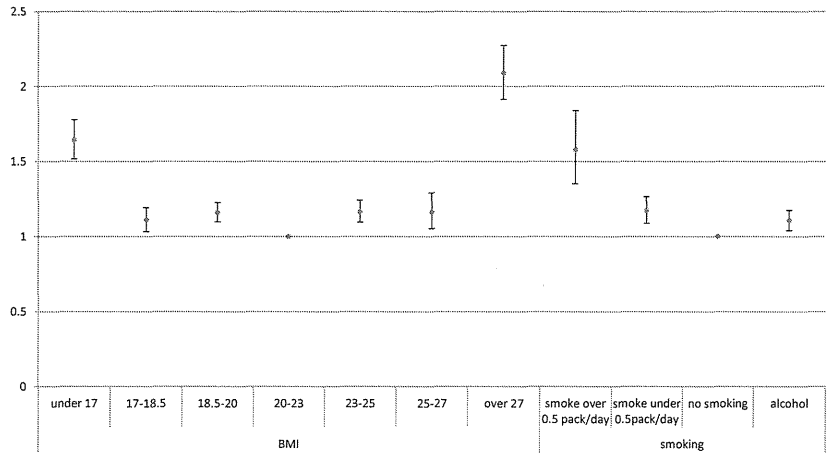
Estimated Effects of other confounders



Overall Summary of trends in Japan

Maternal Characteristics

- Increase in twins
- older maternal age
- # of previous births/stillbirths

play substantial role in shortening gestational length.

Mothers living in major cities are more likely to be older and nulliparous, but with lower risk of preterm birth

Scheduled Deliveries

- Preterm & early term deliveries are more scheduled. Rate higher in major cities
- Full term births have become less likely to be scheduled. Rate similar for residence
- Preterm & early term pre-labor deliveries largely due to
  - medical urgencies
  - breech, multiple pregnancies
  - repeated cesarean section
- Breech mostly delivered by cesarean section before 39 weeks
- Multiple pregnancies mostly delivered before 39 weeks
- Repeated cesarean section mostly operated at early term
- PROM is a main reason for scheduled delivery at full term
- 50% of pre-labor delivery at full term may be elective

P1-073

1979年から2010年における日本全出生の低出生体重児および早産増加の要因分析

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要旨

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

背景

- 近年、先進国で低出生体重児が増加しているのは日本だけであるがいつから増加してきたのか、地域差があるのか、早産が増えているのかなど原因を分析することで今後の予防政策を立案するための重要なデータとなる。
- 低出生体重児は新生児死亡予後リスクだけではなく、将来、心臓病脳梗塞、悪性腫瘍などの成人病発症の素因となり発症のリスクが高くなることが疫学調査から明らかにされている。

目的

1. 1979年から2010年の人口動態調査・出生票を用いて新生児平均体重の経年変化を明らかにする。
2. 近年増加する低出生体重児・早産の増加の経年推移とその要因および地域差があるかどうかを分析する。

方法

人口動態調査の出生票から、単胎で出生した低出生体重児(出生体重が2500g未満）の割合、早産（出生週数が37週未満）の割合、初経産、母親年齢、児性別、出生体重、出生時妊娠週数、出生曜日、出生地域（都市部1, 地方0）などの変数を抽出し、ロジスティック回帰にて要因を分析した。
統計はR(ver:3.0.2)とデータ加工時の使用言語はpython, SQL, AWKを使用した。

結果

図1：平均出生体重増加量（男女別：g）

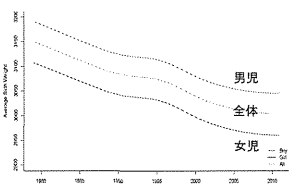

図2：低出生体重児および早産児出生割合（%）

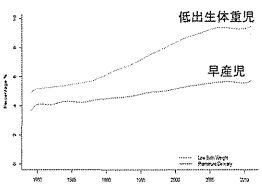

図3：低出生体重児出生週数別出生数

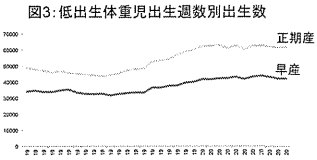

図4：出生曜日別出生割合：低出生体重児

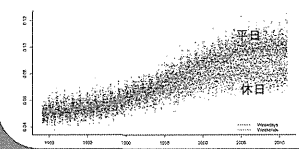

図5：低出生体重児出生と地方・都市部

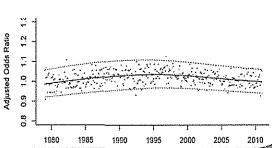

図6：低出生体重児出生と高齢出産（35歳以上）

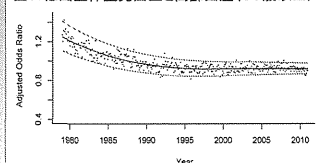

図7：早産児出生と高齢出産（35歳以上）

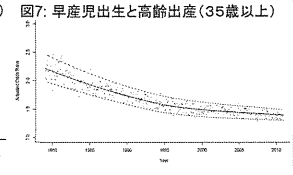

表1：母親年齢別の低出生体重児体重別割合

1979年	0.5kg未満	1.0kg未満	1.5kg未満	2.5kg未満
~19歳	0.00%	0.12%	0.55%	7.63%
20-24	0.00%	0.06%	0.28%	4.92%
25-29	0.00%	0.06%	0.25%	4.05%
30-34	0.00%	0.09%	0.36%	4.36%
35-39	0.01%	0.17%	0.71%	7.12%
40~	0.01%	0.29%	1.19%	10.17%

1990年	0.5kg未満	1.0kg未満	1.5kg未満	2.5kg未満
~19歳	0.01%	0.25%	0.77%	8.38%
20-24	0.00%	0.16%	0.45%	6.31%
25-29	0.00%	0.12%	0.35%	5.33%
30-34	0.01%	0.16%	0.46%	5.06%
35-39	0.01%	0.29%	0.76%	6.76%
40~	0.02%	0.54%	1.36%	10.01%

2010年	0.5kg未満	1.0kg未満	1.5kg未満	2.5kg未満
~19歳	0.04%	0.43%	0.85%	9.93%
20-24	0.01%	0.23%	0.55%	8.04%
25-29	0.02%	0.19%	0.44%	7.73%
30-34	0.02%	0.23%	0.54%	8.09%
35-39	0.03%	0.35%	0.82%	9.19%
40~	0.05%	0.53%	1.41%	11.55%

表2：母親年齢別の低出生体重児週数別割合

1979年	37週未満	37~42週未満	42週以降
~19歳	43.36%	53.95%	2.69%
20-24	37.15%	60.75%	2.10%
25-29	38.21%	59.85%	1.94%
30-34	44.79%	53.52%	1.69%
35-39	47.47%	50.57%	1.96%
40~	52.92%	45.05%	2.04%

1990年	37週未満	37~42週未満	42週以降
~19歳	44.13%	54.85%	1.02%
20-24	37.07%	62.42%	0.51%
25-29	37.14%	62.35%	0.51%
30-34	41.27%	58.33%	0.40%
35-39	49.50%	50.13%	0.37%
40~	56.11%	43.11%	0.77%

2010年	37週未満	37~42週未満	42週以降
~19歳	40.18%	59.75%	0.07%
20-24	33.24%	66.69%	0.08%
25-29	33.33%	66.63%	0.04%
30-34	35.23%	64.73%	0.04%
35-39	39.33%	60.64%	0.03%
40~	45.05%	54.88%	0.07%

考察＆結論

1. 平均出生体重は男女共に年々減少しており、低出生体重児、とくに早産児が増加している。
2. 出生曜日の割合が1990年前後で逆転して増加しているのは、地域のクリニックから病院への転換、産科エコー機器の導入、NICU医療向上などによる影響が考えられる。
3. 低出生体重児と早産児の地方と都市部での出生割合は差はない。
4. 低出生体重児出生と高齢出産は、1980年代は高い割合であったが、2010年以降は調整後のオッズは1に近くまで低下し、母体年齢との関連はみられなかった。これは、20代の低出生体重児出生割合が増加しているためと考えられる。
5. 早産と高齢出産は、1980 年代には２倍以上リスクが高かったが、２０１０年には1.5倍まで低下している。若い世代のやせの増加が低出生と早産に関連している可能性が考えられる。

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研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
なし							

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Strategies of testing for syphilis during pregnancy (Protocol)

Shahrook S, Mori R, Ochirbat T, Gomi H

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[Intervention Protocol]

Strategies of testing for syphilis during pregnancy

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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 effectiveness of maternal syphilis screening strategies.

BACKGROUND

Syphilis is a potentially fatal, sexually transmitted disease (STD) that can be transmitted to the fetus of a pregnant woman infected with syphilis. Though preventable, globally, each year about two million pregnant women become infected with syphilis, the majority of whom live in developing countries (WHO 2011). The yearly toll of adverse birth outcomes associated with untreated maternal syphilis is 730,000 to 1500,000, of which nearly 650,000 deaths occur in fetuses and newborns (Schmid 2007; WHO 2010). Maternal syphilis is less of a concern in developed countries than in developing countries. For example, in congenital syphilis (mother-to-child transmission), the seroprevalence of women with syphilis attending antenatal care is estimated to be highest in Latin America (3.90%) and Africa (1.98%) (Schmid 2007). In Africa alone, syphilis causes nearly 400,000 stillbirths and newborn deaths in a single year (Anonymous 2012). Furthermore, concern is deepening in countries such as China where an increase in the disease incidence has already been observed (Cheng 2007; Tucker 2010). In China in 2008, among 9480 total cases, on average, more than one baby per hour was born with congenital syphilis; the observed amplification rate was by a factor of 12 during the five preceding years (Tucker 2010). Moreover, people with the human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDs) usually become infected with syphilis and vice versa (Walker 2001). As a result, the rise in congenital syphilis in many countries in Sub-Saharan Africa has been aggravated by HIV/AIDs as this region is highly burdened by HIV/AIDs infection (WHO 2010).

The World Health Organization (WHO) has estimated that about 50% of pregnant women with untreated syphilis will transmit the infection to the fetus causing severe birth outcomes such as spontaneous abortion, prematurity, stillbirth, low birthweight, neonatal death, or serious sequelae in liveborn infected children (WHO 2011). However, these adverse outcomes are preventable, and existing health programs such as incorporated sexual and reproductive health programs, antenatal syphilis screening, and timely treatment have been suggested as a means to curtail syphilis-attributable perinatal deaths and stillbirth incidence by about 50% (Bique 2000; Hawkes 2011; Myer 2003; Wilkinson 1998). Hence, every pregnant woman has been urged to undergo routine antenatal

check-up (UNICEF 2009; WHO 2007). Yet, for decades, in spite of the existence of an antenatal screening policy in the majority of the countries, policy implementation is typically lacking (Gloyd 2001; Hossain 2007).

Additionally, the control and elimination of syphilis is hindered by the fact that the majority of infected women are not tested; nearly every one of those who is tested either does not undergo prompt treatment or is missed entirely (WHO 2011). Despite the availability of various improved diagnostic tools and cost-effective prevention therapy (Peeling 2004; WHO 2010), the prevention and elimination of syphilis is predominantly disrupted by the complexity of the natural disease history, coupled with the absence of precise clinical presentation in infected patients (Peeling 2004). It has also been suggested that the absence of antenatal care, and poor quality services are likely to be important factors in raising the number of mothers giving birth to newborns with congenital syphilis (Walker 2002; Wilkinson 1998).

Scientific efforts for the prevention and elimination of congenital syphilis have been accelerated by the development of reliable and improved diagnostic tools such as on-site syphilis testing, providing rapid results and immediate therapy for sero-positive women in primary care settings. In addition to laboratory testing, on-site testing might be a useful strategy to curb congenital syphilis and its associated adverse outcomes by reducing treatment delays and increasing the numbers of sero-positive women treated (Delport 1998; Fitzo 1996; Jenniskens 1995). Although the effects of on-site testing in observational studies (Bique 2000; Temmerman 2000) were positive, one randomised controlled study found no effective impact on either treatment rates or perinatal mortality reduction (Myer 2003). Indeed, in spite of the presence of laboratory access in some developing areas, the number of infected women treated fully is still in the minority (Wilkinson 1997). Furthermore, in developing countries, useful screening tools such as treponemal tests are often obtainable only at reference laboratories or large regional centres (Peeling 2004). Hence, syphilis screening has been constrained by varying dynamics and largely due to the delays in the identification and treatment of the infected women (Rotchford 2000). Therefore, it is crucial to assess the effectiveness of available screening strategies for the detection of syphilis infection in pregnant women.

Description of the condition

Syphilis is caused by the bacterium *Treponema pallidum*. The disease manifestation is protean; involvement of any organs in this disease is possible and it may appear with multiple clinical manifestations resulting in a range of severe health outcomes (CDC 2010). Syphilis infection is transmitted via person-to-person direct contact with a syphilis sore, and during vaginal, anal or oral sexual intercourse. The external genitals, vagina, rectum or anus are the main organs where sores usually occur, including lips and inside the mouth. The risk of acquiring HIV infection in an individual with syphilis is two- to five-fold if exposed when an ulcer is present, and consequently, individuals involving in high-risk sexual behavior are likely to suffer from syphilis and HIV co-infection. Furthermore, the syphilis bacterium can be vertically transmitted to the fetus of a pregnant woman who has a syphilis infection; reportedly, at least two-thirds of all newborns are infected from maternal syphilis (Zenker 1990). The likelihood of fetal involvement occurs among women with active syphilis infection (i.e. rapid plasma reagin (RPR) titre greater than 1:4), specifically, insufficient or untreated infection acquired within the five years prior to the pregnancy (Hawkes 2011). Sixty-nine per cent of such women with active infection may experience a variety of adverse birth outcomes (Ingraham 1950; McDermott 1993), i.e. late miscarriage (after 16 weeks) or stillbirth in 25% cases, neonatal death at term in 11%, preterm or low birthweight in 13%, and classic symptoms and clinical signs of congenital syphilis in 20% (Ingraham 1950; McDermott 1993; Schmid 2004; Watson-Jones 2002). Classically, newborns with congenital syphilis are severely infected premature infants with marasmus, a pot belly, 'old man faces' and withered skin (Walker 2001). The severity of the adverse birth outcomes associated with congenital syphilis is usually determined by the length of the maternal infection as well as pregnancy stage. The majority of the pregnant women with syphilis are asymptomatic and so are many infected newborns at the time of their birth (Peeling 2004). Therefore, if not treated immediately, within a few weeks the disease progression can be fatal (CDC 2010).

Description of the intervention

Early detection and administration of appropriate therapies are at the centre of syphilis prevention strategies: undergoing syphilis screening tests at the first antenatal check-up within the first trimester and again in late stage of pregnancy followed by prompt treatment of sero-positive women with a single dose of long-acting penicillin before the second trimester (WHO 2010).
Serologic testing is the core strategy of syphilis screening and diagnosis (Hook 1992; Peeling 2004). The are two main types of serologic tests: non-treponemal tests and treponemal tests. Non-treponemal tests identify antibodies to reagin, a cholesterol-lecithin-cardiolipin antigen that cross-reacts with antibodies present in the sera of patients with syphilis. Non-treponemal tests such as the RPR test are easy to perform, sensitive, and relatively cheap (Peeling 2004). Furthermore, the non-treponemal test is quantitative and treatment response can be followed over time (Fiumara 1978). On the other hand, in most cases, the treponemal tests remain positive indefinitely, whether the person has been treated or not. In addition, treponemal tests, e.g. enzyme immunoassay (EIAs) are more costly than non-treponemal tests and can be difficult to perform (Peeling 2004). Seroprevalence data from antenatal screening programmes are used as one of the proxy indicators

for monitoring the prevalence of sexually transmitted infections (Peeling 2004). Non-treponemal tests such as RPR can be performed at a local laboratory but one of the major limitations is that RPR can not be carried out on whole blood. Conversely, confirmatory assays such as EIAs, although useful to obtain prevalence rates and surveillance facts, are usually available only at reference or large regional laboratories in resource-poor settings. Currently, numerous improved sero-diagnostic tools are available for the control and treatment of syphilis. For example, nowadays RPR and Venereal Diseases Research Laboratory test (VDRL) reagents can be stored at room-temperature. In addition, existing solar-energy powered rotators have provided the means to carry out these tests in resource-poor settings where there is a lack of, or no electricity (Peeling 2004). Rapid and easy treponemal tests using whole blood, serum or plasma can be stored at room temperature for six to 12 months, are cost-effective (Peeling 2004), and the performance of some of these tests is comparable to laboratory tests (Fenis 2001; Lien 2006). It is noteworthy that syphilis screening and treatment are estimated to be the most cost-effective public health interventions in existence (WHO 2007).

How the intervention might work

Prevention success lies in the early detection of syphilis in pregnant women and prompt treatment management before the second trimester (WHO 2010). As recommended by the WHO, all pregnant women should undergo antenatal syphilis screening tests; however, by some means, women without test results at delivery should also be tested or re-tested. Women should also be well informed about the importance of being tested for HIV infection. Additionally, this treatment should also be offered to their partners and treatment planning should be primed in order to protect their infants at birth. Screening of pregnant women in the early stage of their pregnancy (preferably prior to 24 weeks of gestational age) can substantially avert the burden of associated adverse birth outcomes in many parts of the developing world. Screening pregnant women at the routine antenatal check-up, in the first trimester, and again in the late stage of pregnancy, and finally the prompt treatment of those women detected with syphilis sero-positive results are desirable. Syphilis is curable by administering a single dose of long-acting penicillin, and prevents related consequences in the unborn babies. Either one (primary or secondary disease) or three (latent disease) penicillin doses can be effective to treat maternal syphilis, depending on the disease stage.

Why it is important to do this review

Evidence on the effectiveness of screening strategies for the detection and treatment of maternal syphilis is scarce from randomised controlled trials, and most of the knowledge is derived from observational studies. Moreover, earlier reviews of syphilis screening and treatment detected either no intervention effect on preterm birth reduction (Barros 2010), or high grade of evidence (Menezes 2009). Therefore, this review will attempt to accumulate quality evidence on the effectiveness of syphilis screening strategies in pregnant women and their neonates.

OBJECTIVES

To assess the effectiveness of maternal syphilis screening strategies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised (individual and clustered) controlled trials comparing different syphilis screening strategies during routine antenatal check-up will be sought. The unit of randomisation could be either individual pregnant women or any formal healthcare facilities e.g. health posts/clinics. Studies that have been presented only as abstracts will also be included indicating their appropriate status. Cross-over trials and quasi-randomised experimental study designs will be excluded.

Types of participants

The eligible participants will be either pregnant women or healthcare facilities/clinics depending on the randomisation unit in each included trial.

Types of interventions

We plan to examine the effectiveness of syphilis testing strategies offered to pregnant women attending routine antenatal check-up. We will compare available syphilis screening tests versus no screening tests. However, if we find trials that investigate the effect of combined screening strategies, i.e. syphilis and HIV/AIDs screening, we will consider them for inclusion in the subsequent review, if the only difference between the arms was that of syphilis screening strategies.

Types of outcome measures

Primary outcomes

- Perinatal mortality
- Coverage of different screening tests for the detection and treatment of syphilis infection
- Obstacles/challenges in the uptake of antenatal syphilis screening tests

Secondary outcomes

- Incidence of congenital syphilis
- Incidence of HIV/AIDs in pregnant women and neonates
- Any other adverse outcomes reported in the included studies will be summarised

Economic data for the use of healthcare resources

Mothers

- Antenatal hospital admission

Neonates

- Special care/intensive care admission

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.
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 check the studies cited in relevant review articles.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (S Shahrook (SS) and R Mori (RM)) will independently assess all the potential studies identified from the search methods to be included in the review. Two review authors will obtain the full text of all eligible trials identified by at least one author, and independently review the full copies for eligibility. We will attempt to contact authors of the original studies if we need further clarification for inclusion. We will resolve any disagreement through discussion or, if required, we will consult an arbiter.

Data extraction and management

Data will be extracted using a specified form. For eligible studies, two review authors (SS and RM) will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult an arbiter. We will enter data into Review Manager software (RevMan 2011) 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

SS 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 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 *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 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 *Handbook* 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. 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.

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.

Cross-over trials

We will not include cross-over trials as they are generally considered to be inappropriate while measuring a primary outcome which is irreversible such as mortality as described in the *Cochrane Handbook for Systematic Reviews of Interventions* section 16.4.

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 I^2 is greater than 30% and either 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

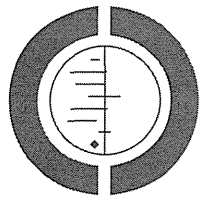
If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2011). 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 its 95% confidence interval, and the estimates of T^2 and I^2.

Interventions for improving outcomes for pregnant women who have experienced genital cutting (Review)

Balogun OO, Hirayama F, Wariki WMV, Koyanagi A, Mori R



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[Intervention Review]

Interventions for improving outcomes for pregnant women who have experienced genital cutting

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ABSTRACT

Background

Female genital cutting (FGC) refers to all procedures that involve the partial or total removal of the external female genitalia, or other injury to the female genital organs for cultural or other non-therapeutic reasons. There are no known medical benefits to FGC, and it can be potentially dangerous for the health and psychological well-being of women and girls who are subjected to the practice resulting in short- and long-term complications. Health problems of significance associated with FGC faced by most women are maternal and neonatal mortality and morbidity, the need for assisted delivery and psychological distress. Under good clinical guidelines for caring for women who have undergone genital cutting, interventions could provide holistic care that is culturally sensitive and non-judgemental to improve outcomes and overall quality of life of women. This review focuses on key interventions carried out to improve outcome and overall quality of life in pregnant women who have undergone FGC.

Objectives

To evaluate the impact of interventions to improve all outcomes in pregnant women or women planning a pregnancy who have undergone genital cutting. The comparison group consisted of those who have undergone FGC but have not received any intervention.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 December 2012) and organisations engaged in projects regarding FGC.

Selection criteria

Randomised controlled trials (RCTs), cluster-randomised trials or quasi-RCTs with reported data comparing intervention outcomes among pregnant women or women planning a pregnancy who have undergone genital cutting compared with those who did not receive any intervention.

Data collection and analysis

We did not identify any RCTs, cluster-randomised trials or quasi-RCTs.

Main results

There are no included studies.

Authors' conclusions

FGC research has focused mainly on observational studies to describe the social and cultural context of the practice, and we found no intervention trials conducted to improve outcomes for pregnant women presenting with complications of FGC. While RCTs will provide the most reliable evidence on the effectiveness of interventions, there remains the issue of what is considered ethically appropriate and the willingness of women to undergo randomisation on an issue that is enmeshed in cultural traditions and beliefs. Consequently, conducting such a study might be difficult.

PLAIN LANGUAGE SUMMARY

Care for pregnant women who have experienced genital cutting

Female genital cutting (FGC) also known as female genital mutilation (FGM) or female circumcision is when some or all of a woman's or girl's external genital organs are cut or damaged for cultural beliefs, or reasons not connected with medical treatments. It is often performed by traditional practitioners such as traditional birth attendants without any form of anaesthesia or analgesia using non-sterile instruments. There are no known medical benefits to FGC, and it can be dangerous for the health and psychological well-being of these women and girls, resulting in both short- and long-term problems. Long-term complications include chronic pelvic infection, formation of cysts, vaginal obstruction and infertility. Some of the greatest health problems associated with FGC and faced by most women arise during pregnancy and when giving birth. In some cases, complications from FGC can result in death.

Care offered to these women may include 1) surgery to widen the vaginal opening (deinfibulation), 2) cutting the perineum during birth to widen the outlet to help the baby to be born (episiotomy), 3) removal of cysts and 4) treatment of infections. Women and their partners may also benefit from counselling to enable them to explore and understand the problems caused by FGC. This may also help them make informed decisions about the care they might receive.

We looked for randomised controlled trials to find out what might work best for women. However, we did not find any studies for inclusion in this review. So, there remains the problem of how best to care for pregnant women and women planning a pregnancy in these circumstances. Trials are urgently needed, although conducting such studies might be difficult. In the meantime, caregivers will do their best to look after these women during pregnancy and childbirth.

BACKGROUND

Worldwide, an estimated 100 to 140 million girls and women have undergone female genital cutting (FGC) and more than three million girls are at risk for FGC each year on the African continent alone (Feldman-Jacobs 2010; WHO 2008). Several other terminologies including female genital mutilation (FGM), female circumcision (FC) (Turner 2007) or female genital surgeries (FGS) have been used to describe this practice (Rahman 2001; WHO 2008), all of which refer to the altering of the external female genitalia (WHO 2008). According to the World Health Organization (WHO) definition, FGC refers to all procedures that involve the partial or total removal of the external female genitalia, or other injury to the female genital organs for cultural or other non-therapeutic reasons (WHO 2008).

Depending on the local customs and circumstances, FGC is usually carried out on girls aged between four and 14 years (UNICEF 2005) but may also be performed on infants, or adult women just prior to marriage, or after the delivery of the first child (Toubia 1994).

It is reported that FGC is primarily practiced in at least 28 countries in Africa (Feldman-Jacobs 2010) and certain countries in Asia (e.g. Indonesia, Malaysia, Pakistan and India) and the Middle East (e.g. Oman, Yemen and the United Arab Emirates) (Ekhalad 1997; Feldman-Jacobs 2010). Nevertheless, FGC is increasingly being regarded as a global issue with the influx of refugees and immigrants from practicing communities to Europe (Jacob 2001; Leye

2008), North America (Burstyn 1995), Australia and New Zealand (Utz-Billing 2008). The prevalence of FGC among women of reproductive age can be as high as 88%, as for example in Somalia (Yoder 2008).

The reasons for FGC include a mix of cultural and social factors within practicing families and communities. FGC is often considered a necessary part of raising a girl properly, and a way to prepare her for adulthood and marriage (Althaus 1997; Dirie 1991; Furuta 2008). It is often motivated by beliefs about what is considered proper sexual behaviour, linking the procedure to premarital virginity (Shandall 1967) and marital fidelity (Gruenbaum 2005; Gruenbaum 2006). It is also associated with the cultural ideals of femininity and modesty, and in areas where FGC is a social convention, the pressure to conform to social norm is a strong motivation to perpetuate the practice (Furuta 2008; Gruenbaum 2005). Furthermore, although FGC is not condoned by any major religion, some societies claim that it is a religious requirement (Chalmers 2000; Dirie 1991; Isa 1999), while others believe that genital cutting enhances fertility and child survival (Turner 2007).

FGC is often performed by traditional practitioners such as traditional birth attendants (Al-Hussaini 2003; Asekun-Olarinmoye 2008; Chalmers 2000; Dirie 1991; Morison 2001; Turner 2007), without any form of anaesthesia or analgesia (Al-Hussaini 2003) using non-sterile instruments such as scissors, razor blades or broken glass (Turner 2007). It is always traumatic and is associated with a series of health risks with short- and long-term consequences (Agugua 1982; Banks 2006; Behrendt 2005; Chalmers 2000; Jones 1999; Morison 2001; Toubia 1994) and even death (Morison 2001). There are no medical benefits, and it can be potentially dangerous for the health and psychological well-being of the women and girls who are subjected to the practice (Lax 2000). At the time of cutting, the women usually experience extreme pain, severe bleeding, urinary retention due to difficulty passing urine and infections, mostly due to the use of contaminated instruments (Hakim 2001; Morison 2001). Long-term complications, often associated with the Type III cut (infibulation) include chronic pelvic infection, formation of cysts, vaginal obstruction and infertility (WHO 2001). Major health problems associated with FGC faced by most African women today are maternal and neonatal mortality and morbidity and the need for assisted delivery (Banks 2006). Other consequences include psychological distress (Behrendt 2005; Chibber 2011), domestic violence (Refaat 2001) and although still controversial, the spread of HIV/AIDS due to the frequent use of unclean and non-sterile instruments (Brady 1999; Yount 2007). Recent findings from a large WHO multi-country hospital-based study showed that the deliveries of women who had undergone FGC were significantly more likely to have adverse health outcomes such as necessity for caesarean section, postpartum haemorrhage, extended maternal hospitalisation, infant resuscitation, stillbirth or early neonatal death compared with those without FGC (Banks 2006). The true magnitude of the harmful effects of FGC may have been underestimated in this study as it was a hospital-based study and institutional delivery rate is low in Africa (Banks 2006). Women who deliver at home may be even more vulnerable to serious complications as they are not under the help of experienced doctors and midwives. Additionally, the traumatic experience of FGC, which is usually carried under force, leaves behind a lasting psychological sequel and may adversely affect their mental health (Behrendt 2005; Chibber 2011). Some studies have reported post-traumatic stress disorder, anxiety, depression and memory loss (Behrendt 2005; Elnashar 2007). Furthermore, decreased quality of sexual life due to memories associated with the procedure, damage to the sensitive genital tissues and scar formation have been reported (Behrendt 2005; Elnashar 2007; Thabet 2003).

Description of the condition

FGC refers to all procedures that involve the partial or total removal of the external female genitalia, or other injury to the female genital organs for cultural or other non-therapeutic reasons (WHO 2008). FGC varies from simple removal of the clitoris and prepuce to more complicated procedures such as infibulations that involve the narrowing of the vaginal orifice with the creation of a covering seal by cutting and appositioning of the labia minora or the labia majora, or both (WHO 2008).

Based on the recent WHO classification (WHO 2008), there are four different forms of FGC depending on the type and degree of cutting.

- Type I: clitoridectomy which involves the partial or total *removal of the clitoris and/or the surrounding tissues.*
- Type II: excision which is the partial or total removal of the clitoris and the labia minora, with or without excision of the labia majora.
- Type III: infibulation involving the narrowing of the vaginal opening with the creation of a covering seal by cutting and appositioning the labia minora and/or the labia majora, with or without excision of the clitoris.
- Type IV: describes all other harmful procedures to the female genitalia for non-medical purposes, e.g. pricking, piercing, incising, scraping and cauterisation.

Recent estimates based on current prevalence data indicate that 91.5 million women and girls above 10 years old in Africa are currently living with the consequences of FGC (Yoder 2008).

Description of the intervention

Interventions to improve outcome in circumcised pregnant women include deinfibulation (McCaffrey 1995; Nour 2006; Penna 2002; Rouzi 2001; WHO 2001) or episiotomy (Widmark 2010), surgical removal of cysts (Penna 2002; Thabet 2003; WHO

2001), and treatment of infections (WHO 2001) as well as counselling by trained healthcare providers or psychologists for women and their partners during antenatal care on the need for deinfibulation and to dissuade them from undergoing reinfibulation after childbirth (Knight 1999; McCaffrey 1995; Rouzi 2001; Rushwan 2000; WHO 2001).

How the intervention might work

Under good clinical guidelines for caring for pregnant women who have undergone genital cutting, interventions would provide holistic care that is culturally sensitive and non-judgemental to improve pregnancy outcomes and the overall quality of life of women. Interventions may help by decreasing the risk of perineal laceration (Nour 2006), reducing the risk of maternal and neonatal mortality and morbidity, improving satisfaction with appearance and sexual function (Nour 2006; Thabet 2003) and treatment of post-traumatic stress disorders.

Why it is important to do this review

Although some reviews have examined the impact of various interventions designed to reduce the prevalence of FGC (Denison 2009; Muteshi 2005), none has been carried out to assess the effectiveness of interventions to improve the outcome in women who have undergone FGC. In this review, we planned to summarise data relating to the key interventions carried out to improve outcome and overall quality of life in pregnant women who have undergone FGC.

OBJECTIVES

To critically assess the impact of interventions to improve all outcomes in pregnant women or women planning a pregnancy who have undergone genital cutting. The comparison group consisted of those who have undergone female genital cutting but who have not received any intervention.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT), cluster-randomised trials or quasi-RCTs.

Types of participants

All pregnant women or women planning pregnancy who experienced genital cutting and who have been identified or examined by a healthcare professional.

Types of interventions

We considered for inclusion studies with all intervention types including, but not limited to:

- deinfibulation;
- management of obstetric and gynaecological complications;
- treatment of infections;
- psychological or counselling and health education.

Types of outcome measures

Primary outcomes

Mother

- Incidence of psychological disorders and/or mental health status measured by validated scales
- Incidences of urinary/faecal problems

Baby

- Perinatal/neonatal mortality

Secondary outcomes

- Mode of birth (caesarean section, operative vaginal birth, normal vaginal birth)
- Incidence of episiotomy
- Incidence of any surgical perineal procedures
- Incidence of third and fourth degree perineal lacerations at birth
- Incidence of postpartum haemorrhage
- Incidence of urinary tract infections
- Incidence of perineal infections
- Incidence of reproductive tract or sexually transmitted infections
- Lesions, scars, cysts and other anatomical damage
- Genital pain
- Infertility
- Women's quality of life measured by validated scales
- Need for neonatal resuscitation (infants)
- Apgar score at five minutes (infants)
- Need for admission to neonatal unit (infants)

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 December 2012).

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.

We did not apply any language restrictions.

Searching other resources

Reports produced by all levels of government, non-governmental organisations and academics, demographic and health surveys, databases of international organisations engaged in projects regarding FGC such as World Health Organisation (WHO), The United Nations Children's Fund (UNICEF), Population Reference Bureau (PRB), Center for Development and Population Activities (CEDPA).

Data collection and analysis

There are no included studies in this review. Data collection and analysis methods to be used in future updates of this review are provided in Appendix 1.

RESULTS

Description of studies

There were no randomised controlled trials (RCTs), cluster-randomised trials or quasi-RCTs identified from the search strategy.

Results of the search

The search retrieved no trial reports.

Risk of bias in included studies

Not applicable.

Effects of interventions

Not applicable.

DISCUSSION

There were no randomised controlled trials (RCTs), cluster-randomised trials or quasi-RCTs identified that compared intervention outcomes for pregnant women or women planning a pregnancy who have experienced genital cutting with those who have not received any intervention. Most female genital cutting (FGC) research to date has looked at issues regarding prevalence, context in which the practice is carried out and the short- and long-term medical consequences in women and their infants. The majority of this research is usually through questionnaire surveys, qualitative research, and anthropological studies (Population Council 2002). In the case of intervention research to improve outcomes for women with genital cutting, medical case histories and case studies have been the norm. We identified one study in which participants were randomly assigned to FGC intervention (Thabet 2003), however, this study did not meet the eligibility criteria for this review. To evaluate the effectiveness of interventions requires a study design that follows the principle of experimentation. However, an important aspect of FGC intervention research that should be given proper consideration are the ethical principles underlying the way the study is designed and the data collected. In this review, this requirement precluded the inclusion of any trial from the onset.

AUTHORS' CONCLUSIONS

Implications for practice

Although female genital cutting (FGC) research has focused mainly on observational studies to describe the social and cultural context of the practice, a few well-designed studies have described

the gynaecological and obstetric sequelae of genital cutting including chronic pelvic infection, formation of cysts, virginal obstruction and infertility, maternal and neonatal mortality and morbidity during pregnancy and the need for assisted delivery. Interventions for improving pregnancy outcomes for women presenting with complications of FGC such as deinfibulation, treatment of infections and the management of obstetric and gynaecological consequences are usually delivered as cases. Therefore, most interventions are case-specific and results and conclusions drawn from those cases must be interpreted within the context and limitation of each case.

Implications for research

The unavailability of randomised controlled trials (RCTs), cluster-randomised trials or quasi-RCTs on interventions to improve outcomes from genital cutting among pregnant women or women planning a pregnancy raises the question of the appropriateness of conducting research within this context. Randomised controlled trials provide the most reliable evidence on the effectiveness of interventions, and it may be possible to conduct an RCT, depending on the topic and research question addressed. However, clinicians and researchers may consider the possibility of valid difficulties in conducting RCTs for some forms of complications resulting from FGC. Furthermore, the willingness of women to undergo randomisation on an issue that is enmeshed in cultural traditions and beliefs, which could also be potentially life-threatening when first encountered by medical practitioners, calls to question the acceptability of this research method, depending on the severity of the case. Alternatively, a cluster-RCT of a policy on clinical management of women with genital cutting might provide information on the success of clinical care for women who have experienced this practice.

ACKNOWLEDGEMENTS

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

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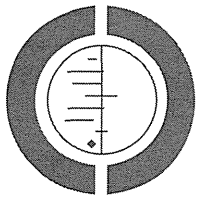
Hydralazine in infants with persistent hypoxemic respiratory failure (Review)

Kawaguchi A, Isayama T, Mori R, Minami H, Yang Y, Tamura M



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[Intervention Review]

Hydralazine in infants with persistent hypoxemic respiratory failure

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ABSTRACT

Background

Most deaths of infants with chronic lung disease (CLD) are caused by respiratory failure, unremitting pulmonary artery hypertension (PAH) with cor pulmonale, or infection. Although the exact prevalence of PAH in infants with CLD is unknown, infants with CLD and severe PAH have a high mortality rate. Except for oxygen supplementation, no specific interventions have been established as effective in the treatment for PAH in premature infants with CLD. Little has been proven regarding the clinical efficacy of vasodilators and concerns remain regarding adverse effects.

Objectives

To review current evidence for the benefits and harms of hydralazine therapy to infants with persistent hypoxemic respiratory failure.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE via PubMed and EMBASE, and other clinical trials registries through November 2011 using the standard search strategy of the Cochrane Neonatal Review Group. We searched these databases using a strategy combining a variation of the Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version with selected MeSH and free-text terms: hydralazine, vasodilator agent, antihypertensive agent, heart diseases, lung diseases, respiratory tract diseases, infant, and randomised controlled trial.

Selection criteria

We considered only randomised controlled trials and quasi-randomised trials for inclusion. We included low birth weight (LBW) infants with persistent hypoxemic respiratory failure who were treated with any type of hydralazine therapy.

Data collection and analysis

Two review authors independently assessed trial quality according to pre-specified criteria.

Main results

We found no studies meeting the criteria for inclusion in this review.

Authors' conclusions

There was insufficient evidence to determine the safety and efficacy of hydralazine in LBW infants with persistent hypoxemic respiratory failure. Since hydralazine is inexpensive and potentially beneficial, randomised controlled trials are recommended. Such trials are particularly needed in settings where other medications such as sildenafil, inhaled nitric oxide (iNO), or extracorporeal membrane oxygenation (ECMO) are not available.

PLAIN LANGUAGE SUMMARY

Hydralazine for pulmonary hypertension in low birth weight infants with chronic lung disease

In premature infants, pulmonary arterial hypertension (PAH) associated with chronic lung disease (CLD) is associated with high mortality rate. With the exception of oxygen supplementation, no specific interventions have been established as an effective treatment for PAH in premature infants with CLD. Vasodilators could be effective treatments to reduce pulmonary arterial pressure, but little has been proven regarding their clinical effectiveness and concern remains regarding adverse effects. This review found no trials of the use of hydralazine for low birth weight infant with PAH related to CLD. However, since hydralazine is inexpensive and potentially beneficial, randomised controlled trials are recommended.

BACKGROUND

Description of the condition

General definition of bronchopulmonary dysplasia and chronic lung disease

In 1967, Northway et al first described bronchopulmonary dysplasia (BPD), a new pulmonary disorder that developed in premature infants exposed to mechanical ventilation and high oxygen supplementation (Northway 1967). In 1988, Shennan and co-workers demonstrated that oxygen dependency at 34 to 36 weeks' postmenstrual age (PMA) predicted worse outcome in premature infants than oxygen dependency at 28 days (Shennan 1988). In 2001, a National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases workshop developed a definition of BPD that has been accepted in the clinical field (Jobe 2001; Jobe 2006). They defined BPD as the need for supplemental oxygen for at least 28 days after birth. As less-mature infants were routinely supported in neonatal intensive care, the deficiencies of using a definition of BPD at 28 days became apparent.

Relatively more mature infants can develop BPD. Although the path to BPD or chronic lung disease (CLD) is most often due to prematurity and respiratory distress syndrome, several other conditions, such as pneumonia, sepsis, aspiration syndromes, pulmonary hypoplasia, diaphragmatic hernia, and congenital heart disease, can be a cause of CLD. The inciting factors are not only the underlying disorder, but also the effects of the supportive treatment, including mechanical ventilation, barotrauma, and oxygen toxicity (Allen 2003). For the purpose of this review, we have defined CLD as oxygen requirement at 36 weeks' PMA.

Chronic lung disease and pulmonary hypertension

Most deaths of infants with CLD are caused by respiratory failure, unremitting pulmonary artery hypertension (PAH) with cor pulmonale, or infection. PAH in infants with CLD results from a combination of factors including an absolute reduction in the size and complexity of the pulmonary vascular bed, increased resting tone of pulmonary artery smooth muscle, and increased reactivity of the arteries to a variety of stimuli (Donahoe-Fillo 1994; Ivy 1998; Hislop 1998; Stenmark 2005). Although the exact prevalence of PAH in infants with CLD is unknown, infants with CLD and severe PAH have a high mortality rate (Shennan 2007; Ali 2010). In a study of infants with BPD treated during the recent surfactant era, those infants who developed PAH had an estimated survival rate of 64% (± 8%) at six months and 53% (± 11%) at two years after diagnosis of PAH. In multivariate analyses, small

birth weight for gestational age and severe PAH (defined as systemic or supra-systemic right ventricular pressure) were associated with worse survival rates (Khemani 2007; Walter 2009).
Pulmonary circulation in patients with BPD is abnormally responsive to oxygen and other pulmonary vasodilators (Abman 1985; Mourani 2004; Stenmark 2005). Despite limited knowledge regarding the risks and benefits, long-term supplemental oxygen therapy is considered the standard treatment for PAH associated with BPD as it could decrease pulmonary vascular resistance (PVR) and thereby decrease the risk of progression to cor pulmonale (Halliday 1980; Abman 1985; Benatar 1995; STOP-ROP 2000).
Multiple other treatment strategies for PAH, including vasodilators such as hydralazine, calcium channel blockers, tolazoline, endothelin antagonists, prostacyclin, phosphodiesterase (PDE) inhibitors, and inhaled nitric oxide (iNO) have been evaluated (Greenough 2005; Oates 2006; Oishi 2011). Nitric oxide (NO) is one of the most promising. It acts as a vasodilator by relaxing the vascular smooth muscle cells by increasing cGMP (cyclic guanosine monophosphate) level. The long-term benefits of iNO are still unclear (Bush 1990; Mourani 2004). There are several adverse effects that need to be considered, such as methaemoglobinaemia (Bizzarro 2005). Tolazoline, one of the former frequently used treatment options, is an α-adrenergic agent and dilates vessels non-specifically. Tolazoline has been used less often because of its now well-known adverse effects, such as gastric bleeding, systemic hypotension, and oliguria. Other vasodilators mentioned above could also be effective treatments to reduce pulmonary arterial pressure, but little has been confirmed regarding their clinical effectiveness, and concern remains regarding adverse effects such as systemic hypotension (Nuntnarumit 2002; Greenough 2005; Oates 2006).

Description of the intervention

Hydralazine is a vasodilator used to treat patients with severe hypertension, pre-eclampsia/eclampsia, or chronic heart failure (Duley 2006; Marik 2007; Hunt 2009). Although many newer drugs have been developed for the treatment of hypertension, hydralazine is still widely used in emergency and critical care fields due to its lower cost and extensive clinical experience (Firush 1997). The usual dose range is 0.1 to 0.2 mg/kg/dose (not to exceed 20 mg) and duration is every four to six hours as needed, up to 1.7 to 3.5 mg/kg/day divided into four to six doses for paediatric patients. The possible route of administration is oral, intramuscular, and intravenous. Known major adverse reactions are heart failure, hypotension, reflex tachycardia, neurological changes, immunological reactions such as drug-induced lupus syndrome, serum sickness, haemolytic anaemia, vasculitis, and rapidly progressive glomerulonephritis (William 2007; Kandler 2011).

How the intervention might work

Hydralazine is thought to reduce peripheral resistance directly by relaxing the smooth muscle cell layer in arterial vessels. Hydralazine does not dilate venous capacitance vessels (McGoon 1983; Zoppa 2008). The mechanism of action has not been identified, but altered Ca^{2+} balance in vascular smooth cells, whereby inhibition of Ca^{2+} release from the sarcoplasmic reticulum prevents contraction mediated by Ca^{2+}-dependent ATPases, kinases, or ion channels (Knowles 2004), may contribute to the effect of hydralazine. Clinically, hydralazine has been used to treat right heart failure caused by pulmonary arterial hypertension. When PVR is elevated, vasodilator therapy helps the failing right ventricle by decreasing afterload. A reduced afterload may also allow a decline in right ventricular end diastolic volume (RVEDV), producing decreased wall tension and myocardial oxygen requirement. The dilated pulmonary vasculature also increases left ventricular preload, which increases mean arterial pressure and right coronary arterial (RCA) perfusion pressure (Subhedar 2000; Slesnick 2006; Mourani 2008).

Why it is important to do this review

No specific interventions have been established as a widely accepted effective treatment for PAH in premature infants with evolving CLD, except oxygen supplementation. Although iNO is achieving the status of primary treatment for PAH in infants (Barrington 2010), hydralazine may have some advantages over iNO, including extremely low cost, a variety of routes of administration, and no possibility of harm for medical staff from passive inhalation.
We planned a review of the current evidence for the benefits and harms of hydralazine therapy in infants with CLD.

OBJECTIVES

Primary

To determine the efficacy and safety of hydralazine compared to placebo or other treatments in infants with persistent hypoxemic respiratory failure.
We also planned to analyse the following subgroups:

1. preterm (< 37 weeks' gestation) versus term infants;
2. gestational age (< 32 weeks versus ≥ 32 weeks);
3. extremely (< 1000 grams at birth); very low birth weight (< 1500 grams at birth); low birth weight (LBW) infants (< 2500 grams);
4. severity of BPD (each level of BPD; using the definition of the National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases Workshop 2001; Jobe 2001; Bancalari 2006);

5. confirmed PAH prior to study entry versus unconfirmed PAH;
6. duration of treatment with hydralazine (< 7 days versus ≥ 7 days);
7. route of administration (oral, intramuscular, and intravenous);
8. dose of treatment with hydralazine (< 2 mg/kg/day versus ≥ 2 mg/kg/day).

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) (including cluster-randomised trials) and quasi-randomised trials for this review.

Types of participants

Infants with persistent hypoxemic failure
Persistent hypoxemic failure was defined as persistent need for supplemental oxygen and assisted ventilation at greater than one week of age for any given causes except known congenital cardiac anomaly. We included all the infants who received the hydralazine treatment, whether or not they had confirmed PAH.

Types of interventions

The intervention of interest was any type of hydralazine therapy, including oral administration.
We considered studies comparing the following interventions:

1. hydralazine compared with placebo or no treatment;
2. hydralazine compared with other potential treatments for pulmonary hypertension with CLD: calcium channel blockers, tolazoline, endothelin antagonists, prostacyclin, PDE inhibitors, and iNO.

We planned to include any dose and duration of hydralazine therapy. The comparison interventions could be either single interventions or combination of therapies or any combination of therapies for PAH (e.g. hydralazine plus calcium blocker versus prostacyclin).

Types of outcome measures

Primary outcomes

1. Survival at 36 weeks' PMA, in-hospital survival at hospital discharge, and at 18 and 36 months of age.

Secondary outcomes

1. Improvement rate of PAH compared before with any timing after the intervention; improvement of PAH is defined as a tricuspid regurgitation (TR) ≤ 2.5 m/s, or a diminished amount of TR, restoration of interventricular septal configuration, regressed right ventricular hypertrophy (RVH) and dilation if using echocardiography, and pulmonary arterial pressure < 25 mmHg if assessed by cardiac catheterization.
2. Neurodevelopment (assessed by Bayley, Griffith, or any other validated tools) assessed at adjusted age of 18 months (Black 1999).
3. Length of hospitalisation (days) after the birth.
4. Length of ventilation (days) after the birth.
5. Length of oxygen supplementation (days) after the birth.
6. Level of oxygen supplementation (FiO_2 or some other measure), or measures of oxygenation (oxygenation index, arterial/alveolar oxygen ratio).
7. Adverse events, such as heart failure, hypotension, reflex tachycardia, neurological changes, immunological reactions such as drug-induced lupus syndrome, serum sickness, haemolytic anaemia, vasculitis, and rapidly progressive glomerulonephritis (or other adverse effects based on reports in the literature).

We defined PAH using either echocardiography or cardiac catheterization. Using echocardiography, we defined PAH as one or both of the following criteria:

1. maximal velocity of the TR jet (≥ 3 m/sec); or
2. flat or left-deviated interventricular septal configuration, and RVH with chamber dilation (Badesch 2009).

If using cardiac catheterization, PAH was defined as pulmonary arterial pressure > 25 to 30 mmHg (Wessel 1997; Adatia 2002; Subhedar 2004).

Search methods for identification of studies

Electronic searches

We used the standard search strategy of the Cochrane Neonatal Review Group as outlined in *The Cochrane Library*. We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE via PubMed and EMBASE (1966 to November 2011), and other clinical trials web sites. We also searched these databases using a strategy combining a variation of the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE: sensitivity-maximising version (Higgins 2011) with selected MeSH and free-text terms: hydralazine, vasodilator agent, antihypertensive agent, heart diseases, lung diseases, respiratory tract diseases, infant, and randomised controlled

trial (publication type). The MEDLINE search strategy translated into the other databases using the appropriate controlled vocabulary as applicable. We did not apply any language restriction. We limited the search to humans and clinical trials. We did a lateral search using the 'related articles' link in PubMed for the articles initially retrieved from the search strategy.
We also reviewed the reference lists of identified articles and handsearch reviews, bibliographies of books, and abstracts. We cross-checked references from identified studies for possible additional studies. We contacted the original manufacturer of hydralazine (Novartis) to identify any additional unpublished or ongoing trials. We also searched the web sites that had registries of ongoing or recently completed trials on this subject.

Data collection and analysis

We followed the methodology for data collection and analysis in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors (Atsushi Kawaguchi and Tetsuya Isayama) independently assessed the eligibility of the trials. We selected studies as being potentially relevant by screening the titles and abstracts. We obtained the full text of the article for review when a decision could not be made by screening the title and the abstract. The two review authors retrieved the full texts of all potentially relevant articles and independently assessed the eligibility by filling out eligibility forms designed in accordance with the specified inclusion criteria. We made efforts to contact the original investigators for additional data and information when required.

Data extraction and management

We planned to extract the data using a data extraction form that was designed by the review authors. The review authors planned to extract the data independently. We made efforts to contact study investigators for additional information or data. We planned to enter data into Review Manager Software (RevMan 5.1) (RevMan 2011).

Assessment of risk of bias in included studies

We planned to use the standard methods of The Cochrane Collaboration and its Neonatal Review Group (neonatal.cochrane.org/en/index.html) to assess the methodological quality of included studies. In addition, we planned to assess study quality and risk of bias using the following criteria documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We also planned to assess eligible studies using the following key criteria: allocation concealment (blinding of randomisation), blinding of intervention, completeness of follow-up, and blinding of outcome measurement, though there was no trial eligible to be included in this review.
We planned to use the 'Risk of bias' table, which addressed the following questions.

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

Was the allocation sequence adequately generated?
For each included study, we planned to categorise the method used to generate the allocation sequence as:

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

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

Was allocation adequately concealed?
For each included study, we planned to categorise the method used to conceal the allocation sequence as:

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

(3) Blinding (checking for possible performance bias)

Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?
For each included study, we planned to categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We planned to assess blinding separately for different outcomes or classes of outcomes.
We planned to categorise the methods as:

- low risk, high risk, or unclear risk for participants;
- low risk, high risk, or unclear risk for outcome assessors;
- low risk, high risk, or unclear risk for personnel.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, drop-outs, protocol deviations)

Were incomplete outcome data adequately addressed?
For each included study, we planned to describe the completeness of data including attrition and exclusions from the analysis. We also planned to note the reason for attrition and exclusions if possible.
We planned to categorise the methods as:

- low risk (< 20% missing data);
- unclear risk; or
- high risk (≥ 20% missing data).

(5) Selective reporting bias

Were reports of the study free of suggestion of selective outcome reporting?
We planned to attempt to contact study authors, asking them to provide missing outcome data, when we suspected reporting bias. When this was not possible, and the missing data was thought to introduce serious bias, we planned to explore the impact of including such trials in the overall assessment of results by a sensitivity analysis.
For each included study, we planned to describe how we investigated the possibility of selective outcome reporting bias.
We planned to assess the methods as:

- low risk (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);
- unclear risk; or
- high risk (where not all the study's pre-specified outcomes have been reported).

(6) Other sources of bias

Was the study apparently free of other problems that could put it at a high risk of bias?
For each included study, we planned to describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We also planned to assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- unclear risk; or
- high risk.

Measures of treatment effect

We planned to use the standard methods of the Cochrane Neonatal Review Group. We planned to analyse categorical data using risk ratio (RR), risk difference (RD), and the number needed to treat for an additional beneficial outcome (NNTB). We also planned to analyse continuous data using the weighted mean difference (WMD) and report the 95% confidence interval (CI) for all estimates.

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis. We planned to explore it by pre-specified subgroup analysis, when we identified substantial heterogeneity (I^2 statistic > 50%). In addition, we also planned to perform all statistical analyses using RevMan 5.1 (RevMan 2011) and Stata version 9.2 for Windows Stata.

Data synthesis

We planned to carry out statistical analysis using RevMan 5.1 (RevMan 2011). We also planned to use fixed-effect inverse variance meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods are judged sufficiently similar. We planned to use fixed-effect meta-analysis where we could not explain heterogeneity between trials' treatment effects.

RESULTS

Description of studies

See: Characteristics of excluded studies.

Results of the search

From an initial search of 1447 citations, three studies were extracted for further examination. All three were excluded from the analysis (see "Characteristics of excluded studies" table below.

Included studies

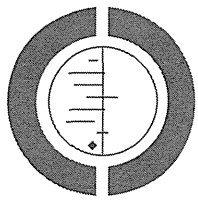
None identified.

Excluded studies

Three studies identified but excluded.
Thompson 1986: One quasi-RCT (Thompson 1986) that met the participants and intervention criteria was excluded for reasons that we could not obtain adequate details of design and outcomes. We made efforts to contact the investigators with no success due to its old published year. No other RCTs and ongoing trials were identified.
This study was conducted in a tertiary children's hospital in the US. It was published in abstract form. Six infants with BPD were allocated to the hydralazine or placebo group in a blinded cross-over manner. It was unclear from the abstract if the study was randomised. Demographic and baseline parameters were as followings; mean body weight 910 ± 200 grams, gestational age 27 ± 2 weeks, postnatal age 57 ± 9 days, and FiO_2 0.57 ± 0.12. Patients received either hydralazine 3.2 mg/kg/day or placebo orally for one week, no drug for one week, and the alternate drug for the third week. Echocardiogram, Doppler flow measurements, and pulmonary function studies were done at the beginning and end of

Methods for administering subcutaneous heparin during pregnancy (Review)

Sasaki H, Yonemoto N, Hanada N, Mori R



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[Intervention Review]

Methods for administering subcutaneous heparin during pregnancy

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ABSTRACT

Background

Pregnant women with a history of venous thromboembolism (VTE), antithrombin deficiency, or other risk factors for VTE, need heparin (unfractionated heparin (UFH) or low-molecular weight heparin (LMWH)) prophylaxis, mainly through administering subcutaneously. Several methods of administering heparin (UFH or LMWH) subcutaneously have been introduced to prevent adverse pregnant outcomes. The effectiveness and safety of different methods administering subcutaneous heparin (UFH or LMWH) during pregnancy have not been systematically evaluated.

Objectives

To compare the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2013) and reference lists of retrieved studies.

Selection criteria

All randomised controlled trials (individual and cluster) comparing the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) during pregnancy. Studies reported only as abstracts were eligible for inclusion and would have been placed in studies awaiting assessment, pending the full publication of their results. Quasi-randomised studies and cross-over trials were not eligible for inclusion..

Methods of administering subcutaneous heparin include intermittent injections versus indwelling catheters or programmable (auto) external infusion pumps, or any other devices to facilitate the subcutaneous administration of heparin (UFH or LMWH) during pregnancy.

Data collection and analysis

If eligible trials had been identified, trial quality would have been assessed and data extracted, unblinded by review authors independently.

Main results

No trials met the inclusion criteria for the review.

Authors' conclusions

There is no evidence from randomised controlled trials to evaluate the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women.

PLAIN LANGUAGE SUMMARY

Methods for administering subcutaneous heparin during pregnancy

There is no evidence from randomised controlled trials to evaluate the best method of administering subcutaneous heparin to pregnant women.

Pregnant women have an increased risk of venous thromboembolism (VTE) when compared with non-pregnant women because of changes in blood clotting. VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a clot in the deep veins of the leg blocking blood flow; parts of the clot may break away and be carried in the blood to the lungs, to form a PE. DVT is potentially, and PE is definitely, life-threatening for both mother and baby. Pregnant women with a history of VTE, antithrombin deficiency, or other risk factors for VTE are at an even greater risk and need heparin for prevention of VTE (prophylaxis). Although receiving subcutaneous heparin (either unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) is the main option in the prevention of VTE during pregnancy, the management of thromboprophylaxis in pregnant women has mostly relied on the evidence from non-pregnant participants. Methods of receiving heparin subcutaneously include giving an injection at regular intervals, or using an indwelling catheter and an infusion pump. Women's satisfaction with receiving subcutaneous heparin is highly important as thromboprophylaxis in pregnancy involves a cost burden, inconvenience, and side effects as a result of a longer duration. Some women may not self-administer heparin and must rely on others to give them their injections otherwise they stop using the heparin, thus exposing themselves to an increased risk of VTE. However, this review found no randomised controlled trials to show which methods of receiving subcutaneous heparin are effective and safe for pregnant women.

BACKGROUND

Description of the condition

Pregnancy is associated with physiologic and anatomic changes that increase the risk of venous thromboembolism (VTE) from the first trimester (James 2011). The true incidence of VTE associated with pregnancy is unknown, yet there is a strong clinical indication of an increased risk when compared with non-pregnant women (Bates 2004). The estimated incidence varies from 0.76 to 1.72 per 1000 pregnancies, which is four times greater than among the non-pregnant population (Marik 2006).

The main reason for the increased risk of VTE in pregnancy is the hypercoagulability that occurs and which protects women from haemorrhaging at the time of miscarriage or childbirth (James 2007). The most important risk factors for VTE in pregnancy are personal history of thrombosis and thrombophilia (a hereditary or acquired predisposition to thrombosis) (James 2006; RCOG 2009). Other risk factors include medical comorbidities (e.g. heart or lung disease, cancer), over 35 years of age, obesity, hypertension, smoking and having a delivery by caesarean section (Bauer 2003; RCOG 2009).

VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the result of an occlusive clot formation in the deep veins of the leg, from which parts of the clot frequently embolise to the lungs resulting in PE (Fauci 2008). From 75% to 80% of pregnancy-associated VTE comes in the form of DVT, while 20% to 25% is PE (James 2006). Because DVT is potentially, and PE is definitely, life-threatening for both mother and fetus, those pregnant women with a high risk of VTE require anticoagulation medications in order to prevent the incidence or recurrence of thrombosis.

Caution is advised in the use of anticoagulation therapy in pregnancy with especial regard to the health of both mother and fetus.

Hepain compounds are the preferred anticoagulants in pregnancy (James 2011). Administering heparin carries the risk of bleeding, osteoporosis and heparin-induced thrombocytopenia (HIT) (Bates 2004). However, James 2009 reported that the rate of recurrent VTE in women who did not receive anticoagulation with heparin varies from 2.4% to 12.2%, while the rate of recurrent VTE *in women who did receive anticoagulation ranges from 0%* to 2.4%. This shows that receiving heparin as an anticoagulant significantly reduced the risk of recurrent VTE during pregnancy.
The signs and symptoms of DVT, such as swelling, pain, redness, superficial venous dilatation, and Homan's sign (a pain in the calf or behind the knee on dorsiflexion of the ankle), are non-specific (Fauci 2008). This is because some of the symptoms of DVT are similar to common symptoms that manifest themselves during pregnancy (Barbour 2001). Clinical suspicions are confirmed in 10% of pregnant women, compared with 25% of non-pregnant participants (Ginsberg 1998).
As regards DVT, compression ultrasonography carries no risk and is the preferred initial test in pregnant women with suspected VTE (Marik 2008). When the results are negative or equivocal and iliac venous thrombosis is suspected, additional confirmatory testing with magnetic resonance imaging (MRI) is recommended (Nijkeuter 2006); MRI does not involve radiation exposure and is not harmful to the fetus (Fraser 2002; Rodger 2006). The use of D-dimer testing in pregnancy is potentially limited by the level of D-dimer which increases with the progression of a normal pregnancy, thus, a combination of the D-dimer level test with other tests is recommended (Nijkeuter 2006).
The signs and symptoms of PE, such as dyspnoea, pleuritic chest pain, cough, and haemoptysis, are also non-specific. Ventilation-perfusion scanning is a reasonable first choice for diagnosing PE in pregnancy that gives less radiation exposure to maternal breast tissue and fetus (Chunilal 2009). Computed tomographic (CT) scanning is also the test of choice with relatively low radiation exposure for the fetus, yet concerns about maternal breast radiation exposure remain (James 2011). Women with suspected PE should be informed that these tests carry the risk of potential radiation exposure.
Although maternal mortality from PE can be reduced by conducting a clinical investigation among symptomatic women and by anticoagulation regimens in women with an increased risk of DVT, PE, or both, it is controversial because a clinical evaluation (e.g. a lung scan) exposes the fetus to radiation, and long-term anticoagulation medications may be inconvenient and painful for women.

Description of the intervention

The anticoagulant, unfractionated heparin (UFH) is administered subcutaneously or intravenously and low molecular weight heparin (LMWH) is usually administered subcutaneously. These are the anticoagulants of choice during pregnancy, due to their established efficacy (Bates 2004) that has been demonstrated in pregnant women with DVT (Fauci 2008). Unlike other anticoagulants such as vitamin K antagonists (e.g. warfarin), both UFH and LMWH have no placental transfer (Bates 2008).
The potential risks of administering heparin - bleeding, osteoporosis and HIT - differ between UFH and LMWH. In one study *(Ginsberg 1989), the rate of major bleeding in pregnant women* receiving UFH was 2%, which is consistent with the reported rates of bleeding associated with administering heparin in non-pregnant women (Hull 1982a) and with warfarin therapy (Hull 1982b) when used for the treatment of DVT. In contrast, complications resulting from bleeding in pregnant women receiving LMWH are uncommon. Moreover, there was no statistically significant difference in bone loss between those who received LMWH and those who were untreated, suggesting that bone loss associated with prophylactic LMWH therapy is no different from the normal physiologic losses that occur during pregnancy (Carlin 2004). However, bone density was significantly lower in those receiving UFH compared with both those who were not treated and those who received the LMWH dalteparin (Monreal 1994). The risk of HIT with heparins is also low and may be lower with LMWH than with UFH, although as yet the actual risk is still unclear (Bates 2008). LMWHs are now commonly used for prophylaxis of maternal thromboembolism (Bates 2012) because they are at least as effective as and safer than UFH (RCOG 2009).
Methods of administering heparin subcutaneously include giving an intermittent injection, or using an indwelling catheter and an infusion pump. For prophylaxis with intermittent subcutaneous injections, UFH is usually given in fixed doses of 5000 U two or three times per day in non-pregnant participants. With these low doses, it is unnecessary to monitor coagulation, but monitoring is required when it is given for treatment (Fauci 2008). However, there is concern that this low dose may be insufficient in high-risk groups, including pregnant women with prior VTE, because it does not reliably produce detectable heparin (UFH) levels (Bates 2008).
The duration and doses of subcutaneous LMWH during pregnancy vary depending on guidelines and studies. For prophylaxis, several dose regimens of LMWHs have been used, including administering subcutaneous enoxaparin 40 mg per 24 hours (Gates 2004), dalteparin 5000 U per 24 hours (Pettila 1999; Key 2000), and an adjusted dose of LMWH to achieve a peak anti-Xa level of 0.2 to 0.4 U/mL (Blomback 1998; Dulitzki 1996).
Key 2000 reported that dalteparin 5000 U per 24 hours was suitable for most pregnant women and did not need to be modified in the third trimester because anti-Xa activity levels did not vary significantly throughout pregnancy. In contrast, with the same regimen, where 5000 U of dalteparin was administered once daily, the mean anti-Xa level at 12, 24, and 36 week's gestation was significantly reduced at two hours post-injection when compared with postpartum (Sephton 2003). This suggests that there are inter- and intra-individual handling differences as pregnancy progresses.

The Duke protocol (James 2005) reflects the increasing requirements for both UFH and LMWH as pregnancy progresses: UFH 5000 U subcutaneously per 12 hours before eight weeks, 7500 U subcutaneously per 12 hours from eight to 28 weeks, then 10,000 U subcutaneously per 12 hours after 28 weeks; or enoxaparin (LMWH) 30 mg twice-daily before 28 weeks, then 40 mg twice *daily after 28 weeks. Although higher dosages ranging from UFH* 13,000 to 40,000 per 24 hours (mean 19,100 U per 24 hours) with 25 weeks of the average duration of prevention have been given, a 2.7% (five out of 184) recurrence of thrombotic events was recorded in spite of the high-dose prophylaxis (Dahlman 1993). Barbour 1995 also concluded that the adjusted high dose of UFH 7500 U to 10,000 per 12 hours may be reasonable in the second and third trimester as long as the activated partial thromboplastin time (aPTT) is not significantly elevated, while prophylaxis with low-dose anticoagulation is recommended for pregnant women with a history of thrombosis (Bates 2004).
One study (Anderson 1993) has investigated the comparative effectiveness and safety of using an indwelling Teflon catheter and a subcutaneous injection. Teflon catheters were inserted over an introducer steel needle at a 30° angle into the subcutaneous tissues of the abdomen by means of a sterile technique. After removal of the needle, the catheter was fixed in place with an adhesive foam pad. UFH was injected slowly, twice daily, through an external port at the proximal end of the indwelling Teflon catheter by means of an insulin syringe and a 25-gauge needle. The entire catheter was 3.5 cm in length with the Teflon portion that was inserted subcutaneously being 2 cm in length. Catheters were changed weekly to reduce the risk of infection. There were no differences in the mean heparin dose or aPTT between the two methods of heparin administration. The study also used a questionnaire to obtain information from women about their preferred route of heparin administration. Of the 12 women interviewed, 11 reported that the catheter caused less pain and bruising than the subcutaneous injections given twice daily, although five women developed urticarial reactions at the sites of the injections and these reactions tended to be more severe when the catheter was used.
Another method of subcutaneous heparin delivery, using a programmable external infusion pump, has been compared with the use of an intermittent subcutaneous injection. In a retrospective study (Floyd 1991), the mean daily dose of UFH when using a subcutaneous infusion pump was higher (29,445 versus 13,822 U), resulting in smoother, more therapeutic heparinisation (mean aPTT, 20.6 versus 10.4 seconds above control) among the subcutaneous infusion pump group when compared with the intermittent subcutaneous injection group. There were two complications (haematoma, site infection) in the intermittent subcutaneous injection group, while none occurred in the subcutaneous infusion pump group. Although the results showed that there was no statistical significance in the smaller number of complications among the subcutaneous infusion pump group, when used in concert with weekly home visits, the subcutaneous infusion pump method nevertheless allowed the administration of the prevention to be more evenly controlled than did the use of intermittent subcutaneous injections.

How the intervention might work

Heparin (UFH and LMWH) acts as an anticoagulant by activating antithrombin and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa (Fauci 2008). The administration of heparin (UFH and LMWH) protects pregnant women against the risk of producing a thrombosis that can develop into thromboembolism (DVT or PE).

Why it is important to do this review

First, although administering subcutaneous heparin (UFH or LMWH) is the main option in the prevention of VTE during pregnancy, the management of thromboprophylaxis in pregnant women has mostly relied on the evidence from non-pregnant participants.
Second, thromboprophylaxis in pregnancy involves a cost burden, inconvenience and side effects as a result for a longer duration. Pregnant women who require anticoagulation therapy, especially those with a history of VTE and those on lifelong anticoagulation, will require a switch from the administration of warfarin to heparin-related compounds (UFH and LMWH) (James 2007; James 2011) when conception has occurred and been detected, because of the effects of warfarin on the fetus. Heparin is more expensive *than warfarin (Bell-Edwards 2000) and LMWH is even more expensive* than UFH (James 2011). There is a report that LMWH is at least 10 times the cost of low-dose heparin in North America (Etchells 1999). It is clear that women who receive insufficient medical cost coverage face financial burdens. Furthermore, women in a region or country where self-administration is not allowed may need to be hospitalised for the management of administering heparin throughout pregnancy. Others who self-administer as outpatients require self-management to inject several times a day depending on agents and dosage used, yet those who do not self-administer heparin must rely on others to give them their injections otherwise they discontinue the administration, thus exposing themselves to an increased risk of VTE (Anderson 1993). Although bleeding in pregnant women receiving LMWH is uncommon, skin complications (Bank 2003) may occur due to repeated and long-term injections.
Having considered the disadvantages and adverse effects of administering subcutaneous heparin (UFH or LMWH), women's satisfaction is highly important, since the effectiveness and safety of administering subcutaneous heparin (UFH or LMWH) during pregnancy using different methods is still not clear. This underscores the importance of conducting a systematic review to investigate the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) in this high-risk *of VTE group of pregnant women.*

OBJECTIVES

To compare the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all randomised controlled trials (individual and clustered) investigating methods for administering sub*cutaneous heparin (UFH or LMWH) during pregnancy. Studies* reported only as abstracts were eligible for inclusion and would have been placed in studies awaiting assessment, pending the full publication of their results. Quasi-randomised studies and cross-over trials were not eligible for inclusion.

Types of participants

Women requiring heparin (UFH or LMWH) during pregnancy. We excluded pregnant women under intensive care.

Types of interventions

Intermittent injections versus indwelling catheters or programmable (auto) external infusion pumps, or any other devices to facilitate the subcutaneous administration of heparin (UFH or LMWH) during pregnancy.

Types of outcome measures

Primary outcomes

1. Women's satisfaction
2. Incidence of VTE

Secondary outcomes

1. Maternal death
2. Local and systemic bleeding (haemorrhage)
3. Pain
4. Urticarial reaction
5. Local and systemic infection and bruising
6. Withdrawal because of adverse events (discontinuation of heparin because of serious and threatened adverse events)
7. Pregnancy outcomes (e.g. miscarriage, fetal death)
8. Any adverse events reported by the included trials (e.g. osteoporosis, HIT)

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 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

We searched the reference lists of relevant studies. We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed the inclusion of the *one potential study identified as a result of the search strategy.* We resolved any disagreement through discussion.
There are no included studies in this review. Full methods of data collection and analysis to be used in future updates of this review are provided in Appendix 1.

RESULTS

Description of studies

See: Characteristics of excluded studies.

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved two reports relating to one trial that we subsequently excluded because the study was a randomised, multiple, cross-over study (Anderson 1993). There are no included studies in this review.

Risk of bias in included studies

There are no included studies in this review.

Effects of interventions

There are no included studies in this review.

DISCUSSION

It is disappointing that no randomised controlled trials are available to assess the effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women.

The lack of relevant studies identified by the review reflects the ethical concerns that emerge in this population requiring heparin (UFH or LMWH) prophylaxis during pregnancy. Random allocation of women at risk of VTE to one method of administering subcutaneous heparin (UFH or LMWH) or another may not be acceptable to women or their families, and therefore, informed consent of the study would be difficult. Although VTE and thrombophilia are not rare, it may be difficult to complete such a trial, because of the difficulty of recruiting pregnant women with a previous VTE or with thrombophilia.

In a randomised, multiple, cross-over study that has been excluded *in this review, women alternated every two weeks between hav*ing heparin administered through the indwelling Teflon catheter and receiving heparin via subcutaneous injections. Ten of the 12 women in this trial preferred to have subcutaneous heparin administered through an indwelling Teflon catheter rather than by twice-daily injections ($P = .04$), and 11 women reported that the catheter caused less pain and bruising than twice-daily injections ($P < .01$). Although the interpretation of the result is limited by the small number of participants, it does indicate that the bioavailability of heparin is not affected by repeated injections into the same subcutaneous site (Anderson 1993).

The risk of severe adverse pregnancy outcomes is lower under the management of heparin prophylaxis during pregnancy but the potential adverse pregnancy outcomes are serious due to discontinuation of heparin prophylaxis. Therefore, large trials would be required to demonstrate that effectiveness and safety of different methods of administering subcutaneous heparin (UFH or LMWH) during pregnancy is assured.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised controlled trials that have shown the effectiveness and/or safety of different methods of administering subcutaneous heparin (UFH or LMWH). Although the risk of severe adverse pregnancy outcomes is generally low under the management of heparin prophylaxis during pregnancy, women's satisfaction seems to be different depending on the methods of administration. Thus, the methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women should be considered, based upon women's informed preference and the risk of adverse outcomes rather than based upon availability of clinical devices or expertise, avoiding discontinuation due to discomfort, pain and financial burden.

Implications for research

There is a need for large scale randomised controlled trials with adequate sample sizes to assess the effectiveness and/or safety of different methods of administering subcutaneous heparin (UFH or LMWH) to pregnant women. Future trials should ideally assess effectiveness of any devices to facilitate the subcutaneous administration of heparin (UFH or LMWH) during pregnancy compared with intermittent injections via indwelling catheters or programmable (auto) external infusion pumps.

ACKNOWLEDGEMENTS

Trained medical interpreters in a face-to-face clinical setting for patients with low proficiency in the local language (Protocol)

Tsuruta H, Karim D, Sawada T, Mori R

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[Intervention Protocol]

Trained medical interpreters in a face-to-face clinical setting for patients with low proficiency in the local language

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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 trained medical interpreters in face-to-face clinical settings for patients with low proficiency in the local language on:

1. the quality of communication between patient and provider (as a precondition for the utilisation of professional knowledge to provide quality health care);
2. the quality of health care, and health outcomes; and
3. the cost benefit, cost effectiveness and cost utility of interventions by trained medical interpreters.

BACKGROUND

Description of the condition

Population mobility is a global phenomenon, with about 214 million people, 3.1% of the world's population, living outside their country of birth (UN 2008). This number is increasing by almost 2% each year (UN 2008), creating various challenges for the countries of origin, host countries, and the migrants themselves (IOM 2010). Among these challenges is migrants' health. When they move, migrants can become vulnerable to disease and may face barriers to accessing appropriate health care due to poverty, marginal status, and/or limited access to social benefits (WHO 2003; IOM 2005; Gbeni 2008). Although several studies have observed that the health of some populations improves after migration (Fris 1998), and that some populations are healthier than others, these positive effects may be lost over time (Ahmad 2004). Because many migrants are not familiar with the local language, in face-to-face clinical settings they face language barriers that can diminish the quality of health care they receive. A number of studies have described the negative impact of language barriers on the quality of health services, on the utilisation of

these services, and on patients' health status as an outcome of service quality. These include excess hospitalisation, medical errors, and drug complications (Hampers 1999; Gandhi 2000; Bard 2004); poor access to medical care (Weinick 2000; Pippins 2007; DuBard 2008; Cruz-Flores 2011), and poor access to services promoting healthy behaviour change (Woloshin 1997; Jacobs 2005; Johnson-Kozlow 2009; Kaur 2009). Language barriers cause communication problems and misunderstanding of patients' explanations of their symptoms and health history. They also inhibit the health provider's presentation of diagnosis, treatment and suggestions for healthful behavioural changes, and the development of a therapeutic patient-provider alliance. In the diagnosis and treatment process, and particularly for illnesses that cannot be identified by observable symptoms, this communication gap can lead to serious problems. The alleviation of language barriers may address these problems. One means of achieving this is by using trained medical interpreters.

Description of the intervention

A 'trained medical interpreter' works to overcome language and cultural barriers in a clinical setting (Hornberger 1997; Flores 2005; Bauer 2010; Leanza 2010) through oral restatement of words from one language into another language, simultaneously or consecutively. Trained medical interpretation is not simply any intervention involving an interpreter to provide a linguistic bridge between patient and health provider. There is no universal definition of the term 'trained medical interpreter', and different standards and training have been required by different institutions, agencies, and in various locations The International Medical Interpreters Association (IMIA) has defined standards of practice in the following three areas (IMIA 2007):

1. clinical interpretation,
2. cultural interface (understanding, attitudes and practices to reduce culturally-based dissimilarities of perception, presentation, course, and outcomes of illness, wellness and treatment as between providers and patients), and
3. ethical behaviour.

Reflecting these standards, we define a trained medical interpreter as an internal (staff member employed in health facility in which a patient receives services) or external interpreter (staff member employed in different organisation from health facility in which a patient receives services), who has received training in clinical interpretation, particularly in some or all of these three areas of practice. It is reasonable to assume that trained medical interpreters provide superior and more accurate interpretation than untrained interpreters.

There is variation in how trained medical interpretation is delivered and utilised. For example, the quality of interpretation may vary depending on the professional interpreter's training. In addition, the cost of using professional interpreters is often regarded as a barrier to use, even though some studies have reported that the use of trained medical interpreters can offer cost benefits to the healthcare system, over other approaches or no interpretation (Hampers 2002; Jacobs 2004). Two obstacles to such positive utilisation, as pointed out in a recent study, are the availability of trained medical interpreters and accessibility to the agencies that provide them (Hadziabdic 2011).

Our review will compare the involvement of trained medical interpreters with other approaches which have similar goals but do not involve trained medical interpreters. These include ad hoc interpreters, bilingual health providers, and translated materials (Riddick 1998; Flores 2005). An ad hoc external interpreter is a friend, family member, relative, etc. who takes on the role of clinical interpreter, but has not received any training in interpretation. Ad hoc interpretation may be more convenient but also problematic, because an ad hoc interpreter may lack appropriate interpretation skills and knowledge of medical terminology. Also, the patient's confidentiality may be compromised, and vital information may be distorted (Launer 1978; Flores 2005; Leanza 2010). A bilingual employee (ad hoc internal interpreter) is a health worker or support worker in a healthcare facility who takes on the role of clinical interpreter without having formal training in interpretation (Johnson 1998; Elderkin-Thompson 2001; Sevilla Matir 2004; Bischoff 2010). Finally, translated materials include documents and flip charts that offer written communication without an interpreter. Health providers and patients can communicate by pointing to an appropriate phrase in their respective languages, but optimal use requires the health provider to be trained to use them effectively as well as the patient to be literate in his/her mother tongue, which is not always the case. Each of the above modes of intervention may be best suited to different circumstances (Garcia-Castillo 2007; Vazquez Navarrete 2009; Manias 2010).

How the intervention might work

One aspect of the quality of health care for migrant patients is the degree to which their specific linguistic, cultural, and any other needs stemming from their migrant status are met in the process of healthcare delivery. Effectively meeting these needs increases the likelihood of achieving desired health outcomes consistent with the current state of professional knowledge (Lohr 1990). Trained medical interpretation can impact on various aspects of healthcare quality. Specifically, it can improve communication quality (Baker 1996; Flores 2003), and patient and healthcare provider satisfaction with communication (Lee 2002; Al-Khathami 2010). The quality of communication can have a substantial influence on: the suitability of clinical responses; diagnostic certainty and the likelihood of testing (David 1984; Drennan 1996; Hampers 2002); timeliness in seeking medical care (Drennan 1996); visit duration (Kravitz 2000; Hampers 2002; Fagan 2003); the utilisation of services including preventive screening (Bell 1999; Jacobs 2001; Bernstein 2002; Dang 2010); appointment keeping (Manson

1988; Server 2009); and the length of stay in hospital (Hampers 2002).
The context in which interpretation takes place can shape its effect, because medical interpretation is practised in different service settings and among different target groups. Our review will consider (in subgroup analyses) the following contextual factors, although we recognise that they may be poorly reported in studies:

- Interpreters' training experience: Fulfilment or non-fulfilment of the three categories of standard practice recommended by IMIA, mentioned above, can influence the interpreter's competency. Interpreters' training experience can vary in terms of the content, duration and intensity of each of the three categories of standard practice (IMIA 2007).
- Gender: The gender of the interpreter, or gender disharmony between the interpreter and patient, may influence their interaction (Bowen 2010).
- Age of patient: Communication can differ between children, adolescents and adults due to differences in emotional development and cognitive ability. Quality of interpretation may influence the emotion and attitude of younger patients to health providers. For example, because paediatric patients may be intimidated in front of adults, they may not be able to verbalise their health condition (Purvis 2009).
- Patient literacy: Information through interpretation for illiterate patients may be limited, since written materials in the patient's own language, for medication and for home follow-up or self-care, cannot be used as a supportive tool for medical interpretation.
- Medical conditions that require sexual/cultural sensitivity: Some conditions such as reproductive illness, which are highly personal, call for sensitivity to sexual issues, which can influence the interaction between interpreter and patient.

Why it is important to do this review

Although some benefits of language interpretation are quite obvious, there is no systematic review of the effects of interpretation on the quality of health services. It is necessary to quantify the impact of interpretation on the quality of health care, in order to clarify its cost-effectiveness and the advantages it offers, as well as any disadvantages.
This review will provide such quantitative information on the impact of trained medical interpreters in face-to-face clinical settings, compared with other interpretation and translation measures. It will also present a subgroup analysis of the contexts in which interpretation takes place.
This information will offer essential assistance to policy makers, health facilities, and patients in the effective and efficient development of interpretation services, particularly in systems with a diversified context that serve patients with low proficiency in the local language.

OBJECTIVES

To assess the effects of trained medical interpreters in face-to-face clinical settings for patients with low proficiency in the local language on:

1. the quality of communication between patient and provider (as a precondition for the utilisation of professional knowledge to provide quality health care);
2. the quality of health care, and health outcomes; and
3. the cost benefit, cost effectiveness and cost utility of interventions by trained medical interpreters.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled trials (RCTs)
2. Cluster RCTs
3. Randomised cross-over trials
4. Quasi-RCTs

We will include quasi-RCTs as there are likely to be few RCTs available for inclusion in the review.

Types of participants

1. Patients of any age with low proficiency in the local language, as determined by the study authors
2. Health personnel who provide services for patients of any age with low proficiency in the local language

Each participant will be analysed separately.

Types of interventions

The main intervention to be considered is interpretation by a trained medical interpreter, in a face-to-face clinical setting.
The trained medical interpreter is an external or internal interpreter who has received training in medical interpretation, especially in all or some of the following areas:

1. clinical interpretation,
2. cultural interface, and
3. ethical behavior (IMIA 2007).

An external interpreter is defined as an individual on dispatch from an outside organization such as a professional interpretation firm. An internal interpreter is defined as an individual employed in the health facility in which a patient receives care.

The intervention will be compared with one of the following control interventions:

- Ad hoc external interpreter: a friend, family member, etc., who takes on the role of medical interpreter, but has not received any training in interpretation.
- Bilingual employee (ad hoc internal interpreter): health worker, support worker at a health facility who takes on the role of medical interpreter, but has not received any training in interpretation.
- Translated materials: document, flip chart, etc. for interpretation without an interpreter.
- No interpretation.

Each comparison group will be analysed separately. We will not include comparison groups assessing remote interpretation via telephone or online.

Types of outcome measures

In accordance with the definition of quality of health care for patients with a low level of proficiency in the local language, we regard quality of communication as the primary outcome, which is a precondition for utilisation of professional knowledge, and can change the quality of health care either directly or indirectly. We regard the provision of health services, patients' health status and cost-benefit/effectiveness of medical interpretation as secondary outcomes. Primary outcomes can be determined by evaluating quality of interpretation, and secondary outcomes can be analysed using various measurements.

Primary outcomes

Quality of communication in medical interpretation

1) Quality of interpretation practice: omission of words or phrases, fluency of interpretation, substitution of words or phrases, editorialisation of words or phrases, addition of words or phrases
Measured by counting from audio or video record, self-report, or health provider report.
Interpretation of the results of analysis for these outcomes will be cautious. Omission, false fluency, substitution, editorialisation, and addition during interpretation are not always errors. They might be required to transform a patient or healthcare provider's discourse to make it understandable. In addition, the person assessing the audio or video record may be a trained interpreter who has a vested interested in showing that trained medical interpreters' have beneficial effects compared to no interpretation or other forms of interpretation (high risk of bias).
2) Quality of interpretation perceived by patient and/or health provider: patient understanding of diagnosis and treatment; patient satisfaction with information provided, decision made and interpretation; health provider satisfaction with information provided, decision made and interpretation; patient's sense of control over communication via interpretation; and health provider's sense of control over communication via interpretation.
Measured by self-report, health provider report, or standardised instruments.
In the table 'Characteristics of Included Studies' we will describe clearly the instruments used for outcome measurement, as well as the translation process to researchers, to achieve transparency of the data because some outcomes may be controversial. For example, patient satisfaction is widely used as an indicator to assess the quality of health care, but it is difficult to define this parameter because satisfaction can be influenced by various factors, such as patient/provider expectation, age, illness, previous experience, patient-health provider relationship, choice of provider, gender, ethnicity, and socio-economic status. In practice, there is no universally accepted method for the measurement of satisfaction (Saila 2006). In addition, articles may not report the details of the measurement and/or instruments used. Patient satisfaction can be low despite high quality interpretation.

Secondary outcomes

1) Patient engagement with health services
Delays in seeking medical care, visit duration, utilisation of health services including preventive screening, missed appointments, length of hospitalisation.
Measured by medical records and the administrative databases of healthcare facilities.
2) Provision of health services
Diagnostic uncertainty, and the amount of medical testing. Communication problems can cause increased diagnostic uncertainty, which can then increase the amount of testing done.
Measured by medical records, and administrative databases of healthcare facilities.
3) Health outcomes (including health behavior, skills acquisition, medical errors, and drug complications).
Measured by medical records, administrative databases of healthcare facilities, standardised instruments, self-report, and provider report.
4) Cost and cost benefits, and effectiveness of medical interpretation
Measured or calculated by the cost of medical interpretation and the effects on health services (i.e. impact on the cost of health services as well as the health outcomes achieved).

Search methods for identification of studies

Electronic searches

We will search for studies using the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*).
- MEDLINE (OvidSP),
- PsycINFO (OvidSP),
- Dissertations & Theses Database (Proquest),
- ERIC (OvidSP),
- Index to Theses,
- Social Services Abstracts (CSA Illumina),
- Sociological Abstracts (CSA Illumina).
- Linguistic and Language Behavior Abstracts (CSA Illumina).

We present the strategy for MEDLINE in *Appendix 1*. Strategies will be tailored to other databases and reported in the review. There will be no language or date restrictions.

Searching other resources

Grey literature

We will search the reports and conference proceedings of IMIA and document resources linked in their web site (e.g. "Annotated Bibliography on Language Access and Interpretation" (http://www.imiaweb.org/resources/AnnotatedBibliography.asp)), and the reports and conference proceedings of Critical Link International (http://criticallink.org/)

Handsearching

We will manually search the following journals: Journal of Immigrant Minority Health (2006 to 2012), Social Science and Medicine (1967 to 2012) and the Journal of General Internal Medicine (1986 to 2012). We will also search reference lists of relevant studies.

Correspondence

We will contact experts in the field and authors of included studies for advice as to other relevant studies.

Data collection and analysis

Selection of studies

Two review authors will screen independently the titles and abstracts of the studies identified by the searches. We will retrieve full copies of all potentially-relevant articles selected by either of the authors. The two authors will then independently determine if studies meet the inclusion criteria mentioned above. We will list studies that initially appear to meet the inclusion criteria but are later excluded in the table 'Characteristics of excluded studies' with reasons for their exclusion. We will settle disagreements between the two authors through discussion with a third author. Potentially-relevant studies in languages other than English will be translated by collaborators within a group and/or translation agency in order to be considered for inclusion. We will provide citation details and any available information about ongoing studies and report details of duplicate publications. In addition, we will report the screening and selection process in an adapted PRISMA flowchart.

Data extraction and management

We will develop a 'data extraction' sheet (based on the Cochrane Consumer and Communication Review Group's data extraction template), pilot test it on ten randomly-selected included studies, and refine it accordingly. Independently, two authors will extract data from the included studies. Information extracted will include study design, information about the participants including patient's language proficiency, type of intervention, setting, and outcomes. We will settle disagreements between the two authors through discussion with a third author.
The patient's language proficiency is assessed by the study authors, who may ask questions in the local language and in the mother tongue of the patients to find whether there are concordant answers between the two languages. However, some studies might not describe how they identified patients with low proficiency in the local language. In this review, we will report on the method used to identify the language proficiency in the table 'Characteristics of Included Studies' and assess it as another source of bias (selection bias) in the assessment of the risk of bias. We will also report on the method used by the study authors to identify the health providers included in the studies.
All data will be entered into RevMan by one review author and checked for accuracy against the data extraction sheets by the other author working independently.

Assessment of risk of bias in included studies

Two review authors will assess the risk of bias of included studies using the criteria from the Cochrane Collaboration's tool (adapted to the Cochrane Consumer and Communication Review Group's data extraction template) as detailed in the Cochrane Consumer and Communication Review Group's Study Quality Guide (CCRG 2011). These criteria consist of the following six domains:

- Sequence generation: judged by the method used to generate the allocation sequence, reported in sufficient detail to allow an assessment of whether it should produce comparable groups. (Quasi-RCTs will be rated as 'high risk' of bias for sequence generation as the methods were not, by definition, truly random).
- Allocation concealment: judged by the method used to conceal the allocation sequence, reported in sufficient detail to determine whether intervention allocation could have been foreseen in advance of, or during, enrolment.
- Blinding of participants and personnel: judged by all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received, and by any information relating whether the intended blinding was effective.
- Blinding of outcome assessment: judged by all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received, and by any information relating whether the intended blinding was effective.
- Incomplete outcome data: judged by the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. If 80% or more of the data are complete, it will be rated as 'low risk' of bias. Otherwise, it will be rated as 'high risk' of bias. If it cannot be identified in a study, it will be rated as being at 'unclear' risk of bias.
- Selective outcome reporting: judged by the review authors' findings about the possibility of selective outcome reporting. If a study protocol is available and all outcomes in the study method are reported by the study report it will be rated as 'low risk' of bias; if no protocol is available and not all outcomes in the method are reported it will be rated as 'high risk' of bias; if no protocol is available but all outcomes in the method are reported it will be rated as being at 'unclear' risk of bias.
- Other sources of bias: the authors will identify any important concerns about bias not addressed in the other domains. For example, we will assess the method used to identify patients' language proficiency as a source of potential selection bias. In addition, we will assess the baseline discordance between groups. If cluster RCTs are included in the review we will also assess and report the risk of bias associated with selective recruitment of cluster participants (CCRG 2011).

Further, as outlined in the Cochrane Handbook (Higgins 2011), we will categorise the risk of bias of included studies as: low risk of bias (plausible bias unlikely to seriously alter the results), unclear risk of bias (plausible bias that raises some doubt about the results), and high risk of bias (plausible bias that seriously weakens confidence in the results).
Two authors will conduct the risk of bias assessment independently. Disagreements will be resolved by discussion between the two review authors; if agreement cannot be reached, a third review author will decide.
The risk of bias of included studies will be used to inform the discussion of the review's findings.

Measures of treatment effect

Continuous data

We anticipate that the majority of outcomes will be measured and reported as continuous data. We will compute a standardised mean difference (SMD) for continuous outcome variables, with a 95% confidence interval (CI). For this review, a corrected Hedges' g will be computed by dividing the difference between intervention means (trained interpreters versus other interpretation) by the pooled and weighted standard deviation of the intervention. Specifically, Hedges' g corrects for a bias (overestimation) that occurs when the uncorrected SMD effect size is used on small samples. The combined effect size for each outcome will be computed as a weighted mean of the effect size for each study, with the weight being the inverse of the square of the standard error. Thus, a study will be given greater weight for a larger sample size and more precise measurement, both of which reduce standard error.

Dichotomous data

We will compute odds ratios (ORs) for dichotomous outcomes with a 95% CI. Based on the assumption of proportional odds, ORs can be compared between variables with different distributions, including very rare and more frequent occurrences.

Unit of analysis issues

Cluster-randomised trials

If the unit of allocation (e.g. hospital) is different from the unit of analysis (e.g. people with low proficiency in the local language), we will seek statistical advice to determine whether appropriate methods were used to avoid unit-of-analysis errors. When suitable cluster analysis is used, effect estimates and their standard errors will be meta-analysed. Otherwise they will be excluded from the meta-analyses unless the review authors can control for the clustering from the available information.

Crossover trials

If studies are conducted in crossover design, we will use the results from the first intervention period.

Multiple intervention groups

Within the intervention and/or control groups mentioned in the section *Types of interventions*, if multiple groups with different individuals are presented in studies, all relevant intervention and/or control groups will be combined into a single group to create a single pair-wise comparison.

Interventions for reduction of stigma in people with HIV/AIDS (Protocol)

Wariki WMV, Nomura S, Ota E, Mori R, Shibuya K

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[Intervention Protocol]

Interventions for reduction of stigma in people with HIV/AIDS

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ABSTRACT

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

1. To assess the effectiveness of interventions to reduce stigma towards people living with HIV/AIDS, improve coping strategies and increase tolerance, compared with a control group.

2. To assess the most effective form of interventions to reduce stigma towards people living with HIV/AIDS, improve coping strategies and increase tolerance, compared with a control group.

BACKGROUND

Description of the condition

First observed in 1981 in the United States, HIV/AIDS has transformed into a global epidemic (UNAIDS 2011). In 2011 alone, an estimated 34.2 million people worldwide were living with HIV/AIDS (UNAIDS 2011). Stigma related to HIV/AIDS was first addressed in a statement at an informal briefing on AIDS to the 42nd Session of the United Nations General Assembly in 1987 (Mann 1988), and there have been a wide range of discussions about effective responses to HIV/AIDS stigma. Despite widespread recognition of the consequences of HIV/AIDS stigma over the first 30 years of the epidemic (Mahajan 2008; Parker 2003; UNAIDS 2011), stigma continues to be an obstacle to HIV prevention efforts (de Bruyn 2004; Rahmati-Najarkolaei 2010; Thi 2008).

Conceptualization of stigma according to Goffman's theory is described as a "dynamic process of devaluation that significantly discredits" an individual from a whole and ordinary person to one tainted (Goffman 1963). On the basis of this traditional perspective, recognition of stigma has increased through various research characterizing it as a social process, including negative social attitudes (perceived stigma) as well as social inequality and discrimination (enacted stigma) towards particular individuals (Corrigan 1999; Pryor 2004). HIV/AIDS-related stigma has been conceptually defined as "a mark of disgrace, which invokes discrimination, prejudice, discounting, discrediting, and negative attitudes, beliefs and behaviours directed at people with or perceived to have HIV/AIDS infection, their families and communities with which they are associated" (Alonzo 1995; Herek 1993; Herek 2007; Parker 2003; Steward 2008). The lack of a comprehensive framework for HIV/AIDS-related stigma precludes meaningful appraisal and

comparisons of interventions that target stigma, and limits the ability to design effective programs and interventions.

In the era of the HIV/AIDS epidemic, recent research to better understand the types of HIV/AIDS-related stigma (e.g., enacted, vicarious, felt normative and internalized) has raised awareness of this complex problem (Corrigan 2004).

Discrimination is a type of stigma towards people living with HIV/AIDS, which can be defined as experiences of stigma (enacted stigma), or prejudicial attitudes and behavior based on their HIV status, such as isolation, exclusion, rejection or harm by other people in the community. Discriminatory behavior, such as loss of jobs, exclusion from community activities, loss of social support, problems in accessing health care or even physical violence (i.e., enacted stigma) and threats to personal well-being because of their serostatus (Gostin 1999; Varas-Díaz 2005; Ziegler 2000) may impact people living with HIV. Exposure to reported stories of discriminatory behavior (vicarious stigma), awareness of people's perceptions of stigma (felt normative stigma) as well as self-stigma or believing the stigma surrounding one's own condition (internalized stigma) are also experienced by people living with HIV/AIDS (Steward 2008).

Globally, stigma may arise through a combined interplay of social interaction practices, structural inequality, cultural differences and relation of power (Castro 2005; de Bruyn 2004; Herek 2002; Letamo 2003; Link 2001; Parker 2003; Unnikrishnan 2010). Stigmatization of people living with HIV/AIDS is positively associated with misconceptions about modes of transmission of the disease, lack of HIV knowledge and accurate information, HIV/AIDS serostatus, fears related to its incurability, poorer mental health, as well as discrimination and prejudice towards risky behavior, though it is manifested differently across settings, groups and individuals (Diaz 2006; Kalichman 2005; Mahajan 2008; Sengupta 2011). Therefore, identifying risk factors for HIV/AIDS-related stigma is important in confronting perceptions that promote stigmatizing behaviours towards people living with HIV/AIDS (Earnshaw 2009; Nyblade 2009).

People who are HIV-positive or who are perceived to have an HIV infection are affected by stigma (Earnshaw 2009), including children and young adults (Boyes 2012; Reyland 2002). In Brazil, children and young people living with or affected by HIV/AIDS can be denied the right to education and job opportunities (Abadía-Barrero 2006). Experiences of stigma and discrimination are also common in pregnant women, and have been reported as a potential barrier to pregnant women's acceptance of HIV testing in antenatal care (Kilewo 2001; Turan 2011), as well as their initial participation in and adherence to a preventing mother-to-child transmission program (Awiti Ujiji 2011; Bwirire 2008; Mepham 2011; Painter 2005). HIV/AIDS-related stigma is common towards men who have sex with men or gay populations, e.g. in India, the United States and Scotland (Chakrapani 2011; Courtenay-Quirk 2006; Diaz 2001; Flowers 2006; Logie 2012). HIV-positive lesbians, bisexuals and transgender women, e.g. in Canada and India (Chakrapani 2011; Logie 2012a), are also affected by stigma. Researchers have highlighted the urgent need to consider the potential effect of stigma amongst sex workers and the implementation of interventions to reduce stigma (Baral 2012; Biradavolu 2012). Necessary HIV preventive interventions related to negative emotion and its association with drug cravings have also been suggested to address HIV/AIDS-related stigma amongst injecting drug users (Mimiaga 2010; Rudolph 2012).

Stigma related to HIV/AIDS is associated with negative health outcomes, such as lack of access to HIV-related prevention (Mahajan 2008; Piot 2006; Rahmati-Najarkolaei 2010; Sengupta 2011), reduced HIV care-seeking behavior (Sayles 2007), fewer treatment efforts (Bogart 2008) and lack of quality services in many settings (Chakrapani 2011; Fox 2010; Li 2012; Ma 2007; Sayles 2007; UNAIDS 2011; Young 2010).

HIV/AIDS-related stigma can be measured effectively using validated survey instruments (Earnshaw 2009). A number of scales have been developed and tested in multiple settings to measure how the social processes of HIV/AIDS-related stigma affect people living with HIV/AIDS. In Thailand and Zimbabwe, a comprehensive 50-item scale was tested measuring three factors associated with HIV/AIDS stigma including shame, blame and social isolation; discrimination; and equity towards people living with HIV/AIDS (Genberg 2008). Although the scale showed good construct validity and high internal consistency, reporting bias due to self-reported HIV stigma could not be avoided (Genberg 2008). In India, Steward and colleagues developed an HIV stigma scale measuring four components of stigma (i.e., enacted, vicarious, felt normative and internalized) and reported an association between HIV/AIDS-related stigma and disclosure, with disclosure avoidance and depression (psychological distress) found among people living with HIV/AIDS (Steward 2008). In South Africa, Swaziland and the United States, the Internalized AIDS-Related Stigma Scale has been used, with results indicating a significant association between internalized stigma, and depression and social support (Kalichman 2009). This scale was also adopted in Uganda and was found to have high internal validity for measuring the outcomes of HIV/AIDS-related stigma (Tsai 2013). In South Africa, the HIV Stigma-by-Association Scale for Adolescents was adapted to measure stigma and symptoms of depression and anxiety (Boyes 2012). This scale assesses associations between stigma-by-association, bullying, peer problems, depression and anxiety symptoms (Boyes 2012).

Description of the intervention

A variety of specific and general intervention campaigns involving individuals living with HIV have been conducted to reduce HIV/AIDS-related stigma, and several underlying factors that may produce stigma have been addressed (Bellingham 1993; Brown 2003). These interventions have reportedly been effective in improving quality of life among people living with HIV/AIDS and

contributing to better health outcomes amongst all populations. In this review, we will focus only on individual interventions that address actionable causes of stigma and discrimination, including behavioral, educational and social interventions in creating awareness of what stigma is, how it manifests, and the resulting negative consequences. It is also interesting to assess the effect of interventions in addressing fears and attitudes of the individual, and their advantages in reducing stigma.

Behavioral intervention efforts have shifted to people living with HIV/AIDS (Earnshaw 2007). "Popular opinion leaders" or peer educators were effective in reducing stigma by improving the attitude and behavior of healthcare providers towards individuals living with HIV in China by focusing on self-protection and occupational safety (Reilly 1991; Li 2013). Education-based interventions, to date, have commonly focused on education workshops, curriculum-based psychosocial support including knowledge of HIV/AIDS transmission and risk behaviours (such as sex outside marriage, having multiple sex partners, substance use, sex work and homosexuality), a preventative vaccine for HIV/AIDS and cultural norms of silence regarding sexuality and sexual practices (de Bruyn 1992; de Bruyn 2004; Liu 2006; Lumoso 2012; Parker 2003; Reardon 2012). Interventions that solely target perceptions of and attitudes towards people living with HIV (Abadía-Barrero 2006), provide sensitivity training related to those living with HIV/AIDS or promote tolerance through individual contact with HIV/AIDS-diagnosed individuals (Brown 2003; Herek 2002) are still limited. For example, an AIDS education program developed in a high school in a socioeconomically disadvantaged urban area in South Africa addressed the whole school community and aimed to raise awareness about HIV/AIDS using a variety of educational methods (Kuhn 1994). Community and home-based care interventions using capacity building, care and support, resource mobilization and income generation were effective in increasing better social and environmental relations of people living with HIV/AIDS in Ethiopia (Okello 2012). Skilled birth attendance is one evidence-based intervention amongst pregnant women with HIV/AIDS aimed at improving maternal and infant health. Women who give birth with the assistance of a healthcare professional are more likely to receive information relating to HIV-related healthcare, which can reduce the fear of HIV/AIDS-related stigma that often presents an added challenge for pregnant women (Gabrysch 2009).

How the intervention might work

By decreasing HIV/AIDS stigma, a challenging impediment to public health programs will be overcome, leading to a reduction in further HIV infections, the provision of adequate health care and support as well as mitigating the impact of HIV/AIDS (Brown 2003).

Interventions that aim to reduce HIV/AIDS-related stigma have been measured (e.g. in randomized controlled trials, pre- and post-test studies with a non-randomized control group, or pre- and post-test studies with one-group designs) and HIV/AIDS stigma is one of the assessed outcomes (Sengupta 2011). Statistics that demonstrate pre- and post-intervention changes in HIV/AIDS stigma outcomes have been used to assess the availability of effective interventions to reduce stigma. The extent to which stigma reduction interventions reduce barriers to an array of positive behaviours including HIV testing, harm reduction, treatment adherence support and prevention of mother-to-child transmission have also been determined (Doherty 2006; Kalichman 2008).

Why it is important to do this review

HIV-AIDS stigma continues to be a significant hurdle to effective treatment. The variability of efforts to reduce stigma in cultural and local settings has led to complexity in assessing the extent of HIV/AIDS-related stigma and its impact on the effectiveness of HIV prevention and treatment programs, as well as the effectiveness of interventions to reduce stigma (Wu 2006). These challenges hamper local, national and global efforts to address HIV/AIDS-related stigma (UNAIDS 2011).

Therefore, it is important to conduct a systematic review to quantitatively document the current state of research, with an emphasis on summarizing the established knowledge of effective interventions, including defining, measuring and assessing the impact of HIV-related stigma. This review will act as a valuable resource to translate evidence into practice in the global response to the HIV/AIDS epidemic.

OBJECTIVES

1. To assess the effectiveness of interventions to reduce stigma towards people living with HIV/AIDS, improve coping strategies and increase tolerance, compared with a control group.

2. To assess the most effective form of interventions to reduce stigma towards people living with HIV/AIDS, improve coping strategies and increase tolerance, compared with a control group.

METHODS

Criteria for considering studies for this review

Types of studies

All identified published, unpublished and ongoing randomized controlled trials (RCTs) to reduce stigma towards people living with HIV/AIDS that compare two different interventions, including individual specific or general intervention campaigns, or one

type of intervention strategy with a control, will be included. The unit of randomization will be individual or cluster level. Quasi-RCTs will be excluded.

Types of participants

The general population living with HIV/AIDS, as well as specific target groups living with the disease, including sex workers, drug users (drug users who inject drugs as well as other drug-using populations), men who have sex with men, bisexual people, pregnant women and adolescents.

Types of interventions

Specific or general intervention campaigns (particularly behavioral-, educational- and social-based interventions) targeted at a population level or at specific target groups, including at an individual level, that aim to reduce stigma. These interventions include lectures, group discussions, individual education, radio, television, print (newspapers, magazines, booklets, leaflets, posters, pamphlets), films, documentaries, billboards, folk media (such as street drama), or a combination of these aimed at achieving behavior change.

The comparison will be other interventions for reduction of HIV/AIDS-related stigma or no intervention.

Types of outcome measures

Primary outcomes

1. Experiences of stigma: prejudicial attitudes and behaviours towards people living with HIV/AIDS, including refusal to provide health care, segregation in healthcare settings, threats of violence, being fired from a job, being refused a job offer, abandonment by family, physical assault, social avoidance, self/ social isolation, secrecy, non-disclosure and sexual abuse-related stigma.
2. Anger symptoms: easy to anger, existential anger.
3. Depressive symptoms: hopelessness about the future, fear, anxiety, frustration, feeling sad, crying easily.

Secondary outcomes

1. Increase in tolerance towards people living with HIV/AIDS in the general population, healthcare providers or any other target groups.
2. Improvement in coping strategies for dealing with HIV/AIDS stigma among people living with HIV/AIDS.

Search methods for identification of studies

The Cochrane HIV/AIDS Group search strategy will be followed.

1. Electronic searches

An exhaustive search strategy in collaboration with the trial search coordinator of the Cochrane HIV Review Group will be formulated to identify all relevant trials regardless of language or publication status (published, unpublished, in press and in progress). The following electronic databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILAC, NLM Gateway, CINAHL, AIDSearch, PsycINFO, Sociological abstracts, and Communication studies. The reference lists of related reviews and all articles obtained will also be reviewed for additional citations. Other relevant websites of international agencies, especially those concerned with the prevention of HIV/AIDS (Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO), United Nations Population Fund (UNFPA), World Bank, and Centers for Disease Control and Prevention) will also be searched.

2. Hand searching

A hand search of key HIV/AIDS research journals will be conducted. The reference list of all studies identified by the above methods and bibliographies of any systematic reviews, meta-analyses, or current guidelines we identify during the search strategy process will be checked.

3. Personal communication

Authors of significant papers and relevant policymakers based in organizations working on HIV/AIDS intervention programs, including UNAIDS and WHO, will be contacted to find other relevant published and unpublished studies.

4. Conference proceedings

Conference proceedings will be searched for relevant abstracts. Conferences include the Conference on Retroviruses and Opportunistic Infections (CROI), 1996-2012; International AIDS Conference (IAC), 1985-2012; and International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS), 2001-2012.

5. Cross-references

Bibliographies of studies identified by the procedures described above will be scrutinized to locate additional studies. The search strategy is iterative in that bibliographies of the included studies will be searched for additional references.

Data collection and analysis

The methodology for data collection and analysis will be based on guidance from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009).

Selection of studies

The selection of potentially relevant studies will be performed in collaboration with the Cochrane HIV/AIDS Group. All identified citations will be appraised independently and critically by two review authors (EO, WW) to determine the potentially eligible studies for inclusion. The titles, abstracts, and descriptor terms of the remaining references will be scanned, and the inclusion criteria will be applied. Irrelevant reports will be discarded, and the full article or abstract obtained for all potentially relevant or uncertain reports will be reviewed for relevance based on study design, types of participants, interventions and outcome measures. No language restrictions will be applied. All disagreements will be resolved by discussion with the third author (RM). Reasons to exclude the potentially relevant trials will be described in an excluded studies table. Reference management software will be used to remove duplicate references.

Data extraction and management

A dedicated pre-designed data extraction sheet for each selected study will be completed by two review authors (EO and WW) independently, after initial search and article screening. The extracted data will include the following information:

- Study details: Study design, type, duration and completeness of follow-up, country and location of the study.
- Participant details: Sociocultural and economic characteristics, inclusion and exclusion criteria including diagnostic criteria for HIV-related stigma.
- Intervention details: Social, behavioral and educational interventions.
- Outcome details: Increase in tolerance towards persons living with HIV/AIDS and improvement in coping strategies for dealing with HIV/AIDS stigma.

Discrepancies will be resolved through discussion or by consulting with the other review author (RM). Data will be entered into the Review Manager software and the accuracy will be checked. When information regarding any of the above is unclear, contact with authors of the original articles will be attempted to elicit further details.

Assessment of risk of bias in included studies

The risk of bias within the included studies against key criteria described below will be assessed independently by two review authors in accordance with methods recommended by the Cochrane Effective Practice and Organization of Care (EPOC) Group and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). The following judgments will be used: low risk of bias, high risk of bias or unclear risk of bias (either because of lack of information or uncertainty over the potential for bias). Disagreements will be resolved by consensus or reconciled with the third reviewer, or an arbitrator will be involved when necessary.

The components of each included study related to risk of bias will be assessed using a standardized form. This will include information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. Methodological components of the studies will be assessed and classified as adequate, inadequate or unclear as explained in the Cochrane Handbook for Systematic Reviews of Interventions and as detailed below:

1. Sequence generation (checking for possible selection bias)
For each included study, the method used to generate the allocation sequence will be described in sufficient detail to allow an assessment to be made of whether it would have produced comparable groups.
Low risk: authors described a random component in the sequence generation process, such as the use of random number tables, tossing coins , or shuffling cards or envelopes.
High risk: authors described a non-random component in the sequence generation process, such as the use of odd or even birth dates or an algorithm based on the day/date of birth, hospital or clinic record number.
Unclear: insufficient information to permit judgment of the sequence generation process.

2. Allocation concealment (checking for possible selection bias)
For each included study, the method used to conceal the allocation sequence will be described and a judgment made as to whether the intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.
Low risk: participants and the investigators enrolling participants could not foresee assignment.
High risk: participants or investigators enrolling participants could foresee assignment.
Unclear: insufficient information to permit judgment of allocation concealment or the method not described.

3. Blinding (checking for possible performance bias)
A description will be provided of the methods used, if any, to blind study participants and personnel from knowing which intervention a participant received.
Low risk: blinding of the participants, key study personnel or outcome assessor; no blinding in the situation where non-blinding is unlikely to introduce bias.
High risk: no blinding or incomplete blinding, whereby the outcome is likely to be influenced by lack of blinding.
Unclear: insufficient information to permit judgment of adequacy or otherwise of the blinding.

4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)
For each included study and for each outcome or class of outcome, *completeness of the data will be assessed including checking* attrition, noting exclusions, checking the numbers included in the analysis at each stage (compared with the total number of randomized participants) as well as reasons for attrition or exclusions where reported, and whether missing data is balanced across groups or is related to outcomes. Where sufficient information is reported, or will be supplied by the trial authors, missing data will be included in the analyses.
Low risk: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data will be balanced in numbers across groups.
High risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers across groups or reasons for missing data.
Unclear: insufficient reporting of attrition/exclusions.

5. Selective reporting bias
For each included study, the possibility of selective outcome reporting bias will be investigated and a conclusion reported.

6. Other sources of bias
For each included study, all other possible sources of bias, including study design and early trial cessation because of data-dependent processes or extreme baseline imbalance, will be reported.

7. Overall risk of bias
Explicit judgements will be made about whether studies are at a high risk of bias according to the criteria given in the handbook (Higgins 2009). With reference to (1) to (6) above, the likely magnitude and direction of the bias and its likely impact on the findings will be assessed and reported.

Measures of treatment effect

1. Dichotomous data
For dichotomous data, results will be presented as summary risk ratios (RR) with a 95% confidence interval (CI).
2. Continuous data
For continuous data, the mean difference (MD) will be used if outcomes are measured in the same way for all trials. Standardized mean differences will be used to combine trials that measured the same outcome with different methods.

Unit of analysis issues

All RCTs including cluster-RCTs will be identified.

Dealing with missing data

For included trials, attrition levels will be noted, and the impact of including trials with high levels of missing data in the overall assessment of the treatment effect will be checked using a sensitivity analysis. For all trials, outcomes analyses will be conducted on an intention-to-treat basis. The denominator for each outcome in each trial will be the randomized number minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

Given that we anticipate heterogeneity between studies, random effects models will be used to generate pooled effects. Statistical heterogeneity amongst trials will be assessed and quantified using an I^2 statistics for heterogeneity (p value<0.1). If there is sufficient data, statistical heterogeneity will be explored by looking at the outcomes of various studies. A narrative form will be provided in the case where we are not able to combine the outcomes of various studies.

Assessment of reporting biases

When reporting bias is suspected, attempts will be made to contact study authors to ask them to provide missing data. If this is not possible and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored through sensitivity analysis.

Data synthesis

The analysis will be performed using the latest version of Review Manager software (RevMan 5). Two authors (EO, WW) will enter the data independently to minimize potential errors leading to heterogeneity.

For each included trial, we will calculate the relative risk, with 95% CI for dichotomous outcomes. For continuous outcomes, weighted mean differences will be used. If studies are considered clinically and methodologically suitable to be combined, a meta-analysis will be conducted. If there are no studies with identical interventions and combinable outcomes, a narrative review will be undertaken.

For the meta-analysis, outcome measures for dichotomous data will be reported as a relative risk with 95% CI. Continuous data will be analysed using the weighted mean difference and standard deviations. If different psychometric scales are used between trials, we will calculate the standardized mean difference (SMD). Survival analysis data (if provided) for time to resolution of symptoms will be analysed using a hazard ratio.

A meta-analysis will be conducted using Review Manager software. Fixed-effect inverse variance meta-analysis will be used for combining data when trials examine the same intervention and their populations and methods are judged sufficiently similar. When heterogeneity between treatment trials is suspected, random-effect meta-analysis will be used. The criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to evaluate the quality of the evidence by outcome will be performed (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be conducted for the primary outcomes of:

Supplementation with multimicronutrients (excluding vitamin A) for breastfeeding women for improving outcomes for the mother and baby (Protocol)

Abe SK, Balogun OO, Ota E, Mori R

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This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 7

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[Intervention Protocol]

Supplementation with multimicronutrients (excluding vitamin A) for breastfeeding women for improving outcomes for the mother and baby

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ABSTRACT

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

To evaluate the effects of multimicronutrient supplementation (excluding vitamin A) in breastfeeding mothers on maternal and infant outcomes.

BACKGROUND

Micronutrients are naturally occurring substances. They are comprised of vitamins and minerals, which are required in small amounts to ensure normal metabolism, physical growth and development. However, due to poor quality of diet and/or inadequate intake of foods, micronutrient deficiency is highly prevalent and constitutes a major global health problem. Globally, more than two billion people are estimated to be deficient in key vitamins and minerals, particularly iodine, iron and zinc (Ritchinsky 2010). The majority of these people live in low-income countries and are typically deficient in more than one micronutrient (WHO 2006). However, micronutrient deficiency among breastfeeding mothers and their infants also remains an issue in high-income settings, specifically among women who avoid meat and/or milk (Allen 2005). These women may have an increased risk of being vitamin B12 (Herrmann 2001), vitamin D and/or iron deficient (Allen 2005). Additionally, postpartum anaemia may be related to postpartum depression (Corwin 2003).

Young children, pregnant and lactating women are particularly vulnerable to micronutrient deficiencies. They not only have a relatively greater need for vitamins and minerals because of their physiological state, but are also more susceptible to the harmful consequences of deficiencies (WHO 2006).

Description of the conditions

The unmet requirements for most micronutrients in lactating women can result in various adverse effects for both mother and

infant as the mother's micronutrient status determines the health and development of her breast-fed infant. Low maternal nutrient intake during lactation remains a problem in many parts of in the world especially in low-income regions such as Sub-Saharan Africa (Lartey 2008). This results in major shortfalls in the concentration of some of these nutrients in breast milk thus providing suboptimal levels of nourishment to the nursing infant (Dijkhuizen 2001; McCullough 1990). At low levels these deficiencies may manifest in one or more clinical symptoms described below. The World Health Organization (WHO) recommends various combinations of multiple-micronutrient supplementation of pregnant mothers, which may also be applicable to breastfeeding women including vitamin A, vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium, iodine; with iron and zinc (UNICEF 1999).

In relation to the level of importance to the mother-infant pair during lactation, micronutrients have been divided into two priority groups defined by maternal status or intake of each nutrient, its concentration in breast milk and the efficacy of supplementation (Allen 1994). Priority group 1 generally includes water-soluble vitamins: B vitamins - thiamin, riboflavin, vitamin B6 and B12 as well as vitamin A, and in endemically-deficient populations, iodine and selenium. Breast milk is the major source of these micronutrients for the infant and the amounts present in breast milk are highly variable depending on maternal intake. Priority group 2 includes folic acid, vitamin D, calcium, iron, copper and zinc. For this group, maternal status or dietary intake has relatively little effect on their concentration in human milk. Consequently, the suckling infant is comparatively well protected from maternal deficiency and the mother runs the greatest risk of depletion during lactation if her intake does not meet requirements. There is some disagreement in which group to categorise folic acid.

Maternal deficiency in vitamin A may prevent vitamin build-up of the infant's liver stores and consequently fail to offer protection from deficiency beyond six months of age. Moreover, vitamin A supplementation for breastfeeding women has been extensively reviewed in an earlier Cochrane systematic review (Oliveira-Menegozzo 2010) and has therefore been excluded from this review. The authors found that a single dose of vitamin A showed no effect on infant death, maternal death or morbidity, while one small study showed an improvement in infant health (Oliveira-Menegozzo 2010). Improvement in maternal serum retinol, breast milk retinol and vitamin A liver stores was demonstrated by the this intervention, however, the review concludes that postpartum supplementation of vitamin A presents limited benefits (Oliveira-Menegozzo 2010). Other Cochrane reviews have examined the effects of vitamin A supplementation during pregnancy (van den Broek 2010), lactation (Gogia 2011), and in newborns (Gogia 2011; Haider 2011) on low birthweight infants' outcomes (Darlow 2011); long chain polyunsaturated fatty acids (LCPUFA) supplementation of breastfeeding mothers (Delgado-Noguera 2010); micronutrient supplementation for pregnant women has also been reviewed (Haider 2006).

Description of the intervention

Generally, B complex vitamin deficiency is partially caused by lack of meat and dairy in the diet. Infants born to mothers whose B vitamin status is inadequate are at high risk of developing a deficiency of these vitamins, because their stores are probably lower at birth and maternal breast milk concentrations are low (Allen 1994).

Thiamine (vitamin B1) deficiency, otherwise known as beri-beri, is characterised by myocardial alterations with congestive heart failure, oedema and peripheral neuritis. It is still relatively common (Harper 2006). Mothers with beri-beri produce breast milk low in vitamin B1, which results in infantile beri-beri as reported in Thailand among breast-fed infants receiving adequate amounts of milk from thiamine-deficient mothers (Thanangkul 1966). However, in mild cases, maternal supplementation with the vitamin increases milk concentration and reduces the risk of infantile thiamine deficiency (WHO 1999).

Riboflavin (vitamin B2) concentrations in breast milk are also sensitive to maternal riboflavin intake. In a study in rural Gambia measuring the riboflavin status in infants between birth and two years of age, infants born to riboflavin-deficient mothers were found to be deficient at birth, and remained so throughout suckling and weaning in comparison to a supplemented group. However, although riboflavin status fell within normal limits in the treatment group for the duration of the supplement, the vitamin levels rapidly deteriorated again once the supplement was withdrawn (Bates 1982). Maternal supplementation with riboflavin also improved clinical signs associated with riboflavin deficiency in the supplemented group reducing the mean activation coefficient (AC) of erythrocyte glutathione reductase from 1.62 to 1.19 within three weeks. Their breast milk riboflavin levels increased, and their infants' AC's were reduced, compared with those of the placebo group (Bates 1982a).

Niacin (vitamin B3) deficiency typically results in pellagra, which is characterised by dementia, dermatitis and diarrhoea (Prakash 2008). Deficiency of vitamin B3 is often interrelated with riboflavin and vitamin B6 deficiencies (WHO 2005), thus multiple-micronutrient supplementation is important. The recommended additional dose for lactating women is 2.4 mg Niacin Equivalents (NE)/day - 1.4 mg of niacin are secreted daily and 1 mg is needed for lactation energy expenditure (WHO 2005). Therefore, the total recommended nutrient intake (RNI) for lactating women is 17 mg/day (WHO 2005).

Vitamin B6 deficiency usually occurs in combination with other B-complex vitamins (McCormick 1988) therefore, multiple-micronutrient supplementation is necessary. Maternal vitamin B6 status was found to correlate strongly with infant behaviour among Egyptian mother-infant pairs. Infants of vitamin B6-deficient mothers were more irritable than infants from mothers with ad-

equate levels of vitamin B6 (McCullough 1990). Therefore, an additional 0.6 mg may be needed for lactating women (Botschel 1995), bringing the total RNI for this subpopulation to 2.0 mg/day (WHO 2005).

Although dietary vitamin B12 deficiency in infancy is rare, a few cases have been reported, most of whom are breast-fed infants of mothers who themselves are deficient in the vitamin (Citak 2011; Emery 1997; Weiss 2004). Clinical manifestations of vitamin B12 deficiency include the development of haematological, neurological and metabolic abnormalities in breast-fed infants of mothers, usually the presenting feature of maternal deficiency upon clinical investigation. In the case of a five month old breast-fed infant, deficiency was due to low vitamin B12 concentrations in the maternal breast milk and treatment of the infant with vitamin B12 resulted in a rapid clinical and haematological improvement (McPhee 1988). Similar recovery was also observed in other reported cases of vitamin B12 deficiency resulting from inadequate maternal intake (Citak 2011; Weiss 2004). The interaction of vitamin B12 with folate or folic acid may be important in the prevention of anaemia (WHO 2005).

Folic acid (folate) needs during lactation are increased due to the important role folate plays in DNA, RNA and protein biosynthesis (O'Connor 1997). Despite maternal intake not affecting concentrations in milk unless the maternal deficiency is severe, there may be consequences for the mother-infant pair which have not been sufficiently researched (O'Connor 1997). The RNI for lactating women is 500 μg/day (WHO 2005).

Vitamin C deficiency presents as scurvy (WHO 2005). The WHO recommends an extra 25 mg of vitamin C for lactating women due to 20 mg daily secretion and an absorption efficiency of 85% (WHO 2005). The total RNI to fulfil the needs of the mother-infant pair is 70 mg/day (WHO 2005).

Breast-fed infants are at high risk for vitamin D deficiency (Specker 1985). Milk content of vitamin D is not very responsive to increased maternal intakes (Picciano 2000). The WHO/FAO (Food and Agriculture Organization) joint report concluded that vitamin D supplementation is not necessary, however, it encourages good nutrition and sunshine exposure to mothers and infants (WHO 2005). Some authors found that vitamin D supplementation during lactation improved the status of mother and infant (Taylor 2003). The RNI for lactating women is 5 μg/day (WHO 2005). Generally, there are no specific recommendations for vitamin E supplementation in lactating women (SACN 2012) however, the Institute of Medicine's recommended dietary allowance (RDA) is 19 mg/day for lactating women up from 15 mg/day for non-lactating, non-pregnant women (SACN 2012).

Copper content in milk decreases throughout the course of lactation (Panel on Micronutrients 2001). Approximately 200 μg/day are secreted and the bioavailability is 65% to 70%. Therefore, an additional 300 μg/day would be needed to replace the copper secreted (Panel on Micronutrients 2001). This assumes there is no increase in copper absorption during lactation, however, animal studies suggest that efficiency of copper may increase. While the WHO/FAO have not set a RNI for copper, the Institutes of Medicine set the RDA at 1300 μg/day for lactating women, up 400 μg/day compared to non-lactating women (SACN 2012).

Selenium RNI for lactating women is 35 μg/day (with nought to six month old infants) and 42 μg/day (with seven to 12 month old infants) (WHO 2005).

Iodine concentration in breast milk is influenced by maternal status (Semba 2001). Infants receiving one third of the recommended 15 μg/kg/day are at risk of developing hyperthyrotropinaemia and brain damage; hypothyroidism leading to endemic cretinism may occur if iodine intake further decreases (WHO 2005). Concentrations of iodine and selenium in breast milk may respond to supplementation in chronically deficient populations (Allen 1994). An Australian study determined maternal and infant iodine status and breast milk iodine concentration over the first six months of breastfeeding. Breast milk iodine levels were found to be 1.3 times and 1.7 times higher in women supplemented with 75 μg I/d ($P = 0.030$) and 150 μg I/d ($P = 0.001$), respectively, than in women who received no supplementation (Mulrine 2010). The RNI for lactating women is 200 μg/day (WHO 2005).

Breast milk content of iron, copper and zinc with their physiological pattern of decline during lactation appear to be uninfluenced by maternal dietary intake making the mother especially vulnerable to depletion during lactation (Allen 1994). Observational studies have found no correlation between maternal mean dietary intake of zinc, copper, and iron with their concentrations in breast milk (Hannan 2009; Mahdavi 2010).

The nutritive demands of lactation are considerably greater than those of pregnancy (IOM 1991). In the first four to six months after birth, infants double their birthweight and lactation is viewed as successful when the fully breast-fed infant is growing well and maintaining appropriate biochemical indexes of nutritional status (Picciano 2003). It is generally assumed that the nutritional demands of lactation are directly proportional to the intensity and duration of breastfeeding and at nutrient intakes less than recommended, maternal intakes of some micronutrients are correspondingly low (Jensen 1995). Breast milk has been proven to be adequate as the sole source of nutrition up to age six months, providing that the maternal diet and reserves are adequate and a sufficient quantity is being transferred to the infant (Kramer 2004). However, measurable differences in milk nutrient content can and do occur due to dietary intake, especially in the vitamin constituents, particularly vitamin A and B (Picciano 2001). The nutritional requirements of the breastfeeding woman thus increase to support infant growth and development as well as maternal metabolism.

How the intervention might work

As highlighted above, lactation involves complex physiological changes associated with increased nutritional needs. Lactating mothers are more likely to suffer from micronutrient deficiencies

than from a shortage of dietary energy or protein. Also, micronutrient deficiencies are more likely to affect breast milk composition and consequently the development and nutritional status of the nursing infant. Micronutrient supplementation can increase the secretion of many of these nutrients in breast milk, and improve infant nutritional status (Allen 1994). Multiple-micronutrient deficiencies often coexist. There is an increased interest in evaluating the benefit of multiple-micronutrient supplements in breastfeeding women because it is possible that deficiencies in one nutrient may be a marker for other nutrient inadequacies. For example, an observational study in Indonesia showed that the micronutrient status of lactating mothers and that of their infants were closely related with deficiencies of vitamin A, iron and zinc occurring concurrently in both mother and infant (Dijkhuizen 2001). Improving intake on multiple nutrients may further enhance understanding of nutrient-nutrient interactions (Kuhena 1996).

Why it is important to do this review

The WHO recommends that infants be exclusively breast-fed for the first six months of life. This feeding strategy has the potential to reduce the risk of infections while benefiting infant health and survival as well as maternal health. Accompanying this recommendation is the emphasis on the importance of the nutritional status in lactating women (Kramer 2004). Lactation is a complex hormonally controlled anabolic state involving the redistribution of nutrients to the mammary glands for transfer to the infant (Picciano 2003). Micronutrients have a special role during lactation for maternal and infant health outcomes (Hermoso 2011). For example, vitamin D is necessary for healthy bone growth and the prevention of rickets and vitamin B6 (pyridoxine) is important for normal brain development and functioning of the central nervous system in infants. Therefore, maintaining adequate levels of essential nutrients in breast milk in lactating mothers is important. Despite this significance, the global status on the prevalence of micronutrient deficiency for various vitamins in lactating women is scarce. Additionally, the extent to which low intakes of micronutrients affect the success of lactation, maternal and infant health has not been sufficiently examined except when a distinct nutritional deficiency is evident in the nursing infant, for example, vitamin B6 (McCullough 1990) and riboflavin (Bates 1982a). Some studies and programs with the aim of improving mother's and infant's health focus on multiple-micronutrient supplementation of breastfeeding women. However, there are no consistent practices or recommendations. A systematic review of the current evidence regarding multiple-micronutrient supplementation for *practice and policy* is warranted.

OBJECTIVES

To evaluate the effects of multimicronutrient supplementation (excluding vitamin A) in breastfeeding mothers on maternal and infant outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All prospective randomised controlled trials evaluating multiple-micronutrient (excluding vitamin A) supplementation of breastfeeding mothers including individually-randomised or cluster-randomised trials, and multi-armed studies. Quasi-randomised trials and cross-over trials will be excluded.

Types of participants

Non-pregnant mothers who are exclusively feeding breast milk or practicing mixed feeding (breast milk and formula). HIV-positive women will be excluded from the review.

Types of interventions

Studies comparing the outcomes of supplementing breastfeeding women who are not pregnant with multiple-micronutrient supplements of three or more micronutrients (excluding vitamin A) compared with placebo, or no supplementation with two or less micronutrients irrespective of dosage of micronutrients. Trials that used less than three supplements in the intervention group will be excluded regardless of their outcome. There will be no limits on the duration of supplementation.

Types of outcome measures

Primary outcomes

Maternal

1. Morbidity (febrile illness, respiratory tract infection, diarrhoea)
2. Adverse effects of micronutrients within three days of receiving the supplement

Infant

1. Infant mortality
2. Child mortality

Secondary outcomes

Maternal

1. Anaemia
2. Satisfaction

Infant

1. Clinical micronutrient deficiency
2. Morbidity episodes (febrile illness, respiratory tract infection, diarrhoea, other)
3. Adverse effects of micronutrients within three days of receiving the supplement

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.

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.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors 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 will extract the 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 2011) 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 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 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 *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 summary risk ratio with 95% confidence intervals.

Continuous data

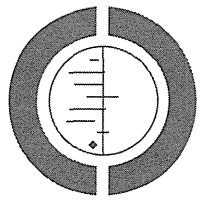
For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

High-dose versus low-dose oxytocin for augmentation of delayed labour (Review)

Kenyon S, Tokumasu H, Dowswell T, Pledge D, Mori R



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[Intervention Review]

High-dose versus low-dose oxytocin for augmentation of delayed labour

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ABSTRACT

Background

A major cause of failure to achieve spontaneous vaginal birth is delay in labour due to presumed inefficient uterine action. Oxytocin is given to increase contractions and high-dose regimens may potentially increase the number of spontaneous vaginal births, but as oxytocin can cause hyperstimulation of the uterus, there is a possibility of increased adverse events.

Objectives

To compare starting dose and increment dose of oxytocin for augmentation for women delayed in labour to determine whether augmentation by high-dose regimens of oxytocin improves labour outcomes and to examine the effect on both maternal/neonatal outcomes and women's birth experiences.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 May 2013) and reference lists of retrieved studies.

Selection criteria

We included all randomised and quasi-randomised controlled trials for women in delayed labour requiring augmentation by oxytocin comparing high-dose regimens (defined as starting dose and increment of equal to or more than 4 mU per minute) with 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-dose regimens is based on an arbitrary decision.

Data collection and analysis

Four review authors undertook assessment of trial eligibility, risk of bias, and data extraction independently.

Main results

We included four studies involving 644 pregnant women. Three studies were randomised controlled trials and one trial was a quasi-randomised study. A higher dose of oxytocin was associated with a significant reduction in length of labour reported from one trial (mean difference (MD) -3.50 hours 95% confidence interval (CI) -6.38 to -0.62; one trial, 40 women). There was a decrease in the rate of caesarean section (risk ratio (RR) 0.62; 95% CI 0.44 to 0.86 four trials, 644 women) and an increase in the rate of spontaneous vaginal birth in the high-dose group (RR 1.35; 95% CI 1.13 to 1.62, three trials, 444 women), although for both of these outcomes there were inconsistencies between studies in the size of effect. When we carried out sensitivity analysis (temporarily removing a study at high risk of bias) the differences between groups were no longer statistically significant

There were no significant differences between high- and low-dose regimens for instrumental vaginal birth, epidural analgesia, hyperstimulation, postpartum haemorrhage, chorioamnionitis or women's perceptions of experiences. For neonatal outcomes, there was no significant difference between groups for Apgar scores, umbilical cord pH, admission to special care baby unit, or neonatal mortality. The following outcomes were not evaluated in the included studies: perinatal mortality, uterine rupture, abnormal cardiotocography, women's pyrexia, dystocia and neonatal neurological morbidity.

Authors' conclusions

Higher-dose regimens of oxytocin (4 mU per minute or more) were associated with a reduction in the length of labour and in caesarean section, and an increase in spontaneous vaginal birth. However, there is insufficient evidence to recommend that high-dose regimens are advised routinely for women with delay in the first stage of labour. Further research should evaluate the effect of high-dose regimens of oxytocin for women delayed in labour and should include maternal and neonatal outcomes as well as the effects on women.

PLAIN LANGUAGE SUMMARY

Oxytocin in high versus low doses for augmentation of delayed labour

Women have different lengths of labour, with first labours lasting on average eight hours (and unlikely to last more than 18 hours) and second and subsequent labours lasting an average of five hours and unlikely to last more than 12 hours. Assessment of progress in labour takes into account not just cervical dilatation, but also descent and rotation of the fetal head and the strength, duration and frequency of contractions. Some evidence suggests that up to one-third of women in their first labour experience delay. They are often given a synthetic version of the hormone oxytocin to increase uterine contractions and shorten labour. Surprisingly for such a routine treatment, the ideal dose at which it should be given is not known, although some comparisons suggest that higher-dose regimens of oxytocin could shorten labour and reduce the chance of caesarean section with an increase in the numbers of women having a spontaneous vaginal birth compared with lower-dose regimens. However, there are potentially harmful side effects as oxytocin may cause the uterus to contract too quickly, and the baby to become distressed. Clinicians attempt to mitigate these side effects by adjusting the dose of oxytocin with the contractions to reduce the chances of the baby being distressed in labour.

From the four randomised controlled trials involving 644 pregnant women that we included in this review, results indicate that a higher dose of oxytocin (4-7 mU per minute, compared with 1-2 mU per minute) reduced the length of labour and the rate of caesarean sections with increased spontaneous vaginal births, but the studies did not provide enough evidence on possible differences between the high- and low-dose regimens on adverse events including hyperstimulation of the uterus, and outcomes for the newborn infant. Only one trial reported on the possible effect on women. The overall quality of the included trials was mixed, but this might reflect how clinical trials were reported in the past.

While the current evidence is promising and suggests that the high-dose regimens reduce the length of labour and the rate of caesarean sections, this evidence is not strong enough to recommend that high-dose regimens are used routinely for women delayed in labour. We recommend that further research is carried out.