Analysis 1.37. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 37 Diarrhoea (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 37 Diarrhoea (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Acute diarrhoea							
Bangladesh 2000	196	1.5 (1.9)	214	1.9 (2.1)		100.0 %	-0.40 [-0.79, -0.01]
Subtotal (95% CI)	**196**		**214**			**100.0 %**	**-0.40 [-0.79, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.02 (P = 0.043)							
2 Persistent diarrhoea							
Bangladesh 2000	196	0.3 (0.7)	214	0.3 (0.6)		100.0 %	0.0 [-0.13, 0.13]
Subtotal (95% CI)	**196**		**214**			**100.0 %**	**0.0 [-0.13, 0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Test for subgroup differences: Chi^2 = 3.70, df = 1 (P = 0.05), I^2 =73%							

Analysis 1.38. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 38 Dysentery (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 38 Dysentery (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	0.04 (0.2)	214	0.1 (0.4)		100.0 %	-0.06 [-0.12, 0.00]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.06 [-0.12, 0.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.94 (P = 0.052)							
Test for subgroup differences: Not applicable							

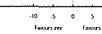
Analysis 1.39. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 39 Cough (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 39 Cough (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	3.9 (1.9)	214	4.1 (1.8)		100.0 %	-0.20 [-0.56, 0.16]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.20 [-0.56, 0.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.09 (P = 0.27)							
Test for subgroup differences: Not applicable							



Analysis 1.40. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 40 Acute lower respiratory infection (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 40 Acute lower respiratory infection (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	0.7 (1.2)	214	0.8 (1.3)		100.0 %	-0.10 [-0.34, 0.14]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.10 [-0.34, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.81 (P = 0.42)							
Test for subgroup differences: Not applicable							

Analysis 1.41. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 41 Impetigo (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 41 Impetigo (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	0.1 (0.6)	214	0.4 (0.8)		100.0 %	-0.30 [-0.44, -0.16]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.30 [-0.44, -0.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.32 (P = 0.000016)							
Test for subgroup differences: Not applicable							

Analysis 1.42. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 42 Infant weight-for-age (Z-score).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 42 Infant weight-for-age (Z-score)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Z-score at 6 months							
Bangladesh 2000	83	1.5 (0.9)	85	1.1 (0.9)		50.4 %	0.40 [0.13, 0.67]
Indonesia 2001	66	-0.17 (0.82)	70	-0.17 (0.85)		49.6 %	0.0 [-0.28, 0.28]
Subtotal (95% CI)	**149**		**155**			**100.0 %**	**0.20 [-0.19, 0.59]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 4.02, df = 1 (P = 0.04); I^2 =75%							
Test for overall effect: Z = 1.01 (P = 0.31)							
2 Z-score at 13 months							
Bangladesh 2000	83	-2.7 (1)	85	-2.3 (1)		100.0 %	-0.40 [-0.70, -0.10]
Subtotal (95% CI)	**83**		**85**			**100.0 %**	**-0.40 [-0.70, -0.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.59 (P = 0.0095)							

Analysis 1.43. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 43 Infant weight-for-height (Z-score).

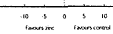
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 43 Infant weight-for-height (Z-score)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Indonesia 2001	66	0.46 (0.89)	70	0.51 (0.77)		100.0 %	-0.05 [-0.33, 0.23]
Total (95% CI)	**66**		**70**			**100.0 %**	**-0.05 [-0.33, 0.23]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 1.44. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 44 Infant mid-upper arm circumference (mm).

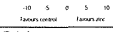
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 44 Infant mid-upper arm circumference (mm)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	194	92 (8)	216	91 (8)		34.3 %	1.00 [-0.55, 2.55]
Peru 1999	445	103 (10)	409	103 (10)		45.8 %	0.0 [-1.34, 1.34]
USA 1995	294	112 (12)	286	110 (13)		19.9 %	2.00 [-0.04, 4.04]
Total (95% CI)	**933**		**911**			**100.0 %**	**0.74 [-0.17, 1.65]**

Heterogeneity: Chi² = 2.74, df = 2 (P = 0.25); I² =27%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 1.45. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 45 Infant mental development index.

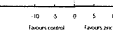
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 45 Infant mental development index

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	99.34 (11.2)	85	102.64 (10)		100.0 %	-3.30 [-6.51, -0.09]
Total (95% CI)	**83**		**85**			**100.0 %**	**-3.30 [-6.51, -0.09]**

Heterogeneity: not applicable
Test for overall effect: Z = 2.01 (P = 0.044)
Test for subgroup differences: Not applicable



Analysis 1.46. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 46 Infant psychomotor development index.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 46 Infant psychomotor development index

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	88.7 (17.4)	85	95.7 (15)		100.0 %	-7.00 [-11.92, -2.08]
Total (95% CI)	**83**		**85**			**100.0 %**	**-7.00 [-11.92, -2.08]**

Heterogeneity: not applicable
Test for overall effect: Z = 2.79 (P = 0.0053)
Test for subgroup differences: Not applicable

Analysis 1.47. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 47 Infant approach.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 47 Infant approach

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	6.63 (1.76)	85	6.53 (1.4)		100.0 %	0.10 [-0.38, 0.58]
Total (95% CI)	**83**		**85**			**100.0 %**	**0.10 [-0.38, 0.58]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable

Analysis 1.48. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 48 Infant emotional tone.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 48 Infant emotional tone

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	5.25 (1)	85	5.9 (2)		100.0 %	-0.65 [-1.13, -0.17]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.65 [-1.13, -0.17]**

Heterogeneity: not applicable
Test for overall effect: Z = 2.67 (P = 0.0075)
Test for subgroup differences: Not applicable

Analysis 1.49. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 49 Infant activity.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 49 Infant activity

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	5.1 (1.2)	85	5.2 (1)		100.0 %	-0.10 [-0.43, 0.23]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.10 [-0.43, 0.23]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

Analysis 1.50. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 50 Infant co-operation.

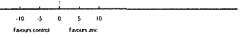
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 50 Infant co-operation

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	5.2 (1.8)	85	5.8 (1.9)		100.0 %	-0.60 [-1.16, -0.04]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.60 [-1.16, -0.04]**

Heterogeneity: not applicable
Test for overall effect: Z = 2.10 (P = 0.036)
Test for subgroup differences: Not applicable



Analysis 1.51. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 51 Infant vocalisation.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 51 Infant vocalisation

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	4.9 (1.3)	85	4.98 (1.7)		100.0 %	-0.08 [-0.54, 0.38]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.08 [-0.54, 0.38]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable

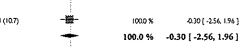
Analysis 1.52. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 52 Differential abilities score at 5 years.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 52 Differential abilities score at 5 years

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Non-verbal ability							
USA 1995	173	86.2 (16.5)	182	88.6 (15.1)		100.0 %	-2.40 [-5.70, 0.90]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**-2.40 [-5.70, 0.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.43 (P = 0.15)							
2 Verbal ability							
USA 1995	173	80 (11)	182	80.3 (10.7)		100.0 %	-0.30 [-2.56, 1.96]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**-0.30 [-2.56, 1.96]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.26 (P = 0.79)							
3 General conceptual ability IQ							
USA 1995	173	81.5 (13.8)	182	82.6 (11.4)		100.0 %	-1.10 [-3.74, 1.54]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**-1.10 [-3.74, 1.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Chi^2 = 1.07, df = 2 (P = 0.59), I^2 =0.0%							



Analysis 1.53. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 53 Visual sequential memory score.

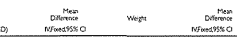
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 53 Visual sequential memory score

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
USA 1995	173	33.7 (7)	182	34.5 (6.8)		100.0 %	-0.80 [-2.24, 0.64]
Total (95% CI)	**173**		**182**			**100.0 %**	**-0.80 [-2.24, 0.64]**

Heterogeneity: not applicable
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 1.54. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 54 Auditory sequential memory score.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 54 Auditory sequential memory score

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
USA 1995	173	36.8 (6.2)	182	36.2 (5.8)		100.0 %	0.60 [-0.65, 1.85]
Total (95% CI)	**173**		**182**			**100.0 %**	**0.60 [-0.65, 1.85]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable

Analysis 1.55. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 55 Knox cube score.

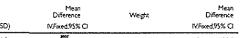
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 55 Knox cube score

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
USA 1995	173	5 (1.5)	182	4.9 (1.3)		100.0 %	0.10 [-0.19, 0.39]
Total (95% CI)	**173**		**182**			**100.0 %**	**0.10 [-0.19, 0.39]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 1.56. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 56 Gross motor scale score.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 56 Gross motor scale score

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
USA 1995	173	331 (16)	182	333 (10)		100.0 %	-2.00 [-4.79, 0.79]
Total (95% CI)	**173**		**182**			**100.0 %**	**-2.00 [-4.79, 0.79]**

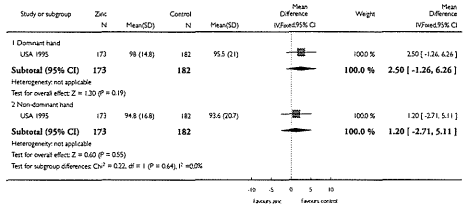
Heterogeneity: not applicable
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable

Analysis 1.57. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 57 Grooved pegboard score.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 57 Grooved pegboard score

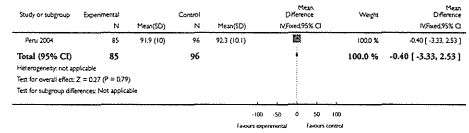


Analysis 1.58. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 58 Intelligence quotient of infants at 54 months.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 58 Intelligence quotient of infants at 54 months



APPENDICES

Appendix 1. Methods used to assess trials included in previous versions of this review

The following methods were used to assess Bangladesh 2000; Chile 2001; Denmark 1956; Indonesia 1999; Indonesia 2001; Nepal 2003; Pakistan 2005; Peru 1999; Peru 2004; S Africa 1985; UK 1989; UK 1991a; UK 1991b; USA 1983; USA 1985; USA 1989; USA 1995.

Selection of studies

Two review authors (K Mahomed, P Middleton) applied the inclusion and exclusion criteria to all identified trials. Disagreements were resolved through discussion.

Data extraction and management

We developed a form for data extraction and two authors independently extracted the data using this form. We contacted, or attempted to contact, authors of the original reports when information regarding a study was unclear.

Assessment of methodological quality of included studies

We assessed the methodological quality of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005).

(1) Selection bias (randomisation and allocation concealment)

We coded each trial as:
(A) adequate concealment of allocation (such as telephone randomisation, consecutively numbered sealed opaque envelopes);
(B) unclear allocation concealment (such as list or table of numbers used, sealed envelopes or trial does not report any approach for concealing allocation);
(C) inadequate concealment of allocation (such as open list of random numbers, dates of birth or days of the week).

(2) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:
(1) blinding of participants (yes/no/unclear);
(2) blinding of caregivers (yes/no/unclear);
(3) blinding of outcome assessment (yes/no/unclear).

(3) Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

We have presented numbers of losses for each study when these have been reported.

Measures of treatment effect

We conducted statistical analysis using the Review Manager software (RevMan 2003). At least two authors independently extracted data. We used a fixed-effect model to combine data since trials appeared to be sufficiently similar (as measured by I^2), except for head circumference and caesarean section where we also calculated this outcome on the basis of a random-effects model.

Dichotomous data

For dichotomous data, we presented results as a summary relative risk with 95% confidence intervals.

Continuous data

For continuous data, we presented results as mean differences with 95% confidence intervals.
One trial (Nepal 2003) used a cluster-randomisation design. The trial was reported with relative risks adjusted to take account of the fact that sectors rather than individuals were randomised to groups. We adjusted the raw data from two of the five arms of this study (in order to compare zinc and no zinc groups). Using the methods outlined in section 8.11.2 of the Handbook (Higgins 2005), we calculated a design effect of 1.067. The average cluster size was 7.66 and we assumed an intra-class coefficient (*e*) of 0.01 and so the design effect was calculated as 1 + (1-7.66) × 0.01 = 1.067. Numerators and denominators of dichotomous outcomes and the sample sizes of the continuous outcomes in Nepal 2003 were reduced by dividing them by the design effect.

Assessment of heterogeneity

We applied tests of heterogeneity between trials using the I^2 statistic. In the event of high levels of heterogeneity among the trials (exceeding 50%), we explored this by prespecified subgroup analysis and performed sensitivity analysis. A random-effects meta-analysis was used as an overall summary when considered appropriate.

Subgroup analyses

The following prespecified subgroup analyses were performed:
- zinc supplementation compared with no zinc or placebo in women likely or shown to be zinc deficient;
- zinc supplementation compared with no zinc or placebo in women in whom compliance with supplementation was good (more than 80%).

WHAT'S NEW

Last assessed as up-to-date: 1 March 2012.

Date	Event	Description
9 November 2011	New search has been performed	Search updated. Three new trials included (China 2011; Ghana 2009; Iran 2010) and four new trials excluded (Mahmoudian 2005; Van Vliet 2003; Villamor 2006; Valda 2010).
9 November 2011	New citation required but conclusions have not changed	New authors helped to update this review.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 3, 1997

Date	Event	Description
1 July 2011	Amended	Search updated. Thirteen trial reports added to Studies awaiting classification
6 November 2008	Amended	Converted to new review format.
20 December 2006	New search has been performed	Search updated. Nine new studies have been added to the original seven included studies, plus one previously excluded study (USA 1985) has now been included, making a total of 17 studies included in the 2006 update. A total of 11 studies have been excluded in this update and two studies have been placed in Studies awaiting classification. The Background and Methods sections have been expanded in this update, and additional outcomes have been added. The title has been changed from 'Zinc supplementation in pregnancy' to 'Zinc supplementation for improving pregnancy and infant outcome'. The conclusions regarding the effect of zinc supplementation on reducing preterm birth have been slightly strengthened

CONTRIBUTIONS OF AUTHORS

R Mori (RM) prepared the first version of this update. RM, R Tobe-Gai, E Ota and P Middleton applied study selection criteria and extracted data from the included studies. Z Bhutta and K Mahomed and all the other authors commented on drafts of the update.

DECLARATIONS OF INTEREST

Kassam Mahomed was principal investigator in a trial included in this review.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.
- Collaboration for Research in Global Women's and Children's Health, Japan.
- The University of Tokyo, Japan.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated our methods to reflect the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Outcomes have been separated into 'Primary' and 'Secondary' outcomes.

We have added 'congenital malformation' to our secondary outcomes.

Given the number of trials identified and the standard methods for the Cochrane Pregnancy and Childbirthbirth Group, quasi-randomised controlled trials have been excluded.

INDEX TERMS

Medical Subject Headings (MeSH)

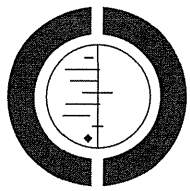
*Dietary Supplements; *Infant, Low Birth Weight; Infant, Newborn; Pregnancy Outcome; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Zinc [*administration & dosage]

MeSH check words

Female; Humans; Pregnancy

Hypnosis during pregnancy, childbirth, and the postnatal period for preventing postnatal depression (Review)

Sado M, Ota E, Stickley A, Mori R



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[Intervention Review]

Hypnosis during pregnancy, childbirth, and the postnatal period for preventing postnatal depression

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ABSTRACT

Background

The morbidity caused by postnatal depression is enormous. Several psychological or psychosocial interventions have appeared to be effective for treating the disorder although they have not shown a clear benefit in preventing the development of PND. As yet however, the effectiveness of hypnosis has not been evaluated in relation to this.

Objectives

To assess the effect of hypnosis for preventing postnatal depression compared with usual antenatal, intranatal, or postnatal care.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2011).

Selection criteria

Randomised controlled trials comparing hypnosis with usual antenatal, intranatal, or postnatal care, where the primary or secondary objective is to assess whether there is a reduced risk of developing postnatal depression.

Data collection and analysis

Two review authors independently assessed trials for inclusion and assessed the one included study for risk of bias. The included study did not contribute any data for analysis.

Main results

There was one included study (involving 63 women). However, as it did not include the outcomes of interest, no data were available for analysis for this review.

Authors' conclusions

There was no evidence available from randomised controlled trials to assess the effectiveness of hypnosis during pregnancy, childbirth, and the postnatal period for preventing postnatal depression. Evidence from randomised controlled trials is needed to evaluate the use and effects of hypnosis during the perinatal period to prevent postnatal depression. Two trials are currently underway which may provide further information in the future.

PLAIN LANGUAGE SUMMARY

Hypnosis during pregnancy, childbirth, and the postnatal period for preventing postnatal depression

Mental illness during pregnancy and the postnatal period can consist of a short period of mood swings, crying spells, irritability (baby blues), depression and postnatal psychosis. Postnatal depression (PND) falls along this spectrum. The morbidity caused by PND is enormous. Possible symptoms can include depressive mood, loss of interest or pleasure in daily activities, anxiety, irritability, insomnia, feelings of guilt, and thoughts of suicide in the first three months after giving birth. These can negatively impact on infant feeding, maternal-infant interaction and the mother's perceptions of infant behaviour. Several psychological or psychosocial interventions appear to be effective for treating the disorder, such as cognitive-behavioural therapy, counselling with or without antidepressants, health visitor-led counselling, peer support, and interpersonal psychotherapy. In regard to prevention however, psychosocial or psychological interventions have not shown a clear benefit in preventing the development of PND. Although hypnosis has been used for a long time to reduce pain during labour and birth, the effectiveness of hypnosis for preventing PND has not yet been evaluated. Hypnosis can be described as a heightened state of focal concentration and receptivity to the suggestions of another person. This person brings about the hypnotic state by focusing the person's attention on a monotonous routine. This review included one study (involving 63 women) but it did not contribute any data to this review. There is insufficient evidence from randomised controlled trials to determine whether hypnosis is effective for preventing PND when compared with usual antenatal, birthing, or postnatal care procedures. Two trials are currently underway however, which may provide further information in the future.

BACKGROUND

Description of the condition

Morbidity from mental illness during pregnancy and the postnatal period can take various forms such as baby blues, postnatal depression (PND), and postnatal psychosis. Baby blues (those mood swings, crying spells, and irritability that may occur just after childbirth) are likely to be mild and disappear within a couple of days, with up to 80% of new mothers reportedly experiencing these transient symptoms to some degree (National Institute of Mental Health 2005). In contrast, postnatal psychosis, while affecting less than 1% of new mothers, usually results in hospitalisation (Evins 1997). Postnatal depression falls along this spectrum. The prevalence of PND ranges from 3% to 25% across studies (O'Hara 1996). Conditions in PND vary and include symptoms such as depressive mood, anhedonia (inability to feel pleasure), anxiety, irritability, insomnia, feelings of guilt, and thoughts of suicide. The first three months after delivery is the period with the highest risk for the development of PND (Cox 1993). Although the definition of PND varies between studies, recent and rigorous research has used standardised self-report measures such as the Edinburgh Postnatal Depression Scale (EPDS) (Cox 1987) or the Beck Depression Inventory (BDI) (Beck 1961) to identify depression. However, the possibility remains that women who are classified as depressed on the basis of a self-report measure may not meet the criteria for depression defined by standardised diagnostic criteria (e.g. the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), (American Psychiatric Association 1994).

Although a number of research studies have been conducted, no specific causative factor has been detected for postnatal depression. However, several studies have indicated that various clinical and psychosocial factors such as substance-use, current or past experiences of abuse (Rosa 2009), stressful life events (Bernazzani 1997; O'Hara 1991), marital conflict (Bernazzani 1997; O'Hara 1986; O'Hara 1991) and a lack of social support (Bernazzani 1997; Brugha 1998; Cooper 1988; O'Hara 1986; Small 1994; Stein 1980; Stuchbery 1998) can all play a significant role in the onset of PND. The enormous burden due to PND is a critical issue across diverse cultures (Alfonso 2009). While the effect this

illness has on mothers is of course immense, the fact that the burden is not restricted to mothers alone is another serious issue. Previous research has suggested for example, that depressive symptomatology in the early postpartum period may increase the risk of negative infant-feeding outcomes (Dennis 2009). It has also been reported that PND can cause impaired maternal-infant interaction (Murray 1996) and negative perceptions of infant behaviour (Mayberry 1993). Moreover, the children of mothers with PND are two to five times more likely to develop long-term behavioural problems (Beck 1998; Orvaschel 1988), which could increase this burden even further.

To reduce the impact of this illness, a number of studies have been undertaken to clarify which types of psychosocial interventions appear to be effective in the treatment of PND. For example, cognitive-behavioural counselling with antidepressants (Appleby 1997), cognitive-behavioural therapy (CBT) and non-directive counselling (Cooper 1997; Cooper 2003), health visitor-led non-directive counselling (Holden 1989; Wickberg 1996), peer support (Dennis 2003), and interpersonal psychotherapy (O'Hara 2000) have been examined and been found to be effective. However, it would be more beneficial if interventions for preventing the development of PND were available.

The effectiveness of a variety of psychosocial and psychological interventions such as antenatal and postnatal classes, professional and lay home visits, continuity of care, early postnatal follow-up, debriefing and interpersonal psychotherapy has already been examined (Dennis 2005). In relation to this, those who experienced such preventive interventions (hypnosis not included) appeared to be just as likely to develop PND as those who had standard care. As regards hypnosis and its role in the birth process, it has been *used for a long time to reduce the pain of labour and delivery,* while it has also been utilised for effective childbirth preparation (Hammond 1990; Hilgard 1994; Ketterlaugen 2002). In connection with this, it has been reported that women have benefited in terms of obstetric outcomes, such as the ability to cope with pain, and have had a shorter period of labour (Jenkins 1994), in addition to less complications and surgical interventions, and a shorter postnatal hospital stay (Martin 2001). However, whether or not hypnosis prevents the onset of PND has not yet been evaluated.

Description of the intervention

Hypnosis is a complex mental state that is normally induced by hypnotic induction. The definition of hypnosis has varied between researchers. While Kaplan 1996 defined hypnosis as "a state of heightened focal concentration and receptivity to the suggestions of another person who brings about the condition by focusing the person's attention on a monotonous routine", Spiegel 2005 described it as "a specialized ability to enhance focal attention and imagination while simultaneously minimizing peripheral awareness." Erickson 1976 also described the process of a clinical trance as "a free period in which individuality can flourish".

How the intervention might work

This form of therapy has been employed to treat a variety of disorders ranging from obesity through to substance-related disorders (Kaplan 1996). Even though there is little evidence that hypnosis has been used for treating depression directly, earlier studies have indicated that hypnosis may be able to reduce symptoms of depression when used in the treatment of other disorders such as anxiety (Crawford 1993), and chronic pain (Lynch 1999). In addition, there has been empirical support for the use of hypnosis in the treatment of specific symptoms related to depression such as insomnia (Anbar 2005; Venmos 2003) and low self-esteem (Torem 1992; Valente 1990). These findings theoretically imply that hypnosis may be potentially important when it comes to preventing the development of PND. As yet, it remains unclear which biological and neurological mechanisms hypnosis acts on in order to improve the symptoms mentioned above. However, it has been suggested that it might regulate the functioning of specific sites in the limbic and cortical regions of the brain as CBT does for depressed patients (Goldapple 2004).

Why it is important to do this review

Postnatal depression is a common complication of childbirth. Dennis 2005 has reviewed the effectiveness of various psychosocial and psychological interventions. They included psychosocial interventions such as antenatal and postnatal classes, lay home visits, early postpartum follow-up, continuity of care, home visits provided by a healthcare professional, and psychological interventions such as interpersonal psychotherapy and debriefing in hospital. While postpartum home visits provided by a healthcare professional had some benefit, other interventions did not reveal any beneficial effects in statistical terms and the overall conclusion of the review was that these various interventions did not reduce the number of women who developed PND. However, the potential effectiveness of hypnosis for preventing the development of PND has never been evaluated, despite it having been previously shown to be beneficial in the treatment of specific symptoms associated with depression. Evaluating the effectiveness of hypnosis for the prevention of PND is therefore of great potential significance.

OBJECTIVES

The primary objective of this review is to assess the effect of hypnosis for preventing PND compared with usual antenatal, intranatal, or postnatal care. Secondary aims are to examine (1) the effects of intervention onset and duration, and (2) whether interventions are more effective in women selected with specific risk factors.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials (RCTs) comparing hypnosis with usual antenatal, intranatal, or postnatal care, to assess whether there was a reduced risk of developing postnatal depression (PND). We planned to include RCTs in which the unit of randomisation could be individuals or clusters (groups or communities). Studies were excluded if they had used a quasi-randomised design.

Types of participants

All pregnant women, women in labour, or new mothers to whom hypnosis was delivered antenatally, intranatally, or within the first postnatal month.

Types of interventions

Hypnosis provided to pregnant women, women in labour, or new mothers within the first postnatal month, compared with usual antenatal, intranatal, or postnatal care.

Types of outcome measures

Primary outcomes

1. The development of PND (defined as a score of more than 12 on the *Edinburgh Postnatal Depression Scale or as a diagnosis* by way of a structured diagnostic interview).

Secondary outcomes

1. Development of postnatal psychosis.
2. Postnatal anxiety disorder.
3. Maternal mortality and serious morbidity including outpatient and inpatient use of psychiatric units, or other health services.
4. Maternal-infant attachment.
5. Suicidal ideation.
6. Death by suicide within one year of the birth.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 2011).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the Specialized Register section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched the reference lists of the studies identified for additional studies. We also made contact with experts for additional information and details of ongoing trials. We did not apply any language restrictions.

Data collection and analysis

The methodology for data collection and analysis was based on the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). We identified only one study for inclusion in this review. We have assessed risk of bias for this study but the review does not contain any analyses. Additional methods of data collection and details of the analysis to be used in future updates of this review, as more data become available, are provided in Appendix 1.

Selection of studies

Two review authors, Mitsuhiro Sado and Erika Ota, independently assessed for inclusion all the potential studies we identified as a result of the search strategy. Any disagreement was solved through discussion or, when required, the other review authors, Andrew Stickley and Rintaro Mori were consulted.

Data extraction and management

A form was designed to extract data. For the one eligible study, two review authors extracted the data using the agreed form. Any

discrepancies were resolved through discussion or, when required, we consulted an additional review author.

The included study did not contribute any data for analysis. In future updates of this review, as more data become available, we will enter data into the Review Manager software (RevMan 2011) and check it for accuracy. If any information regarding data extraction is unclear, we will contact the authors of the original reports to obtain further details.

Assessment of risk of bias in included studies

For the one included study the risk of bias was assessed separately by two review authors using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where there were disagreements, these were resolved by way of discussion or where necessary, by involving a third review author.

(1) Random sequence generation (checking for possible selection bias)

We described for the one included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. The method was assessed as:

- low risk of bias (any truly random process, e.g. random number table);
- high risk of bias (any non-random process, e.g. odd or even date of birth);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For the included study, we described the method used to conceal the allocation to interventions prior to assignment and assessed whether the intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. Methods were assessed as:

- low risk of bias (e.g. telephone or central randomisation);
- high risk of bias (e.g. open random allocation);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described, for the one included study, the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding *separately for different outcomes or classes of outcomes.* We assessed the methods as:

- low, high or unclear risk of bias for participants;
- *low, high or unclear risk of bias for personnel.*

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We describe, for the included study, the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For the included study, and for each outcome, or class of outcomes, information about data completeness including that relating to attrition and exclusions was reported. Where attrition and exclusions are reported, we provide details of how many participants were included in each stage of the analysis. We also give reasons for attrition or exclusion where they were reported, and details of whether data that were missing were related to outcomes or distributed evenly across groups. If the information provided is sufficient or where sufficient information was obtained from study authors, missing data were included in the analyses we performed. Methods will be assessed as:

- low risk of bias (e.g. 20% or less missing data; missing outcome data balanced across groups);
- high risk of bias (e.g. greater than 20% missing data; numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

The possible presence of selective reporting bias was investigated. The methods were assessed as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so cannot be used; the study failed to *include results of a key outcome that would have been expected* to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

Any significant concerns about other potential sources of bias were described for the one study included in the review. Whether these potential biasing factors exist was assessed using the terms:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether the included study is at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it likely to impact on the findings. In future updates of this review, as more data become available, we will explore the impact of the level of bias through undertaking sensitivity analyses -ter Sensitivity analysis'.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

See Characteristics of excluded studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register identified five trials. One study (involving 63 women) was included in this review (Harmon 1990), while two trials were excluded (Guse 2006; Mehl-Madrona 2004). The reasons for exclusion were that one study was not a RCT (Guse 2006) while the other did not assess PND as an outcome (Mehl-Madrona 2004). The two other trials were classified as ongoing studies (Cyna 2006; Downe 2011).

Risk of bias in included studies

One RCT was included in this review. The risk of bias in the study was unclear because all factors other than blinding (allocation sequence, allocation concealment, incomplete outcomes and being free of suggestion of selective outcome reporting) were unclear. Further, although the Minnesota Multiphasic Personality inventory (MMPI) depression scale was used as the measurement instrument and the mean scores were reported, in terms of the *current research it was of little value because we could not evaluate* from the available data whether or not hypnosis reduced the risk of developing PND.

Effects of interventions

In the included study, only the MMPI Depression scale mean scores were reported, and no data were provided regarding whether or not hypnosis reduced the risk of developing PND; therefore, this study was assessed as being unable to contribute to this review and no further analyses were performed.

For reference, in the trial, first, the participants were divided into two groups according to their hypnotic susceptibility (high and low). Then, the participants in each group were randomly allocated to the hypnosis or control group respectively (two treatment conditions x two susceptibility separations). The mean score on the MMPI Depression scale in the highly susceptible hypnosis group was lower than that for the other three groups combined.

DISCUSSION

We identified one randomised controlled trial assessing the potential benefits and harms of hypnosis during pregnancy, childbirth, and the postnatal period for preventing PND. However, this trial showed only the mean score on the MMPI Depression scale, and we thus judged that the data did not contribute to this review and further analyses were not conducted. Consequently, there were no trials which could be used to evaluate *the primary outcomes relevant* to the review. However, we also found that previous studies had provided some indication that hypnosis may help reduce depressive symptoms. For instance, in the included trial of Harmon (Harmon 1990), as previously described, the mean score on the MMPI Depression scale in the highly susceptible hypnosis group was lower than that for the other three groups combined. Similar results were also reported in the Guse study (Guse 2006). The Guse study, which is a quasi-RCT, showed that the mean score on the EPDS in the experimental group (hypnosis) improved significantly compared to that of the comparison group. Although these trials had significant limitations such as providing only the mean scores of continuous scales rather than dichotomous ones (Guse 2006; Harmon 1990), or were not an RCT(Guse 2006), the information obtained from them should be reflected in future research. Finally, two trials are currently underway (Cyna 2006; Downe 2011) and may provide further information in the future.

AUTHORS' CONCLUSIONS

Implications for practice

Although some trials have been undertaken which indicate the possibility that hypnosis may be effective when it comes to re*ducing depressive symptoms, as yet, there is no evidence* available from randomised controlled trials which shows the effectiveness of hypnosis for preventing the development of PND.

Implications for research

Further evidence from randomised controlled trials is needed to evaluate the effects of hypnosis during the perinatal period to prevent PND rather than improve depressive symptoms.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

REFERENCES

References to studies included in this review

Harmon 1990 *(published data only)*
Harmon TM, Hynan MT. Improved obstetric outcomes using hypnotic analgesia and skill mastery combined with childbirth education. *Journal of Consulting and Clinical Psychology* 1990;58:525–30.

References to studies excluded from this review

Gue 2006 *(published data only)*
Gue T, Wissing M, Hartman W. The effect of a prenatal hypnotherapeutic programme on postnatal maternal psychological well-being. *Journal of Reproductive and Infant Psychology* 2006;24(2):163–77.

Mehl-Madrona 2004 *(published data only)*
Mehl-Madrona LE. Hypnosis to facilitate uncomplicated birth. *American Journal of Clinical Hypnosis* 2004;46:299–312.

References to ongoing studies

Cyna 2006 *(published data only)*
Cyna A. Hypnosis antenatal training for childbirth (HATCh): a randomised controlled trial. ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 21 March 2006).
Cyna AM, Andrew MI, Robinson JS, Crowther CA, Baghurst P, Turnbull D, et al.Hypnosis antenatal training for childbirth (HATCh): a randomised controlled trial. *BMC Pregnancy and Childbirth* 2006;6:5.

Downe 2011 *(published data only)*
Downe S. Self-hypnosis for Intrapartum Pain management (SHIP): a single organisation, two-site pragmatic exploratory non-blinded randomised controlled trial with blinded analysis based on intention to treat, and contextualised by interviews, focus groups, logs, and questionnaires. http://www.controlled-trials.com/ISRCTN27575146 (accessed 2011).
Downe S. The SHIP trial - a randomised controlled trial of self-hypnosis during labour. http://www.midirs.org/development/MIDIRSEssence.nsf/articles/F3294343A7FF3E593802578A900528FA5 (accessed 14 December 2011).

Additional references

Affonso 2000
Affonso DD, De AK, Horowitz JA, Mayberry LJ. An international study exploring levels of postpartum depressive symptomatology. *Journal of Psychosomatic Research* 2000;49(3):207–16.

American Psychiatric Association 1994
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth. Washington, DC: APA, 1994.

Anbar 2005
Anbar RD, Savedoff AD. Treatment of binge eating with automatic word processing and self-hypnosis: a case report. *American Journal of Clinical Hypnosis* 2005;48(2-3):191–8.

Appleby 1997
Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. *BMJ* 1997;314(7085):932–6.

Beck 1961
Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961;4:561–9.

Beck 1999
Beck CT. Maternal depression and child behaviour problems: a meta-analysis. *Journal of Advanced Nursing* 1999;29(3):623–9.

Bernazzani 1997
Bernazzani O, Saucier JF, David H, Borgeat F. Psychosocial predictors of depressive symptomatology level in postpartum women. *Journal of Affective Disorders* 1997;46(1):39–49.

Brugha 1998
Brugha TS, Sharp HM, Cooper SA, Weisender C, Britto D, Shinkwin R, et al.The Leicester 500 Project. Social support and the development of postnatal depressive symptoms, a prospective cohort survey. *Psychological Medicine* 1998;28(1):63–79.

Cooper 1997
Cooper PJ, Murray L. The impact of psychological treatments of postpartum depression on maternal mood and infant development. In: Cooper PJ, Murray L editor(s). *Postpartum depression and child development*. New York: Guilford Press, 1997.

Cooper 1998
Cooper PJ, Murray L. Postnatal depression. *BMJ* 1998;316(7148):1884–6.

Cooper 2003
Cooper PJ, Murray L, Wilson A, Romaniuk H. Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression. I. Impact on maternal mood. British Journal of Psychiatry 2003; Vol. 182:412–9.

Cox 1987
Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 1987;150:782–6.

Cox 1993
Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. *British Journal of Psychiatry* 1993;163:27–31.

Crawford 1993
Crawford H, Barabasz A. Phobias and intense fears: facilitating their treatment with hypnosis. In: Rhue J, Lynn, S, Kirsch I editor(s). *Handbook of Clinical Hypnosis*. Washington DC: American Psychological Association, 1993:311–38.

Dennis 2003
Dennis CL. The effect of peer support on postpartum depression: a pilot randomized controlled trial. *Canadian Journal of Psychiatry* 2003;48(2):115–24.

Dennis 2005
Dennis CL. Psychosocial and psychological interventions for prevention of postnatal depression: systematic review. *BMJ* 2005;331(7507):15.

Dennis 2009
Dennis CL, McQueen K. The relationship between infant-feeding outcomes and postpartum depression: a qualitative systematic review. *Pediatrics* 2009;123(4):e736–e751.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629–34.

Erickson 1976
Erickson M, Rossi EL, Rossi SI. *Hypnotic realities: the induction of clinical hypnosis and forms of indirect suggestion*. New York: Irvington, 1976.

Evins 1997
Evins GG, Theofrastous JP. Postpartum depression: a review of postpartum screening. Primary Care Update 1997; Vol. 4, issue 6:241–6.

Goldapple 2004
Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al.Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Archives of General Psychiatry 2004; Vol. 61, issue 1:34–41. [0003–990X: (Print)]

Hammond 1990
Hammond DC. Hypnosis in obstetrics and gynecology. *Handbook of Hypnotic Suggestions and Metaphors*. New York: Norton, 1990.

Harbord 2006
Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;25(20):3443–57.

Higgins 2011
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hilgard 1994
Hilgard ER, Hilgard JR. *Hypnosis in the relief of pain (Revised edition)*. New York: Brunner/Mazel, 1994.

Holden 1989
Holden JM, Sagovsky R, Cox JL. Counselling in a general practice setting: controlled study of health visitor intervention in treatment of postnatal depression. *BMJ* 1989;298(6668):223–6.

Jenkins 1994
Jenkins MW, Pritchard MH. Hypnosis in normal labour. *European Journal of Clinical Hypnosis* 1994;3:22–8.

Kaplan 1996
Kaplan HI, Sadock BJ. Hypnosis. *Synopsis of Psychiatry*. Baltimore: Lippincott Williams & Wilkins, 1996;916–9.

Ketterhagen 2002
Ketterhagen D, Vandevusse L, Berner MA. Self-hypnosis: alternative anesthesia for childbirth. *American Journal of Maternal-Child Nursing* 2002;27:335–40.

Lynch 1999
Lynch DF Jr. Empowering the patient: hypnosis in the management of cancer, surgical disease and chronic pain. *American Journal of Clinical Hypnosis* 1999;42(2):122–30.

Martin 2001
Martin AA, Schauble PG, Rai SH, Curry RW. The effects of hypnosis on the labor processes and birth outcomes of pregnant adolescents. *Journal of Family Practice* 2001;50:441–3.

Mayberry 1993
Mayberry LJ, Affonso DD. Infant temperament and postpartum depression: a review. *Health Care for Women International* 1993;14(2):201–11.

Murray 1996
Murray L, Fiori-Cowley A, Hooper R, Cooper P. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Development* 1996;67(5):2512–26.

National Insitute of Mental Health 2005
National Institute of Mental Health. *Understanding Postpartum Depression*. National Institute of Mental Health, 2005.

O'Hara 1986
O'Hara MW. Social support, life events, and depression during pregnancy and the puerperium. *Archives of General Psychiatry* 1986;43(6):569–73.

O'Hara 1991
O'Hara MW, Schlechte JA, Lewis DA, Wright EJ. Prospective study of postpartum blues. Biologic and psychosocial factors. *Archives of General Psychiatry* 1991;48(9):801–6.

O'Hara 1996
O'Hara MW, Swain AM. Rates and risk of postpartum depression-a meta-analysis. *International Review of Psychiatry* 1996;8(1):37–54.

O'Hara 2000
O'Hara MW, Stuart S, Gorman LL, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. *Archives of General Psychiatry* 2000;57(11):1039–45.

Orvaschel 1988
Orvaschel H, Walsh-Allis G, Ye W). Psychopathology in children of parents with recurrent depression. *Journal of Abnormal Psychology* 1988;16(1):17–28.

RevMan 2011
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Ross 2009
Ross LE, Dennis CL. The prevalence of postpartum depression among women with substance use, an abuse history, or chronic illness: a systematic review. *Journal of Womens Health* 2009;18(4):475–86.

Small 1994
Small R, Astbury J, Brown S, Lumley J. Depression after childbirth. Does social context matter?. *Medical Journal of Australia* 1994;161(8):473–7.

Spiegel 2005
Spiegel H, Greenleaf M, Spiegel D. Hypnosis. In: Kaplan HI, Sadock BJ editor(s). *Comprehensive Textbook of Psychiatry*. 8th Edition. Baltimore: Williams & Wilkins, 2005;2548.

Stein 1989
Stein A, Cooper PJ, Campbell EA, Day A, Altham PM. Social adversity and perinatal complications: their relation to postnatal depression. *BMJ* 1989;298(6680):1073–4.

Stuchbery 1998
Stuchbery M, Matthey S, Barnett B. Postnatal depression and social supports in Vietnamese, Arabic and Anglo-Celtic mothers. *Social Psychiatry and Psychiatric Epidemiology* 1998;33(10):483–90.

Tierney 2005
Tierney JF, Stewart LA. Investigating patient exclusion bias in meta-analysis. *International Journal of Epidemiology* 2005;34:79–87.

Torem 1992
Torem MS. The use of hypnosis with eating disorders. *Psychiatric Medicine* 1992;10(4):105–18.

Valente 1990
Valente SM. Clinical hypnosis with school-age children. *Archives of Psychiatric Nursing* 1990;4(2):151–6.

Wickberg 1996
Wickberg B, Hwang CP. Counselling of postnatal depression: a controlled study on a population based Swedish sample. *Journal of Affective Disorders* 1996;39(3):209–16.

Younus 2003
Younus J, Simpson I, Collins A, Wang X. Mind control of menopause. *Womens Health Issues* 2003;13(2):74–8.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Harmon 1990

Methods	Randomised controlled trial.
Participants	63 nulliparous, married, white women who: 1) were in the end of the second trimester of their pregnancy, 2) were aged from 18 to 35 years, 3) had no reported history of (a) psychiatric hospitalisation, (b) depression during pregnancy, or (c) obstetric risk (e.g., miscarriage, pre-eclampsia, diabetes, etc)
Interventions	The participants were divided into high and low hypnotic susceptibility groups before receiving 6 sessions of childbirth education and skill mastery using an ischaemic pain task. Half of the participants in each group received a hypnotic induction at the beginning of each session (intervention group); the remaining control participants received relaxation and breathing exercises typically used in childbirth education (control group)
Outcomes	Obstetric outcomes, medication usage, and the MMPI depression scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, insufficient information to permit judgement
Other bias	Low risk	Nothing special.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants were not informed that they were in two treatment conditions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	MMPI is a self-reported measure.

MMPI: Minnesota Multiphasic Personality Inventory (depression scale)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Guse 2006	This was not a RCT. The author created 2 groups, an intervention and comparison group. 23 participants were allocated to each. However, 8 participants were allocated to the control group in accordance with the participants' own request. Thus, we judged that this was a quasi-RCT
Mehl-Madrona 2004	This study did not assess the effectiveness of hypnosis for PND and did not meet our inclusion criteria

PND: postnatal depression
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Cyna 2006

Trial name or title	Hypnosis Antenatal Training for Childbirth (HATCh): a randomised controlled trial
Methods	A single centre, randomised controlled trial using a 3-arm parallel group design in the largest tertiary maternity unit in South Australia
Participants	405 women > 34 and < 39 weeks' gestation, planning a vaginal birth, not in active labour, with a singleton, viable fetus of vertex presentation
Interventions	Antenatal hypnosis training in preparation for childbirth administered by a qualified hypnotherapist with the use of an audio compact disc on hypnosis for re-enforcement; antenatal hypnosis training in preparation for childbirth using an audio compact disc on hypnosis administered by a nurse with no training in hypnotherapy; usual preparation for childbirth with no additional intervention
Outcomes	Primary outcome; the use of pharmacological analgesia during labour and childbirth. Secondary outcomes; the use of oxytocics, the mode of delivery, neonatal Apgar score at 5 minutes < 7 and maternal admission to the high dependency unit or the intensive care unit
Starting date	December 2005.
Contact information	Allan M Cyna: cynaa@cywhs.sa.gov.au
Notes	

Downe 2011

Trial name or title	Self-Hypnosis for Intrapartum Pain Management (SHIP): a single organisation, two-site pragmatic exploratory non-blinded randomised controlled trial with blinded analysis based on intention-to-treat, and contextualised by interviews, focus groups, logs, and questionnaires
Methods	Multicentre pragmatic exploratory non-blinded randomised controlled trial
Participants	800 nulliparous women who all: 1. have a singleton, viable, cephalic pregnancy; 2. are planning a vaginal birth in hospital; 3. have no current history of being under treatment for psychiatric disorders or of hypertensive disorders; 4. speak and read English; 5. consent to take part; 6. who are available to attend the intervention sessions; 7. aged between 18 and 45 years.
Interventions	Intervention group: 1. a hypnosis programme will be provided by 1 of 4 midwives with appropriate training; 2. they will not be present during the labour and birth of study participants; 3. the programmes will be provided in addition to usual care; 4. each programme will be delivered on 1 of the 2 Trust sites, with evening or weekend options, to groups of 5-10 women and their planned birth companions (a maximum total of 20 people) in 2 sessions separated by 3 weeks (32 weeks' gestation, 35 weeks' gestation; 5. each session will last 90 minutes; 6. 4 sets of hypnosis programmes will be run every 4 weeks with evening and weekend options; 7. the hypnosis scripts will be adapted from those tested in the current Australian HATCh Trial; 8. the sessions will include self-hypnosis induction techniques, exercises relating to confidence, coping and strength in labour, suggestions for time distortion, a labour rehearsal involving recurrent fractionation and staircase imagery, and pain control and dissociation techniques. Participants will also be asked to listen to a CD of reinforcement exercises at least once a day until their baby is born. Control group: 'Usual care' will consist of attendance at any antenatal classes usually offered to nulliparous women, and standard clinical care. Women in both groups will be free to request any additional pain relief they require during labour, and this will be emphasised in the information leaflets
Outcomes	Primary outcome: 1. Rates of epidural usage in labour on maternal request. Secondary outcomes: 1. Mode of birth and other maternal labour outcomes. 2. Neonatal well-being. 3. Participants' preferences relating to hypnosis. 4. Anxiety and fear about labour. 5. Recall of labour pain. 6. Ability to manage labour. 7. Satisfaction with self during labour. 8.Clinical and psychological morbidity and well-being. 9. Economic cost-benefit analysis. 10. Experiences of women, their birth companions, and their caregivers 11. Follow-up will continue to 6 weeks postnatally.

Downe 2011 *(Continued)*

Starting date	August 2010
Contact information	Professor Soo Downe: sdowne@uclan.ac.uk
Notes	

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Methods of Data Collection and Analysis to be used in future updates of this review

Data collection and analysis

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratios with 95% confidence intervals.

Continuous data

When continuous data are involved, if outcomes are measured in the same manner across different trials the mean difference will be used. Where the same outcome is being examined but different methods are being employed the standardised mean difference will be used.

Unit of analysis issues

We will include individually-randomised and cluster-randomised trials but will exclude cross-over trials.

Cluster-randomised trials

Cluster-randomised trials will be included in the analyses together with individually-randomised trials. Their standard errors will be adjusted using the methods described in the *Handbook* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and an interaction between the effect of the intervention and the choice of randomisation unit is considered unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For those studies that are included, we will note the levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of the treatment effect by undertaking a sensitivity analysis.
For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

In each meta-analysis we will assess statistical heterogeneity by using the T^2, I^2 and Chi^2 test statistics. If the I^2 statistic is greater than 30% and either T^2 is greater than zero, or there is a low P value (less than 0.10) on the Chi^2 test for heterogeneity, then heterogeneity will be regarded as being substantial.

Assessment of reporting biases

Funnel plots will be used to provide information on reporting biases (such as publication bias) if the meta-analysis consists of 10 or more studies. A visual assessment will be made of funnel plot asymmetry in conjunction with more formal tests for funnel plot asymmetry. The test proposed by Egger 1997, will be used for continuous outcomes, while the test suggested by Harbord 2006 will be used for dichotomous outcomes. If we detect asymmetry in any of these tests or by a visual assessment, we will undertake exploratory analyses to investigate it further.

Data synthesis

Statistical analyses will be undertaken by using the Review Manager software (RevMan 2011). Where it is reasonable to suppose that the same underlying treatment effect is being estimated in studies; i.e. where the same intervention is being examined in trials, and the trials' populations and methods are deemed to be sufficiently similar, a fixed-effect meta-analysis will be used for combining data. If the extent of the clinical heterogeneity is sufficient to expect that different trials will result in differing underlying treatment effects, or if the statistical heterogeneity which is detected is substantial, then a random-effects meta-analysis will be used to generate a summary estimate of whether the average treatment effect across trials can be regarded as being meaningful in clinical terms. The summary of random-effects will be regarded as the average range of possible treatment effects, while we will examine treatment effects differing between trials in terms of their clinical implications. Trials will not be combined if the average treatment effect is not deemed to be meaningful in clinical terms.
When using random-effects analyses, the results will be presented as the average treatment effect with its 95% confidence interval, together with the T^2 and I^2 estimates.

Subgroup analysis and investigation of heterogeneity

We will perform the following three subgroup analyses:

1. the effects of intervention onset (e.g. antenatal and postnatal interventions versus postnatal only interventions);
2. the effects of intervention duration (e.g. single-contact interventions versus multiple-contact interventions);
3. the effects of sample selection criteria (e.g. women with specific risk factors versus the general population).

Subgroup analysis will be restricted to the primary outcome: the development of PND.
For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in the treatment effect between the subgroups.

Sensitivity analysis

We will perform a sensitivity analysis based on trial quality, separating high-quality trials from trials of lower quality. We will define the outcome of subgroup analyses as the development of PND. For the purposes of this sensitivity analysis, we will define 'high quality' as a trial having adequate allocation concealment, and where the percentage of missing data is less than 20%, given the stated importance of attrition as a quality measure (Tierney 2005). If we include any cluster-randomised trials, other sensitivity analyses may also be desirable. If cluster trials have been incorporated with an estimate of the ICC borrowed from a different trial, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

HISTORY

Protocol first published: Issue 4, 2011

Review first published: Issue 6, 2012

CONTRIBUTIONS OF AUTHORS

Mitsuhiro Sado (MS) drafted the protocol under the supervision of Erika Ota (EO), Andrew Stickley (AS) and Rintaro Mori (RM). MS and EO selected and classified studies to be included. AS and RM were involved in the discussion when a consensus was needed. MS wrote the first draft of the review. EO, AS and RM commented upon it and provided feedback. All authors read and approved the final version of the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Keio University School of Medicine, Tokyo, Japan.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have deleted 'outcome measures' from 'Selection of studies' in the Appendices. We added 'death by suicide within one year of the birth' as a secondary outcome. We defined the development of PND more specifically as 'a score of more than 12 on the Edinburgh Postnatal Depression Scale or as a diagnosis by way of a structured diagnostic interview'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hypnosis; Delivery, Obstetric [*psychology]; Depression, Postpartum [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

Ⅳ章

平成25年度総括分担研究報告

平成25年度 厚生労働科学研究費補助金（成育疾患克服等次世代育成基盤研究事業）
「母子保健に関する国際的動向及び情報発信に関する研究」

総括研究報告書

研究代表者　森　臨太郎　国立成育医療研究センター研究所　政策科学研究部長

研究要旨

根拠に基づく母子保健を実現するために、母子保健分野に関する科学的根拠について、国内外の情報を網羅的かつ系統的に収集し、定期的に国内外に情報発信する体制を整備することが必要であり、本研究班はこのような体制整備を通して、我が国における根拠に基づく母子保健を推進し、かつ世界の母子保健に貢献することを目的としている。

少子高齢化と社会保障の今後を念頭に置くと、次世代の市民が健全に育っていく社会の実現と、説明責任に耐えうる政策策定が必要であり、根拠に基づく手法が強く求められている。諸外国において、科学的根拠を集積する手法は、診療方針や保健施策策定の方法論として結実しつつあるが、我が国においては、この系統的レビューの基盤整備はいまだ発展途上である。われわれは、海外関連機関の支援のもと20本の母子保健関連系統的レビューを現在まで出版し、我が国が独立して根拠に基づく母子保健政策・医療を実現するには、人材の強化を通した基盤整備の必要性がある。本年度は、コクラン系統的レビューの著者数およびコクラン系統的レビューの出版が増加し、日本コクランブランチに認定され、この研究班の基盤整備への成果は着実に示されている。

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A. 研究目的

根拠に基づく母子保健を実現するために、母子保健分野に関する科学的根拠について、国内外の情報を網羅的かつ系統的に収集し、定期的に国内外に情報発信する体制を整備することが必要であり、本研究はこのような体制整備を通して、我が国における根拠に基づく母子保健を推進し、かつ世界の母子保健に貢献することを目的としている。

B. 研究方法

①所管課や国内外の関連機関と協議し、母子保健の現重要課題に関して、医療系データベース等を網羅的検索し、検索された研究を系統的に批判的吟味し、結果抽出したうえで統計的に統合（メタ解析）、すなわちコクラン共同計画の方法論に沿った系統的レビューを施行・出版し、広く国内外に発信して情報共有を行う。②国内外関連機関と連携して、プロトコール作成、批判的吟味、メタ解析、結果解釈などの方法論に関するワークショップ及び、学会や教育現場における意識啓発・教育・情報提供を定期的に開催し、同時に、

我が国で系統的レビューを行っている著者や研究者へ方法論や発信手法などに関するきめ細かい支援も行うことで、人材強化を行う。③我が国の出生届・死亡届等政府統計の分析を加えることで情報を多角的に強化する。④日本の母子保健における臨床研究を世界に発信するための検討を行う。⑤国内外の機関との関係を強化し、新たに連携できる人材や組織の発掘や育成を行う。

（倫理面への配慮）

系統的レビュー（メタ解析）は、一般的に公開されている研究情報をもとに行う二次データ分析として位置付けられているため、倫理的な問題は少ないが、疫学研究の倫理指針および、コクラン共同計画の国際倫理指針など、国内外の社会的研究に関するガイドラインを遵守した。

倫理的課題が大きい、ヒトゲノム研究、ヒト幹細胞を用いる研究、遺伝子治療研究、動物実験は行っていない。

C. 研究結果

ネットワークメタアナリシスの批判的吟味：古川　壽亮

複数の治療選択肢を同時に比較するネットワークメタアナリシスの発表が急激に増えている。たとえば、大うつ病の急性期の薬物療法について、すでに3本のネットワークメタアナリシスが発表されている。しかし、医学文献のコンシューマ（医師、患者、政策立案者など）から見ると、異なるネットワークメタアナリシスが異なった結論を導いているように読め、実際に結論が異なるのか、もしそうだとしたらどのネットワークメタアナリシスを信用すべきなのか、批判的吟味の指針がほしい。本研究は、上記の大うつ病のネットワークメタアナリシスを例に、批判的吟味の指針を提示した。

同一の疾患に対して複数の治療を比較するネットワークメタアナリシスは臨床判断に不可欠になってくるであろう。今後、ネットワークメタアナリシスを臨床家が利用できるためには、ネットワークメタアナリシスの論文がカバーすべき項目などのガイドラインが必要である。

妊産婦の保健を対象とした系統的レビューに携わる人材発掘の調整と育成（大槻　克文）

日本におけるコクラン共同計画の認知度は低く、特に周産期領域での人材発掘とその育成は喫緊の課題である。本分担研究では、題目の通り『妊産婦の保健を対象とした系統的レビューに携わる人材発掘の調整と育成』を平成25年度の目的とした。

今年度は、1．コクランレビューワークショップ参加者に対する周産期領域、特に産科領域からのサポート、2．周産期領域での学会等における「コクランレビューに関する説明会の開催、3．学会や医局でのロビー活動（啓発活動）、4．次年度の方策検討、について活動を行った。

ワークショップへの出席者には周産期医療の第一線で勤務質ている者は少なく、本邦の医療従事者の職務環境（多忙など）が影響している可能性が垣間見られた。学会や会合で若い先生へ声を掛け、コクラン共同研究の説明を行うも、多忙と英語力への不安あるが故に興味を有することができないという意見が大多数をしてめていた。

以上より、本邦でのコクラン共同研究、特に『妊産婦の保健を対象とした系統的レビューに携わる人材発掘の調整と育成』には多大の労力、時間、臨床家の職務環境整備などが必要であることが改めて認識された。

産科領域での人材発掘と育成に関しては、今一度今後の方策を緻密に考える必要はあることが明らかであった

次世代育成のための社会科学分野における科学的根拠（原田　隆之）

次世代育成のためには社会科学分野においても，医療や公衆衛生分野同様，国内外のエビデンスを収集し，情報発信をする基盤を構

築するとともに，それを元にして我が国におけるエビデンスに基づいた政策決定と母子保健を推進していくことが重要である。本研究では，社会科学分野における系統的レビューの基盤整備を行うことを主たる目的とする。

本年度は，コクランレビューの執筆，キャンベル共同計画との連携，キャンベルレビューの翻訳等を行い，エビデンスの産出，発信，意識啓発などに努めた。我が国の社会科学分野においては，エビデンス・ベーストがまだ十分に浸透していないが，本研究は，ソフト，ハード両面に及ぶ取り組みの基礎を構築するための一助になったと考えられる。

エビデンスに基づく母子保健のための意思決定には，医療分野のみならず，社会科学分野での基盤整備や情報発信が欠かせない。わが国の社会科学分野において，このような取り組みはまだ始まったばかりであるが，今後もコクランレビューやキャンベルレビューの執筆，情報発信，啓発活動など，さらには医療分野との連携等を継続的に実施していくことが必要である。

小児保健に関する科学的根拠に関する研究（田村　正徳、加藤 稲子、照井 克生、松田 祐典）

周産期医療に関する科学的根拠について、系統的に情報を収集し、国内外へ情報発信する。科学的根拠を適切に評価するため、コクラン共同計画へ参加し、方法論や発信手法を習得した人材育成を行う。

本研究では、帝王切開時の全身麻酔薬の選択に関するタイトル登録を完了し，プロトコール投稿を行った。今回のプロトコール登録の際の研究結果より、全身麻酔の導入薬による違いにより、新生児抑制の頻度が異なり、児の予後へ影響する可能性が示唆された。また，揮発性吸入麻酔薬の過剰投与により、分娩後出血量が増加し、母体の予後へ影響する可能性も示唆された。母児双方の予後改善という観点から本研究の有用性は高いと考えられた。

母子保健分野における麻酔科医の役割は、帝王切開の増加とともに、大きくなると予測される。本研究を通じて、科学的根拠に基づく情報を発信することは、帝王切開数が増加の一途を辿っている我が国における母子保健課題に関して、予防介入の施策として非常に有用だろう。

国際蘇生法連絡委員会(International Liaison Committee on Resuscitation: ILCOR) におけるガイドライン策定におけるコクランレビューの活用の検討（田村　正徳、杉浦　崇浩）

国際蘇生法連絡委員会(International Liaison Committee on Resuscitation: ILCOR)では2015年のコンセンサスの改定に向けGRADE(Grading of Recommendations Assessment, Development and Evaluation)システムを導入し、蘇生に関するガイドライン策定予定である。今回ILCORの旧論文評価法の改善のため、GRADEシステムを採用した既存のコクランレビューを活用することが有用かを検討する。その試験導入として2012年12月のILCORの会議においてコクランレビューを活用したGRADE evidence profile およびGRADE finding tableを例として発表した。

コクランレビューを活用することにより、抽出論文が妥当であることが確認できた。またその評価結果はILCOR会議においてけ受け入れ良好であった。コクランレビューを活用することによりILCORガイドライン作成において、よりその質を改善し、また作業をスムースにしうる。

コクランレビューを活用することにより、より対象とする文献抽出の信頼性が確認できた。またその抽出結果はILCOR会議においてけ受け入れ良好であった。このことからコクランレビューを活用することにより

ILCOR ガイドライン作成においてもより作成過程をスムースにしうると推測された。

人材育成および助産ケアに関する科学的根拠（堀内　成子、八重　ゆかり、片岡　弥恵子、江藤　宏美）

コクラン活動に関連するセミナー、シンポジウム開催およびコクラン・システマティック・レビュー作成を通して、看護・助産分野におけるコクラン・コラボレイション活動に関する知識の普及と人材育成を行う。

平成 25 年度は、コクラン・システマティック・レビューワー育成を目指した聖路加コクラン塾で基礎セミナー、第 27 回日本助産学会学術集会プレコングレスおよびシンポジウムを開催した。

レビュー活動の進捗状況では、継続して分析・作成していた【分娩後出血に対する予防介入効果】が遂にコクラン・システマティック・レビューとして 2013 年 11 月に採用された。また【分娩第 3 期における出血に対するホメオパシーの効果】に関するコクラン・システマティック・レビューのタイトル登録申請が受理され、プロトコル作成中である。

非ランダム化研究に対する系統的レビューの方法論の近年の動向に関する研究（米本直裕）

介入効果の比較を行う多くのコクランレビューにおいて、対象とする研究のデザインはランダム化比較試験である。しかし、ランダム化比較試験が行われていない研究テーマの場合においては、ランダム化が行われていない介入研究、観察研究（Non-randomized studies: NRS）を対象とした系統的レビューが行われる場合もある。本研究では、このような NRS に対する系統的レビューについての方法論に関する近年の動向、主にコクラン共同計画の専門グループで行われている議論、バイアス評価のツールについて報告する。

人材育成および日本コクランブランチ設立にむけて（大田えりか、エマ・バーバラ、ガンチメグ・トゴバタラ、シャルーク・サデクア）

網羅的・系統的に集積した科学的根拠の成果は医療文化や経済的背景による科学的根拠を含めて整理されるため、国内外の母子保健・医療へレビューの結果が利用され、我が国の保健医療研究による国際社会への貢献としても大きな波及効果があると考えられる。母子保健分野に関する科学的根拠を定期的に国内外に情報発信する基盤整備のための、コクラン共同計画の啓蒙活動の実施、およびコクラン系統的レビュー出版を通した人材育成、を目的とした。

本分担班では、3 つの活動を行っている。まず第一に、母子保健分野に関する科学的根拠を定期的に国内外に情報発信する基盤整備を目的とし、コクラン系統的レビューを出版するためのセミナー、ワークショップ、講演、講義などを開催し、人材育成、啓蒙活動を行った。第二に、コクラン系統的レビューの出版である。本年度は、妊娠出産グループサテライトからコクラン系統的レビューが 6 本、コクランプロトコールが 6 本の計 12 本出版され、基盤整備の成果がでてきている。第三に、国際社会への貢献として、日本コクランブランチ設立にむけてプロポーザルを、コクラン豪州センターと連携して立案・提出し日本支部としての設立を許可された。また、WHO との連携を行い、WHO の妊娠期感染症のガイドライン作成を行っている。

我が国の政府統計からみた早産と低出生体重予防法の模索（森　臨太郎、大田えりか、森崎　菜穂）

我が国は他の先進国と比べ低出生体重児の増加が著しく、これは早産および子宮内発育不全の双方の増加に起因するものであることが疫学研究により示唆されている。

本研究の目的は、政府統計調査に含まれる周

産期関連情報を解析することにより、我が国における母児の健康状態を把握し、それに基づいた周産期における臨床的介入がを提示することである。

約30年間の我が国の人口動態調査・出生票を分析し、増加している低出生体重児と早産の経年変化とその要因を明らかにした。高齢出産の低出生体重児出生のリスクは、近年減少しており、差はなかった。早産に限ると、高齢出産は1.5倍リスクは高いが、減少傾向であった。これは、20代での早産および低出生体重児出生が増加している影響と考えられる。今後は、若い世代の低出生体重児出生予防の対策が課題となる。

我々は解析において、日本人は喫煙や飲酒などは減少傾向である一方、高齢化や初産など、早産や子宮内発育不全のリスクである母体因子が増えていた。また、リスクがある児において選択的に計画分娩が増加しており、この傾向は主に大都市に顕著にみられた。しかし一方で、1990年を境に大都市と比較し中小都市において、より在胎週数が短縮していた。この原因の一つに、医療施設の偏在によるアクセスの差が計画分娩の施行基準に地域差を与えている可能性がある。

また、研究において日本人女性の独自性としてやせ女性の多さが際立っていた。やせ女性の割合が多い日本においては、妊娠中の体重増加の抑制は低出生体重児出生や早産に繋がる可能性があり、特にやせ気味の女性には妊娠中の栄養摂取に関して適切な指導が必要であると思われる。

D. 考察

所管課からの要望により、緊急帝王切開に伴う母体へのリスクと、施術に合併する出血リスクについてWHO妊産婦調査の2次解析を行い、母子保健行政に貢献した。7月の第49回日本周産期・新生児医学会学術集会（横浜パシフィコ）では、コクラン妊娠出産サテライト日本支部設立記念シンポジウムを開催した。イギリスのコクラン妊娠出産支部から代表のジムネイルソン教授を招聘し、シンポジウムおよび講演会（成育）を行った。

コクランオーストラリアセンターの日本支部ブランチのプロトコールを作成し、申請を行い認定された。系統的レビューの導入ワークショップおよび講義を日本各地の講座・研究所・大学等で、延べ200名以上の参加者を得て開催し、好評を得た。また、定員30名で満員となった系統的レビューのプロトコール作成ワークショップを開催した。2月には、系統的レビューのフルレビューのワークショップの開催を予定している。

本年度は、研究班全体でコクランプロトコールが6本、コクラン系統的レビューが10本出版された。母子保健分野のレビューはその内、コクランプロトコールが4本、コクラン系統的レビューが5本出版を達成し、以下の医療や政策上の重要課題に関して、最新の科学的根拠を質の高い手法でまとめ発信できた。
この研究班のこの基盤整備への成果は着実に示されている。

謝辞

コクラン共同計画の本部、コクラン妊娠出産グループ、世界保健機関、日本医療機能評価機構、ワークショップの参加者、関連研究者に協力を感謝する。

E. 引用文献・出典

なし

F. 研究発表

1. 論文発表

1) Shahrook S, Mori R, Ochirbat T, Gomi H. Strategies of testing for syphilis during pregnancy (Protocol). Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD010385. DOI: 10.1002/14651858.CD010385.

2) Balogun OO, Hirayama F, Wariki WMV, Koyanagi A, Mori R. Interventions for improving outcomes for pregnant women who have experienced genital cutting. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD009872. DOI: 10.1002/14651858.CD009872.pub2.

3) Kawaguchi A, Isayama T, Mori R, Minami H, Yang Y, Tamura M. Hydralazine in infants with persistent hypoxemic respiratory failure. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD009449. DOI: 10.1002/14651858.CD009449.pub2.

4) Sasaki H, Yonemoto N, Hanada N, Mori R. Methods for administering subcutaneous heparin during pregnancy. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD009136. DOI: 10.1002/14651858.CD009136.pub2.

5) Tsuruta H, Karim D, Sawada T, Mori R. Trained medical interpreters in a face-to-face clinical setting for patients with low proficiency in the local language (Protocol). Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD010421. DOI: 10.1002/14651858.CD010421.

6) Wariki WMV, Nomura S, Ota E, Mori R, Shibuya K. Interventions for reduction of stigma in people with HIV/AIDS (Protocol). Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD006735. DOI: 10.1002/14651858.CD006735.pub2.

7) Abe SK, Balogun OO, Ota E, Mori R. Supplementation with multimicronutrients (excluding vitamin A) for breastfeeding women for improving outcomes for the mother and baby (Protocol). Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD010647. DOI: 10.1002/14651858.CD010647.

8) Kenyon S, Tokumasu H, Dowswell T, Pledge D, Mori R. High-dose versus low-dose oxytocin for augmentation of delayed labour. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD007201. DOI: 10.1002/14651858.CD007201.pub3.

9) Yonemoto N, Dowswell T, Nagai S, Mori R. Schedules for home visits in the early postpartum period. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD009326. DOI: 10.1002/14651858.CD009326.pub2.

10) Nishi D, Shirakawa MN, Ota E, Hanada N, Mori R. Hypnosis for induction of labour (Protocol). Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD010852. DOI: 10.1002/14651858.CD010852.

11) Yaju Y, Kataoka Y, Eto H, Horiuchi S, Mori R. Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD009328. DOI: 10.1002/14651858.CD009328.pub2.

12) Shahrook S, Hanada N, Sawada K, Ota E, Mori R. Vitamin K supplementation during pregnancy for improving outcomes (Protocol). Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD010920. DOI: 10.1002/14651858.CD010920.

G. 知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

※ 図表は報告論文の末尾にまとめて掲載

緊急帝王切開に伴う母体へのリスクと、施術に合併する出血リスクについて

世界妊産婦調査に関する日本のデータ分析から

成育疫学研究室・大田えりか

成育政策科学研究部・森臨太郎

背景

分析に使用した調査は、WHO(世界保健機構)が行う「WHO 周産期に関する世界調査(WHO Global Survey on Maternal and Perinatal Health)」の一部で、2008 年に日本国内にて行った部分です。第一回の調査は 2004 年に中南米で行われ、2005 年にはアフリカで、そして 2006 年にアジアで行われました。この WHO 周産期に関する調査は主に、

- 周産期保健サービスと転帰についての全世界的なデータシステムを作ること
- 出産様式、分娩時ケアと母子周産期保健の成果との関係について調べること
- 出産様式の違いと母子周産期保健の成果について各地域の概略を把握すること
- 無作為化比較試験を含む疫学研究を今後行っていけるよう世界中の医療施設の能力を強化しネットワークを構築すること
- 国ごとの援助プログラム策定のための基礎データを得ること

を目的としてされています。

方法としては、国の選定、施設の選定、データ収集、解析という段階が含まれます。

日本における施設の選定

首都のある東京の他、46道府県よりランダムで 2 地域を選択した。選ばれた 3 地域から年間分娩件数 1000 件以上である施設すべてを対象機関として選択した。年間分娩件数が 1000 件以上の施設が一つもない都道府県の場合は、750 件以上の施設すべてを選択し、収集期間を 4 カ月とした。対象は施設内で指定された 3 か月間(年間分娩数 750 以上 1000 未満の場合には 4 カ月)に分娩を経験した妊産婦全員の調査をした。

結果

2008 年に日本で行われた WHO 周産期に関する世界調査から、8 箇所の分娩施設から 3351 名の女性の出産時の情報を収集した。そのうち 2654 名(79.2%)が経膣出産であり、697 名(20.8%)が帝王切開であった。

表 1. 緊急 CS と計画 CS の医学的適応

CS 医学的適応理由	緊急 CS N=286	計画 CS N=411	P value
Suspected fetal growth restiction	15 (5.4%)	15 (3.6%)	0.307
Fetal distress and other fetal indication	132 (46.1%)	9 (2.2%)	<0.001
Other maternal and obstetric compliaction	70 (24.5%)	39 (9.5%)	<0.001
Eclampsia	34 (11.9%)	11 (2.9%)	<0.001

Postterm	0	1 (0.2%)	
3rd trimester vaginal bleeding	9 (3.1%)	2 (0.5%)	0.006
Cephalo-pelvic disproportion	69 (24.1%)	15 (3.6%)	<0.001
Suspected/ imminent uterine rupture	15 (5.2%)	9 (2.2%)	0.03
Postmortem CS	3 (1.1%)	3 (0.7%)	0.654
Breech or other malpresentation	45 (15.7%)	118 (28.7%)	<0.001
Previous CS	26 (9.1%)	201 (48.9%)	<0.001
Failed induction	38 (13.3%)	0	
Tubal ligation	1 (0.4%)	16 (3.9%)	0.003
Maternal request	7 (2.4 %)	1 (0.2%)	0.007
Previous uterine surgery	6 (2.1%)	28 (6.8)	0.004
Multiple	23 (8.0%)	63 (15.3%)	0.004

表 2. 母親の背景因子

Maternal characteristics	全数	計画 CS	緊急 CS	p-value
Delivery	3351	411 (12.3)	286 (8.5%)	
Age				
>20	30 (0.9%)	1 (0.2%)	0	0.099
20-34	2356 (70.3%)	242 (58.9%)	190 (66.4%)	
>35	965 (28.8%)	168 (40.9%)	96 (33.6%)	
Marital status / Single	53 (1.6%)	4 (1.0%)	4 (1.4)	0.604
Eduaction / <=12 years	667 (19.9%)	90 (21.9%)	46 (16.1%)	0.057
Parity				
0	1450 (43.3%)	249 (17.7%)	77 (26.9%)	<0.001
1-2	1813 (54.1%)	151 (36.7%)	207 (72.4%)	
>3	88 (2.6%)	11 (2.7%)	2 (0.7%)	
Twin delivery	110 (3.3%)	63 (15.3%)	26 (9.1%)	0.015
Infant birthweigh >90th (>3486g)	338 (10.1%)	23 (5.6%)	26 (9.1%)	0.076
Breach or malpresentation	169 (5.0%)	40 (14.0%)	117 (28.5%)	<0.001
Maternal height				
<1.50m	134 (4.0%)	31 (7.5%)	16 (5.6)	0.313
>=1.50m	2567 (96.0%)	380 (92.5%)	270 (94.4%)	
BMI				
<18.5kg/m^2	22 (0.7%)	2 (0.7%)	5 (1.2%)	0.552
18.5-25	1950 (58.2%)	150 (52.4%)	201 (48.9%)	
>25	1.379 (41.1%)	134 (46.9%)	205 (49.9%)	
Complications during pregnacy				
No	2361 (89.0%)	254 (61.8%)	178 (62.2%)	0.907
Yes	272 (11.0%)	157 (38.2%)	108 (37.8%)	

Eclampsia (preeclampsia and pregnancy induced hypertension)				
No	2535 (95.5%)	393 (95.6%)	245 (85.7%)	<0.001
Yes	119 (4.5%)	18 (4.4%)	41 (14.4%)	

表 3. 有害なアウトカム

Outcomes	緊急 CS N=286	計画 CS N=411	P value
Maternal outcomes			
Postnatal Antibiotic treatment (as proxy of infection)(A)	89 (31.1%)	119 (28.9%)	0.539
Prophylactic antibiotic	281 (98.2%)	404 (98.3%)	0.964
Maternal admission to ICU (B)	5 (1.8%)	6 (1.5%)	0.893
Days in ICU (>3days)	2 (40%)	6 (100%)	
Uteronic or blood transfusion for postpartum hemorrhage (C)	59 (20.6%)	82 (19.6%)	0.827
Hysterectomy (D)	1 (0.4%)	2 (0.5%)	0.786
Having any of A-D	117 (40.9%)	161 (39.2)	0.697
Having any of A-D (adjusted for age education parity complication during pregnancy)	REF	AOR 0.94 (0.67 – 1.31)	
Perinatal outcomes			
Stillbirth (1)	1 (0.4%)	1 (0.2%)	0.796
Apgar score at 5min <7 (2)	10 (3.5%)	1(0.2%)	0.001
Neonatal admission to ICU (3)	110 (38.5%)	101 (24.6%)	<0.001
7 days at the ICU	65 (59.0%)	34 (32.7%)	
Early neonatal death (4)	1 (0.4%)	1 (0.2%)	0.796
Having any of 1-4	111 (38.8%)	102 (24.8%)	<0.001
Having any of 1-4 r(adjusted for age education parity complication during pregnancy and gestational age at birth)	REF	AOR 0.52 (0.34 -0.78)	

まとめ

緊急 CS では、分娩時に児の状態が悪くなる場合や、妊娠性高血圧症候群などで医学適応になる場合が多く、計画 CS は、逆子や多胎、前回 CS での適応が多かった。そのため、出生児の NICU 入院は緊急 CS で多かったが、それはもともとハイリスク群が多いためである。母親のアウトカムには、統計的な有意差は見られず、特に出血も有意差はなかった。また、術前の抗生剤投与も両群とも98%実施されており、医療提供の差はみられなかった。