-viable fetus

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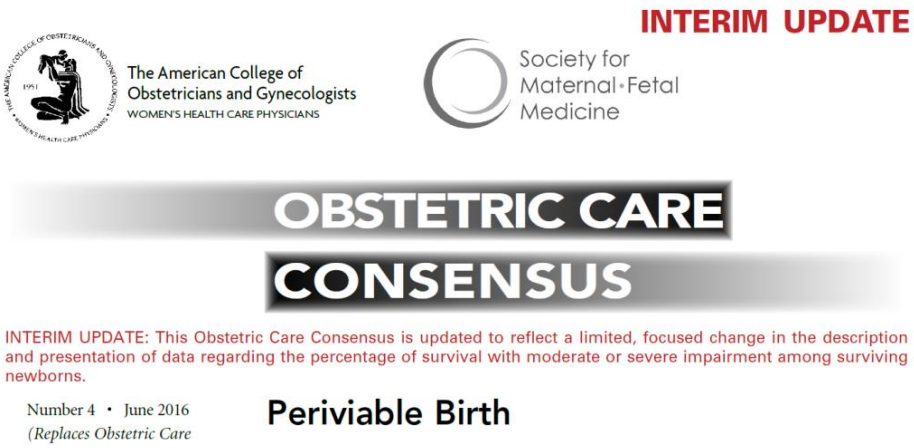
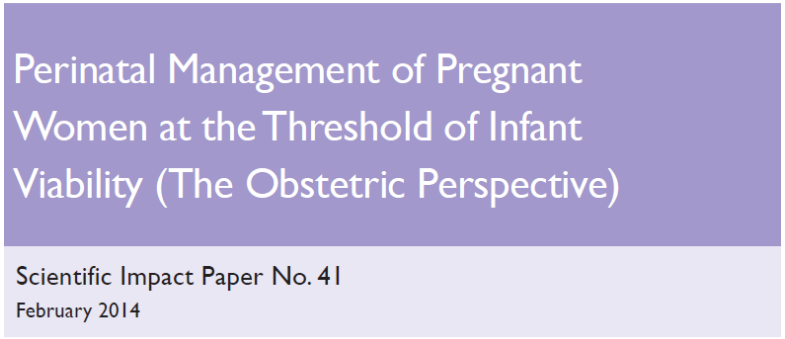
Peri-viable Birth

- Threshold of viability 23^{+0}-24^{+6} weeks to 20^{+0}-25^{+6} weeks
- Poses significant medical and ethical challenges
- A grey zone where the line between patient (parent) autonomy and medical futility/success may be blurred

- Limited evidence to guide practice
- Changing and evolving field
- National consensus statements of expert opinion

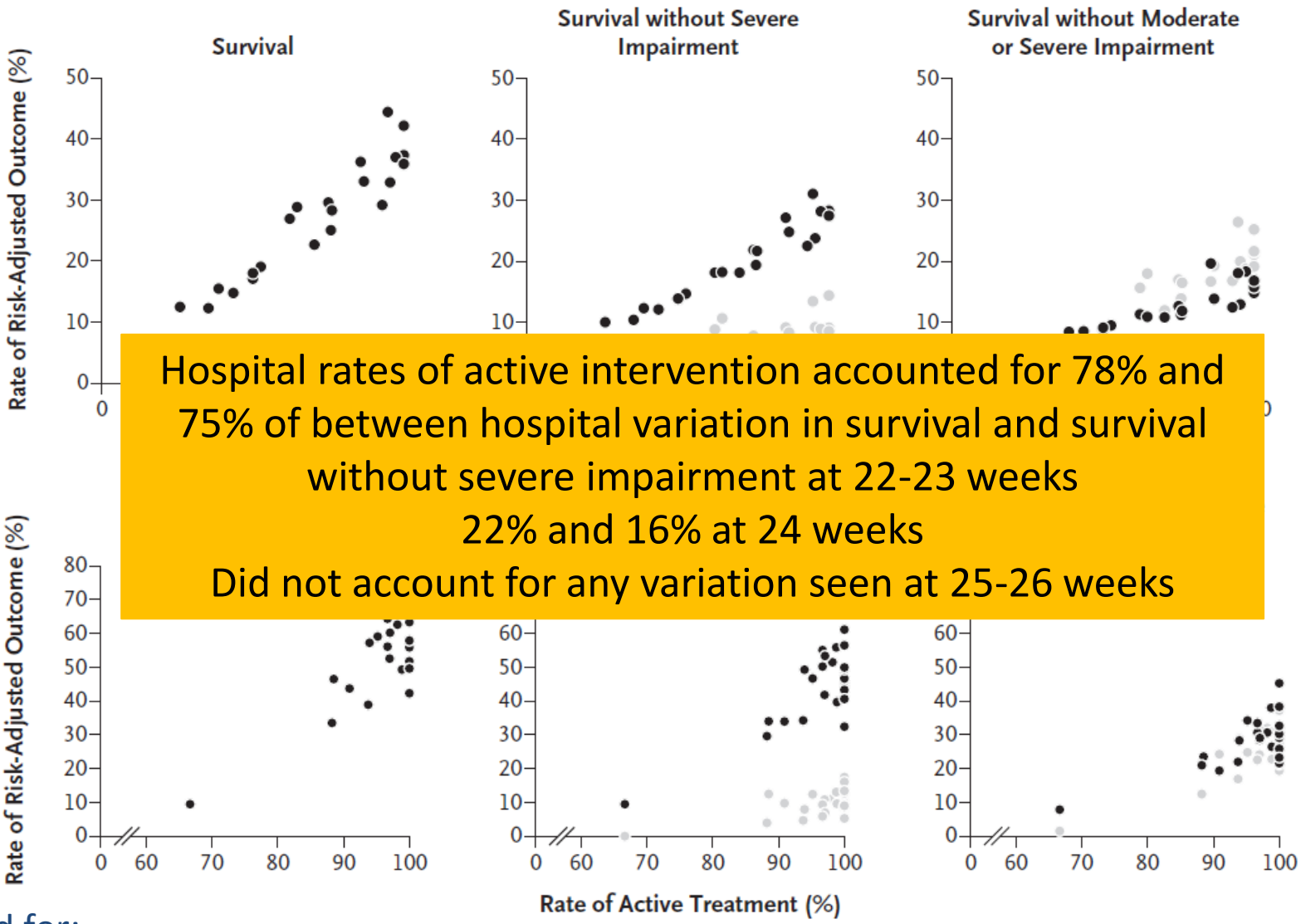




Do outcomes reflect hospital practice?

23 weeks

24 weeks



Hospital rates of active intervention accounted for 78% and 75% of between hospital variation in survival and survival without severe impairment at 22-23 weeks
22% and 16% at 24 weeks
Did not account for any variation seen at 25-26 weeks

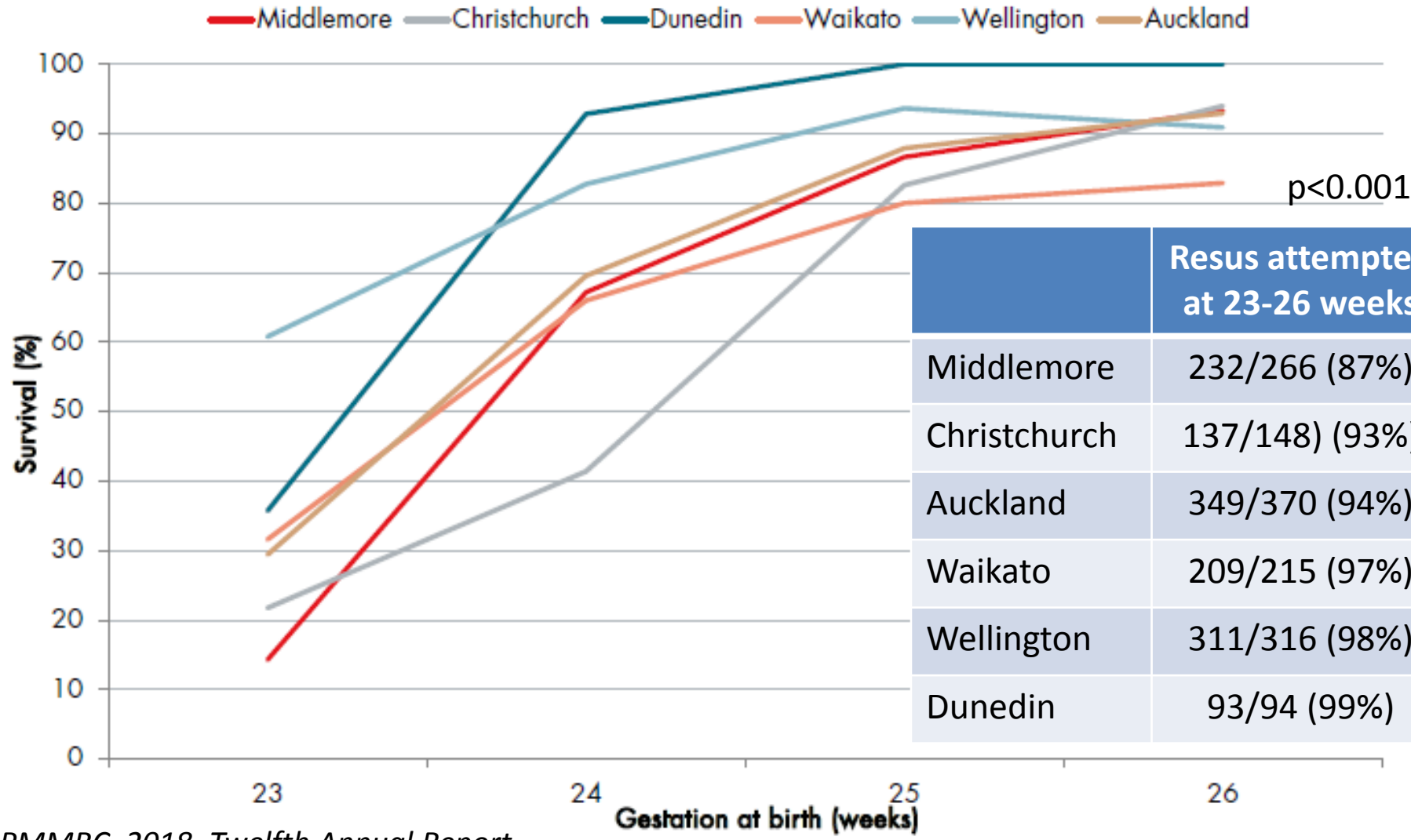
Model adjusted for:

- *Birthweight, sex, plurality, 1-minute Apgar score*
- *Mother's age, race, ethnic group, private health insurance, prenatal care*
- *Antenatal glucocorticoids, maternal hypertension, insulin-dependent diabetes and chorioamnionitis*

Rysavy NEJM 2015;372 (19):1801-1811

Variation in practice and outcomes in New Zealand?

Perinatal and Maternal Mortality Review Committee
He matenga ohorere, he wairua uiui, wairua mutungakore



p<0.001

	Resus attempted at 23-26 weeks
Middlemore	232/266 (87%)
Christchurch	137/148) (93%)
Auckland	349/370 (94%)
Waikato	209/215 (97%)
Wellington	311/316 (98%)
Dunedin	93/94 (99%)

PMMRC. 2018. Twelfth Annual Report
Perinatal and Maternal Mortality Review Committee: Reporting Mortality 2016. Wellington: HQSC

Taking a more proactive approach

What can obstetricians and midwives modify to optimise outcome?

- Antenatal corticosteroids
- Antenatal magnesium sulphate
- Mode of birth
- Intrapartum care
- Timing of cord clamping

What is the evidence?

Antenatal Corticosteroids

Standard of care for women at risk of preterm birth <35 weeks

World Health Organization · RANZCOG · ACOG · Royal College of Obstetricians & Gynaecologists

RCTs not included <24 weeks and limited numbers <26 weeks

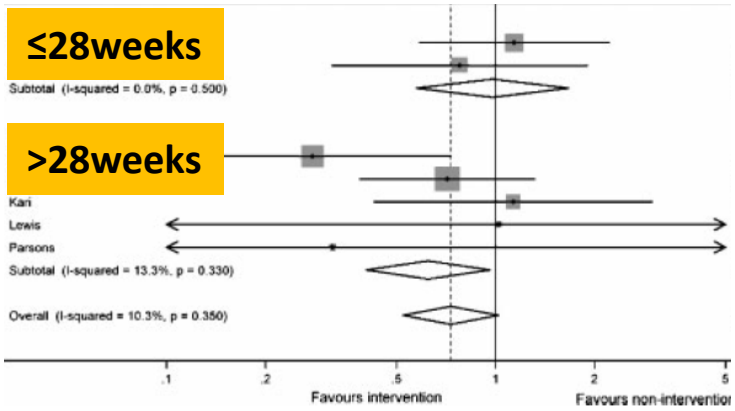
Meta-analysis 2011

- 9 trials (n=1118) including recruits <26 weeks
- ANCS had no effect on death or RDS ≤28 weeks

- No apparent effect at lower gestational ages or no evidence of effect?

Onland *Am J Perinatol* 2011; 28 (1): 33-43

Fetal or Neonatal Death



- Cohort study of 10 541 infants delivered at 22-25 weeks with BW 401-1000g
- 1993-2009 at 23 US centers in NICHD Neonatal Research Network

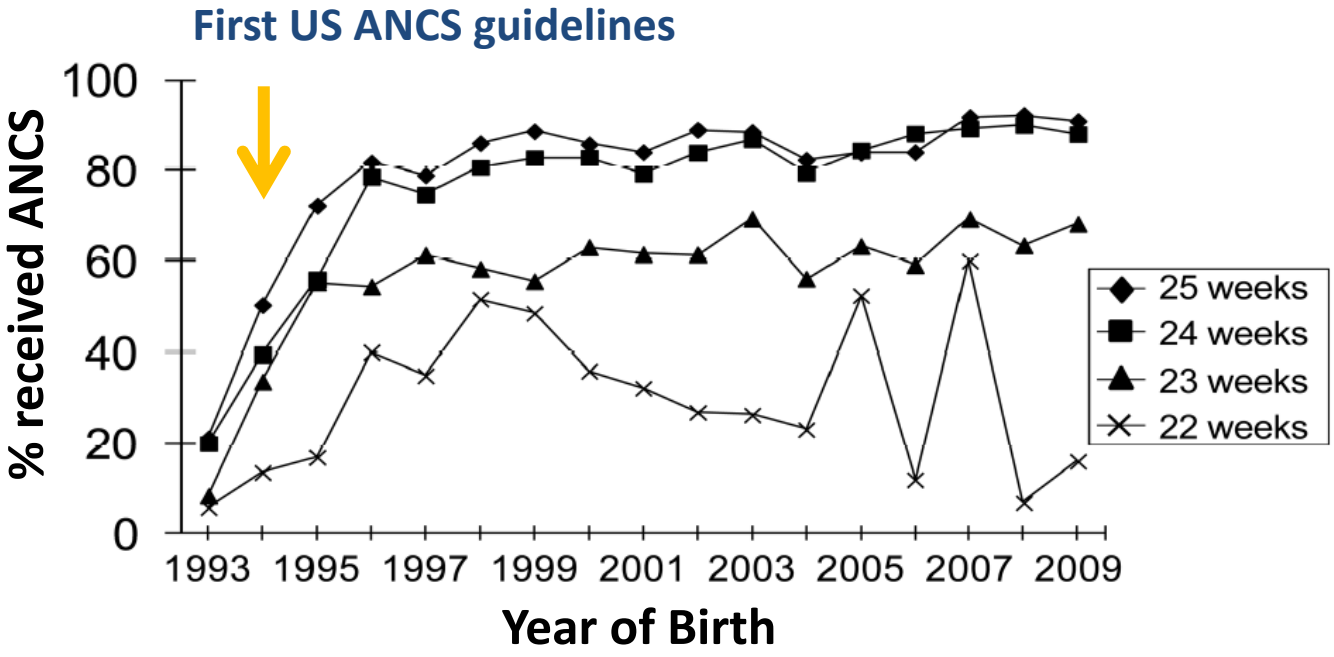
- 18-22 month neurodevelopmental assessment blinded to ANCS use
- Primary outcome: mortality or severe neurodevelopmental impairment (NDI) at 18-22m

Carlo *JAMA* 2011; 306 (21): 2348-2358

74% received one or more doses of corticosteroid

5691 survived to 18-22 months

87% NDI assessment



GA	Rate of death or NDI	Adjusted OR*	95% CI
All	64.2% vs 81.5%	**0.60**	0.53-0.68
22 weeks	90.2% vs 93.1%	0.80	0.29-2.21
23 weeks	83.4% vs 90%	**0.58**	0.42-0.8
24 weeks	68.4% vs 80.3%	**0.62**	0.49-0.78
25 weeks	52.7% vs 67.9%	**0.61**	0.5-0.74

**Adjustment for: maternal age, marital status, race, diabetes, hypertension/preeclampsia, PPROM, APH, mode of delivery, multiple gestation, gender, centre*

Carlo *JAMA* 2011; 306 (21): 2348-2358

Neurodevelopmental impairment in survivors at age 18-22 months

1 or more of the following: a Bayley II MDI <70, PDI score <70, moderate to severe cerebral palsy, blindness (no useful vision in either eye), or deafness (functional hearing impairment with aids in both ears) or after 2005: Bayley III cognitive composite score <70, gross motor function level of ≥2, blindness (some or no useful vision in either eye), or deafness (functional hearing impairment)

GA	Rate of NDI	Adjusted OR*	95% CI
All	38.8% vs 49.2%	**0.83**	0.7-0.99
23 weeks	55% vs 56.2%	1.11	0.71-1.71
24 weeks	41.9% vs 51.9%	0.80	0.60-1.08
25 weeks	33.6% vs 43.5%	0.81	0.62-1.04

Subgroup analysis:

Exposure to ANCS lowered: hospital mortality, mortality at 18-22 months, mortality or NDI at 18-22 months in singleton & multiple births, partial & full ANCS, betamethasone & dexamethasone, mothers with & without diabetes, all durations of PPROM, with or without APH, vaginal delivery or CS, male or female, non-SGA, all racial/ethnic groups

No effect of ANCS seen: SGA, preeclampsia (death & NDI)

Carlo *JAMA* 2011; 306 (21): 2348-2358

Antenatal corticosteroids should be used for same indications & same dosing regime as other preterm births if planning active intervention at 23^{+0} – 24^{+6} weeks

Magnesium Sulphate

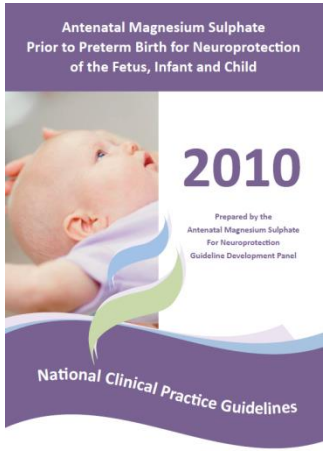
Cochrane Review 2010

4 trials for neuroprotection – range for inclusion <30, 24-32, <33w, <34 weeks

Primary outcomes	RR (95% CI)	Number of trials; participants
Death or cerebral palsy	**0.85 (0.74 to 0.98)***	four trials; 4446 infants
Death (fetal and later)	0.95 (0.80 to 1.12)	four trials; 4446 infants
Cerebral palsy	**0.71 (0.55 to 0.91)***	four trials; 4446 infants
Any neurological impairment	1.03 (0.87 to 1.21)	one trial; 1255 infants
Death or substantial gross motor dysfunction	0.84 (0.71 to 1.00)	three trials; 4387 infants

**significantly in favour of magnesium sulphate*

Doyle *Cochrane Systematic Review* 2009; CD004661



No subgroup analysis <30 weeks

Small numbers at peri-viable gestation

Recommended standard of care for women delivering at <30-32 weeks

World Health Organization

ACOG

Royal College of Obstetricians & Gynaecologists

https://www.adelaide.edu.au/arch/antenatalMagnesiumSulphateGuidlines.pdf

Magnesium sulphate should be used for same indications & same dosing regime as other preterm births if planning active intervention at 23^{+0} – 24^{+6} weeks

Mode of Birth

Harm or Benefit?

No good quality RCT evidence

Royal College of Obstetricians & Gynaecologists

World Health Organization

Routine CS to improve preterm outcome not recommended, regardless of cephalic or breech presentation

ACOG

Routine CS for peri-viable delivery not recommended, no comment on preterm breech presentation

Case dependent

Obstetric and maternal indicators (not fetal)

e.g. fulminating preeclampsia, APH, chorioamnionitis, transverse lie

Mode of Birth for Breech

- Systematic review and meta-analysis
- 23^{+0} – 27^{+6} weeks
- Singleton infants
- Actively resuscitated
- 1994 onwards (standard use of ANCS)

- 15 studies, 12 335 infants (1320 at 23^{+0}-24^{+6} weeks)
- Observational cohort and case-control studies, 1 RCT
- GRADE quality of evidence ‘low’

- Primary outcomes – death and severe IVH

Grabovac *BJOG* 2017 Sep 18. doi: 10.1111/1471-0528.14938 Epub

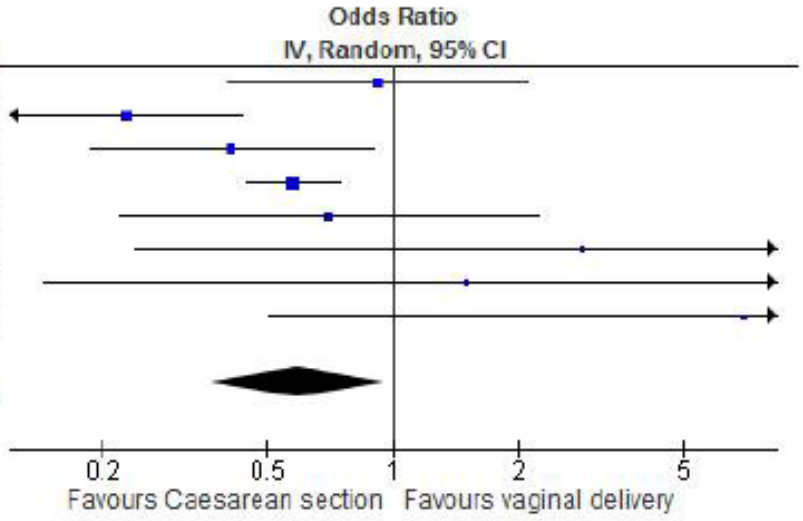
Death before discharge/until 6 months CGA $23^{+0} – 27^{+6}$ weeks

Study or Subgroup	CS Events	CS Total	VD Events	VD Total	Weight	Odds Ratio IV, Random, 95% CI
†Kayem 2015******	20	97	11	50	15.8%	0.92 [0.40, 2.11]
†Herbst 2007******	31	324	20	63	19.3%	0.23 [0.12, 0.43]
Thomas 2016*****						0.89]
§Tucker Edmonds 2015*****						0.74]
Stohl 2011*****						2.24]
†Bruey 2015****						33.90]
†Ghi 2010****						15.46]
Richmond 2002****						97.75]
Total (95% CI)		**1530**		**508**	**100.0%**	**0.59 [0.36, 0.95]**
Total events	451		219			

Heterogeneity: Tau² = 0.20; Chi² = 15.46, df = 7 (P = 0.03); I² = 55%

Test for overall effect: Z = 2.16 (P = 0.03)

30% vs 43%
OR 0.59, 95% 0.36-0.95
NNT=8



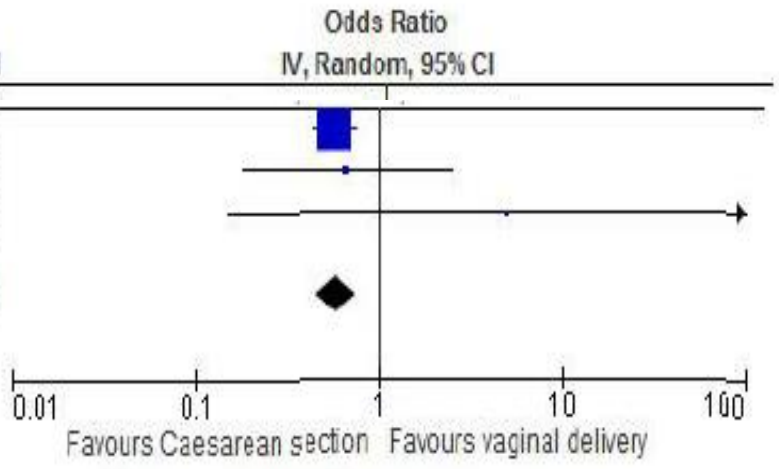
Death before discharge/until 6 months CGA $23^{+0} – 24^{+6}$ weeks

Study or Subgroup	CS Events	CS Total	VD Events	VD Total	Weight	Odds Ratio IV, Random, 95% CI
§Tucker Edmonds 2015*****	352	958	156	310	95.8%	0.57 [0.44, 0.74]
Thomas 2016*****						0]
Richmond 2002****						9]
Total (95% CI)						5]
Total events						

Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 2 (P = 0.47); I² = 0%

Test for overall effect: Z = 4.18 (P < 0.0001)

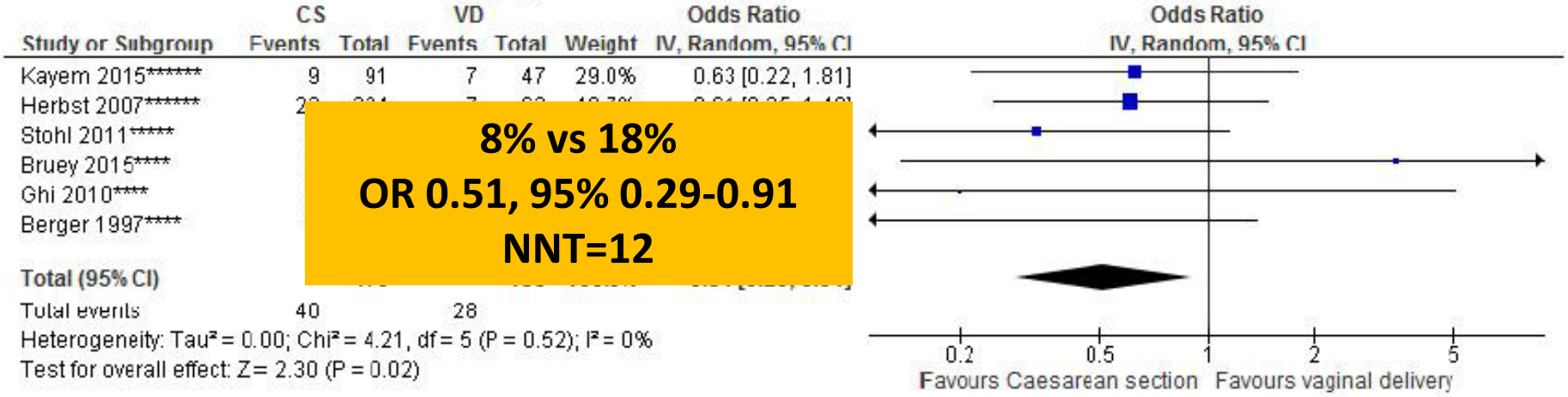
38% vs 51%
OR 0.58, 95% 0.45-0.75
NNT=7



Odds of death were not significantly different between infants born by CS and vaginal birth at $25^{+0} – 26^{+6}$ or $27^{+0} – 27^{+6}$ weeks

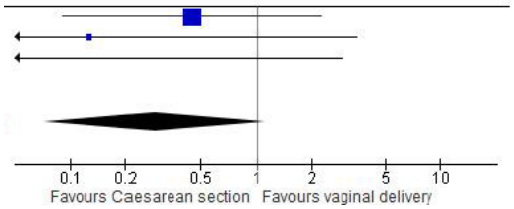
Grabovac *BJOG* 2017 Sep 18. doi: 10.1111/1471-0528.14938

Severe intraventricular haemorrhage 23^{+0} – 27^{+6} weeks

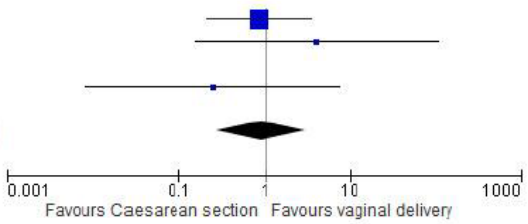


8% vs 18%
OR 0.51, 95% 0.29-0.91
NNT=12

IVH 25^{+0} – 26^{+6} weeks



IVH 27^{+0} – 27^{+6} weeks



No separate data for 23^{+0} – 24^{+6} weeks but non-significant at later ages suggesting effect is greatest in lower gestational age group

Analysis by birthweight

Death only significant at BW 500-999g

16% vs 44%, OR 0.22, 95%CI 0.14-0.36

Maternal outcomes

Very limited, 67% classical CS

Grabovac *BJOG* 2017 Sep 18. doi: 10.1111/1471-0528.14938

? Recommend CS for breech if planning active intervention at 23^{+0}–24^{+6} weeks ?

Intrapartum Care (no evidence specific to peri-viable birth)

Delivery in a unit with neonatal intensive care

Effect only significant <29 weeks

Adjusted Odds Ratios (95% CI) logistic regression to predict mortality and morbidity

Variable	Death in NICU	Severe (≥ grade 3) intraventricular hemorrhage	Patent ductus arteriosus	Respiratory distress syndrome	Nosocomial infection
Outborn					
Yes	1.7 (1.2, 2.5)*	2.2 (1.5, 3.2)*	1.6 (1.2, 2.1)*	4.8 (3.6, 6.3)*	2.5 (1.9, 3.3)*
No	1	1	1	1	1

- Improved outcomes for active intervention
- Optimise care even if planning comfort care only

Chien *Obstet Gynecol* 2001;98:247-252, Lee *AJOG* 2003;188(3):617-622

Intrapartum antibiotics

ACOG RANZCOG Royal College of Obstetricians & Gynaecologists

- Preterm birth <37 weeks is a risk factor for early onset neonatal GBS infection
- Universal screening or risk factor approach start antibiotics in PTL, +/-swabs

Fetal monitoring No evidence that fetal heart rate monitoring is of benefit during labour for peri-viable infants. Continuous monitoring may be appropriate for those planning active intervention including CS for a pathological CTG.

Royal College of Obstetricians & Gynaecologists

- Intermittent auscultation of value to neonatal team.

Labour and delivery

- Analgesia plan, minimise trauma, decision plan for CS (cord prolapse, fetal distress)

Timing of Cord Clamping

Harm or Benefit

Benefits for term and late preterm infants have led to practice change

Very preterm infants likely benefit but not widely accepted practice

60 seconds APTS
Australian Placental Transfusion Study

Largest multicentre trial of ICC vs DCC in infants <30 weeks

Primary outcome: death or major morbidity (severe brain injury, severe ROP, NEC, late onset sepsis) at 36 weeks

	Rate	Relative Risk	95%CI
Death or major morbidity	37.0% vs 37.2%	1.00	0.88-1.13
Death	**9.0% vs 6.4%**	**0.69**	**0.49-0.97**

Effects did not differ according to pre-planned subgroups: sex, <27 v ≥27 weeks or mode of birth

Polycythaemia more common, less red cell transfusions after DCC (52% vs 61%, p=0.001)

No difference in rates of other secondary outcomes:
IVH, ROP, NEC, LOS, PDA and CLD


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Delayed versus Immediate Cord Clamping in Preterm Infants
W. Tarnow-Mordi, J. Morris, A. Kirby, K. Robledo, L. Askie, R. Brown, N. Evans, S. Finlayson, M. Fogarty, V. Gebski, A. Ghadge, W. Hague, D. Isaacs, M. Jeffery, A. Keech, M. Kluckow, H. Popat, L. Sebastian, K. Aagaard, M. Belfort, M. Pammi, M. Abdel-Latif, G. Reynolds, S. Ariff, L. Sheikh, Y. Chen, P. Colditz, H. Lilley, M. Pritchard, D. de Luca, K. de Waal, P. Forder, L. Duley, W. El-Naggar, A. Gill, J. Newnham, K. Simmer, K. Groom, P. Weston, J. Gullam, H. Patel, G. Koh, K. Lui, N. Marlow, S. Morris, A. Sehgal, E. Wallace, R. Soll, L. Young, D. Sweet, S. Walker, A. Watkins, I. Wright, D. Osborn, and J. Simes, for the Australian Placental Transfusion Study Collaborative Group*

Tarnow-Mordi *NEJM* 29 Oct 2017; DOI: 10.1056/NEJMoa1711281

Systematic review and meta-analysis 2017 ICC vs DCC

18 RCTs in 2834 infants <37 weeks

	Rate	Relative Risk	95%CI	NNB
Hospital mortality (All)	8% vs 5%	0.68	0.52-0.90	33
Hospital mortality (<28 weeks*)	17% vs 12%	0.70	0.51-0.95	20

* 3 trials <28 weeks n=996

- No difference in: Apgar scores, intubation, admission temperature, mechanical ventilation, IVH, brain injury, CLD, PDA, LOS, ROP
- DCC increased peak haematocrit by 2.73% (95% CI 1.94 to 3.52; P<0.00001) and reduced proportion receiving blood transfusion by 10% (p<0.00001)
- Increased risk of polycythaemia (3% risk difference) and mean peak bilirubin increased +(4 µmol/L)
- No difference in PPH or maternal blood transfusion rates

Fogarty *AJOG* Nov 2017 doi.org/10.1016/j.ajog.2017.10.231

Delayed cord clamping (60 seconds) should be used for births if planning active intervention at 23^{+0} – 24^{+6} weeks

Offering active neonatal intervention improves outcomes

There is evidence that obstetric interventions improve outcomes

Should we offer active intervention to everyone and how do obstetricians approach care?

- **Likelihood of delivery**
- **Avoid the preterm delivery**
- **Outcome predictors**
- **Multidisciplinary approach**
- **Realistic family centred discussion**
- **Formulate and document plan**
- **On-going review and consideration of plan**

Multidisciplinary approach to family centred discussion

Determine peri-viable delivery is possible/probable
Determine that realistic chance of positive outcome

Involve neonatal team, ensure **consistency in approach**

Multidisciplinary approach to discussion
Individualised and tailored, family-centred discussion

There are options, in a grey-zone, no definite right answers
Provide information and guidance on what is right for each family
Support their decision-making and whatever decision they make

What are the possible outcomes
What can be considered to optimise outcome
What are the options for care

13. Threatened and active PTL at < 24^{+0} weeks

'Active intervention' < 24+0 weeks should not form standard routine care but each case must be individualised and tailored ensuring a multidisciplinary and family-centred approach to the care that is offered.'.

- **Full active intervention** including CS if required on fetal grounds (continuous or intermittent monitoring)
- **Active intervention** no CS on fetal grounds (intermittent monitoring only)
- **Comfort care only**, Individualised compassionate care – provide warmth, minimise discomfort, family time, +/- wish to feed. Palliative care team, perinatal loss team

Clearly documented plan supported by woman, family and staff

Awareness that on-going indicators may require plan to change (antenatal, intrapartum and neonatal) – *'plan for active intervention does not commit caregivers to full resuscitation after birth if it is not deemed to be in baby's best interest, and antenatal counselling should cover this'*

As gestation advances a few days makes a big difference, re-consult, re-discuss and amend plan accordingly

Practice point: Care for women in preterm labour or requiring delivery at 23+0 to 24+6 weeks gestation

Care for pregnant women at risk of birthing at the lower extremes of gestational age (23+0 to 24+6 weeks) remains a complex area of perinatal medicine.

The clinical care pathway is individualised to reflect individual medical complexity and co-morbidity, parental wishes and resource availa

All New Zealand tertiary r and 24 weeks gestation. C high-quality survival is pos

Care of women with threat gestation involves consider part of this discussion as a birth but also has significa

Integrated care for women weeks gestation should inc or paediatric services. Bes specific requirements of ea resuscitation of the newbor

Survival and outcomes for tertiary centre. Early consu

Parents, families and whan prepared for early birth (e Despite this, admission to morbidity and/or mortality

Points for particular consideration in the context of imminent birth at 23+0 to 24+6 weeks gestation

Transfer to a tertiary centre for collaborative discussion and planning is optimal. Transfer is not only for those wanting active management but also for all to have a tertiary consultation. Parents, families and whānau should be counselled antenatally about the possible range of outcomes for the baby and this should be individualised to the clinical setting. These discussions should be led by senior obstetric and neonatal staff and should reflect local institutional outcome data as well as current international data on long-term outcomes, particularly in relation to neurodevelopmental and cognitive outcomes. Parents, families and whānau should be in the centre of decision-making and be aware of the range of possible interventions at this gestation.

Appropriate care options as agreed by parents and senior clinical team include:

1. Palliative
   a. No maternal corticosteroids or magnesium sulphate
   b. No fetal monitoring or operative birth
   c. A palliative care pathway for the baby from birth (stay with parents for comfort cares; no neonatal intensive care unit admission)
2. Active
   a. Maternal corticosteroids and magnesium sulphate
   b. Planning with parents, families and whānau, ideally prior to active labour, regarding whether or not there will be fetal monitoring and intervention (this should include the agreed plan for mode of birth)
   c. Senior neonatal assessment at birth with planned neonatal intensive care unit admission
3. Interim (for parents, families and whanau who require more time to make this decision)
   a. Maternal corticosteroids and magnesium sulphate
   b. Further discussion with parents, families and whānau, regarding whether or not there will be fet monitoring and intervention.

PMMRC. 2018. Twelfth Annual Report of the Perinatal and Maternal Mortality Review Committee: Reporting mortality 2016. Wellington: HQSC

Perinatal and Maternal Mortality Review Committee
He matenga ohorere, he wairua uiui, wairua mutungakore

Just because we can doesn't mean we always should

An approach of active treatment improves survival & survival free of major impairment

Careful consideration and realistic appraisal of antenatal prognostic signs

Consistent message from obstetrics, neonatology, midwifery, support staff

Individualised and tailored, family-centred discussion

Realistic explanations including local outcome data

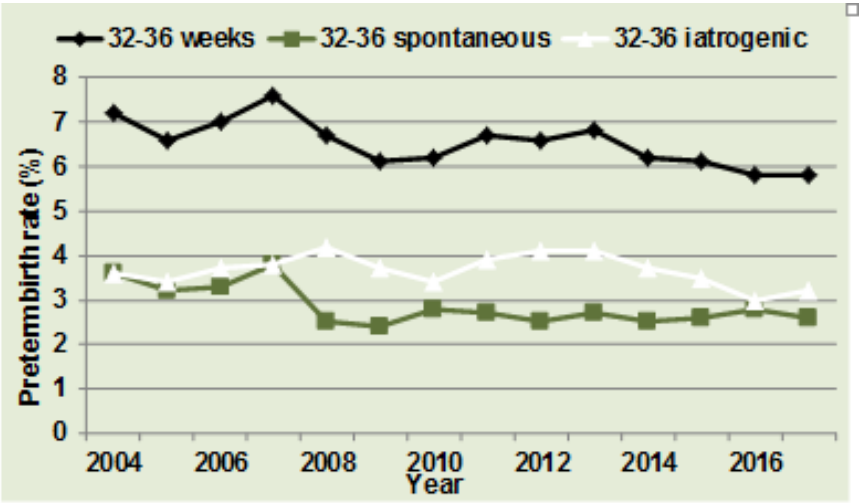
Clear plan of level of intervention

Support family decision

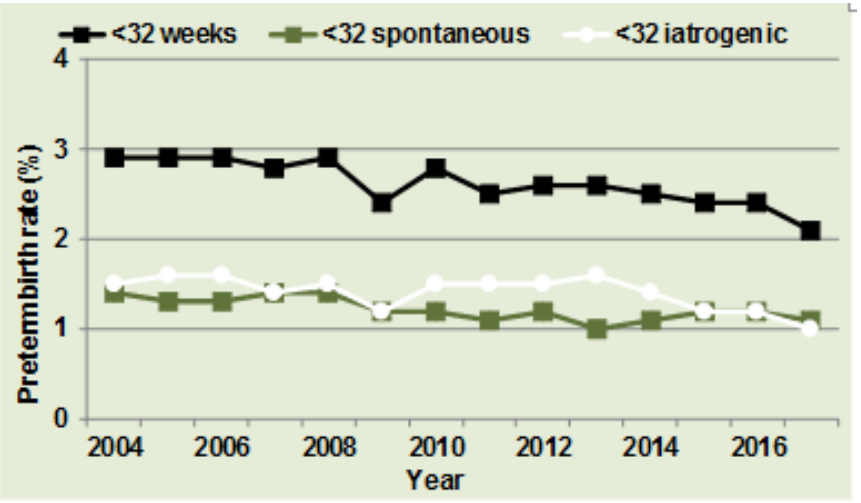
Review and update plan regularly

National Women's Health, Auckland City Hospital

Birth at 32-36 weeks



Birth at <32 weeks



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total birthing women	**7589**	**7735**	**7709**	**7523**	**7695**	**7223**	**7400**	**6933**	**7241**	**6846**
Women birthing preterm (<37) total	733	658	689	684	709	673	647	592	597	542
Incidence %	9.7	8.5	8.9	9.1	9.2	9.3	8.7	8.5	8.2	7.9
Women birthing <32 weeks	222	185	212	190	203	185	185	168	172	144
Incidence %	2.9	2.4	2.8	2.5	2.6	2.6	2.5	2.4	2.4	2.1

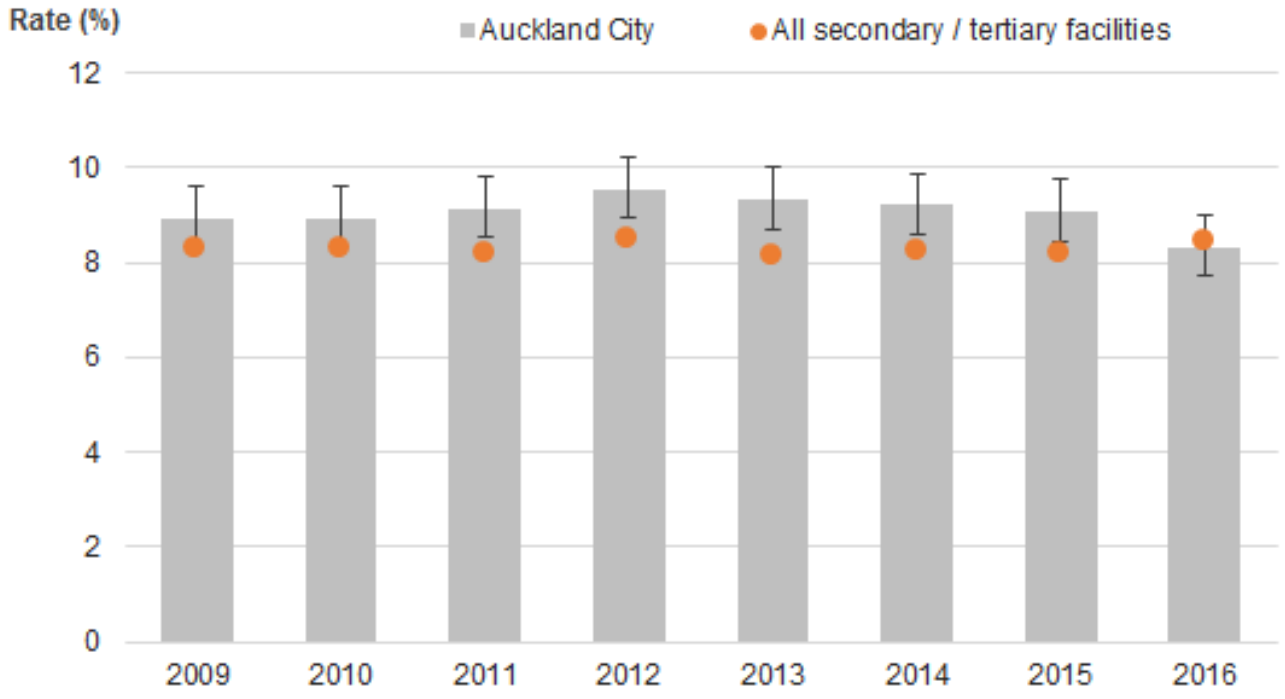
Iatrogenic preterm birth 2006-2017
p=0.005 for <32 weeks
p=0.005 for 32-36 weeks

Spontaneous preterm birth 2006-2017
p=0.03 for <32 weeks
P=0.0003 for 32-36 weeks

National Women's Health Annual Clinical Report 2017

New Zealand Preterm Birth Rates

2009	2010	2011	2012	2013	2014	2015	2016	From 2009 to 2016 (p-value)[1]
7.4	7.4	7.3	7.6	7.4	7.4	7.3	7.5	– (0.689)



Error bars represent the 95% confidence interval for the facility rate.

ISBN: 978-0-9475151-93-5 health.govt.nz
Ministry of Health. 2018. New Zealand Maternity Clinical Indicators 2016. Wellington: Ministry of Health