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# Topical oils for the prevention or treatment of dry skin in term infants (Protocol)

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[Intervention Protocol]

# Topical oils for the prevention or treatment of dry skin in term infants

Alison Cooke[1], Suresh Victor[2], Michael Cork[3], Tina Lavender[4]

[1]School of Nursing, Midwifery & Social Work, The University of Manchester, Manchester, UK. [2]Maternal and Fetal Health Research Group, Neonatal Medical Unit, 5th Floor, St Mary's Hospital, Manchester, UK. [3]Academic Unit of Dermatology Research, Department of Infection and Immunity, The University of Sheffield, Sheffield, UK. [4]School of Nursing, Midwifery and Social Work, The University of Manchester, Manchester, UK

Contact address: Alison Cooke, School of Nursing, Midwifery & Social Work, The University of Manchester, Room 4.338, Jean McFarlane Building, Oxford Road, Manchester, M13 9PL, UK. Alison.Cooke@manchester.ac.uk.

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## ABSTRACT

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

We will assess the effect of the topical application of oils versus that of other topical oils, emollients, placebo or no treatment:

1. in the prevention of dry skin in term (≥ 37 weeks of gestation) newborn infants; and

2. in the treatment of dry skin in term (≥ 37 weeks of gestation) newborn infants.

## BACKGROUND

### Description of the condition

Dry skin is a common occurrence in the first few months of an infant's life (Saijo 1991). Dry skin has been defined as "a cutaneous reaction pattern reflecting abnormal desquamation of diverse etiologies" (Madison 2003). In normal skin, corneocytes are shed from the skin in small enough quantities that they are not visible to the naked eye; however, in dry skin, the skin appearance becomes rough and flaky if this normal process is disturbed in any way. In an infant, this is a normal process of adaptation to life outside the uterus.

Atopic eczema (synonym atopic dermatitis) is an inflammatory skin condition characterised by dry and scaly skin, redness, blistering and itching. It affects up to 30% of children aged 2 to 15 years in the UK (Gupta 2004). Affected children are also predisposed to allergic asthma and allergic rhinitis (Gustafsson 2000). It is suggested that approximately 60% of sufferers develop atopic eczema in their first year of life (Bieber 2008). Prevalence has increased to this current level from approximately 5% of children in the 1940s (Taylor 1984). During that time the genetic structure of skin has not changed; however, the way that we care for an infant's skin has changed, with an increase in use of soaps, other harsh detergents and oils (Cork 2009; Danby 2011a).

Infant skin is physiologically different to adult skin. The stratum corneum is 30% thinner and the epidermis is 20% thinner in in-

fants than in adults (Stamatas 2010). This difference in skin structure results in increases in permeability and dryness in infant skin. Infant skin is also more vulnerable to the use of topical treatments, as the ratio of infant body surface to body weight is higher than that for adults; hence, the risk that such therapies will be absorbed through the skin is greater in infants than in adults (Nikolovski 2008). As the infant skin barrier continues to develop during the first year of life (Stamatas 2011), infants are vulnerable to this risk throughout this period. Infant skin is prone to an increased rate of transepidermal water loss (TEWL) and reduced stratum corneum hydration because it contains fewer lipids and natural moisturising factors, and less melanin than adult skin (Chiou 2004; Nakagawa 2004). Infants may also experience a weakening of the skin barrier due to their elevated skin surface pH. High skin surface pH (low acidity) results in increased activity of proteases, which breakdown corneodesmosomes (the supportive component of the stratum corneum), and hinders the activity of enzymes that are required for lipid processing (Hachem 2003; Cork 2009).

These differences in both structure and function between infant and adult skin suggest that infant skin is more vulnerable to environmental factors, including infant skin care products. The use of some topical oils and emollients on infant skin may therefore contribute to the development of adverse skin conditions, including atopic eczema, whereas other topical oils may have a positive effect and prevent the development of this condition (Danby 2011a; Danby 2011b; Danby 2013).

## Description of the intervention

Parents want to use skin products that make their infant look and smell nice (Lavender 2009; Furber 2012). The application of oil is commonly recommended by health professionals to new parents for use on their newborn infant's skin (Lavender 2009; Cooke 2011), in order to prevent or treat dryness or for massage. The use of emollients is not commonly recommended; however, parents have the choice of a diverse range of emollient infant skin care products from numerous manufacturers. In a UK national survey ( Cooke 2011), 52% of maternity and neonatal units recommended the use of oil; 82% of these units recommended olive oil to parents for use on their infant's skin and 20% recommended sunflower oil. Health professionals, such as midwives and health visitors, believe these oils to be natural and, therefore, not harmful to infant skin (Lavender 2009). Infant skin conditions can cause parental anxiety (Adalat 2007). Parents will often adhere to advice given to them by health professionals with regard to the care of a newborn infant (Lavender 2009).

## How the intervention might work

Some oils have been shown to have a positive effect on skin barrier function (Darmstadt 2004; Darmstadt 2008; Danby 2013), whereas others may impair this function (Naik 1995; Darmstadt 2002a; Jiang 2003; Danby 2013). Research has shown that olive oil of a certain composition (i.e. a high ratio of oleic acid to linoleic acid) may adversely affect skin barrier function in mice (Darmstadt 2002a; Jiang 2003) and adults (Naik 1995; Danby 2013). This composition of oil disrupts the lipid structure of the stratum corneum, and is a potential risk factor in the development or exacerbation of atopic eczema. Optimal sunflower oil (i.e. a high ratio of linoleic acid to oleic acid) has been shown in the same population to promote skin barrier repair (Darmstadt 2004; Darmstadt 2008; Danby 2013).

The use of emollients or moisturisers is common in skin care regimens. They act by preventing water loss or by actively hydrating the skin (Elson 2011). The main reason to use emollients in skin care is to protect the integrity of the skin barrier. For healthy term infants, this is not clinically necessary; however, those infants at risk (such as those with a family history of atopic eczema) may benefit from the regular use of emollients (Frieden 2011). An oil is also an emollient that helps to prevent water loss and lubricates the skin.

## Why it is important to do this review

Societal interest in 'natural' products is high (Allemann 2009), especially in parents of newborn infants (Cottingham 2007). There is a readiness among parents to use oil for infant skin care, and a readiness among maternity professionals to recommend it. There is a misconception that because a product is 'natural' it must be 'safe' (Lavender 2009; Bedwell 2012). Oils have been used in the cosmetic, pharmaceutical and perfumery industries for many years. Although oils are governed by guidelines for the testing and research of cosmetics (Council of the European Communities 1976), these are not as rigorous as those governing the use of medicines in humans (Department of Health 2004). This means that oils have been used as medicinal and homeopathic remedies for many years without any collection and analysis of toxicological data. The infant skin surface area in relation to body weight is high and absorption is relative to the surface area exposed (Rutter 1987). Topical applications may cause irritation, damage or systemic effects through absorption of the oil in to the body.

Infection is one of the leading causes of neonatal morbidity and mortality in low-resource countries (Darmstadt 2002a). The vulnerability of infant skin and the use of oils that may be harmful, combined with poor hygiene conditions, have the potential for increased hazards of infection. Nosocomial sepsis is more common in preterm infants, in whom the stratum corneum is not fully mature (Conner 2009) and the skin does not have the protective benefit of vernix (Yoshio 2003), than in term infants. Several studies (Darmstadt 2002b; Darmstadt 2004; Edwards 2004; Darmstadt 2005; Darmstadt 2008; Kiechl-Kohlendorfer 2008) and a Cochrane systematic review (Conner 2009) have considered

topical applications for preterm infants, but no review has considered the evidence in term infants.

We know that 45% and 60% of atopic eczema cases occur in the first six months and year of life, respectively (Bieber 2008). This period of time is when midwives, maternity workers and other infant health professionals have the most influence with parents. Health professionals find it difficult to give evidence-based advice to new parents, as there is insufficient evidence to guide practice. It is therefore important to systematically review what evidence there is, to provide a high-quality basis for clinical practice and informed decision-making. Some oils are potentially harmful; however, others may provide some benefit. Given the rise in the prevalence of atopic eczema, it is timely to evaluate current evidence in order to provide the most appropriate advice for parents and health professionals.

This review will assess the effects of topical oils and emollients in the prevention or treatment of dry skin compared to the use of alternative oils and emollients or no treatment in term infants. The review will complement the body of work held in the *Cochrane Database of Systematic Reviews*, which includes reviews such as those investigating the prevention of infection in preterm infants (Conner 2009; Seliem 2009) and the prevention of napkin dermatitis in infants (Davies 2009).

A systematic review will provide:

1. an evidence base to inform parents and health professionals in their practice with healthy term newborn infants, rather than remain in confusion regarding which oil or emollient, if any, to recommend or use; and
2. highlight any area that requires further investigation.

## OBJECTIVES

We will assess the effect of the topical application of oils versus that of other topical oils, emollients, placebo or no treatment:

1. in the prevention of dry skin in term (≥ 37 weeks of gestation) newborn infants; and

2. in the treatment of dry skin in term (≥ 37 weeks of gestation) newborn infants.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised and quasirandomised controlled trials (including cluster and parallel trials, and trials in which the infant serves as his/her own control) comparing the topical application of oils with the topical application of other oils, emollients or placebo, or with no treatment will be considered.

#### Types of participants

We will include newborn term (≥ 37 weeks of gestation) infants receiving the application of topical oils or emollients:

1. for the prevention of dry skin within the first 28 days following birth; or

2. for the treatment of dry skin within the first 28 days following birth.

There is no upper gestational age limit for eligibility.

For the purposes of this review, dry skin will be diagnosed using a validated skin assessment scoring tool (Lane 1993; Lund 2001) or skin surface hydration measurement tool (e.g. a Corneometer®), or by clinical observation by a midwifery, neonatal or dermatology health professional.

We will include infants with normal skin and infants with a family history of atopic eczema. Normal infant skin variations, such as erythema neonatorum, erythema toxicum or milia, will not be considered as skin disorders, and will therefore be included. A family history of atopic eczema will be defined as "at least one of mother, father or sibling who has a medical diagnosis of atopic eczema/atopic dermatitis and who is treated with topical steroidal treatment". Infants diagnosed with an impairment of epidermal integrity, abnormal epidermis or dermis, such as collodion infant or congenital ichthyosis, will be excluded.

We will exclude newborn preterm (< 37 weeks of gestation at birth) infants, as this population has been included in another review (Seliem 2009).

#### Types of interventions

All of the stated interventions will be considered separately for both the prevention and treatment of dry skin.

**Intervention**

1. Application of topical oils, which may include any type of oil (such as olive oil, sunflower oil, coconut oil, grape seed oil, borage oil, evening primrose oil, other vegetable oil) compared with placebo or no topical applications
2. Application of topical emollients compared with placebo or no topical applications

**Other Interventions**

1. Intervention oil versus another topical oil
2. Intervention emollient versus another topical application (such as emollient, gel, cream, lotion or powder)
3. Intervention oil versus another topical application (such as emollient, gel, cream, lotion or powder)

It is expected that other products, such as soaps or bathing products, may be used on the infants in the trials. It is also expected that there will be variations in the dose, area, frequency and duration of application of the interventions. If there are substantial

differences across trials, data will not be pooled but reported separately. Where combinations of topical applications are applied, data from a combination of treatments will not be pooled with data for single treatments.

### Types of outcome measures

Where appropriate, data will be pooled or, if necessary (and appropriate), dichotomised. Outcomes will be analysed at baseline and at further time points up to 28 days (e.g. 7, 14, 28 days).

#### Primary outcomes

1. Change in skin surface hydration, measured using a Corneometer® or similar validated tool, within 28 days following birth
2. Change in TEWL, measured using an Aquaflux, Tewameter® or similar validated tool, within 28 days following birth

#### Secondary outcomes

1. Change in skin assessment scores, measured using the Neonatal Skin Condition Score (Lund 2001) or the Skin Condition Grading Scale (Lane 1993) within 28 days following birth.
2. Systemic or cutaneous infection, confirmed by diagnosis more than 48 hours after birth, as determined by culture of swabs from a normally sterile skin site
3. Change in skin surface pH, measured using a Skin-pH-meter or similar validated tool, within 28 days following birth
4. Atopic eczema, confirmed by clinical diagnosis by a dermatologist
5. Clinical observations of adverse skin conditions (visible signs of skin barrier dysfunction such as erythema/rash), measured using a Mexameter® or similar validated tool, or documented clinical examination, within 28 days following birth
6. Maternal satisfaction with regard to using oils for infant skin care or condition of infant's skin, as measured by questionnaire response
7. Other skin-related outcomes not identified a priori by the reviewers but reported by trial authors

## Search methods for identification of studies

We will use the standard search strategy of the Cochrane Neonatal Review Group.

### Electronic searches

We will identify randomised controlled trials from the Cochrane Central Register of Controlled Trials (CENTRAL, latest issue of *The Cochrane Library*). We will identify all other trials from MEDLINE (1966 to current), EMBASE (1980 to current), CINAHL (1982 to current), Dissertation Abstracts (1980 to current) and SIGLE (2000 to current). We will list the full search strategies for these databases in the review. We will identify ongoing clinical trials through searching www.clinicaltrials.gov.

We will not apply any language restrictions. We will use the following text words or medical subject heading terms: infant, neonate, newborn, baby, plant oils, oils, emollients, oleic acid, oleic, linoleic, skin barrier function, epidermal barrier function, skin scores, atopic march, dry skin, atopic eczema, atopic dermatitis.

### Searching other resources

We will search for further studies in the reference lists of all identified articles. We will not apply language, start date or geographical restrictions. We will approach the clinical research departments of all major pharmaceutical and cosmetic companies to request access to their unpublished research (see Appendix 1). We will contact subject experts to identify ongoing, unpublished research. Abstracts presented at the annual meetings of the Society for Pediatric Research, the American Pediatric Society, and the European Society for Paediatric Research, and published in the journal *Pediatric Research,* will be handsearched. We will include trials presented in abstract form only if sufficient data are available from the abstract, or from contact with the author.

## Data collection and analysis

We will use the standard methods of the Cochrane Neonatal Review Group.

### Selection of studies

Two review authors (AC, TL) 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 review author (SV or MC).

### Data extraction and management

We will design a form for the extraction of data. For eligible studies, at least two review authors (AC, TL) will extract data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third review author (SV/MC). We will enter data into Review Manager (RevMan 2011) and check them for accuracy.

We will attempt to contact authors of the original reports to provide further details when information regarding the above is unclear.

## Assessment of risk of bias in included studies

Two review authors (AC, TL) will independently assess the risk of bias in 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 review author (SV/MC).

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

For each included study we will describe 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:

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

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

For each included study we will describe 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 will assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear.

**(3) Blinding (checking for possible performance bias)**

We will describe for each included study the methods used, if any, to blind outcome assessors, participants and personnel from knowledge of which intervention a participant received. We will judge studies at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess the methods for blinding separately under the headings: participants, personnel and outcomes.

We will assess the methods as:

- adequate;
- inadequate;
- unclear.

**(4) Incomplete outcome date (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)**

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, the numbers included in the analysis at each stage (compared with the total numbers of 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 that we undertake.

We will assess the methods as:

- adequate (where fewer than 20% of the data are missing);
- inadequate (where more than 20% of the data are missing);
- unclear.

**(5) Selective 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:

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; 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.

**(6) Other sources of bias**

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 as:

- yes;
- no;
- unclear.

**(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 for Systematic Reviews of Interventions* (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 sensitivity analyses (*see* 'Sensitivity analysis').

## Measures of treatment effect

***Dichotomous data***

We will present results as summary risk ratios and risk differences with 95% confidence intervals for dichotomous data. If statistically significant, we will present the number needed to treat for an additional beneficial or harmful outcome (NNTB/NNTH).

***Continuous data***

We will use the weighted mean difference for continuous data if outcomes are measured in the same way in all trials. We will use the standardised mean difference to combine data from trials that measure the same outcome using different methods. We will present these data with 95% confidence intervals.

### Unit of analysis issues

***Randomised trials where participant serves as own control***

We will include these trials along with individually randomised trials. We will consider it reasonable to combine the results from both types of study if there is little heterogeneity between the study designs.

***Cluster randomised trials***

We will include cluster randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes by means of the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*, using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2011). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster randomised trials and individually randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and an interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will seek statistical advice for this part of the analysis.

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

### Dealing with missing data

For 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 using sensitivity analyses. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis (i.e. we will attempt to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention). The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

### Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the $I^2$ statistic. We will identify heterogeneity using the following categories: less than 25%, no heterogeneity; 25% to 40%, low heterogeneity; 50% to 74%, moderate heterogeneity; and 75% or greater, high heterogeneity. We will explore substantial heterogeneity ($\geq$ 75%), if identified, using subgroup analyses.

### Assessment of reporting biases

Where we suspect reporting bias (*see* 'Selective reporting bias'), we will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results using sensitivity analyses.

We will create funnel plots using Review Manager version 5.2 ( RevMan 2011) and assess the presence of publication bias by visual inspection of the plots for funnel plot asymmetry. Unfortunately, where the effect measure for dichotomous outcomes is the relative risk (or risk ratio), as is the case for potentially two of the outcomes in this review (skin assessment scores and maternal satisfaction), there is limited evidence to underpin the statistical assessment of funnel plot asymmetry (Higgins 2011). Therefore, we will limit our assessment of funnel plot asymmetry to a visual inspection only.

### Data synthesis

Statistical analyses will be performed using the standard methods of the Cochrane Neonatal Review Group. Review Manager version 5.2 (RevMan 2011) will be used for meta-analyses. We will use fixed-effect meta-analyses 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 to be sufficiently similar). If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detect substantial statistical heterogeneity (*see* 'Assessment of heterogeneity'), we will attempt to explain the heterogeneity identified in the fixed-effect model based on differences in clinical, quality or other characteristics between studies.

### Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses based on:

1. setting: high-income countries (gross national income (GNI) per capita $4036 or more) versus low-income countries (GNI per capita $4035 or less (World Bank 2012));
2. ethnicity: white versus black and minority ethnic;
3. family history of atopic eczema ("at least one of father, mother, or sibling, who has a medical diagnosis of atopic eczema and who has had topical steroid treatment") versus no family history of atopic eczema.

For fixed-effect meta-analyses, we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.

### Sensitivity analysis

We will perform sensitivity analyses based on trial quality, separating high-quality trials from trials of lower quality. We will define high quality, for the purposes of this sensitivity analysis, as a trial having adequate allocation concealment and a 'reasonably

expected loss to follow up' (classified as less than 10%). We will restrict sensitivity analyses to primary outcomes.

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* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. Pharmaceutical and Cosmetic Companies approached to access unpublished research

Johnson & Johnson
Pfizer
Roche
GlaxoSmithKline
Novartis
Sanofi Aventis
Astra Zeneca
Abbott Laboratories
Merck
Bayer
Eli Lilly
Bristol-Myers Squibb
Proctor & Gamble
Boehringer
Astellas Pharma Ltd
Unilever
L'Oreal
Shiseido
Estee Lauder
Avon
Beiersdorf
Alberto-Culver
Kao Corporation

## CONTRIBUTIONS OF AUTHORS

Alison Cooke prepared the protocol.

All authors contributed to reviewing all sections of the protocol and reviewed the final version prior to submission.

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