



Birmingham Women's Hospital Journal Club Handbook

Ann Daly
Dr Amer Raza



Birmingham Women's Health Care



NHS Trust

This handbook belongs to



Ann Daly
Clinical Librarian
ann.daly@bwhct.nhs.uk

Dr Amer Raza
Specialist Registrar
amer.raza@bwhct.nhs.uk

© 2008 Ann Daly, Amer Raza

Contents

Contents	i
Glossary of terms used in evidence based medicine	ii
List of acronyms	v
1. Introduction	1
2. What is Journal Club?	1
3. How is Journal Club organised?	1
4. Guidance for the presenter	1
4.1 Identify a knowledge gap and frame a clinical question	2
4.2 Literature search for best evidence to answer the question	3
4.3 Appraise the evidence	5
4.31 The GATE frame	5
4.32 RAAMbo	6
4.33 CASP	6
4.34 CATmaker	6
4.4 Prepare the presentation	7
4.5 Present the findings at Journal Club	10
5. The role of the chairperson	10
6. The role of the consultant	10
7. The role of the clinical librarian	10
8. Frequently asked questions	10
9. Journal Club articles written by members of BWH staff	11
10. Recommended reading	11
11. References	11
List of figures	
Figure 1 Journal Club flow chart	2
Figure 2 The PICOD Model	3
Figure 3 PICOD questions	3
Figure 4 The WHO Reproductive Health Library	4
Figure 5 National Library for Health	5
Figure 6 The GATE Frame	5
List of appendices	
Appendix 1 Record sheet for clinical questions	13
Appendix 2 A working example of a Journal Club presentation	14
Appendix 3 Study paper used to demonstrate a Journal Club presentation	20
Appendix 4 Text copy of a CAT	26
Appendix 5 Criteria for assessing Journal Club presenters	27

Glossary of terms used in evidence based medicine

Absolute risk: measures the probability of an event or outcome occurring, for example, an adverse reaction to the drug being tested.

Absolute risk reduction (ARR): the ARR is the difference in the risk of an event occurring between two groups, for example, if 6% of patients die after receiving a new experimental drug and 10% of patients die after having the existing drug treatment then the ARR is $10\% - 6\% = 4\%$. Therefore, by using the new drug 4% of patients can be prevented from dying.

Bias: influences on a study that can lead to invalid conclusions about a treatment, which can make that treatment appear better or worse than it is. Bias can occur by chance or as a result of a systematic error on the design and execution of a study. It can occur at different stages in the research process, for example, in the collection, analysis, interpretation or publication of research data. See also selection bias, performance bias, information bias, confounding factor and publication bias.

Blinding: the practice of keeping the subjects and / or the investigators of a study ignorant of the group to which a subject has been assigned. For example, a trial in which both the patients and doctors are unaware of whether the patients are taking the experimental or control drugs. The purpose of blinding is to protect against bias. See also double blind, single blind and triple blind study.

Case control study: a study that starts with the identification of a group of individuals sharing the same characteristics (eg people with a particular disease) and a suitable comparison / control group (eg people without the disease). All subjects are then assessed with respect to things that happened in the past that might be related to contracting the disease. These studies are also called retrospective as they look back in time from the outcome to the possible causes.

Clinical governance: a framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care.

Cohort study: an observational study that takes a group (cohort) of patients and follows their progress in order to measure outcomes such as disease or mortality rates, and make comparisons according to the treatments that patients received. Cohorts can be assembled in the present and followed into the future (a concurrent or prospective cohort study) or identified from past records and followed forward from that time up to the present.

Confidence interval: a way of expressing certainty about the findings from a study using statistical measures. A confidence interval describes the range within which the true value of a measurement (eg effect of a treatment) is expected to lie within a given degree of certainty. It is usual to interpret a 95% confidence interval as the range of effects within which we are 95% confident that the true effect lies.

Confounding factor: a factor that influences a study that can contribute to misleading findings. For example, two groups of people - one exercising regularly the other not (the groups have a significant age difference but this is not considered). In relation to cardiovascular events the outcomes are influenced as much by age as exercising. Age is therefore the confounding factor.

Control group: a group of patients recruited to a study that receives no treatment, a treatment of known effect or a placebo – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Controlled clinical trial (CCT): a study testing a specific drug or other treatment involving two or more groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested and the other (the comparison or control group) receives an alternative treatment, a placebo

or no treatment. The two groups are followed to compare differences in outcomes to determine the effectiveness of the experimental treatment.

Cross sectional study: the observation of a defined group at a single point in time – a snapshot. This type of study contrasts with a longitudinal study which follows subjects over a period of time.

Double blind study: a study in which both the subject (patient) and the observer (investigator / clinician) is unaware of which treatment or intervention the patient is receiving. The purpose of this blinding is to protect against bias.

Event rate: the proportion of patients in a group where a specified health event or outcome is observed. For example, if in 100 patients the event is observed in 23, then event rate is 0.23. Control event rate (CER) and experimental event rate (EER) are the terms used in control and experimental groups of patients.

Heterogeneity: when the results or estimates of effects of treatment from separate studies appear to be different.

Homogeneity: when the results from separate studies appear similar.

Information bias: pertinent to all types of study and can be caused by poorly designed questionnaires, observer or interviewer bias, response error and measurement error.

Intention to treat analysis: an analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment or crossed over and received the alternative treatment. Intention to treat analysis are favoured in assessments of clinical effectiveness as they reflect the non compliance and treatment changes that are likely to occur when the treatment is used in practice.

Meta analysis: results from a collection of independent studies (investigating the same treatment) are pooled using statistical techniques to synthesise their findings into a single estimate of treatment effect.

Number needed to treat (NNT): this measures the impact of a treatment or intervention. It states how many patients need to be treated in order to prevent an event that would otherwise occur. For example, if the NNT = 3 then three patients would have to be treated to prevent one adverse outcome. The closer the NNT is to 1, the better the treatment. The number needed to harm (NNH) is the number of patients that would need to receive a treatment to cause one additional adverse event, for example, if the NNH = 4 then four patients would have to be treated for one adverse outcome to occur.

Observational study: a research method that involves watching, listening and recording behaviours and actions.

Odds ratio (OR): odds are a way of representing probability that provides an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of risk and an odds ratio of 1 between two treatment groups, implies that the risks of an adverse outcome is the same in each group.

P value: the *P* value is a measure of probability that a difference between groups happened by chance. It has a value ranging from zero to one. For example, $P= 0.01$ means there is a 1 in 100 chance that the result occurred by chance. The lower the *P* value, the more likely it is that the difference between groups was caused by treatment. *P* values tell us whether an effect can be regarded as statistically significant or not, it does not relate to how large the effect might be, for which we need the confidence interval.

Performance bias: the systematic difference in care provided (apart for the intervention). For example, carers treating patients differently according to which group they are in.

Prospective study: a study in which subjects are entered into research and then followed up over a period of time with future events recorded as they happen.

Publication bias: studies with statistically significant (or positive) results are more likely to be published than those with non significant (or negative) results.

Qualitative research: research used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions.

Quantitative research: research that generates numerical data.

Randomisation: a method that uses the play of chance to assign subjects to groups in a research study, for example, by using a random numbers table or a computer generated random sequence.

Randomised controlled trial (RCT): a study to test a specific drug or other treatment in which subjects are randomly assigned to two or more groups: one (the experimental group) receiving the treatment that is being tested and the other (the comparison or control group) receiving an alternative treatment, a placebo or no treatment. The two groups are followed to compare differences in outcomes to determine the effectiveness of the experimental treatment.

Relative risk (RR): a summary measure that represents the ratio of the risk of a given event or outcome (eg an adverse reaction to the drug being tested) in one group of subjects compared with another. When the risk of events is the same in the two groups the relative risk is one. In a study comparing two treatments, a relative risk of two would indicate that patients receiving one of the treatments had twice the risk of an adverse outcome than those receiving the other treatment.

Retrospective study: a study that deals with the present / past and does not involve studying future events.

Risk ratio: ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group.

Selection bias: selection bias occurs if the characteristics of the sample group differ from those of the wider population or when there are systematic differences between comparison groups of patients in a study in terms of prognosis or responsiveness to treatment.

Sensitivity: in diagnostic testing sensitivity refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a false positive. The sensitivity of a test is also related to its negative predictive value (true negatives) - a test with a sensitivity of 100% means that all those who get a negative test result will not have the disease. To fully judge the accuracy of a test, its specificity must also be considered.

Single blind study: a study in which *either* the subject *or* the observer is unaware of which treatment or intervention the subject is receiving.

Specificity: in diagnostic testing specificity refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result but still have the disease - this is called a false negative. The specificity of a test is also related to its positive predictive value (true positives) – a test with a specificity of 100% means that all those having a positive test result definitely have the disease. To fully judge the accuracy of a test, its sensitivity must also be considered.

Systematic review: a review in which evidence from studies has been identified, appraised and synthesised in a methodical way according to a predetermined criteria.

Triple blind study: a study in which the statistical analysis is carried out without knowing which treatment patients received, in addition to the patients and clinicians being unaware of which treatment was used.

List of acronyms

BWH	Birmingham Women's Hospital
CASP	Critical appraisal skills programme
CAT	Critical appraisal topic
CEBM	Centre for Evidence Based Medicine
EBM	Evidence based medicine
ERC	Education Resource Centre
GATE	Graphical Appraisal Tool for Epidemiological Studies
NICE	National Institute for Health and Clinical Excellence
PICOD	Population, Intervention, Comparison, Outcome, Design – terms used to help formulate a structured clinical question
qds	4 times a day
RAAMbo	Representative, Allocated, Accounted, Measured, blind, objective – terms used to help appraise a study
RCOG	Royal College of Obstetricians and Gynaecologists
RHL	Reproductive Health Library
WHO	World Health Organisation

Birmingham Women's Hospital Journal Club Handbook

1. Introduction

Evidence-based medicine (EBM) integrates current best research evidence with clinical experience in making decisions about patient care. The terms evidence-based *practice* and evidence-based *healthcare* act in accordance with EBM, as does *Clinical Governance*, which is further concerned with quality and safe patient care. West Midlands Deanery regards EBM as an essential competence. Here, at Birmingham Women's Hospital (BWH) we have high regard for evidence-based practice and endeavour to teach EBM skills within the innovative teaching programme known as Journal Club.

2. What is Journal Club?

Journal Club is a teaching programme that supports trainee doctors to learn the principles of evidence-based practice. It is a mandatory feature of a doctor's education that is assessed by the clinical librarian. The format of Journal Club is group, problem-based learning in which a *presenter* (typically a trainee doctor) delivers a structured interactive presentation to an audience of fellow practitioners. The content of the presentation is the critical appraisal of a research paper with the aim of determining research evidence that is trustworthy. The presentation is followed by group discussion in which appraisal is continued in light of the presenter's findings, and application of findings into practice determined.

3. How is Journal Club organised?

A rota is prepared indicating the date individual doctors are required to present in Journal Club which is then issued to presenters, their mentors / chairperson (see section 5) and the clinical librarian. Doctors familiar with the process are allocated first on the rota to enable new doctors an opportunity to look and learn. The Obstetric and Gynaecology Journal Club is held weekly on Monday lunchtime from 12.45 to 1.30 pm at the Seminar Room in the Education Resource Centre (ERC). The ERC staff set-up presentation media and the presenter typically arrives a few minutes early to prepare. The Neonatal Journal Club is held on a Wednesday morning from 8.45 to 9.30 am, in the Neonatal Unit Training Room.

4. Guidance for the Presenter

Presenters should start to prepare approximately four weeks prior to Journal Club. There are five stages to follow:

- Identify a knowledge gap and frame a clinical question
- Literature search for best evidence to answer that question
- Appraise the evidence
- Create a critically appraised topic (CAT) using CATmaker software
- Prepare the presentation and present the findings at Journal Club

Figure 1 provides a Journal Club flow chart.

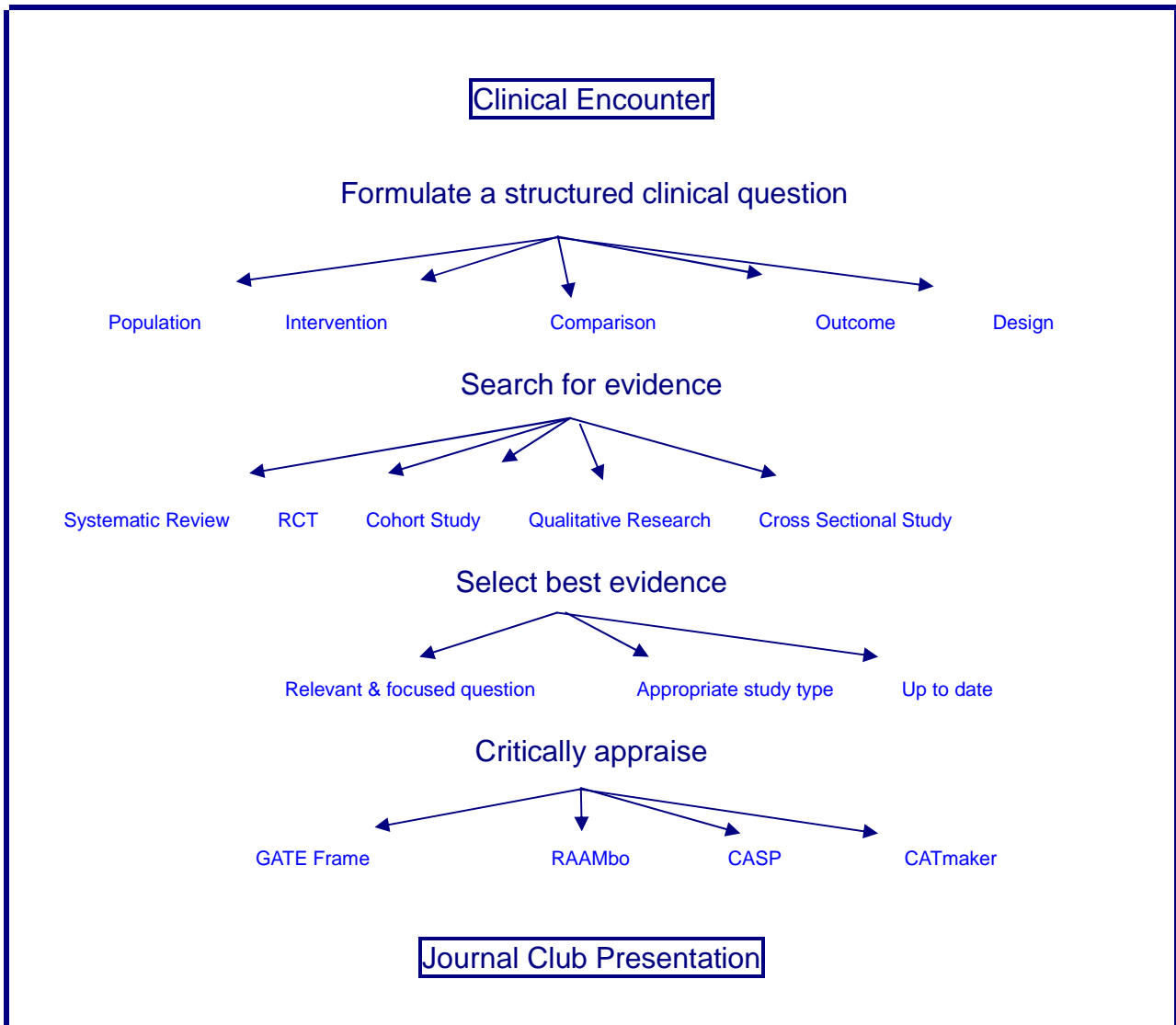


Figure 1 Journal Club flow chart

4.1 Identify a knowledge gap and frame a clinical question

The first step in EBM is to define a structured clinical question. The question should transpire during clinical practice (appendix 1 provides a record sheet for noting clinical questions). Mentors will provide advice as to the choice of question, and the clinical librarian has a list of expired questions / CATs that may be used. The index of CATs is available at <http://www.bwhct.nhs.uk/library-cats.htm>. It is then necessary to frame the question using the PICOD model (**p**opulation, **i**ntervention, **c**omparison, **o**utcome and **d**esign). PICOD is an approach to formulating a structured question and is used to support understanding of the facets or separate parts of a clinical query. It is also useful to help with identifying relevant search terms. Figure 2 provides the facets and an explanation of each.

P I C O D	Explanation
Patient or Population	Which patient group is the question relating to?
Intervention	Which intervention is being used?
Comparison	What is the intervention to compare with?
Outcome	What is the outcome of interest?
Design	The research design is dependent on the type of question: Diagnostic question use a cross sectional study Patient preference question use qualitative research Prognosis question use a cohort study Therapy question use a randomised controlled trial (each study type can be collated in a systematic review)

Figure 2 The PICOD Model, adapted from the CEBM (2007).

It is sometimes difficult to identify the facets of a clinical query; Figure 3 provides a number of examples.

Free form question	Structured PICOD question
Among woman at increased risk of preterm birth is prophylactic administration of progesterone by vaginal suppository effective to reduce the incidence of spontaneous preterm birth?	Population: women at risk of preterm birth Intervention: prophylactic administration of progesterone by vaginal suppository Comparison: placebo Outcome: prolonged gestation Design: a therapy question requiring a RCT
Does sonographic assessment of cervical length or clinical digital examination of the cervix in the second trimester provide better accuracy in the prediction of preterm delivery in a low risk population?	Population: women at low risk of preterm delivery Intervention: sonographic assessment Comparison: clinical digital examination Outcome: accurate prediction of preterm delivery Design: a diagnostic question requiring a cross sectional study
What are the preferences of pregnant women in terms of prenatal testing for chromosomal disorders?	Population: pregnant women undergoing prenatal testing for chromosomal disorders Intervention: as no specific method of scanning / screening is mentioned, consider the range of methods eg foetal ultrasound scanning, amniocentesis, maternal serum screening Comparison: as above, the range of methods Outcome: to identify women's preference of test method Design: a patient preference question requiring qualitative research
What is the outcome of delayed cord clamping in the newborn?	Population: newborns Intervention: a delay in cord clamping Comparison: immediate cord clamping Outcome: risk / benefit of delayed clamping Design: a prognosis question requiring a cohort study

Figure 3 PICOD questions

4.2 Literature search for best evidence to answer the question

The second stage in EBM is a literature search to identify a study that will help answer the question. When searching for evidence use terms identified in PICOD and consider an appropriate research design (cross sectional study, qualitative research, cohort study, randomised controlled trial). A good starting point is PubMed Clinical Queries especially since limits can be applied to enable searching by study type, for example,

etiology, diagnosis, therapy, prognosis and systematic review (each study type can be collated in a systematic review). The Cochrane Library and the Reproductive Health Library (RHL) also provide systematic reviews. The RHL is specific to our subject field here at BWH, therefore content is completely relevant and useful commentary is provided. It is available at <http://www.rhlibrary.com/> (contact library staff for a username and password).



Figure 4 The WHO Reproductive Health Library

The paper selected for presentation at Journal Club should be clinically relevant. It might be that a senior clinician recommends a study, in which case a complete literature search is not necessary. Below is a list of resources to consider referring to for a feel of the literature. During the presentation it is useful to provide details of relevant guidelines, for example, NICE / RCOG / RCPCH / BWH and to identify issues of concern such as that guidelines might be unclear, outdated or unspecific to the question being presented.

BWH Guidelines (see handbooks or U drive)

National Institute for Health and Clinical Excellence (NICE) Guidelines

<http://guidance.nice.org.uk/>

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines

<http://www.rcog.org.uk/index.asp?PageID=1042>

Royal College of Paediatrics and Child Health (RCPCH) Guidelines

<http://www.rcpch.ac.uk/Research/CE/Guidelines/RCPCH-guidelines>

International guidelines, major trials and critically appraised topics TRIP

<http://www.tripdatabase.com/index.html>

The Who Reproductive Health Library <http://www.rhlibrary.com/>

The Cochrane Library

<http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME>

Women's Health Specialist Library <http://www.library.nhs.uk/womenshealth/>

Child Health Specialist Library <http://www.library.nhs.uk/childhealth/>

PubMed Clinical Queries <http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml>

Access to Medline and other bibliographic databases is available from the NLH homepage <http://www.library.nhs.uk> . An Athens password is required.

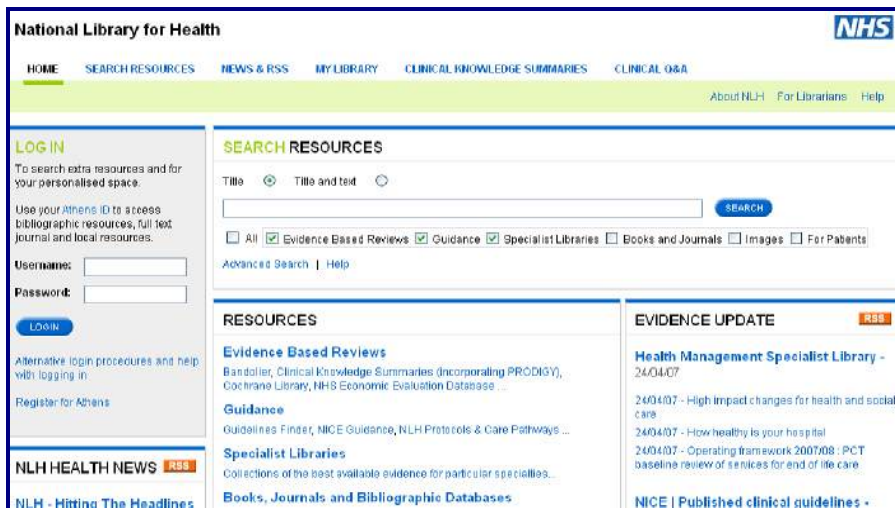


Figure 5 National Library for Health

4.3 Appraise the evidence

The next stage is to critically appraise the selected study using an appraisal tool. One such tool is the **Graphic Appraisal Tool for Epidemiological studies (GATE Frame)** available at <http://ebm.bmj.com/cgi/content/full/11/2/35>, which can be used for therapy and diagnostic questions. A second tool is the **Critical Appraisal Skills Programme (CASP)** available at <http://www.phru.nhs.uk/Pages/PHD/resources.htm> that can be used for all type questions. Finally, **CATmaker**, a computer assisted critical appraisal tool that calculates useful clinical measures can be used to appraise most type questions.

4.31 The GATE Frame

The GATE Frame helps to appraise a paper in a pictorial form using a triangle, circle, square and an X. It is useful as it enables a systematic approach to appraisal, in addition to understanding of the epidemiological design, and assessment of the quality and validity of the entire study.

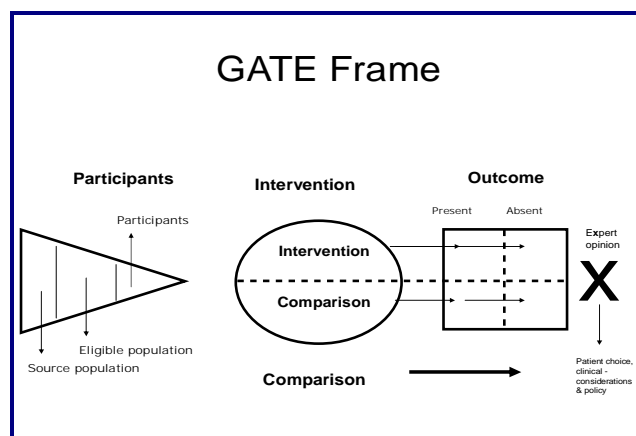


Figure 6 The GATE Frame, adapted from Jackson et al (2006)

The triangle

The triangle represents the population. It is divided into three levels: the whole triangle represents the source population, the middle level represents the population meeting

the eligibility criteria and the lowest level (the tip of the triangle) represents those taking part (the study participants).

The circle and square

The circle is divided into two sections, representing the intervention (or experimental) and the comparison groups. The square represents the study outcome, which is typically divided into four sections showing the present and absent outcome for the intervention and comparison groups.

The X

The X represents the application of evidence into practice, which involves the eXpert practitioner integrating the evidence with important issues; patient choice, and clinical considerations and policy.

4.32 RAAMbo

To complete the Frame link the acronym RAAMbo:

- R** Represent
- A** Allocation or adjustment
- A** Accounted for at completion of the study
- M** Measurements
- b** blinded
- o** objective

This requires the appraiser to weigh-up flaws noted in the study and to consider the impact individual flaws have on the overall validity. A study should provide sufficient detail to determine whom the participants **represent**, which requires information on the source population, eligible population and the participants. The method of **allocation** to the intervention and comparison groups should be stated. Randomised allocation is the best way to avoid imbalance between the two groups since this may influence the outcomes. In non-randomised studies imbalances between the intervention and comparison groups can be reduced by **adjustment** using statistical methods. All participants should be **accounted** for at the completion of a study, and the numbers in the tip of the triangle (study participants) should equal the numbers in the circle (intervention and comparison groups), which should in turn equal the numbers in the square. The accuracy of outcomes **measured** is also a validity issue, and if the study is **blinded** and **objective** there is less likelihood of personal influence (adapted from Jackson et al, 2006).

4.33 CASP

The Critical Appraisal Skills Programme is an appraisal tool to help understanding of medical research. It provides a list of approximately ten questions to help make sense of each type of research, including qualitative and economic evaluation studies. Unlike the GATE Frame it doesn't calculate present and absent outcomes, although it is straight forward to use and provides understanding of the aspects that make a good research study.

4.34 CATmaker

CATmaker is a computer assisted critical appraisal tool that instructs the user to enter information (see slides 2 and 3 below), and calculates useful clinical measures (see

slide 4). It generates a file that can be saved and stored at the BWH library website for all interested parties to view. It is produced by the NHS R&D Centre for EBM in Oxford and is freely available to download at <http://www.cebm/index.aspx?o=1216> (4 files are generated, select catmaker.exe). CATmaker can be used for a single study of therapy, diagnosis, prognosis, aetiology / harm, and a systematic review of therapy.

The information below provides guidance on using CATmaker, and Appendix 4 provides a text copy of a completed CAT.

CATmaker

How do I use CATmaker?

CATmaker prompts you to enter information

At least 12 fields of information need to be entered to complete a therapy CAT

The software isn't difficult to use. However, it may be time consuming drawing the correct information from the study paper to enter into CATmaker

1

What questions does CATmaker ask for a therapy CAT?

- The clinical question
- Search terms used
- Patients' clinical characteristics
- Control regimens and duration
- Experimental regimens and duration
- The study features eg blinded

2

What questions does CATmaker ask for a therapy CAT?

- The number of patients analysed
- The events of interest, and the number or rates of these events
- Bottom line information
- CAT title
- Comments
- Update by (usually period for update is 2 years)

3

What calculations does CATmaker work out?

- Control event rate (CER)
- Experimental event rate (EER)
- Relative risk reduction (RRR)
- Absolute risk reduction (ARR)
- Number needed to treat (NNT)
- Confidence Intervals (CI)

The CEBM provides a glossary of key terms in EBP
<http://www.cebm.net/index.aspx?o=1116>

4

Tips on using CATmaker

- Keep an eye on the message box at the bottom of the screen which displays help information
- Use the TAB key to go from one field to another
- CATmaker provides examples of information to enter into each field, just click the highlighted button on the left hand side

5

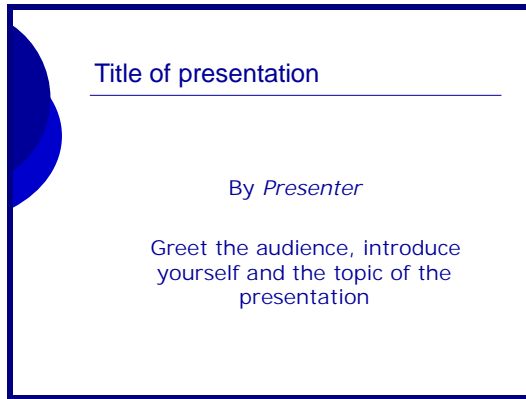
Tips on using CATmaker

- To save your CAT, click on the CATmaker menu in the upper left-hand menu and select one of the actions on the pull-down menu. Save the work as an Unfinished Kitten and use Load Kitten when ready to work on it again.
- When the CAT is complete still save as an Unfinished Kitten as this will allow library staff to re-open it (when emailed) to quality check.
- If you want a text copy of the CAT for your own records or to check content, then select Output as WebCAT, and insert .htm at the end of the file name.

6

4.4 Prepare the presentation

The PowerPoint presentation should last approximately 15 minutes followed by time for discussion. The template below should be used as closely as possible (adapted from Coomarasamy 2005 and Davies 2006). Appendix 2 provides a *working* example of a typical Journal Club presentation, and Appendix 3 is a copy of the study paper that the presentation is based on.

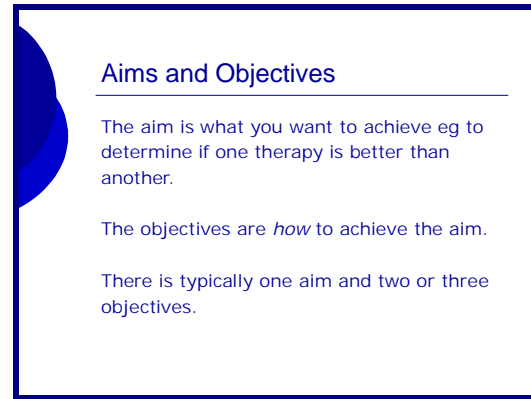


Title of presentation

By *Presenter*

Greet the audience, introduce yourself and the topic of the presentation

1



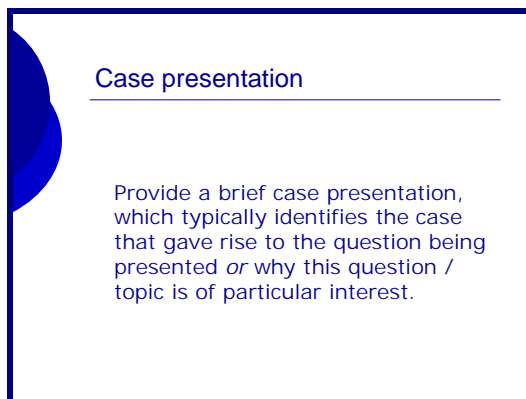
Aims and Objectives

The aim is what you want to achieve eg to determine if one therapy is better than another.

The objectives are *how* to achieve the aim.

There is typically one aim and two or three objectives.

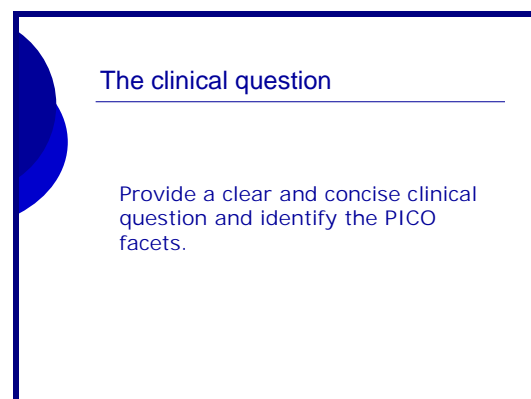
2



Case presentation

Provide a brief case presentation, which typically identifies the case that gave rise to the question being presented *or* why this question / topic is of particular interest.

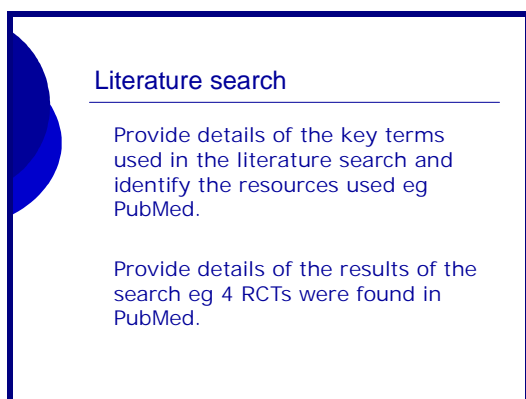
3



The clinical question

Provide a clear and concise clinical question and identify the PICO facets.

4

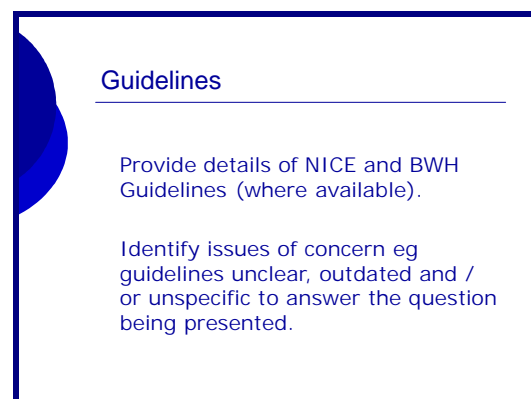


Literature search

Provide details of the key terms used in the literature search and identify the resources used eg PubMed.

Provide details of the results of the search eg 4 RCTs were found in PubMed.

5



Guidelines

Provide details of NICE and BWH Guidelines (where available).

Identify issues of concern eg guidelines unclear, outdated and / or unspecific to answer the question being presented.

6

Paper selected

Provide bibliographic details of the paper selected and state *why* this paper was chosen eg the most relevant paper, up to date, adequate participant numbers, good methodology, etc.

7

Flow chart of the study

Provide a simple flow chart of the study.

Describe the study to the audience to help get a feel of the content and understand the methods used, etc.

8

Details of the study

Copy and paste useful charts or tables from the study paper, and explain their significance to the audience.

This might need 2 or 3 slides.

9

GATE Frame or CASP

If a therapy or diagnostic question, apply the study to the GATE Frame and explain the steps to the audience.

For other type questions use CASP.

10

RAAMbo

When using the GATE Frame list the RAAMbo acronym stating if the study adhered to each aspect:

- Representative
- Allocation or adjustment
- Accounted for
- Measurements
 - blinded
 - objective

11

CATmaker

Provide details of the bottom-line conclusion reached after entering the study data into CATmaker (CATmaker works out the calculations for you).

You can copy and paste the evidence section from a text copy of the Catmaker into the PP presentation

12

Summary and conclusion

- Summarise the findings and provide a conclusion, stating how well the aims and objectives were achieved.
- The findings may prompt change of policy at BWH.
- When insufficient evidence is found recommend audit or further research.
- Thank the audience for listening and ask for questions.

13

4.5 Present the findings at Journal Club

The presenter should arrive five minutes before start time to prepare and test the presentation media. Journal Club represents learning in small group sessions through interaction, discussion, and giving and receiving feedback. Therefore, it is important to listen and take note of feedback. Request clarification or say I don't know if unsure of an answer, and don't feel the need to be positive about the study presented, it isn't uncommon for medical research to be flawed! The chairperson and consultant help to answer the more complicated questions that arise.

5. The role of the chairperson

The chairperson / mentor is responsible for supporting the presenter and will advise on the selection of a paper. However, the presenter is expected to make initial contact with their mentor with thoughts and ideas of a question / topic of interest. The chairperson makes every effort to attend Journal Club, introduce the presenter and play a primary role in the discussion. It is therefore important that the chairperson / mentor is familiar with the paper being presented.

6. The role of the consultant

Consultants attend Journal Club whenever commitments allow, and similar to the chairperson, play an active part in the discussion. Presenters may invite individual consultants known to have a particular interest in the topic being presented.

7. The role of the clinical librarian

The librarian contacts the presenter three or four weeks before he / she is due to present at Journal Club to check preparation has begun, and is available to help with the literature search and to quality check the CAT. The librarian liaises with the chairperson to assess the presentation, and completes the Journal Club assessment form.

8. Frequently asked questions

What if I can't present on the allocated day?

Request a fellow presenter switch days, and inform the chairperson and the librarian.

Can I invite others to my Journal Club presentation?

Yes, invite members of staff that you feel are interested in the topic of the presentation and that might contribute to the discussion. If, for example, the topic relates to radiology, you might want to invite a radiologist, and of course midwives, nurses and other staff are welcome.

Who assesses the presenter and how?

The clinical librarian with the help of the chairperson assesses the presenter. Appendix 5 is a copy of the form used, which becomes part of the 360 Degree Assessment for all trainee doctors. The librarian completes questions 1 – 3 and the chairperson question 4.

9. Journal Club articles written by members of BWH staff

Coomarasamy A, Latthe P, Papaioannou S, Publicover M, Gee H, Khan KS (2001). Critical appraisal in clinical practice: sometimes irrelevant, occasionally invalid. *Journal of the Royal Society of Medicine* 94 (11) 573-7. Available at: <http://ukpmc.ac.uk/picrender.cgi?artid=517767&blobtype=pdf> (NHS Athens password required).

Dwarakanath LS, Khan KS (2000). Modernizing the journal club. *Hospital Medicine* 61 (6) 425-7.

Khan KS, Dwarakanath LS, Pakkal M, Brace V, Awonuga A (1999). Postgraduate journal club as a means of promoting evidence-based obstetrics and gynaecology. *Journal of Obstetrics and Gynaecology* 19 (3) 231-4. Available at: <http://ejcontent.ebsco.com/ContentServer.Net/ContentServer.aspx?target=http%3A%2F%2Fwww%2Einformaworld%2Ecom%2Fsmpp%2Fftinterface%3Fcontent%3Da713681752%26format%3Dpdf%26magic%3Ddebscohostejs%7C%7CAA3D3EFB68C36A3B40C78D54581474B7%26ft%3D%2Epdf> (NHS Athens password required).

10. Recommended reading

Glasziou P et al (2003). *Evidence based medicine*. BMJ Books. London.

Hamer S and G Collinson (2005). *Achieving evidence based practice*, 2nd Edition. Bailliere Tindall. London.

Heneghan C (2006). *Evidence based medicine toolkit*. BMJ Books. London.

Khan KS et al (2003). *Systematic reviews to support evidence based medicine: how to review and apply findings of healthcare research*. The Royal Society of Medicine Press Limited. London.

Straus S et al (2005). *Evidence based medicine: how to practice and teach EBM*, 3rd Edition. Churchill Livingstone. London.

11. References

Centre for Evidence Based Medicine (2007). Available at: <http://www.cebm.net/>

Coomarasamy, A et al (2005). *Journal Club Handbook 2005*.

Da Fonseca E et al (2003). Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomised placebo controlled double blind study. *American Journal of Obstetrics and Gynecology* 188 (2) 419-423. Also available at: http://www2.us.elsevierhealth.com/inst/serve?location=job031882&type=pdf&trueID=pdf_mob0341&id=amob0341&action=get-media&name=x.pdf (Athens password required).

Davies J et al (2006). *Journal Club Handbook 2006*.

Jackson R et al (2006). Evidence-Based Medicine 11 35-38. Also available at: <http://ebm.bmj.com/cgi/content/full/11/2/35?rss=1> (Athens password required).

Sackett DL (1996). Evidence based medicine: what it is and what it isn't. BMJ 312 (7023) 71-72.

Sackett DL (1997). Choosing the best research design for each question. BMJ 315 (7123) 1636. Also available at: <http://www.bmj.com/cgi/content/full/315/7123/1636> (Athens password required).

World Health Organisation (2007). The Who Reproductive Health Library, available at: <http://www.rhlibrary.com/> (contact library staff for username and password).

Appendix 1 Record sheet for clinical questions

Date.....

Question.....

.....
.....
.....
.....

PICO format question:

Population.....

.....
.....

Intervention.....

.....
.....

Comparison.....

.....
.....

Outcome.....

.....
.....

Appendix 2 An example of a presentation

Does prophylactic use of progesterone by vaginal suppository reduce the risk of preterm birth in women at increased risk?

by Ann Daly

Aims and Objectives

AIM

To determine if progesterone by vaginal suppository is effective to reduce the risk of preterm birth

OBJECTIVES

To search for literature relevant to the question presented

To select a useful paper to appraise

To determine the validity of the paper & to identify if the results are reliable enough to help answer the question & subsequently use in clinical practice

Case presentation

During clinical practice, a patient having had two previous preterm births was presented. The use of progesterone by vaginal suppository to reduce the risk of another preterm birth was addressed.

The clinical question

Population

- Women at increased risk of preterm birth

Intervention

- Prophylactic use of progesterone by vaginal suppository

Comparison

- Placebo

Outcome

- Increased gestation

Literature search

Search terms

- preterm delivery OR preterm birth / progesterone AND vaginal suppository / prevention OR risk

Resources searched

- PubMed

Guidelines

NICE

No guidelines available

RCOG

Clinical Guideline no. 1B Oct 2002 Tocolytic Drugs for Women in Preterm Labour

BWH (2007)

- Betamethasone / Erythromycin
- Atosiban – 1st line protocol
- Nifedipine - 2nd line protocol

RCOG 2002: 'If a tocolytic agent is used, ritodrine no longer seems the best choice. Alternatives such as atosiban or nifedipine appear to have comparable effectiveness in terms of delaying delivery for up to seven days and are associated with fewer maternal adverse effects.

Atosiban is licensed for use as a tocolytic but the purchase price is relatively expensive. Nifedipine is not licensed for use as a tocolytic and the ideal dosage and formulation are unclear. For both these agents, further evidence is required about their relative effects on substantive outcomes such as neonatal mortality and morbidity, and on safety and long-term outcome for the child'. **BWH 2007:**

STERIODS: between 24 - 34 weeks

BETAMETHASONE 12mg intramuscular and repeat after 24 hours... In view of evidence that is suggestive of improved outcome regarding neonatal morbidity give **ERYTHROMYCIN** 250mg qds for 10 days. **TOCOLYSIS:** only use to prolong labour to allow steroids to be

administered or permit in utero transfer – Atosiban is 1st line protocol Nifedipine 2nd.

Paper selected

Da Fonseca E, et al (2003). Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increase risk: a randomised placebo-controlled double blind study. *American Journal of Obstetrics and Gynecology* 188 (2) 419 - 423.

NB This paper was selected solely to demonstrate a journal club presentation. See Appendix 3 for the full text of this article

Flow chart of the study

A randomised double blind placebo-controlled study

142 high risk singleton pregnancies
(Hospital das Clinicas, Brazil)

Progesterone 100mg daily versus placebo

Patients underwent uterine contraction monitoring with an external tocodynamometer once a week for 60 minutes, between 24 and 34 weeks of gestation

Control and experimental groups were compared for epidemiologic characteristics, uterine contraction frequency & incidence of preterm birth

Characteristics of women at randomisation

Table II. Characteristics of women at randomization

	<i>Placebo (n = 70)</i>	<i>Progesterone (n = 72)</i>
Age (y)*	26.8	27.6
Ethnicity*		
White	71.4%	68.0%
Nonwhite	28.6%	32.0%
Parity (>1 delivery)*	97.1%	90.2%
Risk factor*		
Previous preterm delivery	97.2%	90.3%
Uterine malformation	1.4%	5.6%
Incompetent cervix	1.4%	4.1%
Gestational age at intake (wk)*	25.2	26.5

*Not significant.

Mean contraction frequency

Table IV. Mean contraction frequency for each gestational week between placebo and progesterone groups

Gestational age (wk)	Placebo	Progesterone	P value
	Mean ± SD	Mean ± SD	
28	4.0 ± 3.6	1.0 ± 0.6	.0001
29	4.0 ± 2.1	1.0 ± 0.9	.0001
30	6.2 ± 3.6	2.8 ± 2.7	.0001
31	5.1 ± 2.5	3.2 ± 2.0	.0001
32	6.5 ± 3.1	2.5 ± 2.5	.01
33	7.0 ± 4.2	2.6 ± 2.4	.0001
34	6.5 ± 3.1	3.5 ± 2.0	.0001

In weeks 28 - 34 the mean contraction frequency is less in the progesterone group than in the placebo.

Frequency of uterine contraction

Table V. Frequency of uterine contraction

Contraction	Placebo (n = 70)	Progesterone (n = 72)	P value
<4	32 (45.7%)	55 (76.4%)	.0001
4-5	12 (17.1%)	3 (4.1%)	.0118
≥6	26 (37.2%)	14 (19.4%)	.0190

Fewer contractions are recorded in the progesterone group.

% of undelivered patients per week

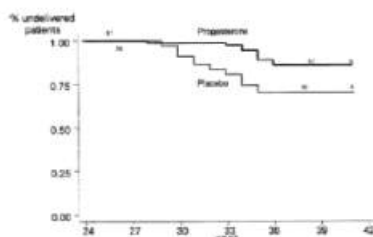
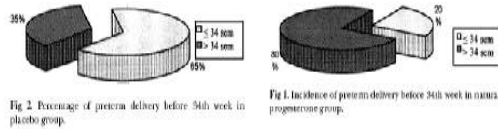


Fig 3. Cumulative percentage of undelivered patients per week, by placebo and progesterone group. Log-rank $\chi^2 = 5.33$, $P = .029$.

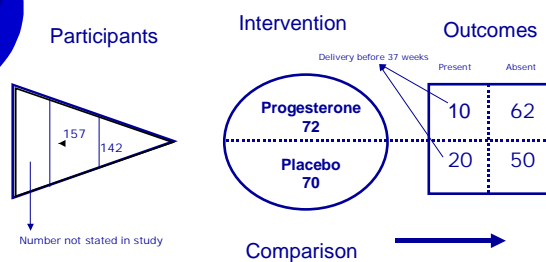
In weeks 24 – 42 there are more patients undelivered in the progesterone group than in the placebo.

Incidence of preterm delivery



There is less incidence of preterm delivery *before 34 weeks* in the progesterone group than in the placebo group.

GATE Frame



The outcome box shows that in the progesterone group there were 10 preterm births and in the placebo there were 20, before 37 weeks gestation.

RAAMbo

Representative

- Source population number not stated, eligible population & no. of participants are stated.

Allocation

- Yes

Accounted

- Yes

Measured

- Blinded – Yes
- Objective - Yes

Representative: source population not stated / eligible 157 / participants 142. Study undertaken in a hospital in Brazil (a developing country, therefore the risk of preterm birth is considered higher than in the UK). Patients were **allocated** to progesterone or placebo according to a randomised number table; the numbers corresponded to sealed envelopes indicating if drug A or B should be used, numbers were given consecutively. All participants were **accounted** for with details of numbers lost to follow-up and numbers withdrawing from the study. **Measurements** in terms of numbers tallying and outcomes are correct. The study was **double blinded** and is considered to be **objective**.



The Evidence (taken from CATmaker)

Contraction frequency at gestational age 28 weeks gestation CER 0.053 / EER 0.012
Contraction frequency at gestational age 30 weeks gestation CER 0.083 / EER 0.034
Contraction frequency at gestational age 32 weeks gestation CER 0.087 / EER 0.030

This evidence shows that contraction frequency is fewer in the experimental (progesterone) group at each gestational age.

Additional evidence (see tables above) indicates fewer preterm births in the progesterone birth.

Summary and conclusion

There were approximately half the number of preterm births in the progesterone group.
The study appears to be well conducted although participant size is small. More similar studies are needed in order to compare results and follow up the long term health of the baby.

Some types of progesterone are *synthetic* and controversies exist about their adverse effects. The progesterone used in this study is *natural*; free of any disturbing teratogenic, metabolic, or hemodynamic effects (Da Fonseca E et al, 2003) so it is *thought* to have less adverse effects. However, further studies need conducting to compare results AND follow up the long term health of the baby.

Appendix 3 Article by Eduardo B da Fonseca (Reproduced with the permission of Elsevier Limited on behalf of the American Journal of Obstetrics and Gynecology)

Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study

Eduardo B da Fonseca, MD, Roberto E Bittar, PhD, MD, Mario HB Carvalho, MD, and Marcelo Zugaib, PhD, MD. *Sao Paulo, Brazil*

Objective: The purpose of this study was to evaluate the effect of prophylactic vaginal progesterone in decreasing preterm birth rate in a high-risk population.

Study design: A randomized, double blind, placebo-controlled study included 142 high-risk singleton pregnancies. Progesterone (100 mg) or placebo was administered daily by vaginal suppository and all patients underwent uterine contraction monitoring with an external tocodynamometer once a week for 60 minutes, between 24 and 34 weeks of gestation. Progesterone (n = 72) and placebo (n = 70) groups were compared for epidemiologic characteristics, uterine contraction frequency, and incidence of preterm birth. Data were compared by χ^2 analysis and Fisher exact test.

Results: The preterm birth rate was 21.1% (30/142). Differences in uterine activity were found between the progesterone and placebo groups (23.6% vs 54.3%, respectively; $P < .05$) and in preterm birth between progesterone and placebo (13.8% vs 28.5%, respectively; $P < .05$). More women were delivered before 34 weeks in the placebo group (18.5%) than in the progesterone group (2.7%) ($P < .05$).

Conclusion: Prophylactic vaginal progesterone reduced the frequency of uterine contractions and the rate of preterm delivery in women at high risk for prematurity. (*Am J Obstet Gynecol* 2003;188: 419-24).

Key words: Preterm delivery, preterm birth, prevention, progesterone.

Preterm delivery is a leading cause of neonatal morbidity and mortality. It is directly responsible for 75% to 95% of all neonatal deaths not resulting from lethal congenital malformations 1, 2. Of the survivors, 10% to 15% have significant handicaps 23. According to the World Health Organization, a preterm birth is defined as birth before 37 completed weeks of gestation 4.

In developed countries, the incidence of preterm birth is about 7% to 12% of all deliveries, 5, 6 and among these one third occur before 34th week 1. The incidence of preterm birth in developing countries is higher than in developed countries 1, 7, 8. In Brazil, preterm birth is a public health problem because of the striking social differences in the population. Because of the high prevalence of high-risk pregnancies, the incidence of preterm birth at Hospital das Clinicas, University of Sao Paulo Medical School, is 22.5%, and half of these resulted from spontaneous preterm labor. Thus, the prevention of preterm delivery has become one of the major objectives of perinatal medicine. Primary prevention is desirable but not always possible 5, 9. The difficulties are due to unawareness of the cause and pathophysiologic mechanisms of preterm birth, and furthermore, it is not only a medical problem, but also a social and educational problem.

The early detection of pregnant women at high risk for preterm delivery 10-14 could be the best way to prevent preterm birth. Thereby, bed rest, cervical cerclage, 15 bacterial vaginosis treatment, and prophylactic use of progesterone could be one of the managements in this high-risk population. Recent studies have shown that an increase in the number of uterine contractions precedes the onset of preterm labor, 13, 16, 17 and the frequency of uterine contractions in pregnancies with preterm delivery is higher than in women with term and post term delivery 18.

Progesterone is useful in allowing pregnancy to reach its physiologic term because at sufficient levels in the myometrium, it blocks the oxytocin effect of prostaglandin $F_{2\alpha}$ and α -adrenergic stimulation and therefore increases the α -adrenergic tocolytic response 6, 19. Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. This is not true for certain artificial progestagens and B -mimetics 1, 20.

Although some studies demonstrate that natural progesterone is effective in the prevention of preterm delivery and can be administered intramuscularly, 21, 22 there are many controversies about their methods. There are few double-blind studies 23, 24 that have only used synthetic progestational agents 21, 23 with a sufficient number of women. To the best of our knowledge, this is the first study that uses natural progestational agents. Therefore, a placebo-controlled clinical trial in asymptomatic high risk women would be of value. The objective of this study was to evaluate whether the prophylactic administration of progesterone by vaginal suppository can reduce the incidence of preterm birth in a high-risk population.

Material and methods

This study was performed in the Obstetrics Clinic, at Hospital das Clinicas, University of Sao Paulo Medical School, a tertiary medical center, in Brazil. A consent form was signed after detailed information was given to every pregnant woman. The study was approved by the Ethical Commission of the hospital. Data available at the start of the study showed that the preterm birth rate in the Obstetrics Clinic, Hospital das Clinicas, University of Sao Paulo Medical School, was 25% 12. Although some studies suggest that the prophylactic administration of progesterone in pregnant women at high risk for preterm birth is associated with a reduction of 60% to 78% in preterm delivery rate, 21, 23, 24 a more realistic assessment of the impact of progesterone may be a reduction of 50% in the preterm rate. Therefore, to calculate the sample size, we have proposed a reduction of 50% in the preterm birth rate for the progesterone group (from 25% to 12.5%) and a reduction of 20% for the placebo group (from 25% to 20%) 24. A power calculation at the start of the study indicated that at least 48 pregnant women would have to be included in each group to obtain a study power of 90% at a significance level of .05 (two tailed) to prove the hypotheses were correct.

Among the women who sought high-risk prenatal care, 157 asymptomatic high-risk singleton pregnant women for preterm delivery were followed up from February 2, 1996, to March 30, 2001. Patients were allocated to progesterone or placebo according to a randomized number table. The numbers corresponded to sealed envelopes that indicated if drug A or drug B should be used. Numbers were given consecutively. Treatment assignment was blinded until the delivery of the last pregnant woman. Both the patients and the staff who were recording the study findings were blinded to the study medication allocation.

Fifteen (9.5%) patients were lost to follow-up or withdrew from the study. Nine (11.1 %) of these were in the progesterone group and 5 (6.5 %) in the placebo group, resulting in 72 assigned to the progesterone group and 70 to the placebo group. None of the patients in either study group had a multiple pregnancy. Women at high risk for preterm delivery were considered to be those in the presence of at least one previous spontaneous preterm birth, prophylactic cervical cerclage, and uterine malformation. Gestational age at a prior preterm birth for the progesterone and placebo groups was 33.3 (± 2.7) and 33.4 (± 2.6) weeks. We did not observe a significant difference in the gestational age of previous preterm birth, uterine malformation, and cervix cerclage in these two groups. Multiple gestation and fetal malformations were excluded. Women allergic to progesterone ($n = 1$), who missed follow-up ($n = 1$), those with preterm rupture of membranes (PROM) ($n = 10$), and those having a therapeutic premature delivery ($n = 3$) were excluded from the study. One hundred forty-two women completed the study, and there was no statistically significant difference for the exclusion cause in both groups (Table I). Gestational age was calculated on the basis of the last menstrual period and ultrasonography up to 12 weeks or by two concordant scans between 12 and 20 weeks.

Table I. Exclusion cause in two study groups

Exclusion cause	Placebo (n = 76)	Progesterone (n = 81)	P value
PROM	4 (5.2%)	6 (7.4%)	NS
Lost follow-up	1 (1.3%)	0	NS
Therapeutic preterm delivery	1 (1.3%)	2 (2.4%)	NS
Allergic process	0	1 (1.2%)	

PROM, Preterm rupture of membranes; NS, not significant.

At the first prenatal visit, a microscopic examination and culture of cervicovaginal secretions for *Trichomonas vaginalis*, *Candida* sp, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Gardnerella vaginalis*, and group B *Streptococcus* were carried out for all patients. Women with positive cultures were treated with specific antibiotics, and repeat cultures were performed to confirm the efficacy of treatment.

All pregnant women were submitted to uterine contraction monitoring by an external tocodynamometer once a week for 60 minutes from 24 to 34 weeks of gestation. We performed uterine monitoring between 8 and 10 a.m. using a Hewlett Packard tocodynamometer 50A series (Hewlett Packard, Houston, Tex) while women were in semi-Fowler position. We determined the frequency of contractions and compared mean values of both study groups. A positive test was considered when there were four or more contractions per hour before the 30th week of gestation and from 30 weeks onward, 6 or more contractions per hour 12, 21, 23.

Preterm labor was defined as two or more regular uterine contractions every 10 minutes, recorded by external tocodynamometer, associated with cervical changes, represented by a dilatation of more than 2 cm, or the presence of progressive dilatation or effacement of the cervix. Women in preterm labor were treated in the hospital with intravenous tocolytic therapy. A preterm delivery was defined as birth before 37 weeks of pregnancy.

Both groups of pregnant women were randomly selected to receive the vaginal progesterone suppository (100 mg) or an identical-looking placebo. The suppositories were identical in appearance and thick. They were applied every night from 24 to 34 weeks of gestation. Patients had a thorough explanation of how to use the suppositories, including an orientation picture. The medication and the placebo were supplied by manipulation pharmacy at Hospital das Clínicas, University of Sao Paulo. Patient treatment was only unblinded after the delivery of the last pregnant women.

The clinical relevance of the prophylactic use of progesterone was determined as it correlated with the evolution of pregnancy to preterm delivery. Statistical analysis was performed with EPI-INFO 2000 1.0 (Centers for Disease Control and Prevention, Atlanta, Ga) and STATA 7.0 (USA) (Stata, College Station, Tex). The χ^2 tests or Fisher exact test were used for categoric variables. The two tailed Student *t* test was used for continuous variables and the Wilcoxon rank sum test was used for interval variables. Kaplan-Meier survival analysis was used to determine the relationship between the administration of prophylactic vaginal progesterone and preterm birth. The log-rank χ^2 test was used to compare the differences in the generated survival curves. A *P* value of .05 was considered significant.

Table II. Characteristics of women at randomization

	Placebo (n = 70)	Progesterone (n = 72)
Age (y)*	26.8	27.6
Ethnicity*		
White	71.4%	68.0%
Nonwhite	28.6%	32.0%
Parity (>1 delivery)*	97.1%	90.2%
Risk factor*		
Previous preterm delivery	97.2%	90.3%
Uterine malformation	1.4%	5.6%
Incompetent cervix	1.4%	4.1%
Gestational age at intake (wk)*	25.2	26.5

*Not significant.

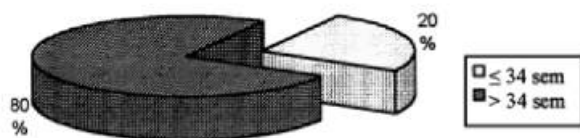


Fig 1. Incidence of preterm delivery before 34th week in natural progesterone group.

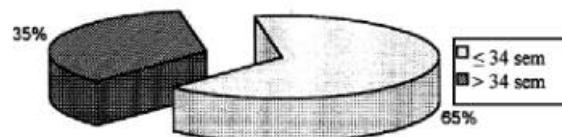


Fig 2. Percentage of preterm delivery before 34th week in placebo group.

Table III. Incidence of preterm delivery

	Placebo (n = 70)	Progesterone (n = 72)	P value
<37 wk	20 (28.5%)	10 (13.8%)	.03
34 wk	13 (18.6%)	2 (2.8%)	.002
Admission for threatened preterm labor	22 (31.4%)	14 (19.4%)	NS

NS, Not significant.

Results

Of 142 cases, there were 30 preterm births (21.1%). The incidence of preterm delivery in the progesterone group was 13.8% (10/72) and 28.5% (20/70) in the placebo group. When comparing these two groups, we observed a statistically significant difference in the preterm delivery rate ($P = .03$). As shown in Table II, the two groups were found similar in regard to age, risk factors for preterm delivery, and obstetric history. There was no significant difference between gestational age at study admission and vaginal infection. Socioeconomic status, estimated by the educational level as well as ethnicity, was similar in both groups. Twenty-two women in the placebo group (31.4%) and 14 in the progesterone group (19.4%) were admitted for preterm labor. However, this difference was not significant. The use of *B*-mimetic drugs in the management of preterm labor demonstrated a significant benefit in the progesterone group ($P = .031$). In the progesterone group, 85.7% of pregnant women had their delivery delayed for more than 72 hours, whereas in the placebo group this was observed in only 36.4% of the patients. Twelve of the 22 pregnant women in the placebo group (54.5%) and 10 of the 14 pregnant women (71.4%) in the progesterone group had a second episode of preterm labor, with an interval time of 3.9 ± 3.2 days and 5.7 ± 2.3 days in the placebo and progesterone groups, respectively ($P = .02$).

The average gestational age for those who had preterm birth was 33.5 ± 2.4 weeks in the progesterone group and 32.0 ± 0.7 weeks in the placebo group. Because preterm birth before 34 weeks is associated with the worst pregnancy outcome, we were especially interested in decreasing preterm birth incidence in this period. In Table III, it can be seen that more women were delivered before 34 weeks in the placebo group (18.6%) than in the progesterone group (2.8%). Figs 1 and 2 show the frequency of preterm delivery before 34 weeks. When the difference in the frequency of preterm birth in the progesterone (2.8%) and placebo (18.8%) groups was compared, a statistically significant difference was observed ($P = .002$).

When survival analysis was used to establish the relationship between prophylactic vaginal progesterone administration and preterm birth, a lower gestational age at delivery correlated with the placebo group (mean 36 ± 3.3 weeks, range 29–41 vs mean 37 ± 2.8 weeks, range 28–41; $P = .029$). The probability of undelivered patients at 34 weeks of gestation was higher in the progesterone group than in the placebo group (97.2% vs 81.4% $P = .029$) (Fig Mean contraction frequency for each gestational week studied was significantly greater for the placebo group than the progesterone group (Table IV). We calculated the maximum number of contractions per hour for each week between 28 and 34 weeks gestation. The frequency of contractions was inferior in the group treated with progesterone than in the placebo group ($P < .004$) (Fig 4). As shown in Table V, the frequency of uterine contractions of more than four contractions per hour was more frequently found in the placebo group than in the progesterone group (54.3% vs 23.6%, respectively; $P = .0001$).

Comment

The results of this study confirm the findings of other studies reporting that progesterone is effective in preventing preterm delivery 20–24. The real mechanism of action of this drug is not well known; however, its clinical usefulness was shown in our study by the decrease in the incidence of preterm birth from 28.1% in the placebo group to 13.8% in the progesterone group.

The difference between the two groups could not be explained in terms of epidemiologic characteristics, obstetric history, or frequency of premature membrane rupture because these parameters were similar in both groups. Our high incidence of spontaneous preterm delivery is related to the presence of a history of at least one preterm birth in the inclusion criteria.

The role of progesterone in pregnancy is unclear; however, we know that the effect of progesterone on the myometrium is 2-fold: it suppresses the action of estrogen by inhibiting the replacement of cytosolic estrogen receptors and it exerts a direct effect on the biosynthetic processes of the uterus through its

own cellular receptor 1,18,19. Thus, the contractile capacity is maintained under the influence of progesterone, as indicated by the development of tension in the electrically stimulated uterus of progesterone-treated rabbits or rats. In the pregnant ewe, very close to the delivery, there is progesterone withdrawal and a surge in estrogen secretion. Myometrial oxytocin receptors appear, gap junctions are developed, and cervical ripening commences 19.

On the other hand, progesterone withdrawal in primates is not an accepted theory, especially when viewed from a classic endocrine aspect 1,19. In humans, serum progesterone-estrogen ratio does not show significant changes. Progesterone level in the blood does not decrease, there is no unusual metabolism of progesterone in the tissues, and there is no major extraplacental site of progesterone production 20, 21. However, a myometrial decrease in progesterone receptors was observed in patients in labor compared with those not in labor in preterm and term pregnancies. This may play a role in the onset of labor in women with term or preterm pregnancies 5, 7,19, 21.

Thus, the concept of progesterone withdrawal as a quiescent biologic phenomenon in humans cannot be easily abandoned. First of all, such mechanisms are dominant in the mammalian world. Second, during the normal menstrual cycle, physiologic progesterone withdrawal occurs after ovulation and before menses 5, 20, 21. Third, corpus luteectomy before the 8th week of gestation is followed by spontaneous abortion 22, 23 and abortion also follows the use of pharmacologic antiprogesterone agents in early pregnancy 22, 23. Some investigators suggest that labor may be stimulated later in pregnancy by these agents 22.

In humans, the effects of progesterone on the frequency of preterm birth were consistent among similar trials. Johnson et al 16 and Yemini et al 14 used 250 mg of 17 α -hydroxyprogesterone caproate by intramuscular injections per week until the 37th week. Papiernik- Berkhauser 24 used the same agent, twice a week, started between 28 and 32 weeks and stopped after eight doses. These authors demonstrated a reduction in preterm delivery rate in the progesterone group and concluded that 17 α -hydroxyprogesterone caproate could be effective in preterm birth prevention.

Daya 22 and Goldstein et al 17 reported separate meta analyses assessing the effects of progestogen administration in pregnancy but reached contradictory conclusions. Daya 22 showed a beneficial effect, whereas Goldstein et al 17 concluded that the data did not support this finding. These authors failed to distinguish between the use of progestogens for early miscarriage because of inadequate luteal phase and the use of progestogens for prophylaxis of preterm labor. Furthermore, in these two meta-analyses, the authors did not compare the same progestational agent. Because there are many differences between these agents, Keirse 25 conducted a third, more restricted meta analysis. He demonstrated that 17 α -hydroxyprogesterone caproate is effective in the prevention of preterm labor and preterm birth with an odds ratio of 0.43 (0.2-0.89) and 0.5 (0.3-0.85), respectively.

The probability to term delivery was higher in the progesterone group; however, there was no significant difference on the incidence of preterm labor in both groups. *B*-Mimetic drugs showed a significant benefit in the management of preterm labor in the progesterone group compared with the placebo group. This important result strongly suggests steroids could be used to stimulate surfactant synthesis in type II alveolar cell in this period.

This study indicates that the prophylactic use of natural progesterone may be associated with the decrease of uterine contractions. However, the lower incidence of preterm delivery in the progesterone group cannot be explained by these findings because uterine activity was only assessed weekly for just 1 hour.

Although we observed better results in the progesterone group, the mechanisms involved are unclear and cannot be explained by this article. Our study strongly suggests that, by administering vaginal natural progesterone in pregnant women with high risk for preterm delivery, it is possible decrease the frequency of preterm birth. However, multicenter randomized clinical trials with others risk factors are required to confirm these results.

References

1. Amon E. Preterm labor. In: Reece EA, Hobbins JC, editors. *Medicine of the fetus and mothers*. Philadelphia: Lippincott-Raven; 1999. p. 1529-79.

2. Rush RW, Davey DA, Segall ML. The effect of preterm delivery on perinatal mortality. *Br J Obstet Gynaecol* 1978;85:806-11.
3. Ehrenhaft PM, Wagner JL, Herdman RC. Changing prognosis for very low birth weight infants. *Obstet Gynecol* 1989;74:528.
4. Challis JRG. Characteristics of parturition. In: Creasy RK, Resnik R, editors. *Maternal fetal medicine*. 4th ed. Philadelphia: WB Saunders; 1999. p. 484-97.
5. Cunningham FG, Macdonald PC, Gant NF, Leveno KJ, Gilstrap LC III, Hankins GDV, et al. Preterm and postterm pregnancy and fetal growth retardation. In: *Williams' obstetrics*. 20th ed. New Jersey: Prentice-Hall International; 1997. p. 797-826.
6. Lockwood CJ, Senyei, AE, Dischie MR, et al. Fetal fibronectina in cervical and vaginal secretions as a predictor of preterm delivery. *N Engl J Med* 1991;325:669-74.
7. Bittar ER, Yamasaki AA, Sasaki S, Zugaib M. Cervical fetal fibronectina in patients at increased risk for preterm delivery. *Am J Obstet Gynecol* 1996;175:178-81.
8. Katz M, Gill P, Newman RB. Detection of preterm labor by ambulatory monitoring of uterine activity: a preliminary report. *Obstet Gynecol* 1986;68:773-8
9. Iams JD. Uterine contraction monitoring and preterm birth. In: Elder MG, Lamont RF, Romero R, editors. *Preterm labor*. Philadelphia: Churchill Livingstone; 1997. p. 185-93.
10. Newman RB, Campbell BA, Stramm SL. Objective tocodynamometry identifies labor onset earlier than subjective maternal perception. *Obstet Gynecol* 1990;76:1089-92.
11. Nageotte MP, Dorchester W, Porto M, Keegan KA, Freeman RK. Quantitation of uterine activity preceding preterm, term and postterm labor. *Am J Obstet Gynecol* 1994;170:20-5.
12. Cunningham FG, Macdonald PC, Gant NF, Leveno KJ, Gilstrap LC III, Hankins GDV, et al. Parturition: biomolecular and physiology processes. In: *Williams' obstetrics*. 20th ed. NJ: Prentice- Hall International; 1997. p. 797-826.
13. Erny R, Pigne A, Prouvost C, Gamerre M, Malet C, Serment H, et al. The effects of oral administration of progesterone for premature labor. *Am J Obstet Gynecol* 1986;154:525.
14. Yemini M, Borestein R, Dreazen E, Apeiman Z, Molginer BM, Kessler I, et al. Prevention of premature labor by 17 x-hydroxyprogesterone caproate. *Am J Obstet Gynecol* 1985;151:574-7.
15. Nobloz G, Andra P, Dargent D, Fagner B, Melner G. The use of micronized progesterone in the treatment of menance of preterm delivery. *Eur J Obstet Gynecol Reprod Biol* 1991;40:203.
16. Johnson JWC, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17-xThydroxyprogesterone caproate in the prevention of premature labor. *N Engl J Med* 1975;293:675-80.
17. Goldstein P, Berrier P, Rosen J, Sachs HS, Chalmers TC. A metaanalysis of randomized control trials of progesterone agents in pregnancy. *Br J Obstet Gynaecol* 1989;96:265-74.
18. Fuchs F, Stakeman G. Treatment of threatened premature labor with large doses of progesterone. *Am J Obstet Gynecol* 1960;79:172.
19. Fuchs AR, Fuchs F. Endocrinology of human parturition: a review. *Br J Obstet Gynaecol* 1984;91:948-67.
20. Keelan JA, Myatt L, Mitchell MD. Endocrinology and paracrinology of parturition. In: Elder MG, Lamont RF, Romero R, editors. *Preterm labor*. Philadelphia: Churchill Livingstone; 1997. p. 457-91.
21. Mazor M, Hershkomitz R, Cham W, Levy S, Sharony Y, Leiberman JR, et al. Human preterm birth is associated with systemic and local changes in progesterone 17 x-estradiol ratios. *Am J Obstet Gynecol* 1994;171:231-6.
22. Daya S. Efficacy of progesterone support for pregnancy in women with recurrent miscarriage: a meta-analysis of controlled trials. *Br J Obstet Gynaecol* 1999;96:275-80.
23. Check JH, Lee G, Epstein R, Vetter B. Increased rate of preterm deliveries in untreated women with luteal phase deficiencies. *Gynecol Obstet Invest* 1992;33:183-4.
24. Papiernik-Berkhauer E. Etude en double aveugle d'un medicament prevenant la survenue prématurée de l'accouchement chez les femmes 'à risque élevé' d'accouchement prématuré. In: Edition Schering, Serie IV, fiche. p. 65-8.
25. Keirse MJN. Progestogen administration in pregnancy may prevent preterm delivery. *Br J Obstet Gynaecol* 1990;97:149-54.

Appendix 4 Text copy of a CAT

Is prophylactic use of progesterone by vaginal suppository useful to reduce the risk of preterm birth in women at increased risk?

The study shows that by administering vaginal progesterone in pregnant women with high risk for preterm delivery, it is possible to decrease the frequency of preterm birth.

Citation/s: Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomised placebo controlled double blind study. Am J Obstet Gynecol 188 (2) 419-424.

Lead author's name and fax: Eduardo B. da Fonseca. **Three-part Clinical Question:** Does (prophylactic use of progesterone by vaginal suppository) (reduce the risk of preterm birth) in (pregnant women at high risk?). **Search Terms:** preterm delivery OR preterm birth / progesterone AND vaginal suppository / prevention OR risk. PubMed searched and limited to randomised controlled trial.

The Study: Double-blinded concealed randomised controlled trial without intention-to-treat.

The Study Patients: Women at high risk of PTB / uterine malformation / incompetent cervix / gestational age at intake was 25.2 to 26.5 weeks. **Control group** (N = 75; 70 analysed): placebo

Experimental group (N = 82; 72 analysed): progesterone 100 mg by vaginal suppository / daily

Outcome	Time to Outcome	CER	EER	RRR	ARR	NNT
Contraction frequency at gestational age 28 weeks	28 weeks	0.053	0.015	72%	0.038	26
	95% Confidence Intervals:			-36% to 100%	-0.019 to 0.095	NNT = 11 to INF; NNH = 52 to INF
Contraction frequency at gestational age 30 weeks	30 weeks	0.079	0.035	56%	0.044	23
	95% Confidence Intervals:			-37% to 100%	-0.029 to 0.117	NNT = 9 to INF; NNH = 35 to INF
32 weeks	32 weeks	0.081				
	95% Confidence Intervals:				NAN to NAN	

Measure	Control Group		Experimental Group		Difference	95% CI
	Mean	SD	Mean	SD		
Contraction freq 28 weeks	4.0	3.0	1.0	0.6	3.000	1.468 to 4.532
30 weeks	6.2	3.0	2.8	2.7	3.400	0.703 to 6.097
32 weeks	6.5	3.1	2.5	2.5	4.000	1.378 to 6.622

Non-Event Outcomes	Time to outcome/s	Control group	Experimental group	P-value
Incidence of preterm delivery	< 37 weeks	20	10	0.03
Incidence of preterm delivery	< 34 weeks	13	2	0.002
Admission for threatened preterm labour		22	14	NS

Comments:

This study shows a decrease in the incidence of preterm birth from 28.1% in the placebo group to 13.8% in the progesterone group. It appears to be well conducted, although the number of participants is small. Further studies are needed in order to compare results, look at the possible adverse effects of progesterone and follow up the long term health of the baby.

Appendix 5 Criteria for assessing Journal Club presenters

Name of presenter.....

Date of presentation

Name of Chair

Question / topic

Study selected.....

.....

1. Were the following slides included in the presentation?

A clear question

Aims and objectives

A case report / context of the question

Literature search (databases / PICO / search terms)

Details of any Guidelines relating to the study

Bibliographic details of the paper selected

A flow chart of the study / details of the study

Appraisal of the study using the GATE Frame

A summary / conclusion

A CAT

2. Quality of the presentation

On a scale of 1 to 4: 1 excellent / 2 good / 3 adequate / 4 needs attention

Clear communication 1 2 3 4

Good use of media 1 2 3 4

Interactive 1 2 3 4

A positive response to comment / criticism 1 2 3 4

3. Did the presenter put enough time and effort into the presentation as a whole?

On a scale of 1 to 3: 1 good time & effort / 2 just enough / 3 more time & effort needed

1

2

3

4. Did the presenter generally demonstrate good knowledge of the topic presented?

On a scale of 1 to 4: 1 good knowledge held / 4 poor knowledge held

1

2

3

4

Comments

.....

.....

Completed by