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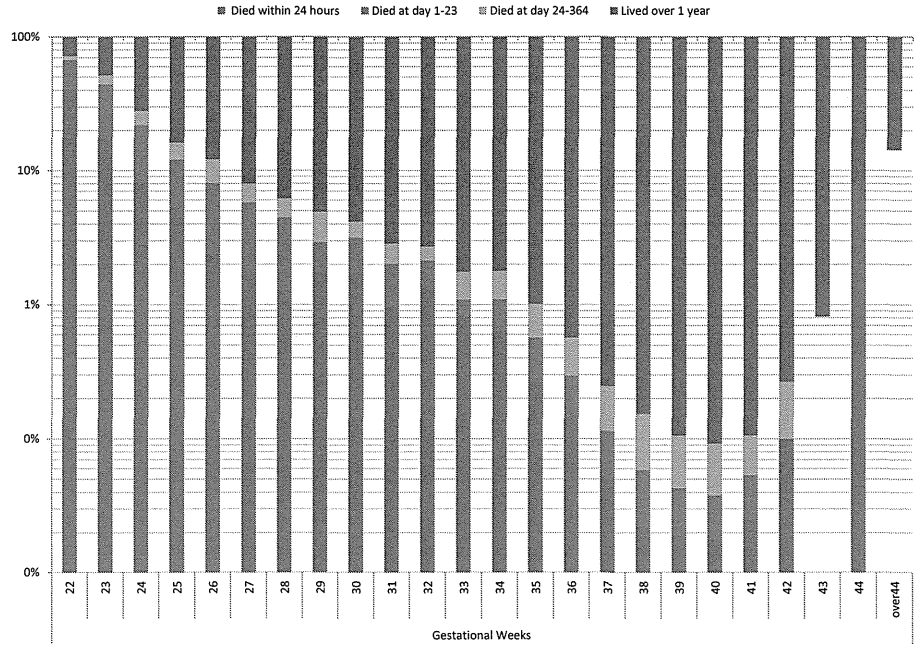
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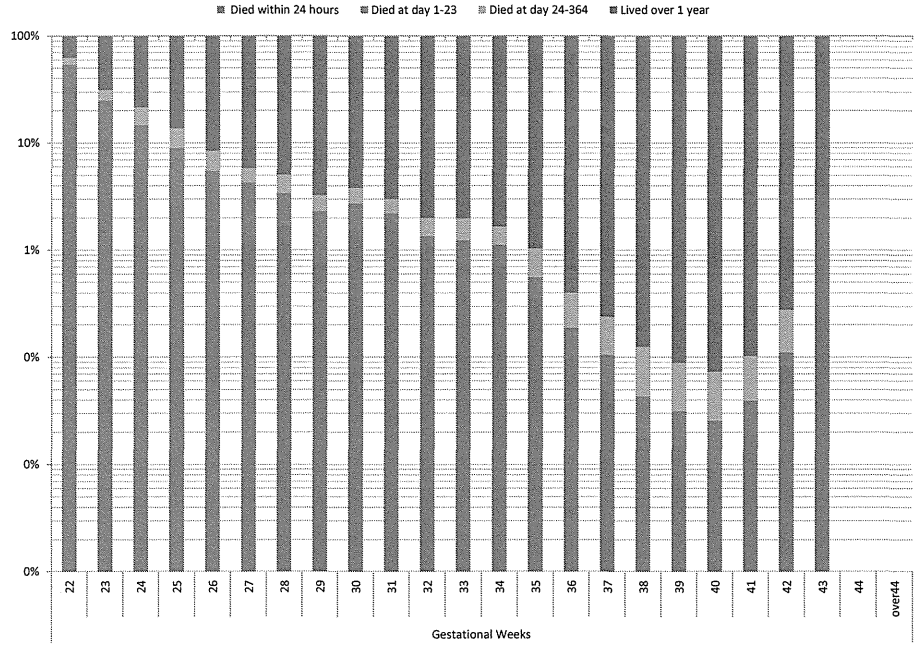
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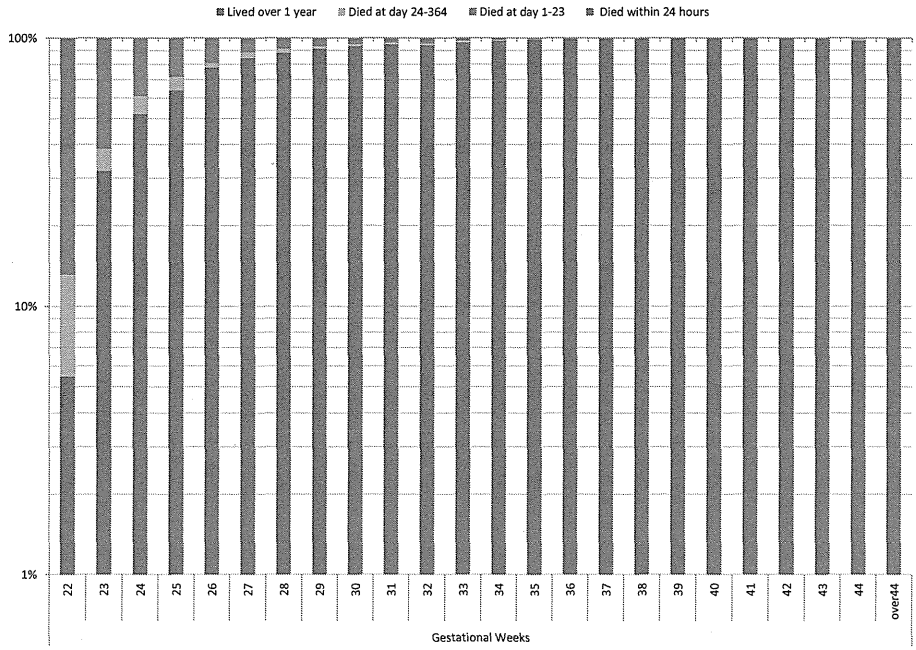
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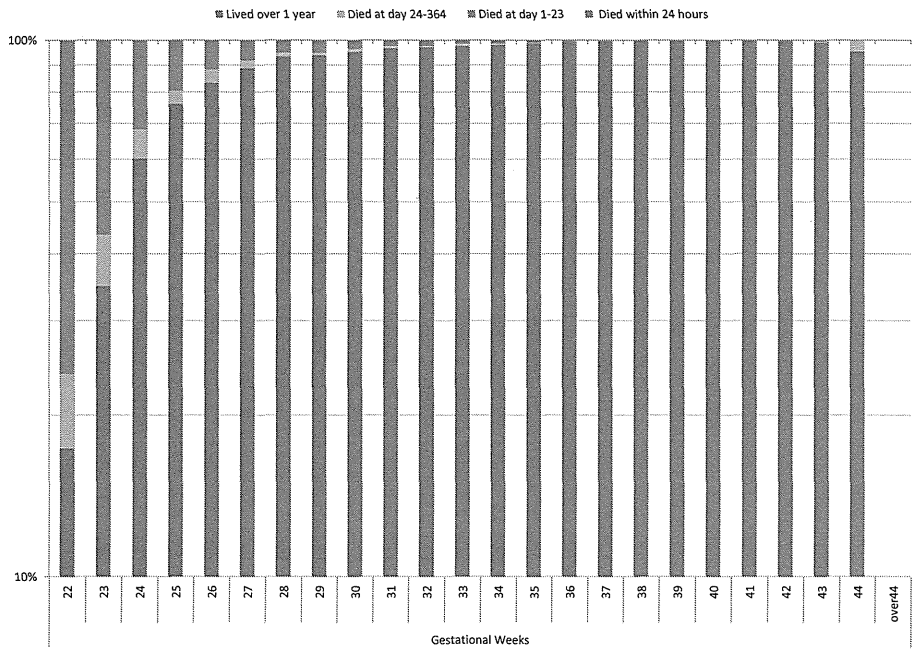
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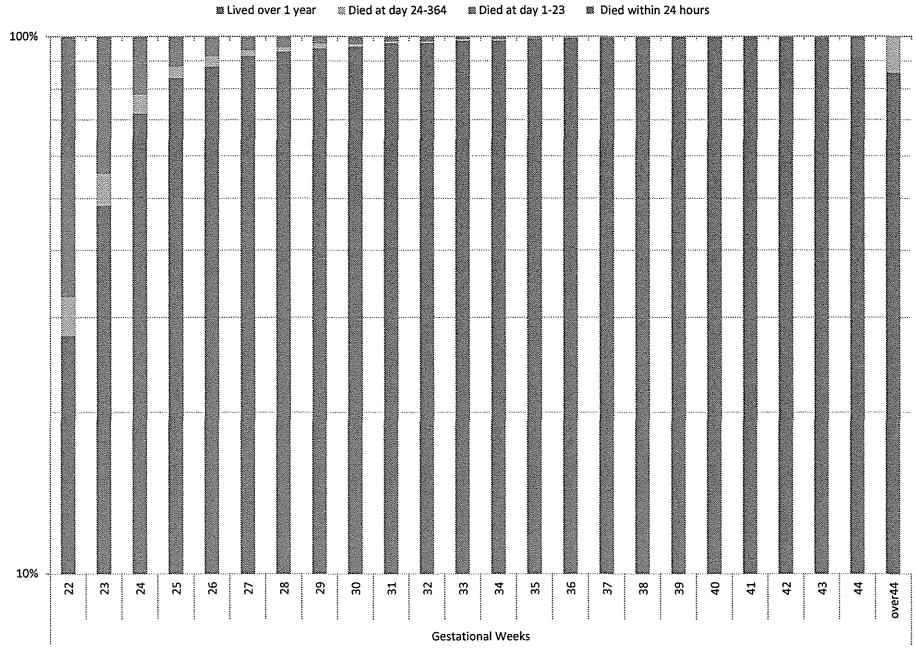
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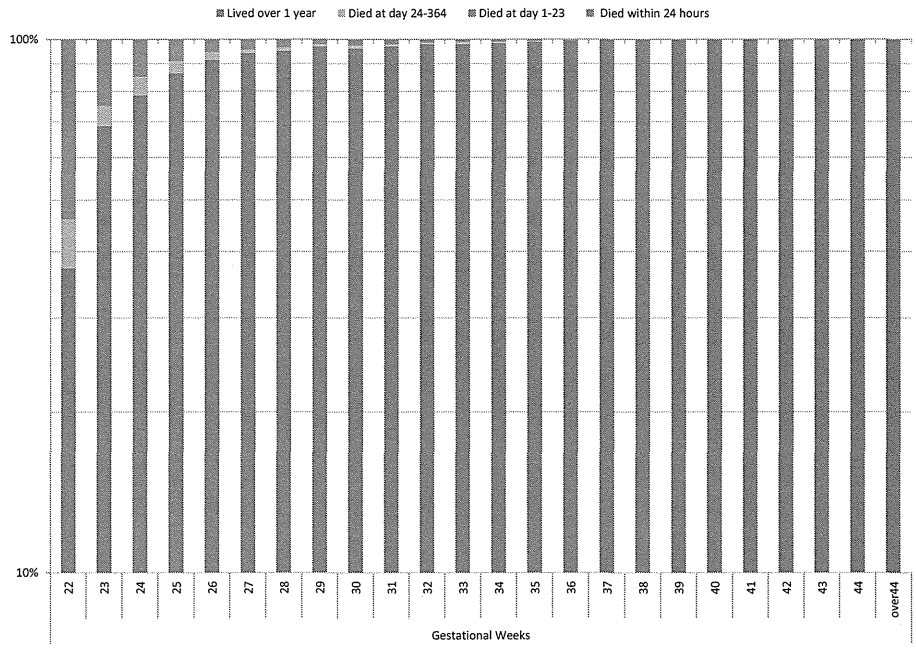
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Gestational Weeks

研究成果の刊行に関する一覧表

書籍

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
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雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Methods for administering subcutaneous heparin during pregnancy (Protocol)

Sasaki H, Yonemoto N, Mori R

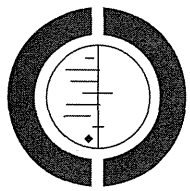

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TABLE OF CONTENTS

[Intervention Protocol]

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

BACKGROUND

Description of the condition

The true incidence of thromboembolism (VTE) associated with pregnancy is unknown, yet there is a strong clinical indication of an increased risk when compared to non-pregnant individuals (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 2008).

The main reason for the increased risk of VTE in pregnancy is the hypercoagulability that occurs which protects women from haemorrhaging at the time of miscarriage or childbirth (James 2009). In developing countries, 20% to 34% of maternal mortality is due to haemorrhaging, while approximately 15% of maternal deaths in developed countries result from a pulmonary embolism (PE) (Khan 2006). Other risk factors for VTE in pregnancy include thrombophilia (an acquired or inherited tendency to develop thrombosis), a history of thrombosis, and antiphospholipid syndrome (a coagulation disorder that causes thrombosis in both arteries and veins) (James 2006). Acquired risk determinates include being aged over 35 years old, obesity, having a delivery by caesarean section, and a personal or family history of VTE (Bauersachs 2007).

Pregnancy leads to a temporary but more than three-fold increase in the risk of recurrent thrombosis compared to its occurrence among non-pregnant women (Pabinger 2002). Those women who develop VTE during their pregnancies require heparin (unfractionated heparin (UFH) or low-molecular weight heparin (LMWH)) as a treatment. Once they have passed through the treatment period, the dose or regimen will switch to a level that is necessary for prevention. Pregnant women requiring heparin prophylaxis are those with a history of VTE, antithrombin deficiency, and other risk factors for VTE such as a high-risk pregnancy.

VTE includes DVT (deep vein thrombosis) and PE. DVT is the result of an occlusive clot formation in the deep veins of the leg, from which parts of the clot frequently embolize to the lungs (PE) (Fauci 2008). From 75% to 80% of pregnancy-associated VTE comes in the form of DVT, while 20% to 25% is PE (James 2009). DVT and PE are life-threatening for both mother and fetus. Although maternal mortality from PE can be reduced by conducting a clinical investigation among symptomatic women and by treatment or prevention 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 treatment or prevention may be inconvenient and painful for patients. 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 PE, such as dyspnoea, pleuritic chest pain, cough, and haemoptysis, are non-specific. 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 also 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 patients (Ginsberg 1998).

The classic gold standard for diagnosing PE is pulmonary angiography, which is an invasive method requiring expertise. Hence, similar to the developments that have occurred in the diagnosis of DVT, two (complementary) strategies have evolved. The first is the combination of the assessment of clinical probability (outcome) and the measurement of the D-dimer blood level; the second is the introduction of spiral CT of the chest. As regards DVT, ultrasonography with non-compressibility of the vein as the sole criterion has largely replaced contrast venography. This method has a very high sensitivity and specificity (95% to 100%) in symptomatic patients for proximal DVT (Fauci 2008). Compression ultrasonography carries no risk and is the preferred test in pregnant patients with suspected venous thromboembolism. Magnetic resonance imaging (MRI) also does not involve radiation exposure and is not harmful to the fetus. Unlike either ultrasonography or MRI, CT scanning is associated with fetal radiation exposure (Marik 2008).

Description of the intervention

UFH and LMWH are usually administered subcutaneously or intravenously for prophylaxis and treatment. These are the anticoagulant of choice during pregnancy, due to their established efficacy (Bates 2004) which has been demonstrated in pregnant women with DVT (Fauci 2008). Unlike other anticoagulants including vitamin K antagonists, warfarin and aspirin, 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). How-

ever, bone density was significantly lower in those receiving UFH compared with both those who were not treated and those who received delteparin (LMWH) (Montreal 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). Even though the risk of severe adverse pregnancy outcomes is low, the use of subcutaneous heparin during pregnancy may cause pain, urticarial reaction, infection, and bruising due to repeated and long-term injections.

Heparin administration increases adverse pregnancy outcomes in women at risk. Women with thrombophilia are at a high risk of fetal loss, intrauterine growth restriction (IUGR), pre-eclampsia, placental abruption, and intrauterine death. Administering a combination of UFH and aspirin in women with thrombophilia has been shown to be effective for miscarriage compared with aspirin alone (Kutteh 1996; Rai 1997). The risk of thromboembolic complications in women with mechanical heart valves receiving heparin has varied across studies. Some studies (Al-Lawati 2002; Gedalia 2005) have reported that there are fewer thromboembolic events among women receiving warfarin than in those treated with UFH, while other research (Nasser 2004) has reported conflicting results. The risk of maternal bleeding, congenital malformations, and fetal loss has been also reported in this high risk group (Bates 2008).

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 patients. With these low doses, it is unnecessary to monitor coagulation, but monitoring is required when it is given for treatment (Fauci 2008). 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 heparin 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; Rey 2000), and an adjusted dose of LMWH to achieve a peak anti-Xa level of 0.2 to 0.4 U/ml (Dahlman 1996; Blomback 1998).

Rey 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 (aPPT) is not significantly elevated, while prophylaxis with low-dose anticoagulation is recommended for pregnant women with a history of thrombosis (Bates 2004).

One study (Andersen 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 the 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 aPPT between the two methods of heparin administration. The study also used a questionnaire to obtain information from patients 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 patients 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 to 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 heparinization (mean aPTT, 20.6 versus 10.6 seconds above control) among the subcutaneous infusion pump group when compared to the intermittent subcutaneous injection group. There were two complications (hematoma, 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 treatment to be more evenly controlled than did the use of intermittent subcutaneous

injections.

How the intervention might work

Heparin 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, which can develop into a DVT or PE.

Why it is important to do this review

Women requiring heparin during pregnancy, especially those with a history of VTE who are likely to be on lifelong anticoagulation, will require a switch from the administration of warfarin to heparin-related compounds (James 2007) when conception has occurred and been detected, because of the effects of warfarin on *the fetus. Although administering subcutaneous heparin (UFH* or LMWH) is the main option in the prevention of VTE during pregnancy, until now the management of thromboprophylaxis in pregnant women has mostly relied on the evidence from non-pregnant patients. Because of the discomfort and side effects due to repeated and long-term injections, some women discontinue administering heparin (UFH or LMWH) subcutaneously. Others may not self-administer heparin and must rely on others to give them their injections or else they discontinue the administration, thus exposing themselves to an increased risk of VTE (Anderson 1993). Women's satisfaction while administering subcutaneous heparin (UFH or LMWH) is highly important, since the effectiveness and safety of administering subcutaneous heparin 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 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 will include all randomized controlled trials (individual and clustered) investigating methods for administering subcutaneous heparin (UFH or LMWH) during pregnancy. We will also include studies that have been reported only as abstracts but indicate that they are studies awaiting assessment, pending the full publication of their results. We will exclude quasi-randomized studies and crossover trials.

Types of participants

Participants will be women requiring heparin (UFH or LMWH) during pregnancy. We will not include 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 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. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

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

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

Searching other resources

(1) References from published studies

We will search the reference lists of relevant trials and reviews identified.

(2) Unpublished literature

If necessary, we will contact the authors for more details about the published trials/ongoing trials.

We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors will independently assess the inclusion of 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 the third review author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult an additional review author. We will enter data into the Review Manager software (RevMan 2008) 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 the risk of bias for each study, as well as for cluster-randomized and crossover trials separately 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 an additional 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) or;
- unclear risk of bias.

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

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

We will assess the methods as:

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

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

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

We will assess the methods as:

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

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

We will describe for each included study the methods used, if any, to blind *outcome assessors from knowledge of which intervention*

a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used *to blind outcome assessment* as:

- low, high or unclear risk of bias.

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

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

We will assess methods as:

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

(5) Selective reporting (checking for reporting bias)

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

We will assess the methods as:

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

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

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

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

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

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the 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 standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We will include cluster-randomized trials in the analyses, along with individually randomized trials and crossover trials. We will adjust their sample sizes using the methods described in the *Handbook* (Higgins 2011), using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both, if there is little heterogeneity between the study designs and an interaction between the effect of the intervention and the choice of the randomization unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomization unit and perform a separate meta-analysis.

Dealing with missing data

For included studies, we will note the levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of the treatment effect by 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 randomized to each group in the analyses, and all participants will be analyzed 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 randomized 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, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out a statistical analysis using the Review Manager software (RevMan 2008). We will use a fixed-effect model for combining data where trials are examining the same intervention, and the trial's populations and methods are judged sufficiently similar. We will weight effect estimates by the inverse of their variance, giving greater weight to larger trials. If we suspect clinical or methodological heterogeneity between treatment effects, we will use a random-effects model. We will carry out meta-analysis by study type (randomized trial, cluster-randomized trial).
If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.
If possible, we plan to carry out subgroup analyses for the primary outcomes and secondary outcomes as follows.

1. Type of heparin (UFH versus LMWH)
2. Previous VTE during pregnancy
3. A family history of VTE
4. Thrombophilia
5. Other risk factors (e.g. age, obesity, antiphospholipid syndrome)

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the effect of trial quality for important outcomes in the review. If there is a risk of bias associated with a particular aspect of study quality (e.g. allocation concealment), we will explore this by sensitivity analysis. We will use primary and secondary outcomes in the sensitivity analysis.

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* *Indicates the major publication for the study*

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DECLARATIONS OF INTEREST

None known.

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

Review information

Review number: 0707

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What's new

Date	Event	Description

History

Date	Event	Description

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) (Elchalal 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 (Bosch 2001; Leye 2006), 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 98%, 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 2006). 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 (Acuguia 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 (McCafrey 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; McCafrey 1995; Rouzi 2001; Rushwan 2009; 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.

Contributions of authors

Olukunmi Balogun with contribution from Ai Koyanagi wrote the first draft of the protocol. Fumi Hirayama, Ai Koyanag, Windy MV Wariki and Rintaro Mori commented on the draft. Windy MV Wariki and Rintaro Mori provided editorial assistance.

Fumi Hirayama worked with Olukunmi Balogun to produce the second draft of the protocol.

All review authors were involved in subsequent modifications and writing of the full review.

Declarations of interest

None known.

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

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Other published versions of this review

Classification pending references

Data and analyses

Figures

Sources of support

Internal sources

- The University of Tokyo, Japan

External sources

- Ministry of Health, Labour and Welfare, Japan

Feedback

Appendices

1 Methods of Data collection and analysis to be used in future updates of this review

Data collection and analysis

Selection of studies

At least 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. If agreement cannot be reached, we would consult a third party.

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. 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) 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 the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as:

- 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 through withdrawals, dropouts, protocol deviations)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total 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. less than 20% 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 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 sources of bias

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

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

(7) Overall risk of bias

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

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

Unit of analysis will be individual women. We will consider cluster-randomised trials if they are identified.

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions Section 16.3.4* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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

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 the I^2 is greater than 30% and either the 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, and use formal tests for funnel plot asymmetry. For continuous outcomes, we will use the test proposed by Egger 1997, and for dichotomous outcomes, we will use the test proposed by Harbord 2006. *If asymmetry is detected in any of these tests or 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.

Subgroup analysis and investigation of heterogeneity

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

We plan to carry out the following subgroup analyses.

- Type I and type II genital cutting.
- Type II and type III genital cutting.
- Type I and type III genital cutting.

The following outcomes will be used in subgroup analysis.

- The need for perineal surgery at birth.
- Incidence of perineal lacerations at birth.
- Psychological disorders.

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

Strategies of testing for syphilis during pregnancy

Review information

Review number: 0683

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Protocol First Published:	Issue 2 , 2013
Review First Published:	Not specified
Last Citation Issue:	Issue 2 , 2013

What's new

Date	Event	Description

History

Date	Event	Description

Abstract

Background

Objectives

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (6 February 2013) and reference lists of retrieved studies.

Selection criteria

Data collection and analysis

Main results

Authors' conclusions

Plain language summary

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 2008; 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; Fann 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 (Hannah 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 (Fears 2001; Lien 2000). 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 contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (6 February 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 checked the studies cited in relevant review articles.

We did 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 co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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.

Subgroup analysis and investigation of heterogeneity

When data are available or appropriate, we plan to carry out the following subgroup analyses.

1. Low-income versus middle-income countries.
2. Study settings, i.e. antenatal clinics versus other healthcare facilities.
3. HIV/AIDs infection status of the pregnant women and neonates.
4. Syphilis screening strategies including HIV/AIDs versus without HIV/AIDs screening.

The following outcomes will be used in subgroup analysis.

- Perinatal mortality.
- Coverage of different syphilis screening tests.
- Obstacles/challenges in the uptake of antenatal syphilis screening tests.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2011). We will report the results of subgroup analyses quoting the χ^2 statistic and p-value, and the interaction test I^2 value.

Sensitivity analysis

Sensitivity analyses will be performed to assess the risk of bias effects (trials with low or unclear sequence generation and allocation concealment and either high levels of attrition or inadequate blinding) on the analyses. If any cluster-randomised trials are identified and included, sensitivity analysis using a range of ICC values will be carried out. We will carry out sensitivity analysis for primary outcomes only.

Results

Description of studies

Results of the search

The search of the Pregnancy and Childbirth Group's Trials Register retrieved three reports (Figure 1).

Included studies

Excluded studies

Risk of bias in included studies

Allocation (selection bias)

Blinding (performance bias and detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other potential sources of bias

Effects of interventions

Discussion

Authors' conclusions

Implications for practice

Implications for research

Acknowledgements

We are thankful for the support provided by the Cochrane Pregnancy and Childbirth group during the protocol development process.

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

Contributions of authors

Sadequa Shahrook drafted the protocol with advice from Rintaro Mori, Tumendemberel Ochirbat and Harumi Gomi assisted in drafting the protocol.

Declarations of interest

None known.

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Munkhuu 2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Myer 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Rotchford 2000

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Excluded studies

Studies awaiting classification

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Ongoing studies

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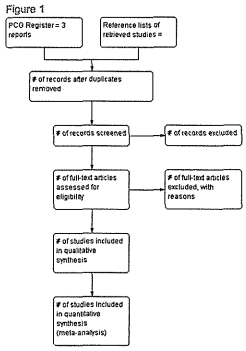
Classification pending references

Data and analyses

Figures

Figure 1



Caption

Study flow diagram.

Sources of support

Internal sources

- National Center for Child Health and Development, Japan

External sources

- Ministry of Health, Labour and Welfare, Japan

Feedback

Appendices

Hydralazine in infants with persistent hypoxemic respiratory failure

Review information

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What's new

Date	Event	Description

History

Date	Event	Description

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; Bancalari 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 (Tomashefski 1984; Bush 1990; Hislop 1990; 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 (Khemani 2007; An 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 1998; 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; Ostrea 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; Ostrea 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 (Fiuush 1987). 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; Zuppa 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; Sleenick 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

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 the treatment period. Their primary and secondary outcomes were unclear from the abstract, and also they did not report mortality at 36 weeks' PMA, at hospital discharge, and at 18 and 36 months of age in either study group. RPET/RVET and AcT/RVET were calculated by echocardiogram and reported for the evaluation of PAH (Kosturakis 1984), but it was not presented with the data that we defined as PAH. Tidal volume, airway pressure, end-tidal PO_2 and PCO_2, dynamic compliance, total resistance,

alveolar ventilation, and venous admixture were measured by pulmonary function test, but data were not presented in the abstract. They reported that AcT/RVET increased significantly with hydralazine, but other parameters were not different significantly between two groups; AcT/RVET increased from 0.18 to 0.23 (P = 0.01; only mean was presented), RPEP/RVET decreased from 0.32 to 0.27 (P = 0.07; only mean was presented). Four patients were extubated during the trial. They concluded that hydralazine did not cause hypoxaemia and did increase mix venous saturation, but again they did not report

the exact data for them. There were no data reported on neurodevelopment assessment, length of hospitalisation, length of ventilation, length of oxygen supplementation, or adverse events.

Goodman 1988: Goodman studied the effects of oxygen and hydralazine on 15 infants with BPD and PAH in a well-organised non-controlled prospective manner. The haemodynamic responses to oxygen and hydralazine (0.3 mg/kg, via intravenous injection) were evaluated by cardiac catheterization. Five patients developed normal pulmonary artery pressure while receiving supplemental oxygen and were not studied further. Of the remaining 10 patients, the six patients with large, haemodynamically significant collateral vessels all had haemodynamically or clinically deleterious reactions to hydralazine. Two of the four patients without collateral pulmonary circulation responded to hydralazine with further reductions in mean pulmonary artery pressure to normal levels.

Martin 1991: Martin studied the effects of hydralazine for the cardiac performance in 23 infants with systemic hypertension undergoing extracorporeal membrane oxygenation (ECMO). Patients were divided into hypertensive group or normotensive group (40 mmHg < mean arterial pressure < 60 mmHg), and several parameters were measured on echocardiogram. The study was excluded because it was conducted in infants with respiratory failure on ECMO and did not address whether these infants were LBW or had CLD.

Ongoing studies

A search of PubMed, ClinicalTrials.gov, and the Clinical Trials Search Portal of the World Health Organization revealed no protocols or ongoing trials on our targeted patient group.

Risk of bias in included studies

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

Effects of interventions

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

Discussion

We found no studies that met our inclusion criteria for this review. Consequently, the review found no RCTs that addressed the use of hydralazine for LBW infant with persistent hypoxemic failure. Therefore, we could not establish if hydralazine treatment reduces mortality or neurodevelopmental impairment in our targeted patients.

Hydralazine has been used for the treatment of a variety of conditions. 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 benefits (Frvath 1997). Despite the benefits of hydralazine in hypertensive crisis and some other conditions (pre-eclampsia/eclampsia or chronic heart disease), it has not been widely used in PAH related to CLD. Following a comprehensive literature search, few clinical studies were identified that examined the effect of hydralazine in the management of PAH with CLD (Thompson 1986; Goodman 1988).

In infants with PAH related to CLD, Thompson (Thompson 1986) demonstrated that hydralazine administration may have potential benefit in PAH without causing hypoxia and haemodynamic instability. They alleged that pulmonary hypertension was improved with hydralazine by using data of RPEP/RVET and AcT/RVET (Kosturakis 1984). In this study, pulmonary function and mixed venous saturation were measured at the same time in order to demonstrate that no haemodynamic instability and complications occurred with hydralazine administration. But there are several potential limitations to this trial. First, only the abstract was obtained, so several points were unclear especially on the methodology. Although the patients' characteristics matched our protocol criteria in terms of prematurity (body weight (mean; 910 ± 200 g), gestational age (mean; 27 ± 2 weeks), and oxygen requirement (FiO_2; 0.57 ± 0.12)), they did not report their exact definition of BPD and

PAH, as well as other patient characteristics such as vital signs, medication used, and patients' oxygenation status. Second, even though the design of the trial was blind and cross-over manner, the number of the included patients was very small, and it was unclear if it was randomised or not. So strong selection bias need to be considered in this trial. Finally, they did not report any concrete data showing if there was any difference in pulmonary function test before and after hydralazine administration.

No other prospective controlled trials have been published on the use of hydralazine to treat PAH related to CLD. Moreover, only a few non-controlled trials are available, one of which showed potential adverse effects of hydralazine especially for the patients with pulmonary collateral shunt (Goodman 1988).

Although the studies suggested an potential improvement in PAH following infusion of hydralazine, there is no evidence from RCTs to support its use. Given the absence of evidence, hydralazine cannot be recommended as a treatment for PAH related to CLD. But since hydralazine is inexpensive and potentially beneficial for the patients group, RCTs are recommended. But such trials have to be carried out in settings where other treatments are not available, such as sildenafil, iNO, or extracorporeal life support, which are currently accepted in wealthy developed countries for the treatment of PAH, with careful monitoring of haemodynamics and complications.

Authors' conclusions

Implications for practice

There is insufficient evidence to determine the safety and efficacy of hydralazine in LBW infants with persistent hypoxemic respiratory failure.

Implications for research

A controlled clinical trial suggested a potential benefit of hydralazine in infants with persistent hypoxemic respiratory failure related to PAH and evolving CLD. Since hydralazine is inexpensive and potentially beneficial, RCTs are recommended. Such trials could be carried out in settings where other treatments such as sildenafil, iNO, or extracorporeal life support are not available, with careful monitoring of haemodynamics and complications.

Acknowledgements

None.

Contributions of authors

Kawaguchi, Atsushi: conceptualised the review and protocol, literature search, reviewing the identified papers data extraction, drafting the manuscript.

Mori, Rintaro: contributed to design of the review and commented on the manuscript.

Isayama, Tetsuya: contributed to literature search, review of the identified papers, and data extraction.

Tamura, Masonori: commented on the manuscript.

Minami, Hirotaka: commented on the manuscript.

Yang, Ying: commented on the manuscript.

Declarations of interest

None.

Differences between protocol and review

None.

Published notes

Characteristics of studies

Characteristics of included studies

Footnotes

Characteristics of excluded studies

Thompson 1986

Reason for exclusion	Quasi-RCT that met the participants and intervention criteria; however, the study was excluded because we could not obtain adequate details regarding study design or relevant clinical outcomes

Goodman 1988

Reason for exclusion	This was a well-organised prospective study that evaluated the effects of oxygen and hydralazine to 15 BPD infants with pulmonary hypertension; however, intervention was not assigned in a random or quasi-random fashion

Martin 1991

Reason for exclusion	Studies the effects of hydralazine for systemic blood pressure in extracorporeal membrane oxygenation patients; no relevant outcomes were reported

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Excluded studies

Goodman 1988

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Classification pending references

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Figures

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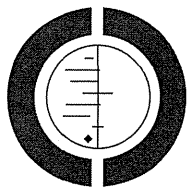
Feedback

Appendices

Antibiotics for treating lower urinary tract infection in children (Review)

Fitzgerald A, Mori R, Lakhanpaul M, Tullus K



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[Intervention Review]

Antibiotics for treating lower urinary tract infection in children

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ABSTRACT

Background

Urinary tract infection (UTI) is one of the most common bacterial infections in infants and children. Lower UTI is the most commonly presenting and in the majority of cases can be easily treated with a course of antibiotic therapy with no further complications. A number of antimicrobials have been used to treat children with lower UTIs; however is it unclear what are the specific benefits and harms of such treatments.

Objectives

This review aims to summarise the benefits and harms of antibiotics for treating lower UTI in children.

Search methods

We searched the Renal Group's Specialised Register (April 2012), CENTRAL (*The Cochrane Library* 2012, Issue 5), MEDLINE OVID SP (from 1966), and EMBASE OVID SP (from 1988) without language restriction.

Date of last search: May 2012.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs in which antibiotic therapy was used to treat bacteriologically proven, symptomatic, lower UTI in children aged zero to 18 years in primary and community healthcare settings were included.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as risk ratios (RR) with 95% confidence intervals (CI).

Main results

Sixteen RCTs, analysing 1,116 children were included. Conventional 10-day antibiotic treatment significantly increased the number of children free of persistent bacteriuria compared to single-dose therapy (6 studies, 228 children: RR 2.01, 95%CI 1.06 to 3.80). No heterogeneity was observed. Persistent bacteriuria at the end of treatment was reported in 24% of children receiving single-dose therapy compared to 10% of children who were randomised to 10-day therapy. There were no significant differences between groups for persistent symptoms, recurrence following treatment, or re-infection following treatment. There was insufficient data to analyse the effect of antibiotics on renal parenchymal damage, compliance, development of resistant organisms or adverse events. Despite the inclusion of 16 RCTs, methodological weakness and small sample sizes made it difficult to conclude if any of the included antibiotics or regimens were superior to another.

Authors' conclusions

Although antibiotic treatment is effective for children with UTI, there are insufficient data to answer the question of which type of antibiotic or which duration is most effective to treat symptomatic lower UTI. This review found that 10-day antibiotic treatment is more likely to eliminate bacteria from the urine than single-dose treatments. No differences were observed for persistent bacteriuria, recurrence or re-infection between short and long-course antibiotics where the antibiotic differed between groups. This data adds to an existing Cochrane review comparing short and long-course treatment of the same antibiotic who also reported no evidence of difference between short and long-course antibiotics.

PLAIN LANGUAGE SUMMARY

Antibiotics for lower urinary tract infection in children

Urinary tract infection (UTI) is one of the most common bacterial infections in infants and children. The most commonly presenting infection of the urinary tract is known as cystitis and in the majority of cases can be easily treated with a course of antibiotic therapy with no further complications. This review identified 16 studies investigating antibiotics for UTI in children. Results suggest that 10-day antibiotic treatment is more likely to eliminate bacteria from the urine than single-dose treatments; there was not enough data to draw conclusions about other treatment durations, or effectiveness of particular antibiotics. Although antibiotic treatment is effective for children with UTI, there are insufficient data to recommend any specific regimen.