POSTPARTUM ANTIBIOTICS FOR INTRAPARTUM CHORIOAMNIONITIS: SYSTEMATIC REVIEW

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Health Development
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ทบทวนวรรณกรรมอย่างเป็นระบบ: การใช้ยาปฏิชีวนะในระยะหลังคลอด เพื่อรักษาภาวะการติดเชื้อของรกและน้ำคร่ำที่เกิดขึ้นในระยะรอคลอด

พันโทหญิงพีระพรรณ พันธุ์ภักดีคุณ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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พีระพรรณ พันธุ์ภักดีคุณ : ทบทวนวรรณกรรมอย่างเป็นระบบ: การใช้ยาปฏิชีวนะในระยะหลังคลอดเพื่อรักษาภาวะการติดเชื้อของรกและน้ำคร่ำที่เกิดขึ้นในระยะรอคลอด. (POSTPARTUM ANTIBIOTICS FOR INTRAPARTUM CHORIOAMNIONITIS: SYSTEMATIC REVIEW) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ.นพ.สุรสิทธ์ ชัยทองวงศ์วัฒนา, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ศ.นพ.ภิเศก ลุมพิกานนท์, 39 หน้า.

ที่มา: ภาวะการติดเชื้อของรกและน้ำคร่ำก่อให้เกิดความทุพพลภาพของมารดาและการติดเชื้อของทารก ตลอดจนเป็นสาเหตุการตาย แต่ยังไม่มีข้อตกลงที่ชัดเจนถึงยาปฏิชีวนะที่ใช้รักษาและระยะเวลาที่เหมาะสมในการให้ยาต่อเนื่องหลังคลอด

จุดประสงค์: เพื่อทบทวนวรรณกรรมอย่างเป็นระบบ ถึงประสิทธิภาพของยาปฏิชีวนะที่ใช้รักษาภาวการณ์ติดเชื้อของรกและน้ำคร่ำในระยะหลังคลอด ที่มีต่อความทุพพลภาพและการตายของมารดา รวมทั้งผลข้างเคียงจากยา

วิธีการทบทวนวรรณกรรม สืบค้นงานวิจัยทางคลินิกชนิดสุ่มตัวอย่างและชนิดกึ่งสุ่มตัวอย่างจากฐานข้อมูล MEDLINE, SCOPUS และ The Cochrane Central Register of Controlled Trial (CENTRAL) ซึ่งทำการศึกษาในมารดาที่ได้รับการวินิจฉัยว่ามีการติดเชื้อของรกและน้ำคร่ำในระยะรอคลอด โดยเปรียบเทียบผลของการรักษาในระยะหลังคลอดด้วยยาปฏิชีวนะกับการรักษาด้วยยาปฏิชีวนะต่างวิธีหรือยาหลอกที่มีต่อภาวะทุพพลภาพของมารดา โดยผู้ทบทวนวรรณกรรม 2 คนพิจารณาแยกกันว่างานวิจัยใดมีลักษณะเข้าได้กับข้อกำหนด ส่วนคุณภาพของงานวิจัยและการนำข้อมูลในงานวิจัยมาวิเคราะห์ทำโดยผู้ทบทวนวรรณกรรม 1 คน และใช้ Review Manager Software (RevMan 2004) ในการวิเคราะห์ทางสถิติ

ผลการศึกษา พบงานวิจัย 3 เรื่องที่มีลักษณะของงานวิจัยเข้าได้กับข้อกำหนด โดยมีผู้ป่วยรวมทั้งสิ้น 517 คน เมื่อทำ meta-analysis งานวิจัย 2 เรื่องที่ศึกษาเปรียบเทียบการรักษาด้วยยาปฏิชีวนะ 1 ครั้งหลังคลอดกับการให้ยาปฏิชีวนะหลายครั้งจนกว่าผู้ป่วยจะไม่มีไข้ พบว่าความล้มเหลวจากการรักษาด้วยวิธีทั้งสองไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (RR 1.78, CI 0.72, 4.40)

ข้อสรุปของผู้ทบทวนวรรณกรรม จากการทบทวนวรรณกรรมนี้ ไม่สามารถให้ข้อแนะนำถึงวิธีการและชนิดของยาปฏิชีวนะที่เหมาะสมซึ่งให้ต่อในระยะหลังคลอด สำหรับมารดาที่มีภาวะการติดเชื้อของรกและน้ำคร่ำในขณะรอคลอด เนื่องจากจำนวนงานวิจัยที่รวบรวมมาวิเคราะห์มีจำนวนน้อยเกินไป

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต.....

ปีการศึกษา 2550 ลายมือชื่ออาจารย์ที่ปรึกษาวิทยานิพนธ์หลัก.....

ลายมือชื่ออาจารย์ที่ปรึกษาวิทยานิพนธ์ร่วม.....

497 50049 30: MAJOR HEALTH DEVELOPMENT

KEY WORD: CHORIOAMNIONITIS/ POSTPARTUM ANTIBIOTICS/ SYSTEMATIC REVIEW

PEERAPUM PUNPUCKDEEKOON: POSTPARTUM ANTIBIOTICS FOR INTRAPARTUM CHORIOAMNIONITIS: SYSTEMATIC REVIEW. THESIS PRINCIPAL ADVISOR: ASSOC. PROF. SURASITH CHAITHONGWONGWATTHANA, THESIS CO-ADVISOR: PROF. PISAKE LUMBIGANON, 39 pp.

Background: Chorioamnionitis is associated with maternal morbidity and neonatal sepsis and death. There is no clear consensus on the most appropriate antibiotics regarding type, dosage and duration.

Objective: This review aims to systematically assess the effectiveness of different postpartum antibiotic regimens in women with intrapartum chorioamnionitis on maternal morbidity and mortality, and their side effects.

Method of review: We searched MEDLINE, SCOPUS, and The Cochrane Central Register of Controlled Trials (CENTRAL). Randomized and quasi-randomized trials that compared the effect of postpartum antibiotics with different antibiotic regimen or placebo on maternal morbidity in women with of intrapartum chorioamnionitis were included. Study eligibility was assessed independently by two reviewers. Trial quality and data were extracted by one reviewer. Data were analyzed using the Review Manager software (RevMan 2004).

Main results: Three eligible trials (517 women) were included in this review. Meta-analysis of two trials comparing single-dose antibiotics with multiple-dose antibiotics after delivery showed no statistically significant difference in treatment failure (RR 1.78, CI 0.72, 4.40).

Authors' conclusions: No recommendation can be made on the most appropriate antibiotic regimen for treating a chorioamnionitis during postpartum period due to limited available information.

Field of Study Health Development Student's Signature:.....

Academic Year 2007 Principal Advisor's Signature:.....

Co-advisor's Signature:.....

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CHAPTER I

INTRODUCTION

BACKGROUND

Chorioamnionitis is designated by microscopical finding when mono- and polymorphonuclear leukocytes infiltrate the chorion *(1)*. This condition is frequently associated with prolonged membrane rupture and long labor. It occurs when several protective mechanisms of the urogenital tract and uterus fail during pregnancy or when increased numbers of microbial flora or highly pathogenic flora residing in the vagina, cervix, or both ascend through intact or ruptured fetal membranes and initiate amniotic fluid infection *(2)*. Infection is often polymicrobial with principal pathogens including Ureaplasma urealyticum, Fusobacterium spp., Mycoplasma Hominis, Escherichia coli, Bacteroides spp., Streptococcus agalactiae, etc *(3)*.

There is a significant risk of both maternal and fetal morbidity and mortality. Maternal mortality from chorioamnionitis is rare, but morbidity and hospital costs are substantial. For the mother with chorioamnionitis, serious infectious complications include endometritis, localized pelvic infections requiring drainage, intra-abdominal infections, septic shock, acute renal failure, and adult respiratory distress syndrome (ARDS) *(4)*. Maternal chorioamnionitis or other secondary infectious complications may cause thrombosis of pelvic vessels and the potential for pulmonary emboli. Furthermore, occult chorioamnionitis is frequently cited as a possible explanation for many otherwise unexplained cases of ruptured membranes, preterm labor, or both.

Clinical signs and symptoms of chorioamnionitis include fever, maternal tachycardia, fetal tachycardia, purulent or foul-smelling amniotic fluid or vaginal discharge, uterine tenderness *(2)*. However, fever is the most frequent sign and the only reliable indicator for this diagnosis.

Management of overt clinical chorioamnionitis is antimicrobial administration and prompt efforts to effect delivery, preferably vaginally *(1, 2)*. Nevertheless, there is little consensus on the most appropriate antibiotic to use, how long the treatment should

continue *(4)*. Randomized trials comparing the effectiveness of various antibiotic regimens either during the intrapartum or postpartum periods have been published in recent decades. There is unclear evidence for the effectiveness of postpartum antibiotics for the treatment of intrapartum chorioamnionitis. Therefore this review aims to systematically assess the effectiveness of antibiotics for the treatment of chorioamnionitis during the postpartum period.

OBJECTIVES

- To assess the effects of different postpartum antibiotic regimens in women diagnosed intrapartum chorioamnionitis on maternal morbidity.
- To assess the effects of different postpartum antibiotic regimens in women diagnosed intrapartum chorioamnionitis on maternal mortality.
- To assess the side effects of different postpartum antibiotic regimens in women diagnosed intrapartum chorioamnionitis.

LIMITATION

- Review, just like every intervention, is based on a theory. This may not be explicit or well explored.
- Quantitative analysis of results from studies of variable validity can result in both false positive and false negative conclusions.
- Limitations of quality assessment: There are 2 major difficulties with assessing the validity of studies; inadequate reporting of trials and limited empirical evidence of a relationship between parameters thought to measure validity and actual study outcomes.

OPERATIVE DEFINITIONS

Randomized controlled trial: An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants.

Quasi-random allocation: Methods of allocating people to a trial that are not random, but were intended to produce similar groups when used to allocate participants. Quasi-random methods include: allocation by the person's date of birth, by the day of the week or month of the year, by a person's medical record number, or just allocating every alternate person.

Random allocation: A method that uses the play of chance to assign participants to comparison groups in a trial, e.g. by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual or unit being entered into a trial has the same chance of receiving each of the possible interventions. It also implies that the probability that an individual will receive a particular intervention is independent of the probability that any other individual will receive the same intervention.

Concealment of allocation: The process used to ensure that the person deciding to enter a participant into a randomized controlled trial does not know the comparison group into which that individual will be allocated.

Blinding: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs.

Attrition bias: Systematic differences between the comparison groups in withdrawals or exclusions of participants from the results of a study.

Performance bias: Systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation.

Selection bias: Systematic differences between comparison groups in prognosis or responsiveness to treatment.

Contamination: The inadvertent application of the intervention being evaluated to people in the control group; or inadvertent failure to apply the intervention to people assigned to the intervention group.

Co-intervention: The application of additional therapeutic procedures to people receiving a particular program of treatment; either or both the experimental and the control groups.

Intention-to-treat analysis: All participants were included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm.

Per protocol analysis: An analysis of the subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. This subset may be defined after considering exposure to treatment, availability of measurements, and absence of major protocol violations. The per protocol analysis strategy may be subject to bias as the reason for non-compliance may be related to treatment.

Fixed-effect model: [In meta-analysis] A model that calculates a pooled effect estimate using the assumption that all observed variation between the studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect.

Random-effects model: [In meta-analysis] A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of included studies beyond chance, random-effects model will give wider confidence intervals than fixed-effect model.

Statistical heterogeneity: The degree of variation in the effect estimates from a set of studies.

CHAPTER II

LITERATURE REVIEW

Clinical chorioamnionitis is a common, acute, clinically detectable infection primarily of the uterus and its contents during pregnancy. Several alternative terms are in widespread use and include clinical intraamniotic infection, amnionitis, amniotic fluid infection, and intrapartum infection *(5, 6)*.

Chorioamnionitis occurs in approximately 1% to 4 % of term pregnancies *(5, 7)* and approaches 25 % in preterm deliveries *(5, 7, 8)*. The majority of cases are associated with polymicrobial with a mixture of aerobic and anaerobic organisms involved. The organisms are anaerobes, group B streptococci, *Mycoplasma hominis*, *Escherichia coli, Gardnerella vaginalis, Bacteroides bivius*, etc *(9-11)*.

Gibbs and Duff *(5)* defined clinical criteria used to make the diagnosis of chorioamnionitis when there is an intrapartum maternal temperature of $\geq$ 37.8 ^{o} C and two or more of the following conditions: maternal tachycardia (> 100 beats/min), fetal tachycardia (> 160 beats/min), uterine tenderness, and foul odor of the amniotic fluid, and a maternal leukocytosis (> 15,000 cells/mm^3), all with or without membrane rupture. Newton *(6)* demonstrated that maternal fever is the index criterion and occurs in virtually all cases. While maternal tachycardia is the most inconsistent criterion and relates more to the assessment of coexisting variables, e.g., pain. Maternal leukocytosis, foul-smelling amniotic fluid and uterine tenderness are found in 70-90%, 5-22%, and 4-25%, consecutively.

Many studies clearly demonstrated the adverse effects of chorioamnionitis in pregnancies. Before 1970 up to 5% of maternal mortality was associated with chorioamnionitis. With the current availability of prenatal care, intensive medical facilities, and broad-spectrum antibiotics, the prospects for survival are greatly increased. Less than 1% of all patients with chorioamnionitis have any severe morbidity, such as septic shock, coagulopathy, and adult respiratory distress syndrome. Currently, most chorioamnionitis is associated with bacteremia, dystocia, cesarean operations,

and potential increases in surgical complications (e.g., blood loss, wound infection, endomyometritis, increased operative duration) *(6)*.

Several studies showed adverse outcome of chorioamnionitis in the fetus and neonate. Ferguson et al. *(12)* reported a case-controlled study of perinatal outcome after chorioamnionitis. The next live-born infant with a birth weight within 100 gm and gestational age within 2 weeks was chosen as a control for each study patient. The chorioamnionitis cases were accompanied by a higher perinatal mortality rate (20% vs. 11%), a higher sepsis rate (6% vs. 2%), and a higher asphyxia rate (27% vs. 16%). Soper et al. *(13)* also shown in a prospective epidemiologic study that the fetus is infected in approximately 5% of the cases. Yoder et al. *(14)* conducted a prospective case-controlled study in 67 matched pairs which showed 5% of bacteremia and 4% of pneumonia among infants with chorioamnionitis.

Delivery of products of conception combined with appropriate antibiotics is imperative to successful treatment of clinical chorioamnionitis *(5)*. Administration of broad spectrum parenteral antibiotics with known ability to cross the placenta and coverage for beta-lactamase producing aerobes and anaerobes should be initiated at diagnosis. In the review by Duff *(15)*, penicillin and ampicillin have excellent activity against group A and group B streptococci but both have only limited activity against anaerobic gram-negative bacilli, particularly Bacteroides and Prevotella species. While the principal spectrum of activity of aminoglycoside antibiotics is the aerobic gram-negative bacilli. On contrary, metronidazole and clindamycin's spectrum of activity includes anaerobic streptococci, anaerobic gram-negative bacilli but no activity against aerobic gram-negative bacilli. Therefore combination regimens such as penicillin or ampicillin and aminoglycoside plus clindamycin or metronidazole are usually administered for treatment of polymicrobial infections such as chorioamnionitis and puerperal endometritis. Alternatively, extended spectrum cephalosporins, penicillins, and carbapenams are also highly effective to be used as single agents in this clinical situation.

Three studies *(16-18)* evaluated intrapartum versus postpartum treatment of chorioamnionitis and consistently demonstrated that initiating intrapartum antibiotic therapy in the presence of chorioamnionitis reduced maternal infectious morbidity to a

minimum, and improved neonatal outcome. In a randomized trial by Gibbs et al. *(16)*, intra-amniotic infection was treated with ampicillin and gentamicin during labor in 26 women and immediately after umbilical cord clamping in 19 women. Intrapartum-treated mothers had a shorter mean postpartum stay, a lower mean number of febrile days, and a lower mean peak postpartum temperature than did postpartum-treated mothers; these differences were all statistically significant ($p < .05$). Neonatal benefits of intrapartum treatment were also confirmed in these studies *(16-18)*, neonatal sepsis occurred 0% to 2.8% if antibiotic therapy was started intrapartum compared with 5.7% to 21% in postpartum treatment group.

However, the appropriate duration of treatment remains debatable. Clinical decision making regarding duration of postpartum antibiotic therapy has been based on level 3 evidence (ie. expert opinion). Several authors have empirically recommended continuing parenteral antibiotics until the patient has been afebrile and asymptomatic for 24 to 48 hours *(19, 20)*. Others believe that once the source of infection is removed, postpartum antibiotics may be superfluous. Furthermore, potential disadvantages with prolonged use of antibiotics include cost of prolonged hospitalization, development of resistant organisms, overgrowth of pathogens, and drug side effects. Whether this postpartum antibiotic therapy is necessary recently has been challenged in some clinical trials *(21, 22)*.

Berry et al. *(21)* addressed the question of antibiotic continuation in vaginally delivered patients who had chorioamnionitis. In a double-blind clinical trial, they administered antibiotics to one group and placebo to the other. Although their sample population was small, there were no cases of endometritis in the patients who were randomized to the placebo arm.

Turnquest et al. *(22)* concluded in their randomized controlled trial study that in patients whose labors were complicated by chorioamnionitis and who underwent cesarean section, the continuation of preoperative clindamycin and gentamicin in the postoperative period did not reduce the risk of endometritis (treatment failure) compared with a single preoperative dose.

In this age of cost containment, various strategies have been proposed for the treatment of chorioamnionitis while maintaining clinical efficacy. Patients with

chorioamnionitis who deliver vaginally may be ideal candidates for abbreviated therapy due to their lower risk of developing serious infectious morbidity compared to the higher risks associated with cesarean delivery *(14, 17)*. In the study by Chapman and Owen *(23)*, single-dose cefotetan was compared with multiple-dose cefotetan for the postpartum treatment in women with a diagnosis of chorioamnionitis and delivered vaginally. A randomized trial in 109 patients revealed that treatment failure was not statistically significant different between two groups but single-dose cefotetan group had the shorter length of hospital stay.

Additionally, the efficacy of abbreviated therapy during postpartum period in the cases that delivered via cesarean section was also reported. Edwards and Duff *(24)* enrolled 292 women who were clinically diagnosed intrapartum chorioamnionitis. Subjects were randomized to continue ampicillin and gentamicin or clindamycin if delivered via cesarean section until afebrile and asymptomatic for 24 hours (control group) or to receive only the next scheduled dose of each drug (study group). The study showed that failure rate did not differ between both groups.

CHAPTER III

METHODS

RESEARCH DESIGN

- Systematic review

HYPOTHESIS

- There is no treatment difference on maternal morbidity in all studies included in this review.

SEARCH STRATEGY

We searched MEDLINE (1966 to December 2007), SCOPUS (1966 to December 2007), and The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2, 2007). In MEDLINE database, the following free-text search terms were used:

1 # postpartum
2 # POSTPARTUM PERIOD (MeSH)
3 # chorioamnionitis
4 # amnionitis
5 # (intra-amniotic infect*)
6 # (puerper* infection)
7 # (obstetric* infection)
8 # antibiotic*
9 # ANTIBACTERIAL AGENTS (MeSH)
10 (# 1 or # 2)
11 (# 3 or # 4 or #5 or # 6 or # 7)
12 (# 8 or # 9)
13 (# 10 and # 11 and # 12)

We also adapted the search strategy to search SCOPUS by selecting appropriate keywords from their respective thesauri and subheadings. In addition, we handsearched journals and conference proceedings. Furthermore, we looked for relevant trials in the references of the retrieved articles. No language restrictions were placed.

CRITERIA FOR CONSIDERING STUDIES FOR THE REVIEW

Type of Studies

- All identified published and unpublished quasi-randomized studies (e.g. using alternation) and randomized controlled trials evaluating the effect of antibiotic therapy in women during postpartum period.

Type of Participants

- Women in the postpartum period who were diagnosed intrapartum chorioamnionitis by the presence of fever plus at least one of: maternal tachycardia, fetal tachycardia, uterine tenderness or foul smell amniotic fluid; either proven or not proven by laboratory investigations, and were treated by any antibiotics during labor.

Type of Interventions

- Intervention: antibiotic therapy (any type, route of administration, dosage, duration)
- Control: placebo, no treatment, or another antibiotic regimen

Type of Outcome Measures

- Primary outcomes: clinical assessment by physician, wound infection, endometritis, other serious infectious complications (e.g. septic shock, renal failure, DIC, ARDS), persistent infection, need for operation, death
- Secondary outcomes: adverse drug reaction following antibiotic therapy , length of hospital stay, cost of treatment

METHODS OF THE REVIEW

One reviewer screened the titles and abstracts from the database searches to determine whether the inclusion criteria were satisfied. When a clear decision could not be made on the basis of the title or abstract, the study would be considered relevant. Without any language restriction, full text of relevant studies was retrieved. If retrieved articles were non-English, an English translation would be obtained. Afterward decisions regarding inclusion were made separately by two reviewers who are content experts using a form prepared for verification of study eligibility **(Appendix A)**. This form had been pilot tested by two reviewers on a sample of articles to clarify the inclusion criteria and to ensure that the criteria could be applied consistently by more than one person. The names of the authors, institutions, journal of publication and results were disclosed. Any disagreement was resolved through discussion between authors. All studies that apparently met the selection criteria but had to be excluded and also any that did not meet all of the criteria but were well known as the review were tabulated along with the reason for their exclusion. **(Appendix C)**.

One reviewer extracted data onto data collection form **(Appendix B)** which had been pilot tested using a representative sample of the studies to be reviewed to identify data that were not needed or were missing. In addition to the main outcomes listed above, information on the setting of the study, a description of the antibiotic regimen (drug, dose, route, frequency and timing), definition of chorioamnionitis was collected. Data were entered onto the Review Manager software (RevMan 2004). When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Trials under consideration were evaluated for methodological quality by one reviewer, without consideration of their results. Each study was assessed for quality of the concealment of allocation, completeness to follow up, blinding of participants, caregivers and outcome assessors to the assigned treatment.

Selection bias (randomization and allocation concealment): A quality score for concealment was assigned to each trial, using the following criteria:

- **A** – adequate concealment of allocation: such as telephone randomization, consecutively numbered sealed opaque envelopes,

centralized or pharmacy-controlled randomization, pre-numbered or coded identical containers which are administered serially to participants

- B – unclear whether adequate concealment of allocation: such as list or table used, sealed envelops, or study does not report any concealment approach
- C – inadequate concealment of allocation: include alternation; use of case record numbers, dates of birth or days of the week, and any procedure that is entirely transparent before allocation, such as open list of random-number tables,

Attrition bias (completeness to follow up): Data were analyzed on an intention-to-treat basis. Completeness to follow up was assessed by using the following criteria:

- A – less than 5 % loss of participants
- B – 5 % to 10 % loss of participants
- C – more than 10% and up to and including 20 % loss of participants
- D – more than 20 % loss of participants: trials would be excluded.

Performance bias (blinding): We assessed blinding using the following criteria:

- Blinding of participants (Yes/ No/ Unclear)
- Blinding of caregiver (Yes/ No/ Unclear)
- Blinding of outcome assessment (Yes/ No/ Unclear)

Overall quality of trial was broadly classified into three categories using the criteria described in **Table 1**.

Table 1 Methodological quality of trials

Risk of bias	Interpretation	Relationship to individual criteria
A. Low risk of bias (high quality trial)	Plausible bias unlikely to seriously alter the results	All of the criteria met
B. Moderate risk of bias	Plausible bias that raises some doubt about the results	One or more criteria partly met
C. High risk of bias	Plausible bias that seriously weakens confidence in the results	One or more criteria not met

DATA ANALYSIS

We analyzed data on an intention-to-treat basis, therefore all participants with available data were included in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analyzed in the group to which they were randomized, and there was sufficient information in the trial report, we would attempt to restore them to the correct group.

If overall results were not calculated in the review, a qualitative assessment or description of the range and pattern of the results was given. If overall results were calculated, we carried out statistical analysis with results reported as risk ratio (RR) with 95% confidence intervals for dichotomous data and weighted mean difference (WMD) with 95% confidence interval for continuous data if outcomes were measured in the same way between trials. The standardized mean difference was used to combine trials that measured the same outcome, but used different methods. If there was evidence of skewness, this would be reported.

We assessed statistical heterogeneity in the treatment difference parameter across the trials using I^2 test. Where significant heterogeneity was found (I^2 greater than 50%), we would explore potential sources including differences in study quality, inclusion criteria or intervention regimens between studies. If heterogeneity could not be explained, individual trial results would be presented.

Fixed effect model would be used unless statistical heterogeneity was found. In case where no reason was found to explain heterogeneity or if no further data were available to explore heterogeneity, a random effects model would be used as an overall summary and instances of discrepancies between the two models would be reported.

If data were available we planned to conduct prespecified subgroup analysis on different routes of delivery and duration from rupture of membranes to delivery.

We would carry out sensitivity analysis to evaluate the effect of trial quality. Study of poor quality was excluded from the analyses (those rated B or C) in order to assess any substantive difference to the overall result. Then we analyzed the impact the inclusion of quasi-controlled trials had on trial quality.

Publication bias and other reporting biases were planned to be assessed by funnel plot. Symmetry would be expected in the absence of any bias although situations other than publication bias may result in asymmetry. However, it was anticipated that the number of eligible studies in this review might be too few to allow adequate assessment.

CHAPTER IV

RESULTS

DESCRIPTION OF STUDIES

Three trials, published from 1997 to 2003 were examined for inclusion in the review but eleven trials were excluded because they were not randomized controlled trials or did not fit the selection criteria specified in the review (for a detailed description of the reasons for exclusion, see table of “Characteristics of excluded studies”). The study by Chapman (1997) enrolled 109 women, 116 women were recruited in the study of Turnquest (1998), and 292 women were included in the study by Edwards (2003).

Criteria listed to define intrapartum chorioamnionitis were consistent in all included studies. The participants with severe complications were excluded in all studies. Study by Chapman et al. enrolled the participants who delivered vaginally, Turnquest et al. limited only to the cases delivered by cesarean section, while Edwards et al. included both routes of delivery.

Turnquest et al. compared postpartum antibiotic treatment with no antibiotic treatment, while the remaining two studies evaluated the results of single-dose regimen and multiple-dose regimen. There was considerable variation in the antibiotic regimen used in the trials. One trial (Turnquest et al.) administered clindamycin and gentamicin while patients in the study of Edwards received ampicillin and gentamicin, but clindamycin would be added for those who required cesarean section. Chapman et al., in contrast to the other studies, used only single drug (cefotetan).

A trial by Turnquest et al. was terminated before the predetermined sample size (N= 244) was reached with the reason mentioned in the article that endometritis rate, the primary outcome variable, was much lower than anticipated. Therefore the study had only a 23% power to detect the difference on the basis of the achieved sample size (N = 116).

In the studies of Chapman et al. and Edwards et al., intention-to-treat analyses were performed, whereas Turnquest et al. used per protocol analysis. However, all participants were analyzed in the group to which they were randomized. All three

studies presented the outcome in terms of failed therapy which referred to febrile morbidity or endometritis. Length of hospital stay was reported as the outcome in every study but in the studies of Chapman et al. and Turnquest et al., this was reported as median and range and we failed to derive the results presented as mean and standard deviation by personal contact with the trialists. Thus we did not pool this outcome for meta-analysis.

A study by Turnquest was not added in meta-analysis for the reason that it was the only one study that compared postpartum treatment with no treatment. Therefore only 401 participants from the two studies (Chapman et al. and Edwards et al.) that compared 2 different antibiotic regimens were brought in meta-analysis.

METHODOLOGICAL QUALITY

All three studies are randomized controlled trials using computer generated set of random numbers with adequate allocation concealment by sealed opaque envelopes. But there was no mention in these three included studies as to whether the participants, providers and outcome assessors were blind to the allocation.

In the study by Turnquest, 14 of 130 women (3.25%) randomized to postpartum treatment were excluded from the analysis because of the protocol violation, co-intervention, data form misplaced, etc. The data to correct this potential bias were not available for reviewers to restore them to the correct group for intention-to-treat analysis. However, the excluded cases of less than 5% should not greatly affect the trial quality.

Protocol violation occurred in 18 out of 292 participants (6.16%) in the study by Edwards. With regards to low rate of treatment failure (4.1%) in the study, this high number of protocol violations had impaired the quality of the study.

Overall methodological quality of the 3 studies included in this review was rated as B in that one or more criteria were partially met.

RESULTS

Three studies involving 517 participants were included. Data were available for only some of the prespecified outcomes. In one trial (n = 116) postoperative administration at least 24 hours of gentamicin and clindamycin was compared with no

treatment and found no statistically significant difference in the occurrence of endomyometritis (relataive risk (RR) 0.68, 95% confidence interval (CI) 0.31, 1.48). This study also reported no statistically significant difference in wound infection, hematoma, seroma events as well. **(Table 2)**

Meta-analysis of two trials (N = 401) which compared treatment failure events between single-dose antibiotic and multiple-dose antibiotic after delivery showed no statistically significant difference (RR 1.78, CI 0.72, 4.40) **(Table 3).** Further subgroup analysis based on route of delivery demonstrated more treatment failure in former group but there was no statistically significant difference; vaginal delivery (RR 1.49, CI 0.54, 4.11) and cesarean section (RR 3.31, CI 0.38, 28.75) **(Figure 1)**. Moderate heterogeneity across trials (I^2 = 35.5%) may be the result of different antibiotic regimens; combined antibiotic in one study and single antibiotic in the other study. However, relative risk of treatment failure events among those who delivered vaginally was similar either using fixed effect model or random effect model (RR 1.46, CI 0.39, 5.51).

In the study of Edwards et al., the length of hospital stay was shorter in women who received treatment with single-dose antibiotics compared with multiple-dose antibiotics and this result reached statistical significance (weighted mean difference (WMD) - 0.90, CI - 1.64, - 0.16). On the other hand, a reduction rate of wound infection and pelvic abscess was in favor of multiple-dose antibiotics although this did not reach statistically significant difference.

None of the included studies compared the effect of different types of antibiotics. Neither maternal serious complications nor death occurred and no data about adverse drug reaction or cost of treatment presented in the three included studies.

Publication bias and other reporting biases were not assessed due to a limited number of eligible studies. Sensitivity analysis was not carried out to evaluate the effect of trial quality since all included studies were of the same quality.

Table 2 Comparison 01. No antibiotic versus any antibiotic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Endomyometritis	1	116	Relative risk (fixed) 95 % CI	0.68 [0.31,1.48]
02 Wound infection	1	116	Relative risk (fixed) 95 % CI	2.70 [0.29 , 25.25]
03 Hematoma	1	116	Relative risk (fixed) 95 % CI	0.90 [0.06 , 14.07]
04 Seroma	1	116	Relative risk (fixed) 95 % CI	0.30 [0.03 , 2.81]

Table 3 Comparison 02. Single-dose antibiotic versus multiple-dose antibiotic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Treatment failure (febrile morbidity or endometritis)	2	401	Relative risk (fixed) 95 % CI	1.78 [0.72 , 4.40]
02 Wound infection	1	292	Relative risk (fixed) 95 % CI	1.87 [0.17, 20.37]
03 Pelvic abscess	1	292	Relative risk (fixed) 95 % CI	2.80 [0.12 , 68.24]
04 Hospital days	1	292	Weighted mean difference (fixed) 95 % CI	-0.90 [-1.64,-0.16]

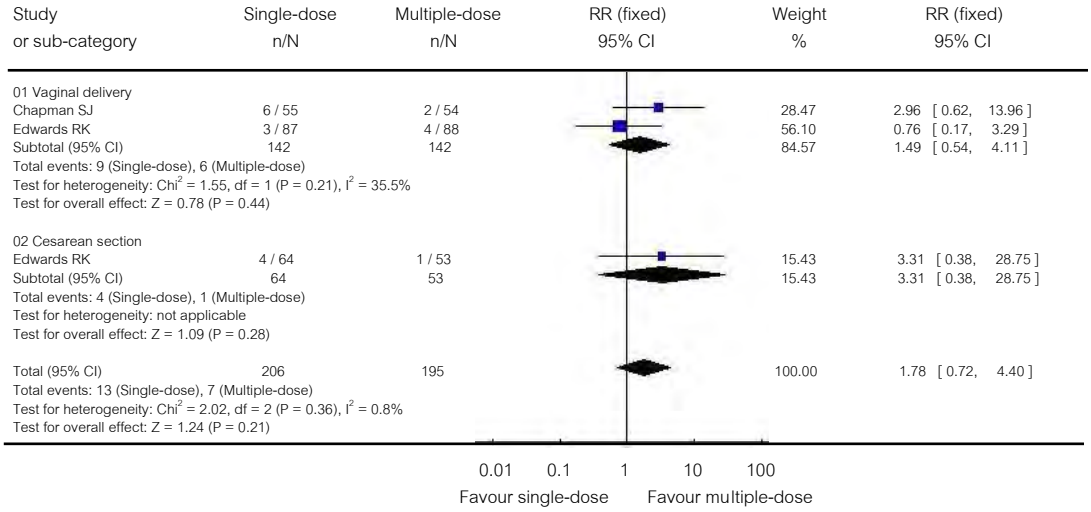
Table 4 Single-dose versus multiple-dose antibiotic: Treatment failure (subgrouped by route of delivery)

Route of delivery	Study	Treatment Outcome	Single-dose	Multiple-dose
Vaginal delivery	Chapman SJ	Failure	6	2
		Success	49	52
		Total (N =109)	55	54
	Edwards RK	Failure	3	4
		Success	84	84
		Total (N = 175)	87	88
	Total (2 studies)	Failure	9	6
		Success	133	136
		Total (N = 284)	**142**	**142**
Cesarean delivery	Edwards RK	Failure	4	1
		Success	60	52
		Total (N = 117)	**64**	**53**
Both routes of delivery	Total (2 studies)	Failure	13	7
		Success	193	188
		Total (N = 401)	**206**	**195**

Figure 1 Analysis 02.01 Single-dose versus multiple-dose antibiotic

Outcome 01 Treatment failure (subgrouped by route of delivery)

Review: Postpartum antibiotics for intrapartum chorioamnionitis
Comparison: 02 Single-dose versus multiple-dose antibiotic
Outcome: 01 Treatment failure (subgrouped by route of delivery)



CHAPTER V

CONCLUSION, DISCUSSION

DISCUSSION

This is the first systematic review of postpartum antibiotics for intrapartum chorioamnionitis. The conclusions for clinical practice that could be drawn from this review are limited due to the small numbers of the studies. Although the finding of no difference would suggest that single-dose antibiotic regimen was as effective as multiple-dose antibiotic regimen in treating chorioamnionitis during postpartum period, the sample sizes were too small in all instances to draw conclusions, as evidences by the wide confidence interval associated with the findings.

Current consensus within the clinical community is the continuation of antibiotic treatment during postpartum period until afebrile for 24-48 hours when the diagnosis of intrapartum chorioamnionitis is done. This approach is not based on the well-designed clinical trials, but rather on expert opinion, descriptive studies, and clinical experience. The results of this review, however, demonstrated the trend in reducing endomyometriitis and febrile morbidity when multiple-dose antibiotics; i.e. administration of antibiotics until afebrile for 24-48 hours, were administered in the group that delivered by cesarean section.

As in all studies, our review has some limitations. First, we try to identify maximum number of eligible trials by using multiple system of retrieval, hoping that the studies included in the review will be a representative sample of all eligible studies. Nevertheless, this depends on thoroughness of the composite search, in terms of number of systems searched and the adequacy of those searches. Second, only few studies were included in our review probably due to the strict inclusion criteria for participants since we would like to get the well-designed studies with homogeneity. The last potential weakness in our study should be noted is that we are not able to get further detailed information from the original authors by personal contact.

AUTHORS' CONCLUSIONS

Implications for Practice

Changes in obstetric practice over time and among centers (eg. conservative management of rupture of membranes at term, use of internal pressure catheters for amnioinfusion) would increase the incidence of chorioamnionitis. This would address the importance of appropriate selection of antibiotic regimens during both intrapartum and postpartum periods.

The results of this review unfortunately can produce very little guidance to neither supports nor refute the current approach of the clinical management of intrapartum chorioamnionitis during postpartum period. No recommendations can be made on the most appropriate postpartum antibiotic regimen in terms of both health gains and cost-effectiveness.

From the review, we conclude that single-dose and multiple-dose postpartum antibiotic administration for women with intrapartum chorioamnionitis who deliver vaginally provide no difference in treatment failure which is consistent with level of evidence (Oxford-Centre for evidence based medicine) 1a.

Implications for Research

It would have been useful for researchers to undertake appropriately sized randomized controlled trials to compare postpartum antibiotic treatment with placebo or different antibiotic regimen. Regarding the low incidence of chorioamnionitis, enrollment adequate number of patients might be resolved by multi-center studies.

In light of the developments in the pharmacology of antibiotics, future trials should be designed to compare the effectiveness of traditional combined antibiotic regimens with the modern single antibiotic regimens with broad spectrum coverage for chorioamnionitis. If the treatment failure and the complications are not different between 2 regimens, single antibiotic regimens should be selected due to the less administration charges.

Finally, since the wholesale acquisition cost of an antibiotic represents only a fraction of the charge actually incurred by the patient, other costs, such as markup above wholesale, pharmaceutical dispensing fees, dose preparation fees, and nursing

administration charges must be considered. Therefore cost analysis should be the part of evaluation in future trials.

POTENTIAL CONFLICT OF INTEREST

None known.

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APPENDICES

Appendix A

Verification of study eligibility

Information about study references and authors			
Trial ID……	Name of author who is abstracting data……		
Title of review Author (s) Year of publication			
Notes specific to the study			
Source of key information			
Personal communication			
Verification of study eligibility			
Type of study • Randomized / quasi-randomized	Yes	No	Unclear
Type of participants			
• Chorioamnionitis	Yes	No	Unclear
• Postpartum	Yes	No	Unclear
Type of interventions			
• At least 1 group treated by antibiotic	Yes	No	
Study meets inclusion criteria	Yes	No	
Reason for exclusion (if select No)			

Appendix B

Data collection form prepared for this review

Study characteristics			
Methods			
• Randomized	Describe:		
	Adequate	Unclear	Inadequate
• Conceal allocation	Describe:		
	Adequate	Unclear	Inadequate
• Blinding			
Participant	Yes	Unclear	No
Provider	Yes	Unclear	No
Outcome assessor	Yes	Unclear	No
Number of participants			
• Drop-outs			
• Cross-overs			
• Co-intervention			
Participants			
• Inclusion			
• Exclusion			
• Setting of studies			
• Diagnostic criteria			
Interventions	**(type, dose, route, frequency, duration)**		
• Study gr. 1			
• Study gr. 2			
• Study gr. 3			

Outcomes measures and results						
Dichotomous	N =					
	Study gr. 1 n =		Study gr. 2 n =		Study gr. 3 n =	
	events	total	events	total	events	total
Primary outcome						
●						
Secondary outcome						
●						
●						
●						
Continuous	N =					
	Study gr. 1 n =		Study gr. 2 n =		Study gr. 3 n =	
	mean	SD	mean	SD	mean	SD
Primary outcome						
●						
Secondary outcome						
●						
●						
●						
Conclusion:						

Methodological quality				
Selection bias ● Allocation concealment	Adequate (A)	Unclear (B)	Inadequate (C)	
Performance bias ● Blinding	Yes (A)	Unclear (B)	No (C)	
Attrition bias ● Loss of participants	< 5% (A)	5% - 10 % (B)	> 10% - 20% (C)	> 20% (D)

Appendix C

Characteristics of included studies

Study	Chapman 1997
Methods	**Randomization**: computer generated random number sequence **Allocation**: consecutively numbered, sealed, opaque envelopes **Blinding**: not stated **Study period**: January 1995 to November 1996 **Analysis**: intention to treat
Participants	**Inclusion criteria**: A clinical diagnosis of intrapartum amnionitis treated intrapartum with ampicillin and gentamicin and delivered vaginally **Exclusion criteria**: Septic shock, another source of infection, or penicillin allergy **Number of participants**: N = 109
Interventions	**Group 1**: Cefotetan 2 gm IV q 12 hrs for a minimum of 48 hrs after an initial dose in the recovery room (n = 54) **Group 2**: Cefotetan 2 gm IV single dose immediately postpartum (n = 55)
Outcomes	Failed therapy (febrile morbidity or readmission for endometritis): Group 1: 2/54 vs. Group 2: 6/55 Length of postpartum hospital stay (median, range): Group 1: 57 [36-190] vs. Group 2: 33 [16-190] hrs Duration of maternal febrile morbidity: Group 1: 12 [-2 to 158] vs. Group 2: 7 [-3 to 175] hrs
Notes	A study was conducted at 2 hospitals, a tertiary care and a nearby county hospital, using the same protocol.
Allocation concealment	A - Adequate

gm = gram IV = intravenous

hrs = hours vs. = versus

Study	Edwards 2003
Methods	**Randomization**: random number generating software program **Allocation**: next sealed opaque envelope containing order sheets to 1 of 2 groups **Blinding**: not stated **Study period**: December 26, 1999 to March 18, 2003 **Analysis**: Intention-to-treat
Participants	**Inclusion criteria**: A diagnosis of clinical chorioamnionitis and received intravenous ampicillin 2 gm every 6 hrs, and gentamicin 1.5 mg/kg every 8 hrs until delivery **Exclusion criteria**: β-lactam allergy, immunocompromised, at risk for bacterial endocarditis, receive β-mimetic drug in preceding 8 hrs, concurrent febrile illness **Number of participants**: 292
Interventions	**Group 1**: Ampicillin 2 gm IV every 6 hrs plus gentamicin 1.5 mg/ kg IV every 8 hrs, if delivered vaginally. Clindamycin 900 mg IV at umbilical cord clamping then every 8 hrs plus ampicillin 2 gm IV every 6 hrs and gentamicin 1.5 mg/ kg IV every 8 hrs, if delivered by cesarean section. Until afebrile, asymptomatic for 24 hrs (n = 141) **Group 2**: Same antibiotic regimen as in group 1 but received only next schedule dose of each drug (n = 151)
Outcomes	Treatment failure (febrile morbidity): Group 1: 5/141 vs. Group 2: 7/151 Duration of hospital stay: Group 1: 5.1 ± 4.3 vs. Group 2: 4.2 ± 1.4 d Wound infection: Group 1: 1/141 vs. Group 2: 2/151 Pelvic abscess: Group 1: 0/141 vs. Group 2: 1/151
Notes	Different antibiotic regimen between vaginal delivery and cesarean section. Protocol violation: Group 1: 13/141 vs. Group 2: 5/151
Allocation concealment	A - Adequate

mg = milligram mg/kg = milligram per kilogram

gm = gram IV = intravenous

vs. = versus hrs = hours

Study	Turnquest 1998
Methods	**Randomization**: computer generated set of random numbers **Allocation**: sealed opaque envelopes & opened in consecutive order **Blinding**: not stated **Study period**: May 1992 to May 1996 **Analysis**: per protocol
Participants	**Inclusion criteria**: A diagnosis of clinical chorioamnionitis treated with ampicillin during labor and required cesarean delivery **Exclusion criteria**: Receive antibiotic no less than 7 days before enrollment, allergy to penicillin, ampicillin, gentamicin, or clindamycin, insulin-dependent diabetes, connective tissue disorder, or positive HIV test,impaired renal function **Number of participants**: N = 130 (116 remained eligible for statistical analysis)
Interventions	**Group 1**: Clindamycin 900 mg IV and gentamicin 2 mg/ kg IV preoperative No scheduled postoperative antibiotics (n = 61) **Group 2**: Clindamycin 900 mg IV and gentamicin 2 mg/ kg IV preoperative Clindamycin 900 mg IV every 8 hrs and gentamicin 1.5 mg/ kg IV every 8 hrs until afebrile for a minimum of 24 hrs (n = 55)
Outcomes	Postpartum endometritis: Group 1: 9/61 vs. Group 2: 12/55 Wound infection: Group 1: 3/61 vs. Group 2: 1/55 Hematoma: Group 1: 1/61 vs. Group 2: 1/55 Seroma: Group 1: 1/61 vs. Group 2: 3/55 Duration of fever (median, range): Group 1: 14 [0-216] vs. Group 2: 24 [0-246] hrs Length of stay (median, range): Group 1: 4 [2-12] vs. Group 2: 4 [2-13] d
Notes	The study was conducted at 2 institutions; both of which are teaching hospitals. Failure to obtain the predetermined sample size (N = 244) Fourteen patients were excluded from the analysis: 7 protocol violations (incorrect antibiotic regimen or timing), 1 deliver vaginally after enrollment, 6 data form misplaced after randomization
Allocation concealment	A - Adequate

mg = milligram mg/kg = milligram per kilogram

IV = intravenous vs. = versus

hrs = hours d = days

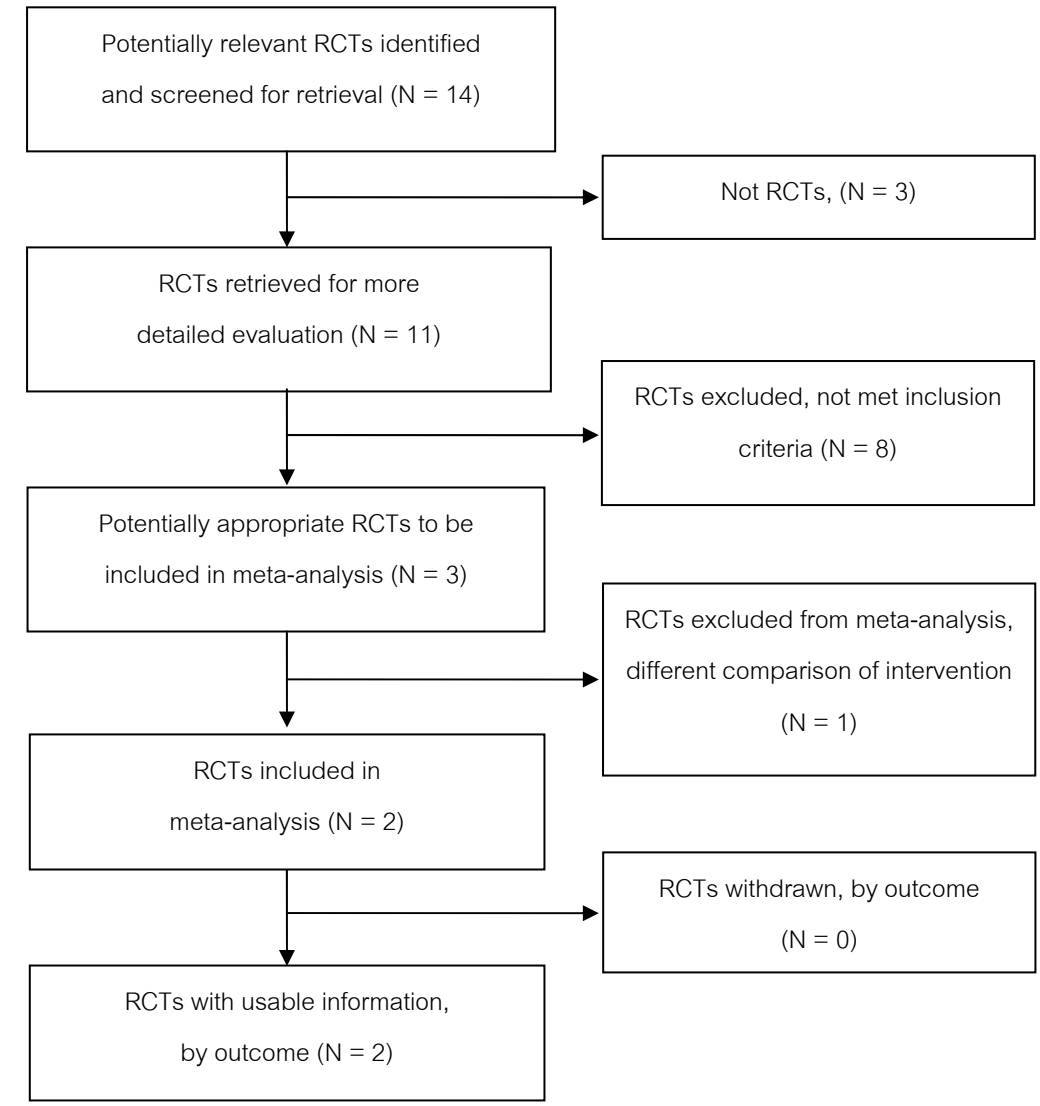
Characteristics of excluded studies

Study	Reason for exclusion
Berry 1994	This randomized controlled trial used the criteria of maternal fever and ruptured membranes for the diagnosis of chorioamnionitis without the presence of maternal or fetal tachycardia, uterine tenderness, or foul smell amniotic fluid.
Del Priore 1996	The study included women diagnosed as having postpartum endometritis. Patients diagnosed with chorioamnionitis during labor were eligible for the study only if they had remained afebrile for longer than 8 hours, had antibiotics discontinued after delivery, and subsequently developed signs and symptoms of endometritis.
Gibbs 1988	The study did not compare 2 different therapies during postpartum period for patients diagnosed intrapartum intra-amniotic infection.
Hager 1989	This randomized study enrolled the patients on the obstetrics and gynecology services who had a clinical diagnosis of chorioamnionitis, endomyometritis, or post-hysterctomy cuff cellulites or cuff abscess.
Knuppel 1988	53 participants enrolled in this study included 47 cases of endometritis, 3 cases of pelvic inflammatory disease, and 3 cases of chorioamnionitis, and all were randomized to receive either cefotetan or cefoxitin.
Livingston 2003	This prospective, placebo-controlled, double-blinded study included women diagnosed as having postpartum endometritis.
Morales 1989	The study included patients with the diagnosis of postpartum endomyometritis.
Soper 1987	This was a case-control study which included women diagnosed as having postpartum endometritis.
Sperling 1987	The study was a clinical trial comparing effect of intrapartum with immediate postpartum treatment of intra-amniotic infection on maternal and neonatal morbidity and mortality, but the timing of the treatment was determined at the physician's discretion.

Stovall 1988	This was the case-control study which included both chorioamnionitis & postpartum endomyometritis.
Sweet 1985	The study was a randomized trial that included 60 cases of tuboovarian abscess, severe pelvic inflammatory disease with peritonitis, postpartum and postabortal endomyometritis, and wound abscess.

Appendix D

Flow diagram of the review



RCTs = randomized controlled trials

VITAE

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