BACKGROUND

Description of the condition

Length of labour varies between women, with first labours lasting on average eight hours (and unlikely to last more than 18) and second and subsequent labours lasting on average five hours (and unlikely to last more than 12 hours). Progress in labour should take into account not just cervical dilatation, but also descent and rotation of the fetal head and strength, duration and frequency of contractions. The definition of delay varies, but cervical dilatation of 2 cm in four hours is widely accepted as being normal (NICE 2007). The incidence of delay in labour is not accurately known. Some evidence suggests that up to one-third of women in their first labours experience delay (Williams 1998). Other evidence suggests the incidence of prolonged labour is more than 10% of women (DGH 2004), and about 40% to 60% of these women have their labour augmented with oxytocin due to slow progress or other reasons in first stage of labour (Gottvall 1997; Impey 2000). Many women would have already had their membranes ruptured spontaneously, and amniotomy is not recommended as routine practice (Smyth 2007).

Description of the intervention

Oxytocin has been widely used in obstetric practice and increases both the frequency and strength of uterine contractions in labour. In doses under 4 mU/min, it has been shown to shorten labour but not alter mode of birth (Wei 2007).

How the intervention might work

It is plausible that increasing both the dose and speed of the oxytocin will increase the number of women having a spontaneous vaginal birth. It is currently routine treatment for women delayed in labour, and while it does carry potentially harmful side effects, clinicians routinely effectively titrate the dose against uterine contractions.

Why it is important to do this review

Evidence suggests that high doses of oxytocin may increase spontaneous vaginal birth but not enough is known about neonatal outcomes or how this might affect women's birth experience. One non-Cochrane systematic review included trials that compared high versus low doses of oxytocin for augmentation of labour (Wei 2010) but some of the trials were undertaken in the context of active management of labour.
This review intends to assess the risks and benefits of high- and low-dose regimens of oxytocin for augmentation of labour due to delayed first stage of labour. We have excluded trials undertaken in the context of active management of labour (one-to-one continuous support, strict definition of established labour, early amniotomy, routine two-hourly vaginal examinations and oxytocin if labour becomes slow), or as part of induction of labour.

OBJECTIVES

To compare starting dose as well as increment dose of oxytocin for augmentation in delayed labour to determine whether augmentation by high dose of oxytocin improves labour outcomes and women's satisfaction.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials. We intended to include both published or unpublished trials.

Types of participants

Women in labour assessed as requiring augmentation by oxytocin for delay or slow progress in labour. We only included women with live fetuses.

Types of interventions

High starting and increment dose (6 micro unit (mU) per minute or more) of oxytocin for augmentation in delayed labour compared with low dose (less than 4 mU per minute). We defined amount of oxytocin as below:

- high-dose regimens: defined as starting dose and increment of equal to or more than 6 mU per minute;
- low-dose regimens: defined as starting dose and an increment of less than 4 mU per minute;
- increase interval: between 15 and 40 minutes.

The separation of low and high doses is based on an arbitrary decision.

Types of outcome measures

Primary outcomes

1. Perinatal mortality rate (as defined by trial authors)
2. Neonatal mortality rate

3. Caesarean section rate
4. Women's satisfaction (measured quantitatively using validated questionnaires)
5. Length of labour

Secondary outcomes

1. Spontaneous vaginal birth
2. Instrumental vaginal birth
3. Incidence of hyperstimulation (contracting greater than five in 10 minutes for at least 20 minutes with fetal heart rate changes)
4. Incidence of ruptured uterus
5. Diagnosis of chorioamnionitis
6. Incidence of postpartum haemorrhage (blood loss more than 500/1000 mL)
7. Use of epidural analgesia
8. Incidence of abnormal cardiotocography (considered only if blindly assessed)
9. Incidence of women's pyrexia
10. Incidence of dystocia
11. Neonatal outcomes of Apgar scores, umbilical cord pH, neurological morbidity, admission to special care baby units

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (31 May 2013).
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 retrieved studies.
We did not apply any language restrictions.

Data collection and analysis

We used the following methods when assessing the reports identified by the search.

Selection of studies

Review authors Rintaro Mori (RM), Hironobu Tokumasu (HT), Therese Dowswell (TD) and Sara Kenyon (SK) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We intended to resolve any disagreement through discussion or, if required, consult Debbie Pledge (DP); there was no disagreement found.

Data extraction and management

We designed a form to extract data prior to the review. For eligible studies, RM, HT and TD extracted the data using the agreed form, which was checked by SK. We resolved discrepancies through discussion or, if required, we planned to consult DP (though we were able to resolve all discrepancies by discussion). We entered data into Review Manager software (RevMan 2012) and checked for accuracy.

Assessment of risk of bias in included studies

RM, HT, TD and SK independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved all disagreement by discussion.

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

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

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

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

We describe for each included study the method used to conceal allocation to interventions prior to assignment and assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding of participants, personnel and outcome assessment (checking for possible performance bias)

We describe for each 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;
- low, high or unclear risk of bias for outcome assessment.

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

We describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or was supplied by the trial authors, we re-included missing data in the analyses which we have undertaken.
We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. 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)

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

- low risk of bias (where it is 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 are reported incompletely and so cannot be used; study fails 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)

We describe for each included study any important concerns we had about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- 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 studies are 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 considered it is likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where trials examined the same intervention, and the trials' populations and methods were judged to be sufficiently similar. Where we suspected clinical or statistical heterogeneity between studies, sufficient to suggest that treatment effects might differ between trials, we carried out random-effects meta-analysis.

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this review. However, if we identify cluster-randomised trials for inclusion in future updates, we will include them in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* 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 the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

Cross-over trials

We did not include cross-over trials.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data (over 10% for outcomes where data were collected in labour) in the overall assessment of treatment effect by using Sensitivity analysis. In this version of the review we did not carry out planned sensitivity analysis because labour outcomes studies were rated as being at low risk of bias with little loss of follow-up or missing data reported.
For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and analysed 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 was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if a T^2 was greater than zero and either an I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

Where we suspected reporting biases (such as publication bias), we attempted to contact study authors asking them to provide missing outcome data.
In future updates of this review, if more data become available and there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes, we will use the test proposed by Egger 1997, and for dichotomous outcomes, we will use the test proposed by Harbord 2006. If we detect asymmetry in any of these tests or by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if high statistical heterogeneity was identified, we planned to use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. For random-effects analysis the effect estimate represents the average treatment effect and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.
If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We intended to conduct planned subgroup analysis using the methods described by Deeks 2001 and set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. By parity (nulliparous versus multiparous women).
2. By previous experience of caesarean section (women who had a caesarean before this delivery versus those who had not).

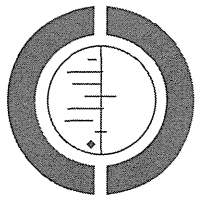
We planned to use the following outcomes in subgroup analysis.

- Perinatal mortality rate.
- Neonatal mortality rate.
- Women's satisfaction.
- Mode of birth.

We were only able to carry out limited subgroup analysis due to insufficient data. We assessed differences between subgroups using the subgroup interaction tests available in Revman (RevMan 2012).

Schedules for home visits in the early postpartum period (Review)

Yonemoto N, Dowswell T, Nagai S, Mori R



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[Intervention Review]

Schedules for home visits in the early postpartum period

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ABSTRACT

Background

Maternal complications including psychological and mental health problems and neonatal morbidity have been commonly observed in the postpartum period. Home visits by health professionals or lay supporters in the weeks following the birth may prevent health problems from becoming chronic with long-term effects on women, their babies, and their families.

Objectives

To assess outcomes for women and babies of different home-visiting schedules during the early postpartum period. The review focuses on the frequency of home visits, the duration (when visits ended) and intensity, and on different types of home-visiting interventions.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (28 January 2013) and reference lists of retrieved articles.

Selection criteria

Randomised controlled trials (RCTs) (including cluster-RCTs) comparing different types of home-visiting interventions enrolling participants in the early postpartum period (up to 42 days after birth). We excluded studies in which women were enrolled and received an intervention during the antenatal period (even if the intervention continued into the postnatal period) and studies recruiting only women from specific high-risk groups, (e.g. women with alcohol or drug problems).

Data collection and analysis

Study eligibility was assessed by at least two review authors. Data extraction and assessment of risk of bias were carried out independently by at least two review authors. Data were entered into Review Manager software.

Main results

We included data from 12 randomised trials with data for more than 11,000 women. The trials were carried out in countries across the world, and in both high- and low-resource settings. In low-resource settings women receiving usual care may have received no additional postnatal care after early hospital discharge.

The interventions and control conditions varied considerably across studies with trials focusing on three broad types of comparisons: schedules involving more versus fewer postnatal home visits (five studies), schedules involving different models of care (three studies), and home versus hospital clinic postnatal check-ups (four studies). In all but two of the included studies, postnatal care at home was delivered by healthcare professionals. The aim of all interventions was broadly to assess the wellbeing of mothers and babies, and to provide education and support, although some interventions had more specific aims such as to encourage breastfeeding, or to provide practical support.

For most of our outcomes only one or two studies provided data, and overall results were inconsistent.

There was no evidence that home visits were associated with improvements in maternal and neonatal mortality, and no strong evidence that more postnatal visits at home were associated with improvements in maternal health. More intensive schedules of home visits did not appear to improve maternal psychological health and results from two studies suggested that women receiving more visits had higher mean depression scores. The reason for this finding was not clear. There was some evidence that postnatal care at home may reduce infant health service utilisation in the weeks following the birth, and that more home visits may encourage more women to exclusively breastfeed their babies. There was some evidence that home visits are associated with increased maternal satisfaction with postnatal care.

Authors' conclusions

Overall, findings were inconsistent. Postnatal home visits *may* promote infant health and maternal satisfaction. However, the frequency, timing, duration and intensity of such postnatal care visits should be based upon local needs. Further well designed RCTs evaluating this complex intervention will be required to formulate the optimal package.

PLAIN LANGUAGE SUMMARY

Home visits in the early period after the birth of a baby

Health problems for mothers and babies commonly occur or become apparent in the weeks following the birth. For the mothers these include postpartum haemorrhage, fever and infection, abdominal and back pain, abnormal discharge, thromboembolism, and urinary tract complications, as well as psychological and mental health problems such as postnatal depression. Mothers may also need support to establish breastfeeding. Babies are at risk of death related to infections, asphyxia, and preterm birth. Home visits by health professionals or *lay supporters in the early postpartum period may prevent health problems from becoming long-term, with effects on women, their* babies, and their families. This review looked at different home-visiting schedules in the weeks following the birth.

We included 12 randomized trials with data for more than 11,000 women. Some trials focused on physical checks of the mother and newborn, while others provided support for breastfeeding, and one included the provision of practical support with housework and childcare. They were carried out in both high-resource countries and low-resource settings where women receiving usual care may not have received additional postnatal care after early hospital discharge.

The trials focused on three broad types of comparisons: schedules involving more versus less postnatal home visits (five studies), schedules involving different models of care (three studies), and home versus hospital clinic postnatal check-ups (four studies). In all but two of the included studies postnatal care at home was delivered by healthcare professionals. For most of our outcomes only one or two studies provided data and overall results were inconsistent.

There was no evidence that home visits were associated with reduced newborn deaths or serious health problems for the mothers. Women's physical and psychological health were not improved with more intensive schedules of home visits. Overall, babies were less likely to have emergency medical care if their mothers received more postnatal home visits. More home visits may have encouraged more women to exclusively breastfeed their babies. The different outcomes reported in different studies, how the outcomes were measured, and the considerable variation in the interventions and control conditions across studies were limitations of this review. The studies were of mixed quality as regards risk of bias.

More research is needed before any particular schedule of postnatal care can be recommended

BACKGROUND

Description of the condition

The postpartum period, defined by the World Health Organization (WHO) as *the period from childbirth* to the 42nd day following delivery (WHO 2005), is critical for both mothers and newborns. An estimated 529,000 maternal deaths occur worldwide each year because of pregnancy-related complications in the antenatal, intrapartum, and postpartum periods, especially in resource-limited settings (WHO 2005).These deaths are often sudden and unpredictable, with 11% to 17% occurring during childbirth itself and 50% to 71% occurring during the postpartum period (WHO 2005). Maternal health problems commonly observed in the postpartum period include postpartum haemorrhage, fever, abdominal and back pain, abnormal discharge, puerperal genital infection, thromboembolic disease, and urinary tract complications (Barlow 2008), as well as psychological and mental health problems such as postnatal depression. The postpartum period is also critical for newborns. Every year approximately 3.7 million babies die in the first four weeks of life. Most of these infants are born in developing countries and most die at home. Nearly 40% of all deaths of children younger than five years old occur within the first 28 days of life (neonatal or newborn period), but three causes-infections, asphyxia, and preterm birth-account for nearly 80% of these deaths (WHO/UNICEF 2009). Moreover, the postpartum period is a time of transition for women and their families, who are adjusting on physical, psychological, and social levels (Shaw 2006). In most developed countries, postpartum hospital stays are often shorter than 48 hours following a vaginal birth; thus most postpartum care is provided in community and ambulatory-care settings. Early intervention in the postpartum period may prevent health problems from becoming chronic with long-term effects on women, their babies, and their families.

Description of the intervention

The purpose of a home-visiting program is to provide support at home for mothers, babies, and families by health professionals or skilled attendants. However, a single clearly defined methodology for this intervention does not exist. Further, the term "home visiting" is used differently in various contexts (AAP 2009). Since the 1970s, the length of hospital stay after childbirth has fallen dramatically in many high-resource settings. Early postnatal discharge of healthy mothers and term infants does not appear to have adverse effects on breastfeeding or maternal depression when women are offered at least one nurse-midwife home visit after discharge (Brown 2002). Home-visiting programs provide breastfeeding and hygiene education, parenting and child health instruction, and general support to families, successfully addressing many of the barriers to access including transportation issues, initiation of timely care, and completeness of services (AAP 1998; AAP 2009). Several trials have assessed the impact of home-visiting programs, especially effects on child abuse and neglect in vulnerable families (Donovan 2007; Olds 1997; Quinlivan 2003). Others focused on the effectiveness and cost-effectiveness of intensive home-visiting programs (Barlow 2006; Carabin 2009; McIntosh 2009). Some home-visiting programs have specifically targeted high risk groups such as women suffering domestic abuse (intimate partner violence) or families that are economically or socially disadvantaged. Home-visiting programs for high risk groups or those by child health nurses may include components during pregnancy and may continue over many months or years; such programs are outside the scope of this review and have been addressed in other Cochrane reviews (Bennett 2006; Bilukha 2013; Macdonald 2005; Turnbull 2012). In this review we focus on the early postnatal period following discharge from hospital.

In 2009, WHO and the United Nations Children's Fund recommended home visits by a skilled attendant in resource-limited settings. In high-mortality settings and where access to facility-based care is limited, at least two home visits are recommended for all home births: the first visit should occur within 24 hours of the birth, the second visit on day three, and if possible, a third visit should be made before the end of the first week of life (day seven). For babies born in a healthcare facility, the first home visit was recommended to be made as soon as possible after the mother and baby return home with remaining visits following the same schedule as for home births (WHO/UNICEF 2009).

A recent review demonstrated the effectiveness of community-based intervention packages in improving neonatal outcomes and reducing maternal and neonatal morbidity and mortality in resource-limited settings; home visiting is the one of the main components in each of these intervention packages. This review offers encouraging evidence of the value of integrating maternal and newborn care in community settings (Lassi 2010). We, therefore, did not include intervention packages of continuous care with components of antenatal or hospital care in our review.

How the intervention might work

In high-resource settings healthy women and babies are frequently discharged from hospital within one or two days of the birth, and in low-resource settings women may be discharged within hours of the birth or give birth at home (Brown 2002). Potentially, home visits in the first few days of the birth by healthcare professions or trained support workers offer opportunities for assessment of the mother and newborn, health education, infant feeding support, emotional or practical support and, if necessary, referral to other health professionals or agencies (Carabin 2009; Donovan 2007; Lassi 2010; Shaw 2006). Postpartum visits may prevent health

problems developing or reduce their impact by early intervention or referral. Home visits have improved coverage of key maternal and newborn care practices such as early initiation of breastfeeding, exclusive breastfeeding, skin-to-skin contact, delayed bathing, attention to hygiene (e.g. hand washing and water quality), umbilical cord care, infant skin care. In addition, home visits may identify conditions that require additional care or check-up, as well as counselling regarding when to take the mother and newborn to a healthcare facility (WHO/UNICEF 2009). Home visits may involve not only the assessment of the mother and newborn for physical problems but also assessment of maternal mental health, family circumstances and the home environment.

Depending on the context, home visits may take a non-judgmental and supportive role or a more directive approach in which the goals are to monitor family compliance with standards of parenting care and ensure the newborn's health and welfare. The type of approach used can influence the ability of the carers to engage mothers and newborns, resulting in acceptance or rejection of the help offered and potential for further disengagement (Doggett 2005).

Why it is important to do this review

Despite many studies and reviews, evidence regarding the effectiveness of different types of home-visiting programs in the early postnatal period is not sufficient. In some contexts once women have been discharged from hospital there may be no, or very limited postnatal follow-up. In higher-resource settings once women are at home, services may be provided by a range of health and social care agencies (newborn health visitors, social workers, paediatricians and general practitioners) and may be fragmented; postnatal home visits potentially allow continuity of care after hospital discharge and for the assessment and referral of the mother and newborn.

This review addresses the following questions: do different schedules of postpartum home-visiting programs reduce maternal/neonatal mortality and morbidities, and if they do, what is the optimal schedule for postpartum home visits? This review includes reports evaluating the frequency, timing, duration and intensity of home visits.The optimal schedule has been set out by WHO/UNICEF 2009, however, there was no clear evidence underpinning recommendations.

OBJECTIVES

The primary objective of this review is to assess outcomes (maternal and newborn mortality) of different home-visiting schedules during the early postpartum period. The review focuses on the frequency of home visits (how many home visits altogether), the timing (when visits started, e.g. within 48 hours of the birth), duration (when visits ended), intensity (how many visits per week), and different types of home-visiting interventions.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies that compared outcomes after home visits with outcomes of no home visits or different types of home-visiting interventions: studies that used random or quasi-random allocations of participants; and those in which the unit of allocation was the individual or group (cluster-randomised). We also planned to include studies available only as abstracts, noting that these studies were awaiting assessment, pending publication of the full report. There was, however, no such study identified.

Types of participants

Eligible studies were ones that enrolled participants in the early postpartum period (up to 42 days after birth). We excluded studies in which women were enrolled and received an intervention during the antenatal period, even those in which the intervention continued into the postnatal period.

We planned to exclude studies that only recruited women from specific high-risk groups (e.g. women identified with alcohol or drug problems) as interventions to support such women have been addressed elsewhere (Turnbull 2012).

Types of interventions

Interventions included scheduled home visiting in the postpartum period (excluding studies with antenatal home visiting in which the visits continued over many months). Interventions were home visits with various frequency, timings, duration and intensity.

We planned to include studies with co-intervention(s). Home visits may include outreach visits to non-healthcare facilities. Trials including a group that did not receive home visits would have been eligible but would have been analysed separately.

Types of outcome measures

Primary outcomes

1. Maternal mortality at 42 days post birth.
2. Neonatal mortality.

Secondary outcomes

Maternal outcomes

1. Maternal morbidities (postpartum haemorrhage, puerperal fever, abdominal and back pain, abnormal discharge, puerperal genital infection, thromboembolic disease, and urinary tract complications) within 42 days after birth.
2. Maternal mental health (depression, anxiety) and related problems (intimate partner violence, drug use) at 42 days after birth.
3. Satisfaction with overall care and service at 42 days after birth.

Neonatal outcomes

1. Neonatal morbidities (pneumonia, upper respiratory tract infection, diarrhoea, septic meningitis, encephalopathy or cerebral injury, and jaundice) within 28 days after birth.
2. Established feeding regimen (e.g. exclusive breastfeeding) at 28 days after birth.
3. Incomplete immunisation.
4. Failure to thrive, abuse, neglect, domestic violence from parents for any reason within 28 days after birth.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (28 January 2013).

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

(1) References from published studies

We searched the reference lists of relevant trials and reviews identified.

(2) Unpublished literature

We planned to contact the authors for more details about the published trials/ongoing trials.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (NY and SN) independently assessed eligibility for inclusion for all studies identified as a result of the search strategy. We resolved discrepancies by discussion and by consulting a third review author (RM).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (NY and SN) extracted the data using the agreed form. We resolved discrepancies through discussion. We entered data into the Review Manager (RevMan) software (RevMan 2012) and checked for accuracy.

If information regarding any of the above had been unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (TD and NY) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving an additional assessor (RM).

(1) Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

Hypnosis for induction of labour (Protocol)

Nishi D, Shirakawa MN, Ota E, Hanada N, Mori R

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[Intervention Protocol]

Hypnosis for induction of labour

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective of the study is to investigate whether hypnosis is an effective means of inducing labour.

BACKGROUND

Description of the condition

Labour induction is a method to artificially stimulate uterine contractions in order to bring about childbirth. This method is a common obstetric intervention carried out to address a variety of complications, such as prolonged pregnancy, maternal illness or fetal death. In recent years the rate of labour induction has been rapidly increasing (Grobman 2007) and approximately 10% of 300,000 deliveries across 24 countries were induced, ranging from 1.4% in Niger to 35.5% in Sri Lanka (WHO 2011). Possible complications that lead to induction of labour include post-term pregnancy, prelabour rupture of membranes, hypertensive disorders (e.g. gestational hypertension, pre-eclampsia, or eclampsia), maternal medical complications (e.g. diabetes mellitus, abruptio placentae), fetal death, fetal growth restriction, suspected fetal macrosomia (large baby), chorioamnionitis (inflammation of the fetal membranes), multiple pregnancy, vaginal bleeding and other complications (ACOG 2009; WHO 2011). A related Cochrane review shows that a policy of labour induction compared with expectant management in postterm women is associated with fewer perinatal deaths and fewer caesarean sections (Gülmezoglu 2012). However, induced labour can also give rise to increased complications, such as bleeding, caesarean section, uterine hyperstimulation and rupture (WHO 2011). Although not advocated in current guidelines, induction of labour is sometimes elected by pregnant women, or for the convenience of clinicians (WHO 2011).

There are a variety of methods available for induction, including the following: pharmacological methods (e.g. administration of oxytocin, prostaglandins, hyaluronidase, corticosteroids, or oestrogen); mechanical methods (e.g. manually rupturing the amniotic membranes, membrane sweeping, laminaria tents or balloon catheters); and alternative medicine methods (e.g. acupuncture, hypnosis or non-invasive interventions). It can be complicated to balance the benefits and risks of each method. For instance, a recent systematic review suggested that prostaglandin E2 (PGE2) reduced the possibility of failure to deliver vaginally within 24

hours and vaginal misoprostol reduced the need for caesarean deliveries, but both interventions heightened the risk of uterine hyperstimulation (Mozurkewich 2011). Mechanical methods such as laminaria tents and balloon catheters reduced uterine hyperstimulation, but increased maternal and neonatal infectious complications (Mozurkewich 2011). Given these possible problems, complementary and alternative medicine (CAM) methods may provide a safer strategy. Hypnosis comes under this category. Up to now, it has been used mostly during active labour while its effectiveness in the induction of labour is largely unknown. The purpose of this protocol is to search out evidence of its use and benefits, if any, in induction.

Description of the intervention

Hypnosis is a technique that enhances concentration and increases suggestibility, while simultaneously decreasing sensory awareness (Burrows 2001).

According to the Society for Psychological Hypnosis, Division 30 of the American Psychological Association, a definition of hypnosis is as follows: "Hypnosis typically involves an introduction to the procedure during which the subject is told that suggestions for imaginative experiences will be presented. The hypnotic induction is an extended initial suggestion for using one's imagination, and may contain further elaborations of the introduction. A hypnotic procedure is used to encourage and evaluate responses to suggestions. When using hypnosis, one person (the subject) is guided by another (the hypnotist) to respond to suggestions for changes in subjective experience, alterations in perception, sensation, emotion, thought or behavior. Persons can also learn self-hypnosis, which is the act of administering hypnotic procedures on one's own. If the subject responds to hypnotic suggestions, it is generally inferred that hypnosis has been induced" (Green 2005).

Hypnosis is practiced as hypnotherapy in psychotherapy and has applications in many other fields, including pain management (Montgomery 2000). The effect of hypnosis is thought to be mediated by the brain's anterior cingulate cortex (ACC) (Faymonville 2000), which is understood to be involved in processing negative emotional responses (Etkin 2011). A growing body of literature suggests that the ACC in the brain is critically involved in the processing of anxiety (Allman 2001; Shin 2010), meaning that hypnosis could play a role in minimising an anxious emotional response from this part of the brain. The method can be administered either by a hypnotherapist or through self-hypnosis, which women can learn to master during their pregnancy.

How the intervention might work

It is currently unknown how hypnosis works for induction of labour. However, a case report suggests that hypnosis might effect better relaxation of the cervix (Fist 1960). Also, hypnosis may enhance self-esteem (Torem 1992; Valente 1990), self-confidence, mastery and well-being (Simkin 2004), which can help to reduce anxiety in pregnant women. Maternal conditions of anxiety were significantly associated with the onset of labour in a comparative analysis of induced and spontaneous labours in the UK (Humphrey 2009). Recently, oxytocin has been considered to have anxiolytic or anxiety-relieving effects (Matarazzo 2008; Neumann 2011), and a previous study showed a significant negative correlation between oxytocin and anxiety (Scantamburlo 2007). Thus it might be plausible to hypothesise that women who are extremely anxious about their impending labour are unable to produce the oxytocin necessary to stimulate contractions, and therefore, may find the relaxant properties of hypnosis beneficial. These findings hold promise for the application of hypnosis as a potentially effective technique to induce labour by decreasing stress in pregnant women.

Why it is important to do this review

Although there have been various reviews of CAM methods to manage pain during labour and childbirth (Cyna 2004; Jones 2012; Madden 2012), randomised controlled trials on hypnosis related to labour induction have not been fully evaluated. There have been some case reports or series on the effects of hypnosis on labour induction (Cyna 2003; Fist 1960; Rice 1961), but a lack of formal evidence. As induced labour is a standard obstetric intervention experienced by pregnant women when complications arise during pregnancy, it is important to find methods of labour induction that have minimal significant side effects. Hypnotic techniques have been used in obstetrics for over a 100 years (Werner 1982). A meta-analysis conducted by Cyna 2004 showed significantly less use of labour augmentation by oxytocin and an increased incidence of women delivering spontaneously in the hypnosis usage group. Reducing pharmaceutical interventions will prevent associated side effects. Few previous studies reported the costs of providing hypnosis in labour (Jones 2012). However, Cyna suggested that it was expected to be low in relation to the total costs of an episode of care, so it may be associated with substantial decreased costs to the healthcare system if effective (Cyna 2006).This review will set out a clear summary of the effectiveness of hypnosis for induction of labour and its potential significance to healthcare professionals and consumers who are seeking safe, alternative methods of labour induction.

OBJECTIVES

The primary objective of the study is to investigate whether hypnosis is an effective means of inducing labour.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials (RCTs) of acceptable quality comparing hypnosis with no intervention or any other interventions, where the primary outcome is to assess whether there is labour induction. We will include RCTs in which the unit of randomisation is individuals and clusters. We will exclude quasi-RCTs or cross-over trials.

Types of participants

Pregnant women.

Types of interventions

We will include studies comparing pregnant women receiving hypnosis as a method of labour induction with those receiving no intervention or any other interventions for labour induction.

Types of outcome measures

Primary outcomes

1. Vaginal delivery within 96 hours or within the duration defined by the trialist
2. Caesarean section

Secondary outcomes

Maternal outcomes

1. Serious maternal morbidity or death (e.g., uterine rupture, admission to intensive care unit, septicaemia)
2. Uterine hyperstimulation
3. Epidural analgesia
4. Instrumental vaginal delivery
5. Postpartum haemorrhage defined by the trial authors
6. Maternal satisfaction
7. Caregiver satisfaction
8. Chorioamnionitis

Neonatal outcomes

1. Serious neonatal morbidity or perinatal death (e.g., seizures, birth asphyxia defined by the trial authors, neonatal encephalopathy, disability in childhood)
2. Neonatal admission to special care and/or intensive care unit
3. Apgar score at five minutes less than seven

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. This 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. The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

a) Handsearching: we will handsearch relevant journals and other sources including cross-references.

b) Personal communication: we will contact key personnel and organizations in the relevant field for published and unpublished references.

c) We will search conference proceedings of national and international conferences related to hypnosis interventions and will list these in the review.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (D Nishi, MN Shirakawa) will independently assess for inclusion all potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third author (E Ota).

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third author. We will enter data into Review Manager software (RevMan 2012) and check it for accuracy.

When information regarding any of the above is unclear e.g. abstracts only, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (DN, MNS) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement through discussion or by involving a third assessor (EO).

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

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

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

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

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

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

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

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

We will assess 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)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is 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 are reported incompletely and so cannot be used; study fails 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)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

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

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see Sensitivity analysis*.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* 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 the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Multi-armed trials

We will include multi-armed trials in the analyses. We will combine all relevant methods of hypnosis into a single group and incorporate all relevant control groups into a single group. Any other different intervention will be addressed in different meta-analyses. If one of the arms is irrelevant, we will exclude it from the analysis.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using 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 all participants will be analysed 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

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry

is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2012). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses:

1. previous caesarean section versus no previous caesarean section;
2. nulliparity versus multiparity;
3. membranes intact versus ruptured;
4. cervix favourable versus unfavourable or undefined;
5. history of previous induction of labour versus no history of induction;
6. preterm (36 weeks or less) delivery versus term delivery (37 weeks to 41 weeks) versus postterm delivery (42 weeks or more).

Only the primary outcome will be included in the subgroup analyses. We will assess subgroup differences using interaction tests available within RevMan (RevMan 2012). We will report the results of subgroup analyses quoting the $\chi 2$ statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will perform a sensitivity analysis if the review might affect the results due to the high risk of bias of some of the included trials. For the purpose of this sensitivity analysis, we will define 'high quality' as a trial having low risk of random sequence generation, adequate allocation concealment and the percentage of missing data less than 20%, given the stated importance of attrition as a quality measure (Tierney 2005). Only the primary outcome will be included in the sensitivity analyses. If statistical heterogeneity exists in outcomes, we will carry out the sensitivity analysis to explore the effects of fixed- or random-effects analyses. Furthermore, if there are any assumptions for ICC value used in cluster-randomised trials, we will perform a sensitivity analysis.

ACKNOWLEDGEMENTS

We thank Ms Emma Barber for her editorial support.

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

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pregnancy and Childbirth Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

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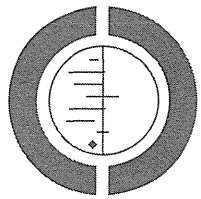
Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period (Review)

Yaju Y, Kataoka Y, Eto H, Horiuchi S, Mori R



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[Intervention Review]

Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period

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ABSTRACT

Background

There are several Cochrane systematic reviews looking at postpartum haemorrhage (PPH) prophylaxis in the third stage of labour and another Cochrane review investigating the timing of prophylactic uterotonics in the third stage of labour (i.e. before or after delivery of the placenta). There are, however, no Cochrane reviews looking at the use of interventions given purely after delivery of the placenta. Ergometrine or methylergometrine are used for the prevention of PPH in the postpartum period (the period after delivery of the infant) after delivery of the placenta in some countries. There are, furthermore, no Cochrane reviews that have so far considered herbal therapies or homeopathic remedies for the prevention of PPH after delivery of the placenta.

Objectives

To assess the effectiveness of available prophylactic interventions for PPH including prophylactic use of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies, administered after delivery of the placenta, compared with no uterotonic agents as well as with different routes of administration for prevension of PPH after delivery of the placenta.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2013), The Food and Drug Administration (FDA) (USA), Medicines and Healthcare Products Regulatory Agency (MHRA) (UK), European Medicines Agency (EMA) (EU), Pharmaceuticals and Medical Devices Agency (PMDA) (Japan), Therapeutic Goods Administration (TGA) (Australia), ClinicalTrials.gov, Current Controlled Trials, WHO International Clinical Trials Registry Platform (ICTRP), University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; Japan), Japan Pharmaceutical Information Center Clinical Trials Information (Japic-CTI; Japan), Japan Medical Association Clinical Trial Registration (JMACCT CTR; Japan) (all on 30 April 2013) and reference lists of retrieved studies

Selection criteria

All randomised or quasi-randomised controlled trials comparing prophylactic ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies (using any route and timing of administration) during the postpartum period after delivery of the placenta with no uterotonic agents or trials comparing different routes or timing of administration of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies, during the postpartum period after delivery of the placenta.

Data collection and analysis

Two review authors independently assessed trial eligibility and the methodological quality of trials, extracted data using the agreed form. Data were checked for accuracy.

Main results

Five randomised studies involving 1466 women met the inclusion criteria. All studies were classified as having an unclear risk of bias. Two studies (involving 1097 women) compared oral methylergometrine with a placebo, and one (involving 171 women) compared oral methylergometrine with Kyuki-choukeisu-in, a Japanese traditional herbal medicine. The remaining two studies (involving 198 women) did not report the outcomes of interest for this review. None of the included studies reported primary outcomes prespecified in the review protocol (blood loss of 1000 mL or more over the period of observation, maternal death or severe morbidity). Overall, there was no clear evidence of differences between groups in the following PPH outcomes: blood loss of 500 mL or more (risk ratio (RR) 1.45; 95% confidence interval (CI) 0.39 to 5.47, two studies), amount of lochia during the first 72 hours of the puerperium (mean difference (MD) -25.00 g; 95% CI -69.79 to 19.79, one study), or amount of lochia by four weeks postpartum (MD -7.00 g; 95% CI -23.99 to 9.99).

The Japanese study with a relatively small sample size comparing oral methylergometrine with a Japanese traditional herbal medicine found that oral methylergometrine significantly increased the blood haemoglobin concentration at day one postpartum (MD 0.50 g/dL; 95% CI 0.11 to 0.89) compared to herbal medicine. Adverse events were not well-reported in the included studies. We did not find any studies comparing homeopathic remedies with either a placebo or no treatment.

Authors' conclusions

There was insufficient evidence to support the use of prophylactic oral methylergometrine given after delivery of the placenta for the prevention of PPH. Additionally, the effectiveness of prophylactic use of herbal medicine or homeopathic remedies for PPH is still unclear as we could not find any clear evidence. Trials to assess the effectiveness of herbal medicines and homeopathic remedies in preventing PPH are warranted.

PLAIN LANGUAGE SUMMARY

Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period

Haemorrhage following childbirth (postpartum haemorrhage) is a major cause of maternal death and health problems in resource-poor settings in both low- and high-income countries. Postpartum haemorrhage is defined as blood loss from the genital tract of more than 500 mL, generally occurring within the first 24 hours after delivering the placenta and occasionally between 24 hours and six to 12 weeks. Possible causes are the uterus (womb) failing to contract after delivery (uterine atony), a retained placenta, inverted or ruptured uterus, and cervical, vaginal, or perineal lacerations. To address these issues, the joint policy statements between the International Confederation of Midwives, the International Federation of Gynecology and Obstetrics, and the World Health Organization recommend 'active management of third stage of labour', which includes the administration of a uterotonic drug (intravenous oxytocin), just before or just after delivery in order to help the uterine muscles to contract. The use of oral uterotonic drugs such as methylergometrine for the prevention of postpartum haemorrhage after delivery of the placenta is not recommended in the joint policy statements. Yet orally delivered uterotonic drugs, such as ergot alkaloids (including methylergometrine), herbal therapies, or homeopathic remedies are easy-to-administer agents that may be considered as possible alternatives after delivery of the placenta in developing countries, as in Japan. We set out to determine whether such agents are effective in preventing haemorrhage after childbirth. We found a total of five randomised clinical trials (involving 1466 women). In three of the trials (involving 1268 women), oral methylergometrine was compared with placebo (two trials) or the Japanese traditional herbal medicine Kyuki-choukeisu-in (one trial). The other two trials (involving 198 women) did not report information on relevant outcomes of interest for this review. Overall, there was no clear evidence that prophylactic oral methylergometrine was effective in reducing haemorrhage after childbirth. The trials were not of good quality

and adverse events were not well-reported. We did not find any completed trials looking at the effectiveness of homeopathic remedies in reducing haemorrhage after childbirth. The effectiveness of such remedies warrants further investigation.

BACKGROUND

Description of the condition

Postpartum haemorrhage (PPH), or excessive bleeding at or after childbirth is a leading cause of maternal mortality and morbidity worldwide, accounting for approximately a quarter of deaths that occur as a consequence of complicated pregnancy (WHO 2005). Although the majority of these deaths occur in developing countries, industrialised countries also suffer from direct cause-related maternal mortality such as PPH. Several recent publications have documented an increasing incidence in PPH over time in resource-affluent settings (Cameron 2006; Ford 2007; Joseph 2007), including Australia, Canada, the UK, and the USA (Knight 2009). The postpartum period is generally deemed to start after delivery of the infant. PPH is generally defined as blood loss from the genital tract in excess of 500 mL with severe postpartum haemorrhage (SPPH) being a loss of 1000 mL or more, and very SPPH being a loss of 2500 mL or more. PPH in the third stage of labour and PPH within the first 24 hours following delivery of the placenta (so called immediate PPH or primary PPH) form the majority of postpartum complications (Cunningham 2010). PPH or SPPH, however, occasionally develop even in the postpartum period between 24 hours and six to 12 weeks (so called delayed/late PPH or secondary PPH) (ACOG 2006). Therefore, the postpartum period between 24 hours and six to 12 weeks can also be a potentially hazardous period during childbirth. The dominant cause of primary PPH is uterine atony, whereas, secondary PPH can be associated with various causes. Secondary PPH is caused due to subinvolution of the placental site, retained products of conception, infection and inherited coagulation defects (ACOG 2006). Clinically problematic uterine haemorrhage develops within one to two weeks in 1% of women. Such bleeding predominantly occurs due to the abnormal involution of the placental site (Cunningham 2010).

Common causes of primary or secondary PPH include failure of the uterus to contract adequately after birth (atonic PPH), genital tract trauma (traumatic PPH), bleeding due to retention of placental tissue and coagulation disorders. Atonic PPH is the most prevalent among all of these conditions. In an effort to prevent uterine atony and associated bleeding, administering oxytocin soon after delivery is a routine management therapy (ACOG 2006). The joint policy statements between the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) have recommended active management of the third stage of labour that includes the administration of oxytocin or another uterotonic drug within one minute after the birth of the child, early umbilical cord clamping and cutting, controlled cord traction, and uterine massage after delivery of the placenta, as deemed appropriate. However, use of uterotonic drugs for the prevention of PPH after delivery of the placenta was not recommended in the statements (ICM-FIGO 2003; ICM-FIGO 2006; WHO 2009). The use and management of drug therapies to prevent PPH after delivery of the placenta remains unclear. However, some studies (Andersen 1998; De Groot 1996a; Van Selm 1995) have reported different types of ergot alkaloids, and varying routes and timing of administration of prophylactic measures. Oral ergometrine or methylergometrine were considered as possible alternative prophylactic oxytocics that were easy to administer and suitable for use in developing countries (De Groot 1996b). Likewise, in a resource-affluent country such as Japan, the use of these prophylactic medications following delivery of the placenta is routinely administered (Okada 2005).

According to the published reviews investigating the role of oral ergometrine or methylergometrine, these medications are not satisfactory alternatives to parenteral prophylactic oxytocic drugs for the prevention of PPH for at least three reasons: using the tablets orally, they are less effective, unstable, and pharmacokinetically unreliable (De Groot 1996b; De Groot 1998). Therefore, effectiveness and safety of the prophylactic use of ergometrine following delivery of the placenta needs to be backed up by clear evidence.

Moreover, a varying number of agents are administered either in herbal forms or as homeopathic remedies for the third stage of labour management (Brucker 2001). Therefore, it can be assumed that apart from ergot alkaloids, numerous prophylactic interventions (e.g. herbal therapies, homeopathic remedies, and other oxytocic drugs) do exist to help with the prevention of PPH after delivery of the placenta. However, the effectiveness and safety of these prophylactic interventions are yet to be investigated.

Description of the intervention

Intramuscular or intravenous ergometrine and methylergometrine are, in general, used in the management of the third stage of labour

and for the prevention of puerperal haemorrhage (WHO 2009). Oral ergometrine or methylergometrine were considered to be possible alternative oxytocics that were easy to administer and suitable for use in developing countries (De Groot 1996b). In Japan, methylergometrine is administered orally for the prevention of secondary PPH in women in the postnatal period after delivery of the placenta (Okada 2005).

Furthermore, herbal medicines or homeopathic remedies in the forms of tablets, tea or other preparations can also be used during the third stage of labour (Brucker 2001).

How the intervention might work

There are three groups of uterotonic agents: ergot alkaloids, oxytocin, and prostaglandins. The mechanisms through which these uterotonic agents work for the prevention of PPH are however, different. Oxytocin and prostaglandin function through oxytocin/prostaglandin receptors in the myometrium leading to fast and long-lasting rhythmic contractions. Ergometrine and methylergometrine are the most common types of ergot alkaloids and increase the muscle tone of the uterus with continuous (not rhythmic) tetanic contractions resulting in compressed myometrial blood vessels (De Groot 1998).

Ergometrine and methylergometrine improve uterine involution contributing to secondary PPH prevention, in which uterine subinvolution of the placental site is likely to be the underlying cause (ACOG 2006; Cunningham 2010). However, administration of ergometrine and methylergometrine may increase the risk of hazardous side effects in mothers such as hypertension and other complications of vasoconstriction. Moreover, intoxicated cases with severe complications including apnoea, coma, and convulsions in newborns have also been documented (Aeby 2003).

Prescribing herbal or homeopathic medicines on the other hand, depends on the characteristics of individual patients. Therefore, the overall concept of administering herbal or homeopathic medicines for PPH prevention is different to conservative Western medication therapies. Yet, herbal or homeopathic medicines must be considered as drug therapies, and therefore, evaluating the effectiveness of the usage of these non-conventional agents is equally important.

Why it is important to do this review

PPH continues to be a challenge in the prevention of maternal morbidity and mortality. Establishing useful methods for preventing PPH that are effective and safe are of vital importance. Administration of ergometrine or methylergometrine in the postpartum period might be one such useful method. Several Cochrane reviews investigating PPH prophylaxis in the third stage of labour (i.e., before or after the delivery of the placenta) looked at both of these drugs (Begley 2011; Cotter 2010; Liabsuetrakul 2011; McDonald 2009; Mori 2012; Novikova 2011; Oladapo 2012; Pohwer 2012; Su 2012; Tunçalp 2012) as well as other measures (Hofmeyr 2010; Peña-Martí 2010; Soltani 2011). Another Cochrane review examined the timing of prophylactic uterotonics in the third stage of labour (Soltani 2010). Current evidence provided from these Cochrane reviews, in general, favours active management over passive management of this stage of labour, involving administration of a prophylactic oxytocic before delivery of the placenta. However, there are no Cochrane reviews looking at the use of prophylactic interventions given purely after delivery of the placenta. In addition, there are no Cochrane reviews investigating herbal therapies or homeopathic remedies for the prevention of PPH after delivery of the placenta.

Existing evidence indicates that ergometrine or methylergometrine are used for the prevention of PPH in the postpartum period after delivery of the placenta in developing countries, including a high-income country, Japan. However, the effectiveness and safety of prophylactic usage of these drugs are not clear and must therefore be systematically assessed. Furthermore, understanding the balance between the risks and benefits of such an intervention is crucial.

OBJECTIVES

To assess the effectiveness of available prophylactic interventions for PPH including prophylactic use of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies, administered after delivery of the placenta, compared with no uterotonic agents as well as with different routes of administration for prevention of PPH after delivery of the placenta.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised or quasi-randomised (such as alternate allocation or allocation by health insurance number, hospital record, etc.) controlled trials comparing prophylactic ergometrine, methylergometrine, or other agents (using any route and timing of administration) with no uterotonic agents during the postpartum period after delivery of the placenta, or comparing different routes or timing of administration of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies during the postpartum period after delivery of the placenta. We included well-conceptualised studies that provided sufficient information for the targeted evaluation. Studies that did not provide sufficient

information for the targeted evaluation were incorporated into the 'Studies awaiting classification' category until they are published as full reports.

Types of participants

Women who have had a spontaneous vaginal delivery.

Types of interventions

Ergometrine, methylergometrine, or other agents administered by any route or timing of administration for the prevention of postpartum haemorrhage after delivery of the placenta.

Comparisons

1. Ergometrine/methylergometrine versus placebo/no treatment.
2. Ergometrine/methylergometrine administration via different routes: oral versus intravenous, oral versus intramuscular or subcutaneous, intravenous versus intramuscular or subcutaneous.
3. Herbal medicine versus ergometrine/methylergometrine (any route or dosage), or versus placebo/no treatment.
4. Homeopathic remedy versus one of the following: ergometrine/methylergometrine (any route or dosage), herbal medicine, placebo/no treatment.
5. Other agents versus ergometrine/methylergometrine (any route or dosage), or versus placebo/no treatment.

Types of outcome measures

Primary outcomes

- Blood loss of 1000 mL or more over the period of observation (as determined by the trial investigator)
- Maternal death or severe morbidity (e.g., major surgery, organ failure, hyperpyrexia, intensive care unit admission, hysterectomy, compression sutures, artery ligations, or as defined by trial authors)

Secondary outcomes

- Maternal death; individual components of severe morbidity (as listed above or as defined by the trial authors)
- Blood loss of 500 mL or more over the period of observation (as determined by the trial investigator)
- Blood transfusion
- Use of therapeutic uterotonics
- Additional treatment for postpartum haemorrhage (uterine tamponade, X-ray, embolisation)
- Side effects reported either individually or combined, when appropriate, e.g., vomiting, nausea, elevation of diastolic blood pressure, shivering, headache, chest pain, shortness of breath, pyrexia, and diarrhoea
- Postnatal anaemia (defined by trial authors, absolute or relative drop in haemoglobin)
- Thromboembolic events
- Cost involved in the treatment sought
- Amount of lochia (vaginal discharge after giving birth) during the first 72 hours postpartum (outcome not prespecified)
- Amount of lochia by four weeks postpartum (outcome not prespecified)
- Duration of lochia of more than four weeks (outcome not prespecified)
- Endometritis (outcome not prespecified)
- Pain requiring analgesia (outcome not prespecified)

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 April 2013).

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.

To find clinical trials for approval of new drugs, we also searched the following databases through 30 April 2013:

- The Food and Drug Administration (FDA) in the USA
- The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK
- The European Medicines Agency (EMA) in the EU

- The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan
- The Therapeutic Goods Administration (TGA) in Australia

For ongoing trials, we searched the following trial registers through 30 April 2013:

- ClinicalTrials.gov
- *Current Controlled Trials*
- The WHO International Clinical Trials Registry Platform (ICTRP)
- University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; Japan)
- Japan Pharmaceutical Information Center Clinical Trials Information (Japic-CTI; Japan)
- Japan Medical Association Clinical Trial Registration (JMACCT CTR; Japan)

Searching other resources

We checked references cited in papers identified through the above search strategy to retrieve additional relevant studies.

We also considered abstracts for inclusion, if sufficient information was provided.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

The inclusion of studies identified through the search strategy was independently assessed by two review authors, Yukari Yaju (YY) and Yaeko Kataoka (YK). We resolved any disagreement through discussion among the review authors.

Data extraction and management

We designed a form that would enable us to extract data. For eligible studies, two review authors (YY, YK) used the form to extract the data independently. We resolved discrepancies through discussion among the review authors. We used the Review Manager software (RevMan 2011) for data entry and checked the accuracy of the data entry. When information about the studies was unclear, we contacted the authors of the original reports to obtain further details. We contacted the authors of two studies (Andersen 1998; Arabin 1986) to request details on random sequence generation and prespecified outcomes and received a satisfactory answer from the author of one study (Arabin 1986). We contacted the author of one study (Ushiroyama 2003) to ask about inconsistency in blood haemoglobin concentrations reported in his article and he provided an appropriate answer. Further, we contacted the author of one study (Grünberger 1983) to request details of outcomes but received no reply. The review authors were not blinded to the names of authors, journals, or institutions.

Assessment of risk of bias in included studies

Two review authors (YY, YK) independently assessed risk of bias in each included study using The Cochrane Collaboration's tool for assessing risk of bias, outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and contained in RevMan (RevMan 2011). Any disagreement was resolved by discussion.

(1) Sequence generation (checking for possible selection bias)

For each included study, we described the method used in the sequence generation process in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the methods as:

- yes (low risk of bias) (any truly random process, e.g. referring to a random number table, using a computer random number generator, minimisation method);
- no (high risk of bias) (any non-random process, e.g. odd or even date of birth, some rule based on date or day of admission, some rule based on hospital or clinic record number); or
- unclear (uncertain risk of bias) (insufficient information about the sequence generation process to permit judgement of 'yes' or 'no').

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

For each included study, we described the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

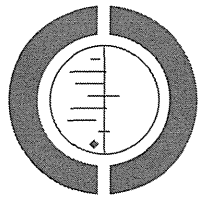
We assessed the methods as:

- yes (low risk of bias) (e.g. central allocation including telephone, web-based and pharmacy-controlled randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes);
- no (high risk of bias) (using an open random allocation schedule such as a list of random numbers, assignment envelopes without appropriate safeguards (e.g., unsealed or non-opaque), alternation or rotation, date of birth, case record number, any other explicitly unconcealed procedure); or
- unclear (uncertain risk of bias) (insufficient information to permit judgement of 'yes' or 'no').

(3) Blinding of participants, personnel and outcome assessors (checking for possible performance bias)

Vitamin K supplementation during pregnancy for improving outcomes (Protocol)

Shahrook S, Hanada N, Sawada K, Ota E, Mori R



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[Intervention Protocol]

Vitamin K supplementation during pregnancy for improving outcomes

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of vitamin K supplementation administered to pregnant women for improving maternal and neonatal outcomes.

BACKGROUND

Description of the condition

Vitamin K deficiency can present a serious health risk to pregnant women and their babies that may lead to haemorrhage, especially in newborns. Haemorrhaging occurs due to reduced levels of prothrombin - an important element of the blood dependent on vitamin K for coagulation - that slows down the blood-clotting process and may result in excessive maternal or neonatal bleeding (Shirk 2006). Vitamin K deficiency is extremely rare among the general adult population, although it may occur when vitamin absorption is impaired due to an underlying pathology (Food and Nutrition Board 2001; WHO/FAO 2004). It is largely unknown what type of crucial role vitamin K plays during pregnancy (UMMC 2011). However, as nutritional requirements generally increase in pregnancy, the risks of clinically relevant deficiencies also escalate, especially among pregnant women with poor nutritional status (Guelinckx 2012).

Ingestion of certain therapeutic drugs such as carbamazepine and heparin anticonvulsants may also impede vitamin K metabolism in pregnant women and give rise to vitamin K deficiency (Davidson 1986; Shih 2006). Women's exposure to vitamin K anticoagulants during pregnancy may affect the fetus in utero, resulting in coumarin embryopathy (CE) (Hetzel 2006). Approximately 6% of newborns exposed to maternal coumarin intake during pregnancy develop CE, with skeletal anomalies (e.g. midfacial hypoplasia and epiphyseal calcifications) found in 80% of these babies. Central nervous malformations (e.g. midline structural defects) were detected in 45% of babies diagnosed with CE; and signs of intracranial haemorrhage were observed in 10% (Van Driel 2002). Moreover, since coumarins cross into the placenta, they later affect fetal coagulation which increases the risk of intracranial haemorrhage before birth (Van Driel 2002). Women's consumption of therapeutic drugs during pregnancy may be associated with maxillonasal hypoplasia in newborns in the first trimester, which can lead to problems with facial and orthodontic development (Hanss 1994). Van Driel 2002 and colleagues observed that of the pregnant women who were administered with coumarins, a vitamin K anticoagulant or blood-thinning medicine, 22% experienced miscarriage (Van Driel 2002). However, there is insufficient evidence to support a link between vitamin K deficiency and miscarriage.

Women of reproductive age undergoing bariatric surgeries for obesity-related morbidity treatment may also experience adverse pregnancy outcomes associated with various nutritional deficiencies (ACOG 2013). Women are likely to experience frequent nutritional shortages following bariatric surgery, but the risks of severe deficiencies are greater after malabsorption-inducing surgery rather than procedures that are solely restrictive (Guelinckx 2009). Deficiencies of vitamin K, vitamin B_{12}, and some trace minerals have previously been reported in pregnant women who have undergone bariatric surgery (Guelinckx 2009; Shankar 2010).

Vitamin K deficiency bleeding (VKDB) is a bleeding disorder in young infants with inadequate levels of vitamin K that can lead to haemorrhaging inside the infant's skull soon after birth (Shearer 2009). Infants are born with naturally low levels of vitamin K and do not receive adequate amounts from breast milk due to the slower transfer rate through the placenta (Shearer 2009). Premature infants with vitamin K shortages and impaired oral absorption are more susceptible to vitamin K deficiency immediately following birth (Shearer 1992). The onset of early VKDB, for example, occurs among infants from birth or 24 hours immediately prior to delivery (Lane 1985). Maternal drug consumption affecting vitamin K metabolism may typically increase this condition among infants (McNinch 1985; Severinsen 1980). Therefore, coagulation disorders require immediate treatment with vitamin K administration prior to diagnosis. In Western European countries, the incidence of late VKDB in infants without vitamin K prophylaxis was found to be 5/105 births versus 11 and 72/105 births in Japan and Thailand, respectively (Shearer 2009). Immediately following birth, the proportion of VKDB infants who received no vitamin K administration was estimated to be 0.01% to 0.44% (Yamin 2010). A mortality rate of 20% was also estimated in newborns with severe bleeding disorders, including intracranial haemorrhage (50%), and common persistent neurologic impairment (McNinch 1991; Van Kalen 1992).

Several adverse pregnancy outcomes affect babies born to women with epilepsy (WWE). Evidence suggests that anticonvulsant drugs may impede folic acid and phytomenadione (vitamin K) metabolism causing higher risks of neural tube defects and early haemorrhage among newborns (Nelson 1972). It has been recommended that pregnant women who take phenobarbital, carbamazepine or phenytoin should commence maternal phytomenadione supplementation four weeks prior to the delivery due date (Sabers 1999). Although uncommon, the use of vitamin K antagonists during pregnancy can give rise to liver disease in neonates (Hetzel 2006). Hetzel 2006 suggests that vitamin K antagonists should be highly controlled during anti-coagulation in pregnant women with mechanical heart valves.

Description of the intervention

Pregnant women deficient in vitamin K may need to incorporate vitamin K supplements into their prenatal vitamin regimen. In certain disease conditions such as cystic fibrosis, coeliac disease, or Crohn's disease in which sufficient vitamin K absorption is impaired, vitamin K supplementations are essential, especially in the form of a multivitamin that contains vitamin K, which is regarded as more beneficial than vitamin K supplementation alone (UMMC 2011). Pregnant women taking anticonvulsant drugs are recommended to take vitamin K two weeks prior to delivery (UMMC 2011). Vitamin K status in pregnant women who take prothrombin-depressing anticoagulants, such as coumarin, should be carefully assessed (Institute of Medicine 1999). Women without these conditions who experience a normal pregnancy are generally not required to take vitamin K supplements unless, for example, they are diagnosed with malabsorption syndrome or are taking antibiotics such as cephalosporins, which inhibit vitamin K absorption by destroying vitamin K-forming bacteria as well as bacteria that is harmful to the body (UMMC 2011).

Vitamin K formulation and prophylactic administration differ by country (WHO/FAO 2004). For example, in the United States, vitamin K1 or phylloquinone is available as a supplement either separately or as a component of a multivitamin complex in 5 mg tablets (UMMC 2011). Vitamin K is widely sold over the counter as water-soluble chlorophyll tablets, capsules, or liquid (UMMC 2011). Vitamin K is administered parenterally or orally, and various reported doses have been administered to pregnant women: for example, 10 mg of intravenous or intramuscular vitamin K daily for two to seven days (Lee 2006); one 10 mg dose of vitamin K intramuscularly, repeated again after four days followed by 20 mg daily of oral vitamin K (Lane 1985); 10 mg of intramuscular vitamin K between four and 96 hours before delivery (Puhan 1990); and 10 mg of vitamin K1 daily is recommended for pregnant women on anticonvulsant therapy from 36 weeks of pregnancy onwards (Greenhalgh 1993).

There is insufficient evidence to show that excessive vitamin K ingestion has toxic effects on the human body. As vitamin K passes through the placenta and is found in breast milk, pregnant and lactating women should seek advice from their health practitioner before commencing vitamin K supplements (UMMC 2011). However, oxidative damage, red cell fragility, and methaemoglobin may develop in cases of high doses of water-soluble vitamin K3 (menadione) consumption, and local hypersensitivity reactions, mostly due to vitamin K1 dermal injections, may also occur (Expert Group on Vitamins and Minerals 2003). A daily intake of 1 mg or less is unlikely to have any harmful effects according to guidelines from the United Kingdom (NHS 2011). Also, as toxicity for the oral consumption of vitamin K remains unknown, 10 to 20 mg or more of phylloquinone is recommended to be safe for common clinical administration in the United States (WHO/FAO 2004). Furthermore, patients with chronic fat malabsorption who take such doses have shown no evidence of side

effects (WHO/FAO 2004). Synthetic menadione and its derivatives are not recommended, particularly for vitamin supplements in newborns (WHO/FAO 2004). Moreover, due to interactions with certain drugs and the potential for side effects, vitamin K supplements are restricted for pregnant and lactating women, as vitamin K passes through the placenta and is found in breast milk; warfarin consumers; and those with a rare metabolic disease called glucose-6-phosphate dehydrogenase (G6PD) deficiency (UMMC 2012).

How the intervention might work

Antenatal administration of vitamin K supplementation for pregnant women may provide significant benefits for improving both maternal and neonatal outcomes. Vitamin K supplementation may improve the deficiency of factor VII in megaloblastic anaemia of pregnancy with thrombocytopenia (Metri. 1969). Adequate supplementation that includes vitamin K and other essential micronutrients has been recommended for pregnant women who have undergone bariatric surgery in order to remedy maternal and fetal complications such as severe anaemia, congenital abnormalities and low birthweight (Goodnicks 2009; Shankar 2010). Furthermore, maternal administration of vitamin K has been suggested to improve prothrombin and partial thromboplastin activities and reduce the incidence and severity of intraventricular haemorrhage (IVH) in infants (Morales 1988; Pomerance 1967) although a Cochrane review (Crowther 2010) shows no impact of vitamin K in preventing IVH. Antenatal vitamin K supplementation may help to reduce the risk of haemorrhagic complications in infants born to WWE who take antiepileptic drugs during pregnancy (Chaudhry 2004; Kaaja 2002), including a reduction in the occurrence of vitamin K deficiency in such infants (Cornelissen 1993).

Why it is important to do this review

The effects of vitamin K deficiency, especially haemorrhagic complications, other adverse outcomes and the need for vitamin K supplementation, have mostly been reported in relation to neonates. Vitamin K deficiency, remedial supplementation and associated morbidities in women of reproductive age, specifically during pregnancy, have not been well described. Evaluation of the efficacy and safety of different treatment regimens for vitamin K supplementation during pregnancy is therefore crucial to improve maternal and neonatal outcomes. A previous Cochrane review examined the effect of vitamin K supplementation, including women at risk of imminent very preterm birth in the prevention of neonatal periventricular haemorrhage (PVH) and associated adverse outcomes in preterm neonates (Crowther 2010). Therefore, in this protocol and subsequent review, we will include all pregnant women regardless of their pregnancy stage and we will aim to assess the effects of vitamin K supplementation on a set of neonatal and maternal outcomes that were not covered by earlier reviews, specifically by Crowther 2010.

OBJECTIVES

To assess the effects of vitamin K supplementation administered to pregnant women for improving maternal and neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised (individual and cluster) or quasi-randomised controlled trials assessing the effect of vitamin K supplementation during pregnancy. We will also consider trials presented only as abstracts. We will exclude cross-over trials.

Types of participants

All pregnant women in any stage of their pregnancy and their infants. We will include trials in which pregnant women are a subset of the participants included in the study, if reported in a way that relevant data can be extracted. This review will exclude studies in which vitamin K was given to women at risk of imminent preterm birth for preventing neonatal PVH, as this is covered in an existing review by Crowther 2010.

Types of interventions

We will assess the effects of vitamin K administered orally, intramuscularly or intravenously to pregnant women during any stage of their pregnancy. This review will exclude studies in which vitamin K was administered to women at risk of imminent preterm birth for the prevention of neonatal PVH, as this has already been evaluated in an existing review by Crowther 2010. The intervention group will be pregnant women who have received prenatal vitamin K supplementation alone or in combination with micronutrients, regardless of the dosages, frequency, duration and timing of delivery. The three comparison groups will consist of pregnant women receiving any dosage of vitamin K supplements versus no vitamin K supplements; micronutrients including vitamin K versus micronutrients without vitamin K; and vitamin K versus a placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Perinatal death.
2. Neonatal bleeding.
3. Maternal bleeding incidence, e.g. during pregnancy, intrapartum haemorrhage and postpartum haemorrhage.

Secondary outcomes

Newborns

1. Stillbirth.
2. Neonatal death.
3. Infant death.
4. Subcategories of neonatal bleeding: a) very early onset (nought to 24 hours after birth), b) classic haemolytic disease of the newborn (24 hours to seven days of life), and c) late haemolytic disease or acquired protein C deficiency (APCD) of the newborn (two to 12 weeks of life).
5. Preterm birth (less than 37 weeks of gestation).
6. Low birthweight.
7. Long-term neurodevelopment.
8. Congenital malformation.
9. Severe liver disease: a) induced intrahepatic biliary obstruction, b) cholestatic disease.
10. Malabsorption of vitamin K, e.g. gut resection.
11. Biliary atresia (congenital absence or closure of the major bile ducts, the ducts that drain bile from the liver).
12. Other morbid conditions, e.g. low Apgar score at five minutes, vitamin K deficiency.

We will summarise any adverse outcomes reported in the included studies.

Mothers

1. Vitamin K deficiency in pregnant women.
2. Anaemia, e.g. megaloblastic anaemia.
3. Hypoprothrombinemia.
4. Thrombocytopenia.
5. Other morbid conditions, e.g. spontaneous abortion.

We will summarise any adverse outcomes reported in the included studies.

Economic data for the use of healthcare resources

Newborns

Special care/intensive care admission: length of hospitalisations; length of other treatment care after hospital discharge; and length of mechanical ventilation.

Mothers

Antenatal hospital admission: utilisation of intensive care units; use of daycare units; and ventilation and dialysis.

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.

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.

We will apply no date restrictions on the searches. 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 will also search reference lists of retrieved trials, included trials and relevant review papers.

We will not apply any language restrictions.

We will contact researchers in the area, if needed.

Data collection and analysis

Selection of studies

Two review authors (S Shahrook (SS), N Hanada (NH), K Sawada (KS), E Ota (EO) and R Mori (RM)) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors (SS, NH, KS, EO and RM) will extract data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2012) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (SS, NH, KS, EO and RM) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

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

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

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

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

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

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

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

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

We will assess 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)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. 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)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is 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 of the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; the study fails 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)

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:

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

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias by undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. To take account of design effect, we will adjust their sample sizes using the methods described in the *Cochrane Handbook* 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 if the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Trials with more than two treatment groups

If trials with more than two intervention groups (multi-arm studies) are identified, only directly relevant arms will be included. If studies with various relevant arms are identified, groups will be combined to generate a single pair-wise comparison (Higgins 2011), and the disaggregated data in the corresponding subgroup category will be included. If the control group is shared by two or more study arms, the control group over the number of relevant subgroup categories will be divided to avoid double counting the participants (for dichotomous data, we will divide the events and the total population, and for continuous data, we will assume the same mean and standard deviation but will divide the total population). The details will be described in the 'Characteristics of included studies' tables.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

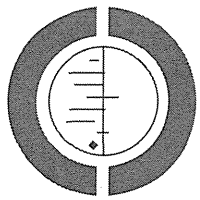
For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they 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

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as

'Third wave' cognitive and behavioural therapies versus treatment as usual for depression (Review)

Churchill R, Moore THM, Furukawa TA, Caldwell DM, Davies P, Jones H, Shinohara K, Imai H, Lewis G, Hunot V



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[Intervention Review]

'Third wave' cognitive and behavioural therapies versus treatment as usual for depression

Rachel Churchill[1], Theresa HM Moore[2], Toshi A Furukawa[3], Deborah M Caldwell[2], Philippa Davies[2], Hannah Jones[4], Kiyomi Shinohara[5], Hissei Imai[6], Glyn Lewis[7], Vivien Hunot[1]

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ABSTRACT

Background

So-called 'third wave' cognitive and behavioural therapies represent a new generation of psychological therapies that are increasingly being used in the treatment of psychological problems. However, the effectiveness and acceptability of third-wave cognitive and behavioural therapy (CBT) approaches as treatment for acute depression remain unclear.

Objectives

1. To examine the effects of all third wave CBT approaches compared with treatment as usual/waiting list/attention placebo/psychological placebo control conditions for acute depression.

2. To examine the effects of different third wave CBT approaches (ACT, compassionate mind training, functional analytic psychotherapy, dialectical behaviour therapy, MBCT, extended behavioural activation and metacognitive therapy) compared with treatment as usual/waiting list/attention placebo/psychological placebo control conditions for acute depression.

3. To examine the effects of all third wave CBT approaches compared with different types of comparators (treatment as usual, no treatment, waiting list, attention placebo, psychological placebo) for acute depression.

Search methods

We searched the Cochrane Depression Anxiety and Neurosis Group Trials Specialised Register (CCDANCTR to 01/01/12), which includes relevant randomised controlled trials from *The Cochrane Library* (all years), EMBASE, (1974-), MEDLINE (1950-) and PsycINFO (1967-). We also searched CINAHL (May 2010) and PSYNDEX (June 2010) and reference lists of the included studies and relevant reviews for additional published and unpublished studies. An updated search of CCDANCTR restricted to search terms relevant to third wave CBT therapies was conducted in March 2013 (CCDANCTR to 01/02/13).

Selection criteria

Randomised controlled trials that compared third wave CBT therapies with control conditions for acute depression in adults.

Data collection and analysis

Two review authors independently identified studies, assessed trial quality and extracted data. Study authors were contacted for additional information when required. We rated the quality of evidence using GRADE methods.

Main results

Four small studies (224 participants) were included in the review. Little information was provided about the process of allocating participants to groups. None of the studies used independent outcome assessors, and evidence suggested researcher allegiance towards the active treatments. The four studies examined a diversity of third wave CBT approaches (extended behavioural activation, acceptance and commitment therapy and competitive memory training) and control conditions. None of the studies conducted follow-up assessments. The results showed a significant difference in clinical response rates in favour of third wave CBT when compared with treatment as usual (TAU) conditions (three studies, 170 participants, risk ratio (RR) 0.51, 95% confidence interval (CI) 0.27 to 0.95; very low quality). No significant difference in treatment acceptability based on dropout rates was found between third wave CBT approaches and TAU (four studies, 224 participants, RR 1.01, 95% CI 0.08 to 12.30; very low quality). Both analyses showed substantial statistical heterogeneity.

Authors' conclusions

Very low quality evidence suggests that third wave CBT approaches appear to be more effective than treatment as usual in the treatment of acute depression. The very small number of available studies and the diverse types of interventions and control comparators, together with methodological limitations, limit the ability to draw any conclusions on their effect in the short term or over a longer term. The increasing popularity of third wave CBT approaches in clinical practice underscores the importance of completing further studies of third wave CBT approaches in the treatment of acute depression, on a short- and long-term basis, to provide evidence of their effectiveness to policy-makers, clinicians and users of services.

PLAIN LANGUAGE SUMMARY

'Third wave' cognitive and behavioural therapies versus treatment as usual for depression

Major depression is a very common condition in which people experience a persistently low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death. Psychological therapies are an important and popular alternative to antidepressants in the treatment of depression. Many different psychological therapy approaches have been developed over the past century, including cognitive-behavioural (CBT), behavioural, 'third wave' CBT, psychodynamic, humanistic and integrative therapies.

In this review, we focused on third wave CBT approaches, a group of psychological therapies that target the process of thoughts (rather than their content, as in CBT), helping people to become aware of their thoughts and to accept them in a non-judgemental way. The aim of the review was to find out whether third wave CBT was effective and acceptable to people in the acute phase of depression. The review included four studies, involving a total of 224 people. The studies examined three different forms of third wave CBT, consisting of extended behavioural activation (two studies), acceptance and commitment therapy (ACT) (one study) and another form of third wave CBT called competitive mind training (one study). Three of the studies compared third wave CBT approaches with treatment as usual control conditions. The fourth study compared ACT with a psychological placebo condition. The results suggested that third wave CBT approaches were effective on a short-term basis in treating depression. However, the quality of evidence was very low because of the small number of studies/participants included in the review, together with the diverse client groups, interventions and control conditions used and possible allegiance of researchers towards the active treatments, making it difficult to draw conclusions with any confidence. It is notable, too, that none of the studies looked at the long-term effect of third wave CBT approaches. Given the increasing popularity of third wave CBT approaches in clinical practice, further well-designed studies should be prioritised to establish whether third wave CBT approaches are helpful in treating people with acute depression.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Third wave CBT versus TAU for depression

Patient or population: depression
Settings: primary, secondary and community care
Intervention: third wave CBT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Third wave CBT				
Clinical non-response at post-treatment	Study population		RR 0.51 (0.27 to 0.95)	170 (3 studies)	⊕○○○ very low[a,b,c]	
	800 per 1000	408 per 1000 (216 to 760)				
	Moderate					
	688 per 1000	351 per 1000 (186 to 654)				
Treatment acceptability (dropout) at post-treatment	Study population		RR 1.01 (0.08 to 12.3)	224 (4 studies)	⊕○○○ very low[a,b,d,e,f]	
	206 per 1000	208 per 1000 (16 to 1000)				
	Moderate					
	42 per 1000	42 per 1000 (3 to 517)				
Clinical non-remission at post-treatment	Study population		RR 0.77 (0.67 to 0.88)	140 (2 studies)	⊕○○○ very low[a,c,d,f]	

Outcomes	Assumed risk (Control)	Corresponding risk (Third wave CBT)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	953 per 1000	734 per 1000 (639 to 839)				
	Moderate					
	938 per 1000	722 per 1000 (628 to 825)				
Depression levels at post-treatment		Mean depression levels at post-treatment in the intervention groups were **1.12 standard deviations lower** (1.53 to 0.71 lower)		211 (4 studies)	⊕○○○ very low[a,d,f,g]	SMD -1.12 (-1.53 to -0.71)
Anxiety levels at post-treatment-behavioural activation vs TAU Beck Anxiety Inventory (BAI)		Mean anxiety levels at post-treatment-behavioural activation vs tau in the intervention groups was **5.5 lower** (10.01 to 0.99 lower)		30 (1 study)	⊕○○○ very low[a,f,h]	
Social adjustment levels at post-treatment- behavioural activation vs TAU Work and Social Ajustment Scale (WSAS)		Mean social adjustment levels at post-treatment-behavioural activation vs tau in the intervention groups was **11.56 lower** (17.89 to 5.23 lower)		38 (1 study)	⊕○○○ very low[a,b,d,f]	

*The basis for the **assumed risk** (eg, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **risk ratio** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Method of sequence generation/allocation concealment unclear. As with all psychological therapy trials, blinding of clinicians/participants was not achievable. The risk of bias was assessed as high for researcher allegiance and as unclear for therapist qualifications.
[b] Substantial statistical heterogeneity indicated. Diverse study settings and participants (use of student population vs older age population). Treatment length varied from a single session to 12 sessions over 3 months.
[c] Only two third wave CBT approaches included.
[d] High proportion of participants prescribed antidepressants naturalistically.
[e] One study used a single-session intervention; therefore no dropouts from treatment. One study had 50% dropout rate in TAU group vs 8% in third wave CBT group.
[f] Small to very small sample sizes with wide confidence intervals.
[g] Moderate statistical heterogeneity indicated. Treatment length varied from a single session to 12 sessions over 3 months.
[h] One study limited to single-session intervention with college students reporting mild depression.

BACKGROUND

Description of the condition

Major depression is characterised by persistent low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms, including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death (APA 2000). Somatic complaints are also a common feature of depression, and people with severe depression might develop psychotic symptoms (APA 2000).

Depression is the third leading cause of disease burden worldwide and is expected to show a rising trend over the next 20 years (WHO 2004; WHO 2008). A recent European study has estimated the point prevalence of major depression and dysthymia (a mild long-term form of depression) at 3.9% and 1.1%, respectively (ESEMeD/MHEDEA 2004). As the largest source of non-fatal disease burden in the world, accounting for 12% of years lived with disability (Ustun 2004), depression is associated with marked personal, social and economic morbidity and loss of functioning and productivity and creates significant demands on service providers in terms of workload (NICE 2009). Depression is also associated with a significantly increased risk of mortality (Cuijpers 2002). The strength of this association, even when confounders such as physical impairment, health-related behaviours and socio-economic factors are taken into account, has been shown to be comparable with, or greater than, the strength of the association between smoking and mortality (Mykletun 2009).

Description of the intervention

Clinical guidelines recommend pharmacological and psychological interventions, alone or in combination, in the treatment of moderate to severe depression (NICE 2009). The prescribing of antidepressants has increased dramatically in many Western countries over the past 20 years, mainly with the advent of selective serotonin reuptake inhibitors and newer agents such as venlafaxine, and antidepressants continue to be the mainstay of treatment for depression in healthcare settings (Ellis 2004; NICE 2009).

Whilst antidepressants are of proven efficacy in acute depression (Cipriani 2005; Guaiana 2007; Arroll 2009; Cipriani 2009; Cipriani 2009a; Cipriani 2009b), adherence rates remain very low (Hunot 2007; van Geffen 2009), in part because of patients' concerns about side effects and possible dependency (Hunot 2007). Furthermore, surveys consistently demonstrate patients' preference for psychological therapies over antidepressants (Churchill 2000; Riedel-Heller 2005). Therefore, psychological therapies can provide an important alternative or adjunctive intervention for depressive disorders.

A diverse range of psychological therapies is now available for the treatment of common mental disorders (Pilgrim 2002). Psychological therapies may be broadly categorised into four separate philosophical and theoretical schools, comprising psychoanalytic/dynamic (Freud 1949; Klein 1960; Jung 1963), behavioural (Watson 1924; Skinner 1953; Wolpe 1958), humanistic (Maslow 1943; Rogers 1951; May 1961) and cognitive approaches (Lazarus 1971; Beck 1979). Each of these four schools incorporates several differing and overlapping psychotherapeutic approaches. Some psychotherapeutic approaches, such as cognitive analytic therapy (Ryle 1990), explicitly integrate components from several theoretical schools. Other approaches, such as interpersonal therapy for depression (Klerman 1984), have been developed to address characteristics considered to be specific to the disorder of interest.

Increasing interest in the role of cognition gave rise to a 'cognitive revolution' in the field of psychology in the 1970s (Mahoney 1978). The most influential approaches were rational emotive behaviour therapy (Ellis 1962), cognitive behaviour modification (Meichenbaum 1977) and cognitive therapy (Beck 1979). The latter developed as an approach to understanding and treating depression. However, both Beck and Ellis acknowledged the value of behaviour therapy (Rachman 1997), and during the 1980s and 1990s, the two approaches were merged to form cognitive-behavioural therapy (CBT).

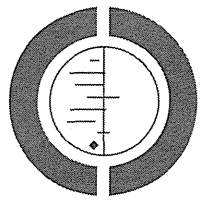
CBT is generally regarded as a family of allied therapies (Mansell 2008) that draw on a common base of behavioural and cognitive models of psychological disorders and utilise a set of overlapping techniques (Roth 2008). In CBT, cognition is central to the treatment of psychological disorders, with emotions and behaviour thought to be mediated by cognitive processes. The fundamental aim of CBT is to identify unhelpful cognitions or 'negative automatic thoughts' derived from long-standing negative beliefs/assumptions about the self, other people or the world. The CBT model proposes that by challenging their meaning and eliciting more realistic thoughts and assumptions, emotions and behaviour can be changed (Clark 1995). An extensive evidence base is available on the effectiveness of CBT, which is recommended as the first-line psychological therapy approach for depression (NICE 2009).

Although the evolution of CBT over the past three decades has tended to overshadow approaches that are more behavioural in nature, evidence supporting purely behavioural approaches has continued to emerge. The findings from Jacobson 1996, a component analysis trial of CBT, suggested that behavioural components alone might work just as well as CBT. These findings revitalised interest in purely behavioural treatments for depression and the development of a more fully realised behavioural intervention based on a contextual approach (Martell 2001).

Prompted by continuing debate in this area, a recent systematic review of 17 randomised controlled trials (RCTs) demonstrated equivalence between CBT and behavioural therapy in terms of depression recovery rates, symptom levels and participant dropout (Ekers 2008). Proponents of a new generation of behavioural therapies, the 'third wave' of CBT (Hayes 2004; Hofmann 2010),

'Third wave' cognitive and behavioural therapies versus other psychological therapies for depression (Review)

Hunot V, Moore THM, Caldwell DM, Furukawa TA, Davies P, Jones H, Honyashiki M, Chen P, Lewis G, Churchill R



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[Intervention Review]

'Third wave' cognitive and behavioural therapies versus other psychological therapies for depression

Vivien Hunot[1], Theresa HM Moore[2], Deborah M Caldwell[2], Toshi A Furukawa[3], Philippa Davies[2], Hannah Jones[4], Mina Honyashiki [5], Peiyao Chen[2], Glyn Lewis[6], Rachel Churchill[1]

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ABSTRACT

Background

So-called 'third wave' cognitive and behavioural therapies represents a new generation of psychological therapies that are increasingly being used in the treatment of psychological problems. However, the effectiveness and acceptability of third wave cognitive and behavioural therapy (CBT) approaches as a treatment for depression compared with other psychological therapies remain unclear.

Objectives

1. To examine the effects of all third wave CBT approaches compared with all other psychological therapy approaches for acute depression.

2. To examine the effects of different third wave CBT approaches (ACT, compassionate mind training, functional analytic psychotherapy, extended behavioural activation and metacognitive therapy) compared with all other psychological therapy approaches for acute depression.

3. To examine the effects of all third wave CBT approaches compared with different psychological therapy approaches (psychodynamic, behavioural, humanistic, integrative, cognitive-behavioural) for acute depression.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Group Specialised Register (CCDANCTR to 01/01/12), which includes relevant randomised controlled trials from *The Cochrane Library* (all years), EMBASE (1974-), MEDLINE (1956-) and PsycINFO (1967-). We also searched CINAHL (May 2010) and PSYNDEX (June 2010) and reference lists of the included studies and relevant reviews for additional published and unpublished studies. An updated search of CCDANCTR restricted to search terms relevant to third wave CBT was conducted in March 2013 (CCDANCTR to 01/02/13).

Selection criteria

Randomised controlled trials that compared various third wave CBT with other psychological therapies for acute depression in adults.

Data collection and analysis

Two review authors independently identified studies, assessed trial quality and extracted data. Study authors were contacted for additional information where required. We rated the quality of evidence using GRADE methods.

Main results

A total of three studies involving 144 eligible participants were included in the review. Two of the studies (56 participants) compared an early version of acceptance and commitment therapy (ACT) with CBT, and one study (88 eligible participants) compared extended behavioural activation with CBT. No other studies of third wave CBT were identified. The two ACT studies were assessed as being at high risk of performance bias and researcher allegiance. Post-treatment results, which were based on dropout rates, showed no evidence of any difference between third wave CBT and other psychological therapies for the primary outcomes of efficacy (risk ratio (RR) of clinical response 1.14, 95% confidence interval (CI) 0.79 to 1.64; very low quality) and acceptability. Results at two-month follow-up showed no evidence of any difference between third wave CBT and other psychological therapies for clinical response (2 studies, 56 participants, RR 0.22, 95% CI 0.04 to 1.15). Moderate statistical heterogeneity was indicated in the acceptability analyses (I^2 = 41%).

Authors' conclusions

Very low quality evidence suggests that third wave CBT and CBT approaches are equally effective and acceptable in the treatment of acute depression. Evidence is limited in quantity, quality and breadth of available studies, precluding us from drawing any conclusions as to their short- or longer-term equivalence. The increasing popularity of third wave CBT approaches in clinical practice underscores the importance of completing further studies to compare various third wave CBT approaches with other psychological therapy approaches to inform clinicians and policymakers on the most effective forms of psychological therapy in treating depression.

PLAIN LANGUAGE SUMMARY

'Third wave' cognitive and behavioural therapies versus other psychological therapies for depression

Major depression is a very common condition, in which people experience persistently low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death. Psychological therapies are an important and popular alternative to antidepressants in the treatment of depression. Many different psychological therapy approaches have been developed over the past century, including behavioural, cognitive-behavioural (CBT), 'third wave' CBT, psychodynamic, humanistic and integrative therapies.

In this review, we focused on third wave CBT approaches, a group of psychological therapies that target the process of thoughts (rather than their content, as in CBT) to help people become aware of their thoughts and accept them in a non-judgemental way. The aim of the review was to find out whether third wave CBT was more effective and acceptable than other psychological therapy approaches for people with acute depression. The review included three studies, involving a total of 144 people. The studies examined two different forms of third wave CBT, consisting of acceptance and commitment therapy (ACT) (two studies) and extended behavioural activation (BA) (one study). All three studies compared these third wave CBT approaches with CBT. The results suggested that third wave CBT and CBT approaches were equally effective in treating depression. However, the quality of evidence was very low because of the small number of studies of poor quality that we included in the review; therefore it is not possible to conclude whether third wave CBT approaches might be more effective and acceptable than other psychological therapies in the short term or over a longer period of time. Given the increasing popularity of third wave CBT approaches in clinical practice, further studies should be prioritised to establish whether third wave CBT approaches are more helpful than other psychological therapies in treating people with acute depression.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Mindfulness-based 'third wave' cognitive and behavioural therapies compared with other psychological therapies for depression

Patient or population: individuals with depression
Settings: primary, secondary and community care
Intervention: mindfulness-based 'third wave' cognitive and behavioural therapies
Comparison: other psychological therapies

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other psychological therapies	Mindfulness-based 'third wave' cognitive and behavioural therapies				
Clinical non-response at post-treatment	**Study population**		RR 1.14 (0.79 to 1.64)	144 (3 studies)	⊕○○○ **very low**[a,b,c]	
	427 per 1000	**487 per 1000** (337 to 700)				
	Moderate					
	422 per 1000	**481 per 1000** (333 to 692)				
Clinical non-response at follow-up: ACT vs other psychological therapies Follow-up: 2 months	**Study population**		RR 0.31 (0.08 to 1.26)	56 (2 studies)	⊕○○○ **very low**[a,b,c]	
	351 per 1000	**109 per 1000** (28 to 443)				
	Moderate					
	347 per 1000	**108 per 1000** (28 to 437)				

Treatment acceptability at post-treatment Dropout rates	**Study population**		RR 1.12 (0.47 to 2.67)	144 (3 studies)	⊕○○○ **very low**[a,b,c]	
	134 per 1000	**150 per 1000** (63 to 358)				
	Moderate					
	133 per 1000	**149 per 1000** (63 to 355)				
Treatment acceptability at follow-up: ACT versus other psychological therapies Dropout rates Follow-up: 2 months	**Study population**		RR 1.07 (0.1 to 11.23)	56 (2 studies)	⊕○○○ **very low**[a,c,d,e]	
	135 per 1000	**145 per 1000** (14 to 1000)				
	Moderate					
	100 per 1000	**107 per 1000** (10 to 1000)				
Non-remission at post-treatment	**Study population**		RR 0.89 (0.6 to 1.3)	88 (1 study)	⊕○○○ **very low**[c,f,g]	
	578 per 1000	**514 per 1000** (347 to 751)				
	Moderate					
	578 per 1000	**514 per 1000** (347 to 751)				
Depression levels at post-treatment (HAM-D)		Mean depression levels at post-treatment in the intervention groups was **1.65 lower** (4.17 lower to 0.88 higher)		113 (3 studies)	⊕○○○ **very low**[a,b,c]	

Depression levels at follow-up: ACT vs other psychological therapies (HAM-D) Follow-up: 2 months		Mean depression levels at follow-up of ACT vs other psychological therapies in the intervention groups were **4.51 lower** (7.47 to 1.55 lower)		49 (2 studies)	⊕○○○ **very low**[a,c,e]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **risk ratio** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] The method of sequence generation/allocation concealment was unclear in two studies. As with all psychological therapy trials, blinding of clinicians/participants was not achievable. The risk of bias was assessed as high for researcher allegiance and as unclear for treatment fidelity and therapist qualifications.
[b] Only two third wave approaches were included and/or the comparator psychological therapy approaches were limited to CBT.
[c] Sample sizes were small and/or confidence intervals were wide.
[d] Moderate statistical heterogeneity was indicated.
[e] Compared against only one other psychological therapy approach.
[f] As with all psychological therapy trials, blinding of clinicians/participants was not achievable. The risk of bias was assessed as high for researcher allegiance and as unclear for treatment fidelity and therapist qualifications.
[g] Only one study provided clinical remission data.

BACKGROUND

Description of the condition

Major depression is characterised by persistent low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms, including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death (APA 2000). Somatic complaints are also a common feature of depression, and people with severe depression might develop psychotic symptoms (APA 2000).

Depression is the third leading cause of disease burden worldwide and is expected to show a rising trend over the next 20 years (WHO 2004; WHO 2008). A recent European study has estimated the point prevalence of major depression and dysthymia (a mild long-term form of depression) at 3.9% and 1.1%, respectively (ESEMeD/MHEDEA 2004). As the largest source of non-fatal disease burden in the world, accounting for 12% of years lived with disability (Ustun 2004), depression is associated with marked personal, social and economic morbidity and loss of functioning and productivity and creates significant demands on service providers in terms of workload (NICE 2009). Depression is also associated with a significantly increased risk of mortality (Cuijpers 2002). The strength of this association, even when confounders such as physical impairment, health-related behaviours and socio-economic factors are taken into account, has been shown to be comparable with, or greater than, the strength of the association between smoking and mortality (Mykletun 2009).

Description of the intervention

Clinical guidelines recommend pharmacological and psychological interventions, alone or in combination, for the treatment of moderate to severe depression (NICE 2009). The prescribing of antidepressants has increased dramatically in many Western countries over the past 20 years, mainly with the advent of selective serotonin reuptake inhibitors and newer agents such as venlafaxine, and antidepressants remain the mainstay of treatment for depression in healthcare settings (Ellis 2004; NICE 2009).

Whilst antidepressants are of proven efficacy in acute depression (Cipriani 2005; Gartlehner 2007; Arroll 2009; Cipriani 2009; Cipriani 2009a; Cipriani 2009b), adherence rates remain very low (Hunot 2007; van Geffen 2009), in part because of patients' concerns about side effects and possible dependency (Hunot 2007). Furthermore, surveys consistently demonstrate patients' preference for psychological therapies over antidepressants (Churchill 2000; Riedel-Heller 2005). Therefore, psychological therapies can provide an important alternative or adjunctive intervention for depressive disorders.

A diverse range of psychological therapies is now available for the treatment of common mental disorders (Pilgrim 2002). Psychological therapies may be broadly categorised into four separate philosophical and theoretical schools, comprising psychoanalytic/dynamic (Freud 1949; Klein 1960; Jung 1963), behavioural (Watson 1924; Skinner 1953; Wolpe 1958), humanistic (Maslow 1943; Rogers 1951; May 1961) and cognitive approaches (Lazarus 1971; Beck 1979). Each of these four schools incorporates several differing and overlapping psychotherapeutic approaches. Some psychotherapeutic approaches, such as cognitive analytic therapy (Ryle 1990), explicitly integrate components from several theoretical schools. Other approaches, such as interpersonal therapy for depression (Klerman 1984), have been developed to address characteristics considered to be specific to the disorder of interest.

Increasing interest in the role of cognition gave rise to a 'cognitive revolution' in the field of psychology in the 1970s (Mahoney 1978). The most influential approaches were rational emotive behaviour therapy (Ellis 1962), cognitive behaviour modification (Meichenbaum 1977) and cognitive therapy (Beck 1979). The latter developed as an approach to understanding and treating depression. However, both Beck and Ellis acknowledged the value of behaviour therapy (Pachman 1997), and during the 1980s and 1990s, the two approaches were merged to form cognitive-behavioural therapy (CBT).

CBT is generally regarded as a family of allied therapies (Mansell 2008) that draw on a common base of behavioural and cognitive models of psychological disorders and utilise a set of overlapping techniques (Roth 2005). In CBT, cognition is central to the treatment of psychological disorders, with emotions and behaviour thought to be mediated by cognitive processes. The fundamental aim of CBT is to identify unhelpful cognitions or 'negative automatic thoughts' derived from long-standing negative beliefs/assumptions about the self, other people or the world. The CBT model proposes that by challenging their meaning and eliciting more realistic thoughts and assumptions, emotions and behaviours can be changed (Clark 1995). An extensive evidence base is available on the effectiveness of CBT, which is recommended as the first-line psychological therapy approach for depression (NICE 2009).

Although the evolution of CBT over the past three decades has tended to overshadow approaches that are more behavioural in nature, evidence supporting purely behavioural approaches has continued to emerge. The findings from Jacobson 1996, a component analysis trial of CBT, suggested that behavioural components alone might work just as well as CBT. These findings revitalised interest in purely behavioural treatments for depression and the development of a more fully realised behavioural intervention based on a contextual approach (Martell 2001).

Prompted by continuing debate in this area, a recent systematic review of 17 randomised controlled trials (RCTs) demonstrated equivalence between CBT and behavioural therapy in terms of depression recovery rates, symptom levels and participant dropout (Ekers 2008). Proponents of a new generation of behavioural therapies, the 'third wave' of CBT (Hayes 2004; Hofmann 2010),

Ⅴ章

平成26年度総括分担研究報告

平成26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（健やか次世代育成総合研究事業）)
「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」分担研究報告書

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。
本年度は、所管課と連携して、母子保健行政上重要課題と考えられる自閉症や発達障害の子どもとアレルギー等の関連について系統的レビューを実施し、政策に寄与した。
われわれは、海外関連機関の支援のもと17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を明らかにしてきた。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の活動により、本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および小児死因分析調査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づけられているため、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順守した。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、動物事件は行っていない。

C. 研究結果

ネットワークメタアナリシスの応用と批判的吟味ガイドライン（古川壽亮）

本分担班のこれまでの経験に基づき、臨床家がネットワークメタアナリシスを臨床で利用するための批判的吟味のガイドラインを作成した。このガイドラインは、メタアナリシスのユーザーズガイドにならい、2部に分かれる。

第1部は、系統的レビューの過程の方法論的妥当性に関するチェックポイントで、通常のペアワイズ・メタアナリシスと同様である。第2部は、得られた結果の質、つまり得られた結果の確実性に関するチェックポイントで、GRADEをネットワークメタアナリシスに適用したものである。ひとつの臨床疑問に関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今後、臨床判断にますます重要となってくるであろう。今回われわれはさらに進んで、ネットワークメタアナリシスを理論的研究に応用する研究を行った。また、ネットワークメタアナリシスを臨床家が適切に利用できるためのガイドラインを作成した。

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）

コクランレビューワークショップに出席し、本研究への理解を深めるとともに、参加者とのコミュニケーションを介して、周産期領域、特に産科領域からのサポートを行うこととした。平成27年4月に横浜で開催される第67回日本産科婦人科学会（学術集会会長：峰岸　敬教授（群馬大学））事務局に対して、日本におけるコクラン共同研究の主旨を説明し、当該学術集会内での「コクランレビューに関する説明会の開催」開催許可を依頼した。また、本邦で開催される周産期領域、産婦人科領域での学会や研究会主催者に働きかけ、「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」を試みた。周産期領域での各種学会や医局において、「日本におけるコクラン共同計画の認知度」を高めるべく、啓発活動を実施した。上記検討結果を踏まえて、主任研究者である森臨太郎先生と問題点の抽出と協議を行い、平成27年度の方策を検討した。

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

ILCORワークシートの1例作成にあたり、網羅的文献検索、1次・2次スクリーニングを実施し、最終的に12文献を採用

した。ここで既存のコクランレビューの採用文献と比較したところ、コクランレビューでは16文献を採用しており、うち11文献は一致していた。今回我々の採用文献に含まれなかった5文献の内、臍帯ミルキングの文献はPICOの観点から除外されて妥当と考えられた。またコクランレビューで採用されていた文献に代わり、その後アップデートされた論文が採用されており、採用文献として内容的には一致していることが確認できた。その他の4論文はILCORのPICOのOutcomeにそぐわず除外されていたことが確認できた。その後コクランには含まれていない非ランダム化試験3文献を採用し、各論文につきGRADEシステムに従いコクランレビューと照らし合わせながらアウトカム毎に基づいたGRADE bias table およびGRADE finding tableを作成し、2014年12月7日のアメリカ合衆国、ワシントンD.CでのILCOR新生児部門会議にて発表した。会議参加者よりその作成過程でのコクランレビューの有用性が認められ、多くの賛同が得られた。

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った。

平成26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セミナーを2回、第28回日本助産学会学術集会（長崎）において、プレコングレス・セミナーを開催した。

レビュー作成の進捗状況は、【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を行った結果アクセプトされ、プロトコル査読結果を受け取り、現在修正中である。

また、「日本助産学会　エビデンスに基づく助産ガイドライン：分娩期2012」の改訂作業を進めている。同時に、「ガイドライン-妊娠期」の作成準備が始まっている。妊婦健診では、助産師健診も増加しており、さまざまな妊婦の疑問に回答できるよう、適切な情報提供ができるようなガイドラインの作成を目指している。日本産婦人科学会のガイドラインの横に助産学会ガイドラインがならび、多様なCQに対するエビデンスの紹介ができるよう作業を進めている。

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）

「Cognitive-behavioural treatment for amphetamine-type stimulants (ATS) use disorders」（アンフェタミン・タイプ刺激剤使用障害に対する認知行動療法）というタイトルで、コクラン薬物・アルコールグループにタイトル登録、プロトコールの執筆を行った。タイトル登録は、平成25年2月に完了し、プロトコールは同年5月に提出した。さらに、キャンベル共同計画への同時登録の許可も双方から得た。

プロトコールについては、同年10月にコクラン・ライブラリーにおいて公表された。今後は、プロトコールにしたがってレビュー本体の執筆を行う。

キャンベル共同計画の翻訳については、既に英語で発表されている教育，刑事司法，社会福祉分野等のレビュー本体、および抄録の翻訳を実施した。また、既存のウエブサイトの見直しと整備を行った。

さらに、社会科学分野におけるエビデンス・ベーストの重要性について広く啓蒙するための学会発表や論文執筆を行った。

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、シャルーク・サデクア、佐々木八十子）

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、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。

本年度は、コクラン日本支部を設立し、プレスリリースを行った。５月にコクランの CEO であるマークウィルソンが来日し、厚生労働省にて記者会見を行った。また、成育にてコクランのワークショップを３回（タイトルレジストレーション６月、プロトコール９月、フルレビュー2月）実施した。また国立精神神経センターと、国立がんセンターと国立成育医療研究センターと３ナショセン合同で、昨年度に引き続き 12 月に第二回メタアナリシス入門講座を実施した。成育医療研究センターのセミナー、東京大学大学院、東京医科歯科大学大学院、大分県立看護大学にて系統的レビュー作成およびコクラン共同計画に関する講義を行いワークショップ等を含め、延べ 300 名以上が参加した。また助産学雑誌に、日本語でコクラン系統的レビューの解説特集の連載を１年間行い啓蒙活動を行った。日本からのコクラン共同計画の著者数は、2015 年２月でおよそ 200 名となり順調に増加している。日本からのコクラン Archie 登録者数は 300 名となった。

本年度の６月には、所管課と連携して、母子保健行政上重要課題と考えられる自閉症や発達障害の子どもとアレルギー等の関連について系統的レビューを実施し、政策に寄与した。（参考資料１：自閉症や発達障害の子どもとアレルギー等の関連について）

国際共同研究としては、WHO の妊娠期の感染症のガイドライン作成のためのコクランレビューを７月から３か月イギリスの妊娠出産グループに行き、関連する２０論文 update しすべて出版された。

D. 考察

本年度は、コクラン日本支部のプレスリリースをはじめとして、ワークショップ、講演、講義などでコクラン共同計画の認知度を高め、系統的レビューの方法論を多くの参加者に伝えることができた。ワークショップの開催も、コクラン系統的レビューの著者が増加し、チューターや講師として参加し協力を得ることができている。また、２月には、成育にてコクランレビューの読み方・使い方のセミナーを開催した。６月には、韓国にて日・中・韓・豪合同のレビューコンプリーションワークショップ開催を予定している。

コクラン系統的レビューは、著者の増加に伴い、順調に出版数を増加させている。本年度は、研究班全体でコクランプロトコールが７本、コクランの手法を用いたプロトコールが１本、コクラン系統的レビューが９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７本、コクラン系統的レビューが７本出版が達成し、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。本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

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E. 引用文献・出典

なし

F. 研究発表

1. 論文発表

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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