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Fetal fibronectin testing for reducing the risk of preterm birth (Review)

Berghella V, Hayes E, Visintine J, Baxter JK

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Vincenzo Berghella[1], Edward Hayes[2], John Visintine[2], Jason K Baxter[2]

[1]Director, Division of Maternal Fetal Medicine, Thomas Jefferson University, Philadelphia, USA. [2]Department of Obstetrics and Gynecology, Thomas Jefferson University, Philadelphia, USA

Contact address: Vincenzo Berghella, Director, Division of Maternal Fetal Medicine, Thomas Jefferson University, 834 Chestnut Street, Suite 400, Philadelphia, PA 19107, USA. vincenzo.berghella@jefferson.edu.

A B S T R A C T

Background

Fetal fibronectin (FFN) is an extracellular matrix glycoprotein localized at the maternal-fetal interface of the amniotic membranes, between chorion and decidua, where it is concentrated in this area between decidua and trophoblast. In normal conditions, FFN is found at very low levels in cervico-vaginal secretions. Levels greater than or equal to 50 ng/mL at or after 22 weeks have been associated with an increased risk of spontaneous preterm birth. In fact, FFN is one of the best predictors of preterm birth in all populations studied so far, and can help selecting which women are at significant risk for preterm birth.

Objectives

To assess the effectiveness of management based on knowledge of FFN testing results for preventing preterm birth.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (January 2008), MEDLINE (1966 to December 2007) and all references in identified articles.

Selection criteria

Randomized controlled trials of pregnant women between the gestational ages of 22 and 34 weeks screened with FFN for risk of preterm birth. Studies included are based exclusively on knowledge of FFN results versus no such knowledge, and we have excluded studies including women with only positive or only negative FFN results.

Data collection and analysis

All four authors assessed studies for inclusion and quality and extracted data.

Main results

We identified 13 trials, of which five were eligible for inclusion. The five included studies randomized 474 women, of which 235 were randomized to knowledge and 249 to no knowledge of FFN.

Preterm birth less than 37 weeks was significantly decreased with management based on knowledge of FFN results (15.6%) versus controls without such knowledge (28.6%; risk ratio 0.54; 95% confidence interval 0.34 to 0.87). All other outcomes for which there were available data (preterm birth at less than 34, 32, or 28 weeks; gestational age at delivery; birthweight less than 2500 grams; perinatal death; maternal hospitalization; tocolysis; steroids for fetal lung maturity; and time to evaluate) were similar in the two groups. No other maternal or neonatal outcome was available for meaningful analysis.

Authors' conclusions

Although FFN is commonly used in labor and delivery units to help in the management of women with symptoms of preterm labor, currently there is not sufficient evidence to recommend its use. Since this review found an association between knowledge of FFN results and a lower incidence of preterm birth before 37 weeks, further research should be encouraged.

PLAIN LANGUAGE SUMMARY

Fetal fibronectin testing for reducing the risk of preterm birth

Preterm birth before 37 weeks is the main cause of death and sickness for newborn infants. While most women have preterm labor symptoms such as contractions before having a preterm birth, most such women with symptoms deliver at term (greater than or equal to 37 weeks). Fetal fibronectin is a test that can identify the women with symptoms of preterm labor most at risk for preterm birth by measuring the level in secretions from the vagina and/or cervix. This review of five controlled studies that randomised 474 pregnant women did not find enough evidence to support or refute the use of the fetal fibronectin test for the management of women with symptoms of preterm labor. Further research should be encouraged.

BACKGROUND

Importance of preterm birth

Preterm birth is defined by the World Health Organization as birth between 20 and 36 6/7 weeks. Its incidence is about 5% to 8% in most developed and developing countries. This incidence is increasing in many countries, including developing countries.

Preterm birth is the main cause of neonatal morbidity and mortalities in most countries, especially in developed countries. In the USA, 75% of perinatal mortality occurs in preterm babies; more than two-thirds of perinatal mortality (60% of total) occurs in infants born at less than 32 week. Mortality and morbidities are inversely associated with gestational age at birth. Morbidities include respiratory distress syndrome (RDS), bronchopulmonary dysplasia, intraventricular haemorrhage (IVH), necrotizing enterocolitis, sepsis, retinopathy, etc. All members of a family in which a preterm birth occurs suffer greatly, in several aspects, including medically, socially, psychologically, and financially.

Interventions to reduce preterm birth

Despite extensive research efforts, the incidence of preterm birth is increasing in many countries. It has increased to 12.9% in 2006 in the USA (a greater than 20% increase in the last 10 years), representing more than 500,000 births in this nation alone. Preterm birth can be spontaneous, and follow preterm labor (50%), or

preterm premature rupture of membranes (30%); or be iatrogenic (20%). The interventions that have been shown to effectively reduce the risk of preterm birth or improve outcomes for babies born preterm in asymptomatic women have been smoking cessation counselling for smokers (Lumley 2004); antibiotics for asymptomatic bacteriuria (Smaill 2001); intramuscular progesterone for women with prior preterm birth now carrying a singleton gestation (Dodd 2006); ultrasound-indicated cerclage in women with both a prior preterm birth and shortening of cervical length less than 25 mm before 24 weeks in the current singleton pregnancy (Berghella 2005); and history-indicated cerclage in women with three or more prior preterm births or second trimester losses (Drakeley 2003). In symptomatic women, corticosteroids (betamethasone 12 mg intramuscularly for 2 doses 24 hours apart between 24 and 33 6/7 weeks is preferred if available) given to mother prior to preterm birth are effective in preventing RDS, IVH, and neonatal mortality (Roberts 2006). Cyclo-oxygenase inhibitors are the only class of primary tocolysis shown to decrease preterm birth before 37 weeks in women with preterm labor compared to placebo, but this effectiveness is based on less than 100 randomized women (King 2005).

Fetal fibronectin to predict and reduce preterm birth

Fetal fibronectin is an extracellular matrix glycoprotein. Fetal fibronectin in biologic fluids is produced by amniocytes and by cytotrophoblast. It is present throughout gestation in all pregnancies. It is not subject to genetic polymorphism. There are very high

levels in amniotic fluid (100 μg/mL) in the second trimester, and 30 μg/mL at term. It is localized at the maternal-fetal interface of the amniotic membranes, between chorion and decidua, where it is concentrated in this area between decidua and trophoblast. Here it acts as a 'glue' between the pregnancy and the uterus. Concentration of fetal fibronectin protein found in blood is 1/5 that found in amniotic fluid; it is not present in urine. In normal conditions, this glycoprotein remains in this area between chorion and decidua, and very low levels are found in cervico-vaginal secretions after 22 weeks (less than 50 ng/mL). Levels above this value (greater than or equal to 50 ng/mL) at or after 22 weeks in the cervico-vaginal secretions collected by a swab have been associated with an increased risk of spontaneous preterm birth.

The fetal fibronectin test assesses risk of preterm labor and preterm birth by measuring amount of fetal fibronectin in cervicovaginal secretions. In fact, fetal fibronectin is one of the best predictors of preterm birth in all populations studied so far, including low- and high-risk women without preterm labor, twins, and women in preterm labor (Leitich 1999). The overall sensitivity and specificity are 56% and 84% for preterm before 37 weeks, respectively, but vary according to gestational age at collection, population studied, prevalence of preterm birth, single versus multiple screening, etc (Leitich 1999). Its positive predictive value varies from about 9% to 46% depending on the incidence of preterm labor in the population studies (Leitich 1999). Even at 13 to 22 weeks, higher (using 90th percentile) fetal fibronectin levels are associated with a two- to three-fold increase risk in subsequent spontaneous preterm labor.

OBJECTIVES

To assess the outcome of management based on knowledge of fetal fibronectin testing results for preventing preterm birth.

METHODS

Criteria for considering studies for this review

Types of studies
Published and unpublished randomized and quasi-randomized controlled trials.

Types of participants
Pregnant women between the gestational ages of 22 and 34 weeks screened with fetal fibronectin for risk of preterm birth.

Types of interventions
A screening test such as fetal fibronectin can only be considered effective if interventions based on fetal fibronectin screening results reduce the outcome of preterm birth. Interventions based on fetal fibronectin screening results can also be classified as:

1. interventions based on knowledge of fetal fibronectin results (e.g. fetal fibronectin is collected on all women, but women are randomized so that in 50% of them the result is available to them and the managing obstetrician, while in 50% the fetal fibronectin is blind to them and the managing obstetrician; or fetal fibronectin screening is done only on half of the women);
2. interventions based on positive fetal fibronectin;
3. interventions based on negative fetal fibronectin.

This review focuses exclusively on (1), i.e. interventions based on knowledge of fetal fibronectin results.

Types of outcome measures

Primary outcomes
(1) Preterm birth (less than 37 weeks)

Secondary outcomes
(2) Preterm birth less than 34 weeks
(3) Preterm birth less than 32 weeks
(4) Preterm birth less than 28 weeks
(5) Gestational age at delivery
(6) Birthweight less than 2500 grams
(7) Perinatal death (fetal death and neonatal death)
(8) Maternal hospitalisation
(9) Tocolysis
(10) Steroids for fetal lung maturity
(11) Time to evaluate (time from arrival to hospital for evaluation of preterm labor to decision regarding admission, discharge, or extended monitoring)
(12) Respiratory distress syndrome
(13) Intraventricular haemorrhage
(14) Necrotizing enterocolitis
(15) Sepsis
(16) Neonatal intensive care unit (NICU) admission
(17) NICU days
(18) Maternal well-being (e.g. stress level, etc)
(19) Economic analysis (cost effectiveness, cost utility)

We will report outcomes 1,2,3,4,5,8,9,10,11,18, and 19 with 'mothers' are the denominators. We will report outcomes 6,7,12,13,14,15,16, and 17 with 'fetuses/neonates' as denominator.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (January 2008).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);

2. weekly searches of MEDLINE;

3. handsearches of 30 journals and the proceedings of major conferences;

4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

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

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

In addition, we searched MEDLINE (January 1966 to December 2007) using the search strategy detailed in Appendix 1.

We reviewed the reference list of all articles, in particular trials and review articles. We contacted all researchers of included trials to provide actual databases and any pertinent further information. We contacted experts in the field for additional and ongoing trials. We did not apply any language restrictions.

Data collection and analysis

Selection of studies

We assessed for inclusion all potential studies we identified as a result of the search strategy. Independently, all authors assessed studies for inclusion in the review using the inclusion criteria. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. All authors independently extracted the data using the agreed form. We resolved any disagreement through discussion. We used the Review Manager software (RevMan 2008) to double enter all the data or a subsample.

When information regarding any of the above is unclear, or to obtain additional data not published, we contacted authors of the original reports to provide further details.

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). Methods used for generation of the randomization sequence were described for each trial.

(1) Selection bias (allocation concealment)

We assigned a quality score for each trial, using the following criteria:

(A) adequate concealment of allocation: such as telephone randomization, consecutively-numbered, sealed opaque envelopes;

(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;

(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:

(A) less than 5% loss of participants;

(B) 5% to 9.9% loss of participants;

(C) 10% to 19.9% loss of participants;

(D) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:

(1) blinding of participants (yes/no/unclear);

(2) blinding of caregiver (yes/no/unclear);

(3) blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. If heterogeneity was found, we explored this by sensitivity analysis followed by random-effects if required.

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardized mean difference to combine trials that measure the same outcome, but used different methods. If there was evidence of skew ness, we reported this.

Unit of analysis issues

Cluster-randomized trials

We identified no cluster-randomized trials.

Dealing with missing data

We analysed data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analysed in the group to which they were randomized, and there was sufficient information in the trial report or in the databases submitted, we attempted to restore them to the correct group.

Assessment of heterogeneity

We applied tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we identified high levels of heterogeneity among the trials (exceeding 50%), we explored it by prespecified subgroup analysis and performed sensitivity analysis. A random-effects meta-analysis was used as an overall summary if this was considered appropriate.

Subgroup analyses

We planned to conduct subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. We planned to carry out the following group analyses:

1. asymptomatic compared with signs and symptoms of preterm labor;
2. low-risk singleton gestations compared with high-risk (e.g. prior preterm labor) singleton gestations;
3. singleton pregnancies compared with multiple gestations;
4. timing of availability of results;
5. gestational age at collection of fetal fibronectin (22 to 23, 24 to 28, more than 28 weeks).

Sensitivity analyses

We carried out sensitivity analysis to explore the effect of trial quality. This involved analysis based on an A, B, C, or D rating of selection bias and attrition bias. We excluded studies of poor quality in the analysis (those rating B, C, or D) in order to assess for any substantive difference to the overall result.

We carried out sensitivity analysis to explore the effect of trial quality assessed by concealment of allocation, by excluding studies with clearly inadequate allocation of concealment (rated C).

If we included quasi-randomized trials in the review, we planned to perform a sensitivity analysis by trial quality.

R E S U L T S

Description of studies

Our search identified 13 trials, of which five were eligible for inclusion. We identified no quasi-randomized trials. We excluded seven of the eight excluded studies because they only included women with positive or only with negative fetal fibronectin (FFN) results. The other excluded study (Kalchbrenner 1999) did not report data regarding the results of the FFN test, with no management reported based on FFN results.

The five included studies randomized 474 women, of which 235 were randomized to knowledge and 249 to no knowledge of FFN. Of the included studies, one study (Ness 2007) used knowledge of both FFN and transvaginal ultrasound cervical length for management interventions. We requested patient-level databases from all authors, and obtained them from two trials (Ness 2007; Plaut 2003), and additional information (but not the database) from one other trial (Grobman 2004), despite multiple attempts with the other authors. Our analysis was based on singleton gestations, and this was possible for all included studies, except for Nguyen 2002 (unclear if twins included) and Lowe 2004 (eight twins included). We avoided repeated entries of the same patients, which was possible since we had patient-level data for the one trial where this occurred (Plaut 2003).

Risk of bias in included studies

Risk of selection bias was not present in four of the five included studies. The fifth study (Nguyen 2002) did not describe allocation concealment (only the abstract of this study has been published). All randomized patients were included in an intention-to-treat analysis in two trials (Grobman 2004; Ness 2007). This could not be assessed in one trial (Nguyen 2002), which was reported only as an abstract. Approximately 12% of randomized patients were excluded from analysis after randomization in the other two included trials (Lowe 2004; Plaut 2003). Attrition bias in terms

of loss of data on outcomes analysed was 21% in Plaut 2003, and even higher for some outcomes in Ness 2007.

Performance bias was present in all trials, as participants and researchers were aware of the arm to which they were randomized, but this was inevitable.

Effects of interventions

Preterm birth before 37 weeks was significantly decreased with management based on knowledge of FFN results (15.6%) versus controls without such knowledge (28.6%; risk ratio (RR) 0.54; 95% confidence interval 0.34 to 0.87). All trials had RRs less than one, with no significant heterogeneity. All other outcomes for which there were available data (preterm birth less than 34, 32, or 28 weeks; gestational age at delivery (weeks); birthweight less than 2500 grams; perinatal death; maternal hospitalisation; tocolysis; steroids for fetal lung maturity; and time to evaluate) were similar in the two groups. No other maternal or neonatal outcome was available for meaningful analysis.

Subgroup analyses were not feasible, since all women included had signs and symptoms of preterm labor; low-risk singleton gestations were not reported separately from high-risk (e.g. prior preterm labor) singleton gestations; there were insufficient data for multiple gestations, timing of availability of results, and gestational age at collection of FFN to make meaningful comparisons.

DISCUSSION

Knowledge of fetal fibronectin results in the management of women with symptoms of preterm labor is associated with a lower incidence of preterm birth before 37 weeks. As all our available outcomes were not affected, and no perinatal outcome other than perinatal death was reported, further research is necessary before fetal fibronectin testing can be recommended in this clinical scenario. Furthermore, it is still unclear which interventions are most beneficial once fetal fibronectin results are known. In fact, only one

study (Ness 2007) reported a detailed protocol of management based on fetal fibronectin (and cervical length) results, and could be replicated in further research trials or clinical management. Our review did not include, by design, assessment of effectiveness of interventions based on positive fetal fibronectin testing, or negative fetal fibronectin testing. We identified no trials on women without signs or symptoms of labor.

AUTHORS' CONCLUSIONS

Implications for practice

Although fetal fibronectin is marketed and commonly used in labor and delivery units to help in the management of women with symptoms of preterm labor, currently there is not sufficient evidence to recommend its use.

Implications for research

Since this review found an association between knowledge of fetal fibronectin results and a lower incidence of preterm birth before 37 weeks, further research should be encouraged, minimizing attrition bias. Future studies should include specific populations (e.g. singleton gestations with symptoms of preterm labor), a study group managed with a protocol based on the fetal fibronectin results, and report not only maternal but also significant perinatal outcomes. Cost-effect analyses are also needed.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Grobman 2004

Methods	Randomized controlled trial.
Participants	24-34 week singletons with > 6 contractions/hour. Twins excluded Number of participants: 100 (50/50: knowledge/no knowledge).
Interventions	FFN knowledge or not. Time FFN results available: unknown. Protocol for FFN knowledge group: no.
Outcomes	Primary: total costs.
Notes	Intention to treat; only singletons; no protocol. Positive FFN test in each group: 5 (10%) in knowledge, 3 (6%) in no knowledge group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Computer-generated, opaque envelopes.

Lowe 2004

Methods	Randomized controlled trial.
Participants	23-34 week singletons/twins with contractions +/- cervical change Number of participants: 97 [89 singletons/8 twins] (46/51: knowledge/no knowledge)
Interventions	FFN knowledge or not. Time FFN results available: < 1 hour. Protocol for FFN knowledge group: no.
Outcomes	Primary: length of stay.
Notes	13/110 excluded post-randomization: not intention to treat; included twins; no protocol Positive FFN test in each group: 11 (24%) in knowledge group; FFN test not performed in no knowledge group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Computer-generated, opaque envelopes, blocks of 10.

Ness 2007

Methods	Randomized controlled trial.
Participants	24-33 6/7 week singletons/twins with >= 6 contractions/hour or symptoms of PTL Number of participants: 100 [97 singletons, 3 twins] (49/51: knowledge/no knowledge)
Interventions	FFN (and cervical length) knowledge versus not. Time FFN results available: < 1 hour. Protocol for FFN knowledge group: yes.
Outcomes	Primary: time from initial evaluation to discharge from triage area
Notes	Intention to treat; included twins; protocol. Positive FFN test in each group: 10 (20%) in knowledge, 10 (22%) in no knowledge group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Computer-generated, opaque envelopes.

Nguyen 2002

Methods	Randomized controlled trial.
Participants	24-35 week (unclear if twins included) with symptoms of PTL. Number of participants: 77 (42/35: knowledge/no knowledge).
Interventions	FFN testing done (and knowledge available) versus not done (so knowledge not available) Time FFN results available: unknown. Protocol for FFN knowledge group: yes.
Outcomes	Primary: cost-effectiveness.
Notes	Abstract only; unclear if intention to treat, twins included, protocol, etc Positive FFN test in each group: not available in knowledge group; FFN not performed in no knowledge group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	No description available (only abstract published).

Plaut 2003

Methods	Randomized controlled trial.
Participants	24-34 6/7 week singletons/twins with 'symptoms of PTL'. Number of participants: 114 (unclear from text) randomized [96 singleton, 12 twins] (analysed: 51/57: knowledge/no knowledge)
Interventions	FFN knowledge or not. Time FFN results available: 1-2 hours. Protocol for FFN knowledge group: no.
Outcomes	Primary: transport rates (not reported).
Notes	6/114 (?) excluded post-randomization: not intention to treat; 8 patients entered in study twice!; stopped trial prematurely; sponsored by Adeza; included twins; no protocol Positive FFN test in each group: 6 (12%) in knowledge, 6 (10.5%) in no knowledge group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Computerized opaque envelopes.

FFN: fetal fibronectin
PTL: preterm labor

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andrews 2001	Only women with positive FFN were included.
Bisits 2004	Only women with positive FFN were included. They were randomized to tocolysis or not
Elliott 2005	Only women with negative FFN were included.
Goldenberg 2001	Only women with positive FFN were included (secondary analysis of NICHD BV/TV study)
Hauth 2001	Only women with positive FFN were included.
Kalchbrenner 1999	This was a trial comparing speculum versus digital collection of FFN. There were no data regarding the results of the FFN test, and no intervention was reported based on FFN results
Lachelin 2004	Only women with positive FFN were included. This is an ongoing trial not yet published

Shennan 2006	Only women with positive FFN were included.

FFN: fetal fibronectin

DATA AND ANALYSES

Comparison 1. Comparison 01 FFN knowledge versus no knowledge, Outcome 01 Preterm birth < 37 week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 01 Preterm birth < 37 weeks	3	275	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.34, 0.87]

Comparison 2. Comparison 01 FFN knowledge versus no knowledge, Outcome 02 Preterm birth < 34 week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 02 Preterm birth < 34 week	3	281	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.41, 2.47]

Comparison 3. Comparison 01 FFN knowledge versus no knowledge, Outcome 03 Preterm birth < 32 week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 03 Preterm birth < 32 week	3	282	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.28, 2.58]

Comparison 4. Comparison 01 FFN knowledge versus no knowledge, Outcome 04 Preterm birth < 28 week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 04 Preterm birth < 28 week	3	284	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.82]

Comparison 5. Comparison 01 FFN knowledge versus no knowledge, Outcome 05 Gestational age at delivery (weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 05 Gestational age at delivery	3	288	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.35, 0.93]

Comparison 6. Comparison 01 FFN knowledge versus no knowledge, Outcome 06 Birthweight 2500 grams

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 06 Birthweight < 2500 g	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.21, 2.44]

Comparison 7. Comparison 01 FFN knowledge versus no knowledge, Outcome 07 Perinatal death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 07 Perinatal death	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 8. Comparison 01 FFN knowledge versus no knowledge, Outcome 08 Maternal hospitalization

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 08 Maternal hospitalization	3	290	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.90, 2.07]

Comparison 9.   Comparison 01 FFN knowledge versus no knowledge, Outcome 09 Tocolysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 09 Tocolysis	4	350	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.30]

Comparison 10.   Comparison 01 FFN knowledge versus no knowledge, Outcome 10 Steroids for fetal lung maturity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 10 Steroids for Fetal Lung Maturity	3	270	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.85, 1.79]

Comparison 11.   Comparison 01 FFN knowledge versus no knowledge, Outcome 11 Time to evaluate (hours)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome 11 Time to evaluate	3	234	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.39, 0.47]

Analysis 1.1.   Comparison 1 Comparison 01 FFN knowledge versus no knowledge, Outcome 01 Preterm birth < 37 week, Outcome 1 Outcome 01 Preterm birth < 37 weeks.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 1 Comparison 01 FFN knowledge versus no knowledge, Outcome 01 Preterm birth < 37 week

Outcome: 1 Outcome 01 Preterm birth < 37 weeks

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grobman 2004	10/50	13/50		33.1 %	0.77 [0.37, 1.59]
Ness 2007	6/42	15/43		37.7 %	0.41 [0.18, 0.95]
Plaut 2003	5/43	12/47		29.2 %	0.46 [0.17, 1.19]
Total (95% CI)	**135**	**140**		**100.0 %**	**0.54 [0.34, 0.87]**

Total events: 21 (Treatment), 40 (Control)

Heterogeneity: Chi² = 1.44, df = 2 (P = 0.49); I² =0.0%

Test for overall effect: Z = 2.53 (P = 0.011)

Test for subgroup differences: Not applicable

```
        0.05   0.2    1    5    20
     Favours treatment    Favours control
```
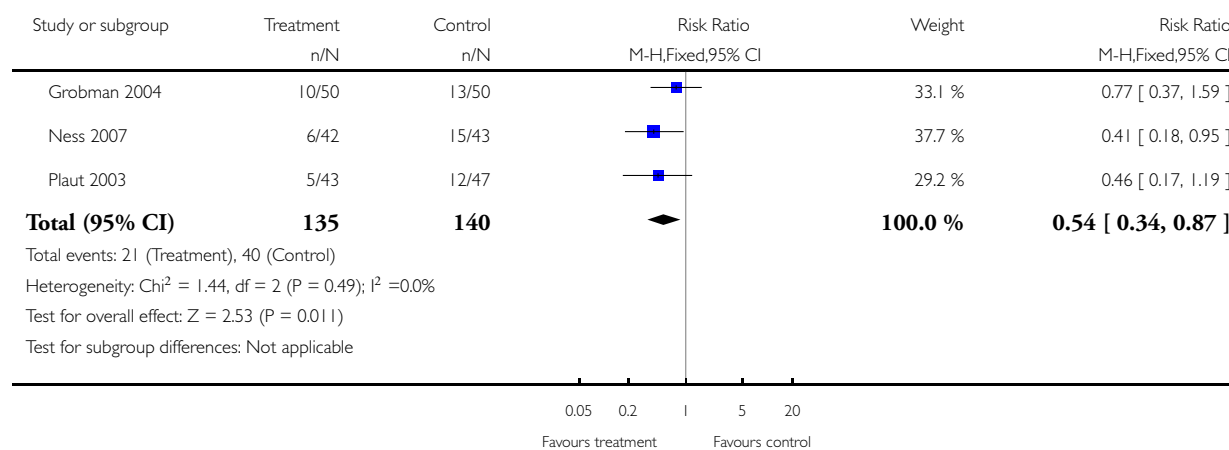
Analysis 2.1. Comparison 2 Comparison 01 FFN knowledge versus no knowledge, Outcome 02 Preterm birth < 34 week, Outcome 1 Outcome 02 Preterm birth < 34 week.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 2 Comparison 01 FFN knowledge versus no knowledge, Outcome 02 Preterm birth < 34 week

Outcome: 1 Outcome 02 Preterm birth < 34 week

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grobman 2004	5/50	3/50		33.5 %	1.67 [0.42, 6.60]
Ness 2007	2/46	4/45		45.2 %	0.49 [0.09, 2.54]
Plaut 2003	2/43	2/47		21.3 %	1.09 [0.16, 7.42]
Total (95% CI)	**139**	**142**		**100.0 %**	**1.01 [0.41, 2.47]**

Total events: 9 (Treatment), 9 (Control)

Heterogeneity: Chi^2 = 1.26, df = 2 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 0.03 (P = 0.98)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1      10    100
      Favours treatment    Favours control
```
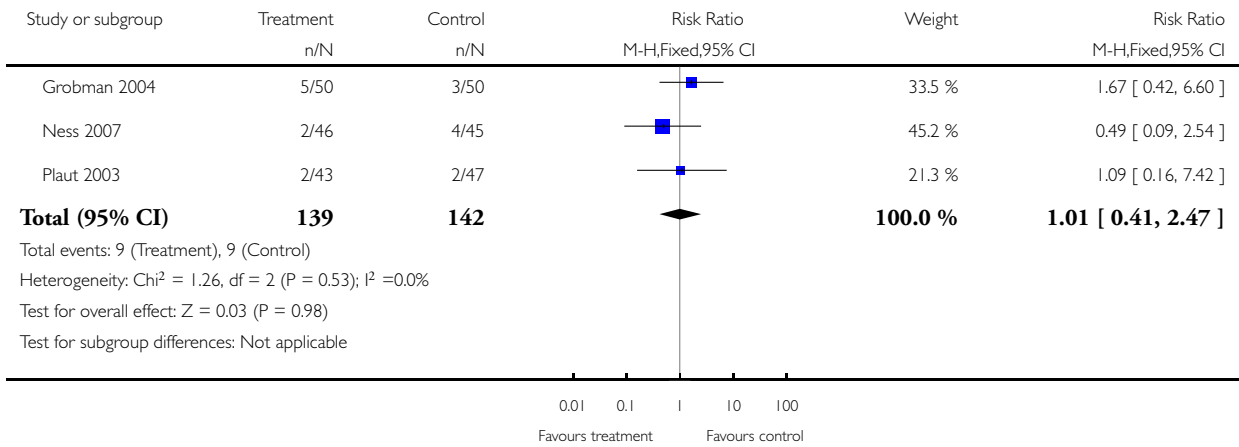
Analysis 3.1.   Comparison 3 Comparison 01 FFN knowledge versus no knowledge, Outcome 03 Preterm birth < 32 week, Outcome 1 Outcome 03 Preterm birth < 32 week.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 3 Comparison 01 FFN knowledge versus no knowledge, Outcome 03 Preterm birth < 32 week

Outcome: 1 Outcome 03 Preterm birth < 32 week

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Grobman 2004	3/50	2/50		30.6 %	1.50 [0.26, 8.60]
Ness 2007	0/47	3/45		54.7 %	0.14 [0.01, 2.58]
Plaut 2003	2/43	1/47		14.6 %	2.19 [0.21, 23.26]
Total (95% CI)	**140**	**142**		**100.0 %**	**0.85 [0.28, 2.58]**

Total events: 5 (Treatment), 6 (Control)

Heterogeneity: Chi^2 = 2.50, df = 2 (P = 0.29); I^2 =20%

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours treatment   Favours control
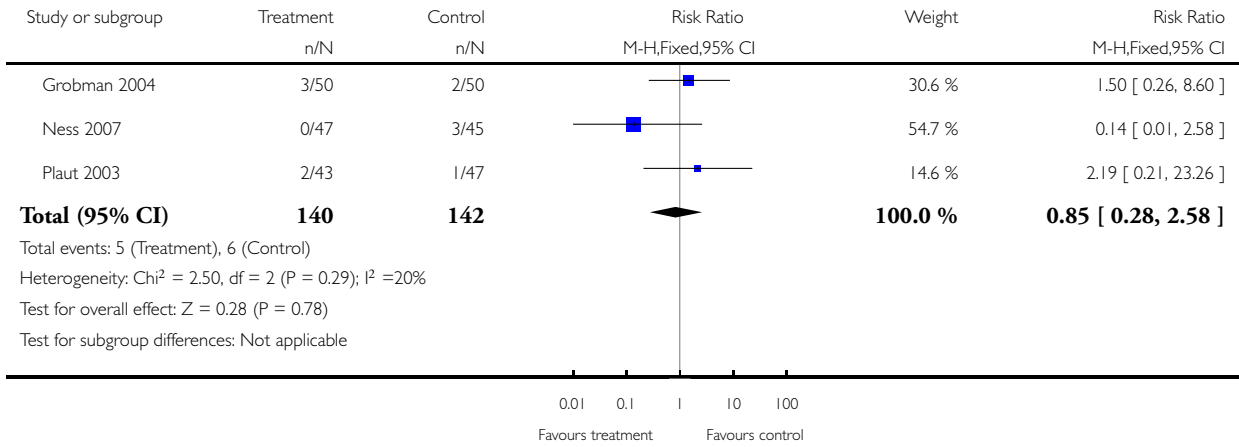
Analysis 4.1.   Comparison 4 Comparison 01 FFN knowledge versus no knowledge, Outcome 04 Preterm birth < 28 week, Outcome 1 Outcome 04 Preterm birth < 28 week.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 4 Comparison 01 FFN knowledge versus no knowledge, Outcome 04 Preterm birth < 28 week

Outcome: 1 Outcome 04 Preterm birth < 28 week

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Grobman 2004	2/50	2/50		100.0 %	1.00 [0.15, 6.82]
Ness 2007	0/48	0/46			Not estimable
Plaut 2003	0/43	0/47			Not estimable
Total (95% CI)	**141**	**143**		**100.0 %**	**1.00 [0.15, 6.82]**

Total events: 2 (Treatment), 2 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100

     Favours treatment      Favours control
```
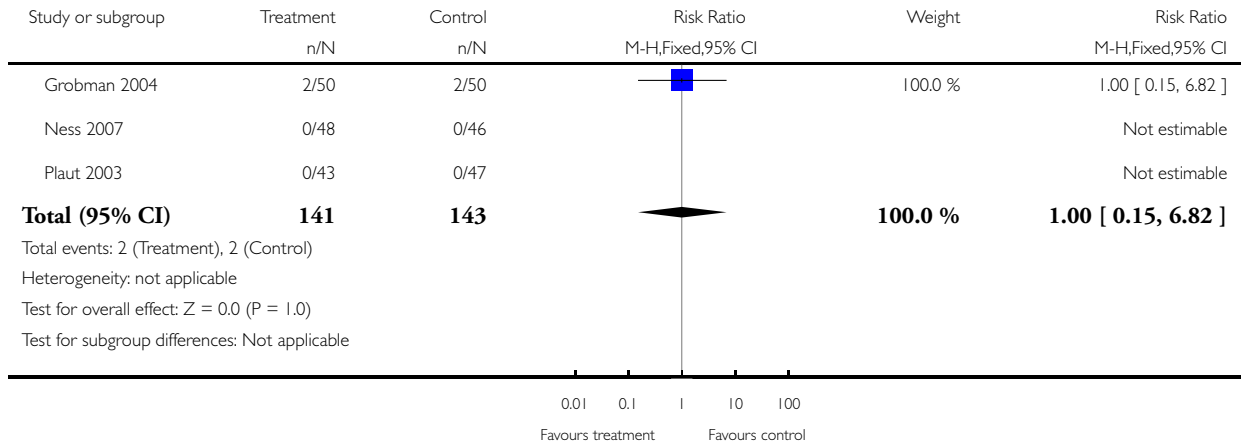
Analysis 5.1. Comparison 5 Comparison 01 FFN knowledge versus no knowledge, Outcome 05 Gestational age at delivery (weeks), Outcome 1 Outcome 05 Gestational age at delivery.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 5 Comparison 01 FFN knowledge versus no knowledge, Outcome 05 Gestational age at delivery (weeks)

Outcome: 1 Outcome 05 Gestational age at delivery

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Grobman 2004	50	38 (3)	50	38 (3)		29.7 %	0.0 [-1.18, 1.18]
Ness 2007	42	38.4 (1.8)	38	37.2 (2.8)		37.7 %	1.20 [0.16, 2.24]
Plaut 2003	51	29.9 (3.2)	57	30.4 (2.7)		32.5 %	-0.50 [-1.62, 0.62]
Total (95% CI)	**143**		**145**			**100.0 %**	**0.29 [-0.35, 0.93]**

Heterogeneity: Chi² = 5.05, df = 2 (P = 0.08); I² =60%

Test for overall effect: Z = 0.89 (P = 0.38)

Test for subgroup differences: Not applicable

```
     -1   -0.5    0    0.5    1
   Favours treatment   Favours control
```
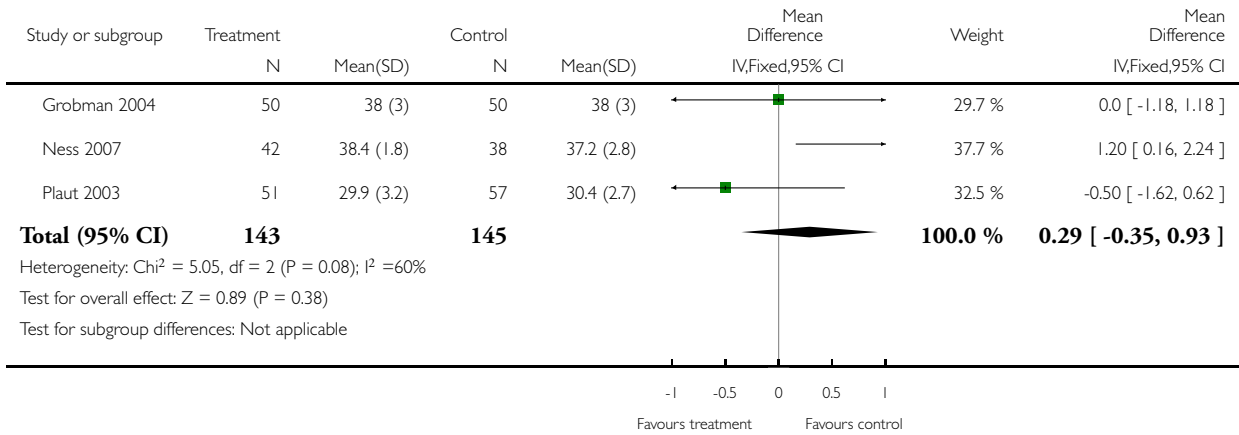
Analysis 6.1. Comparison 6 Comparison 01 FFN knowledge versus no knowledge, Outcome 06 Birthweight 2500 grams, Outcome 1 Outcome 06 Birthweight < 2500 g.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 6 Comparison 01 FFN knowledge versus no knowledge, Outcome 06 Birthweight 2500 grams

Outcome: 1 Outcome 06 Birthweight < 2500 g

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Ness 2007	4/37	5/33		100.0 %	0.71 [0.21, 2.44]
Total (95% CI)	**37**	**33**		**100.0 %**	**0.71 [0.21, 2.44]**

Total events: 4 (Treatment), 5 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

```
   0.01   0.1    1    10    100
   Favours treatment   Favours control
```
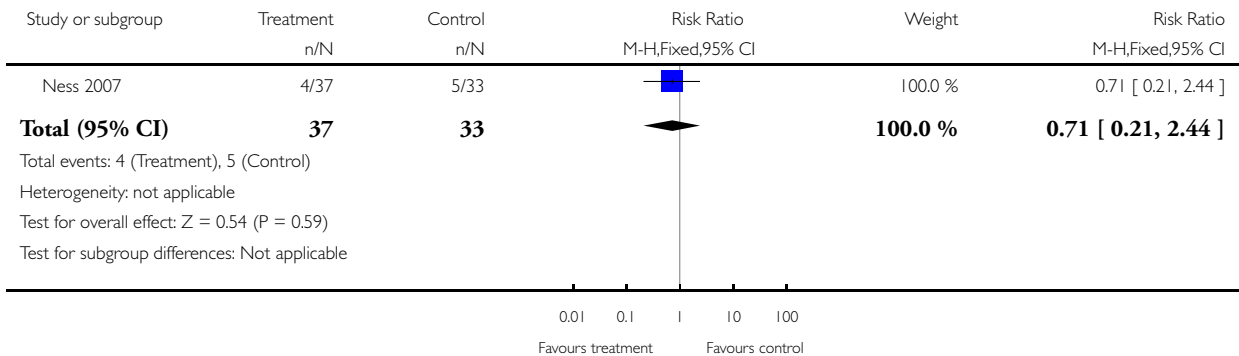
Analysis 7.1.   Comparison 7 Comparison 01 FFN knowledge versus no knowledge, Outcome 07 Perinatal death, Outcome 1 Outcome 07 Perinatal death.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 7 Comparison 01 FFN knowledge versus no knowledge, Outcome 07 Perinatal death

Outcome: 1 Outcome 07 Perinatal death

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ness 2007	0/49	0/48			Not estimable
Total (95% CI)	**49**	**48**			**Not estimable**

Total events: 0 (Treatment), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours treatment   Favours control
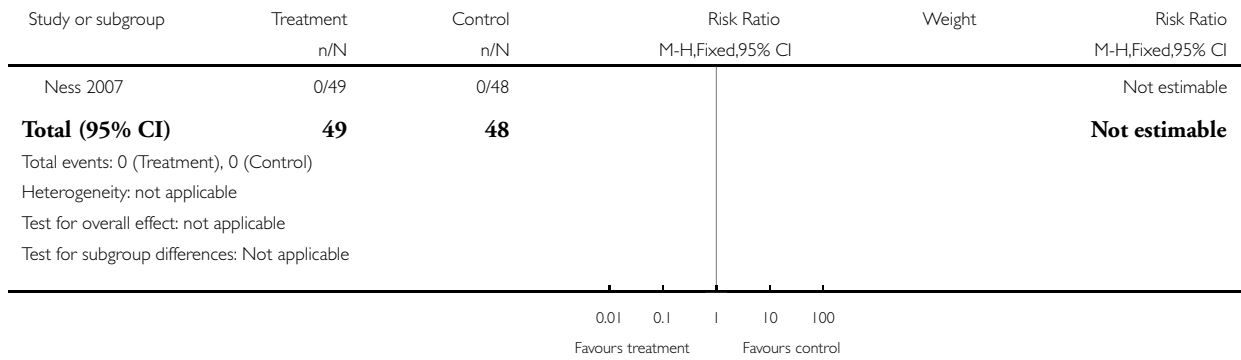
Analysis 8.1.   Comparison 8 Comparison 01 FFN knowledge versus no knowledge, Outcome 08 Maternal hospitalization, Outcome 1 Outcome 08 Maternal hospitalization.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 8 Comparison 01 FFN knowledge versus no knowledge, Outcome 08 Maternal hospitalization

Outcome: 1 Outcome 08 Maternal hospitalization

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grobman 2004	13/50	14/50		49.3 %	0.93 [0.49, 1.77]
Lowe 2004	16/46	12/51		40.1 %	1.48 [0.78, 2.79]
Ness 2007	9/47	3/46		10.7 %	2.94 [0.85, 10.16]
Total (95% CI)	**143**	**147**		**100.0 %**	**1.36 [0.90, 2.07]**

Total events: 38 (Treatment), 29 (Control)

Heterogeneity: Chi² = 2.89, df = 2 (P = 0.24); I² =31%

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours treatment   Favours control
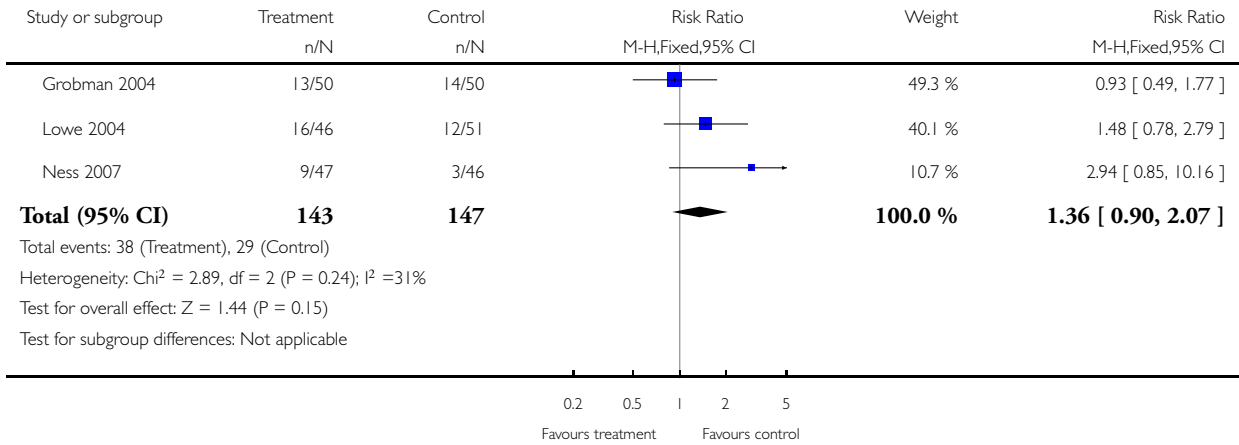
Analysis 9.1.   Comparison 9 Comparison 01 FFN knowledge versus no knowledge, Outcome 09 Tocolysis, Outcome 1 Outcome 09 Tocolysis.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 9 Comparison 01 FFN knowledge versus no knowledge, Outcome 09 Tocolysis

Outcome: 1 Outcome 09 Tocolysis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grobman 2004	8/50	9/50		14.0 %	0.89 [0.37, 2.12]
Lowe 2004	22/46	23/51		33.9 %	1.06 [0.69, 1.63]
Ness 2007	9/36	6/27		10.6 %	1.13 [0.46, 2.78]
Plaut 2003	25/43	28/47		41.5 %	0.98 [0.69, 1.38]
Total (95% CI)	**175**	**175**		**100.0 %**	**1.01 [0.78, 1.30]**

Total events: 64 (Treatment), 66 (Control)

Heterogeneity: Chi² = 0.23, df = 3 (P = 0.97); I² =0.0%

Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours treatment   Favours control

Analysis 10.1. Comparison 10 Comparison 01 FFN knowledge versus no knowledge, Outcome 10 Steroids for fetal lung maturity, Outcome 1 Outcome 10 Steroids for Fetal Lung Maturity.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 10 Comparison 01 FFN knowledge versus no knowledge, Outcome 10 Steroids for fetal lung maturity
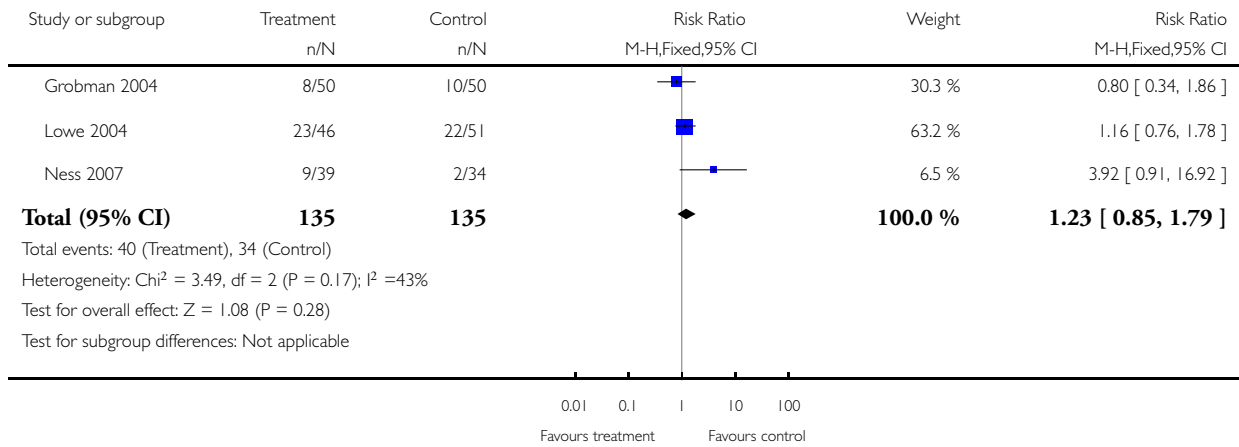
Outcome: 1 Outcome 10 Steroids for Fetal Lung Maturity

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grobman 2004	8/50	10/50		30.3 %	0.80 [0.34, 1.86]
Lowe 2004	23/46	22/51		63.2 %	1.16 [0.76, 1.78]
Ness 2007	9/39	2/34		6.5 %	3.92 [0.91, 16.92]
Total (95% CI)	**135**	**135**		**100.0 %**	**1.23 [0.85, 1.79]**

Total events: 40 (Treatment), 34 (Control)

Heterogeneity: Chi² = 3.49, df = 2 (P = 0.17); I² =43%

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1      10     100
     Favours treatment      Favours control
```
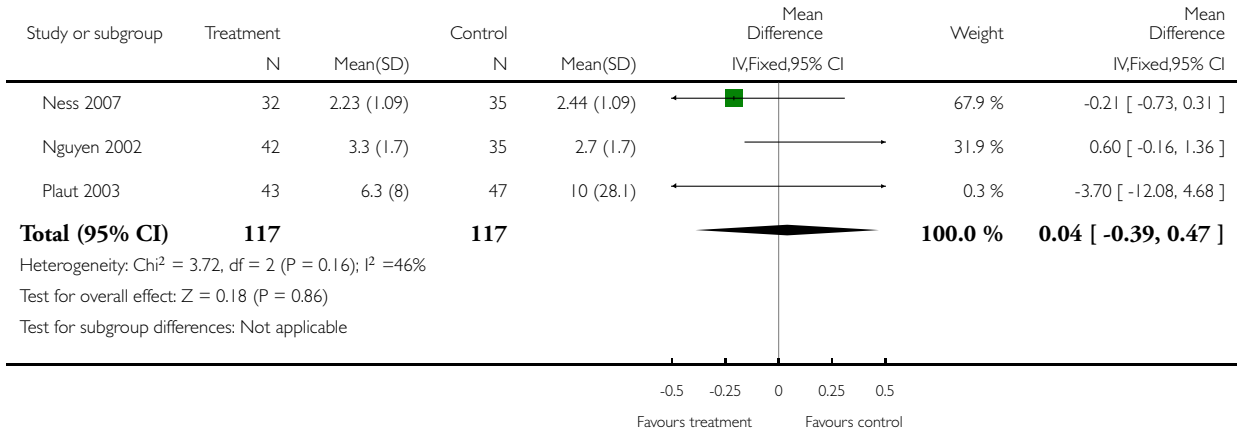
Analysis 11.1. Comparison 11 Comparison 01 FFN knowledge versus no knowledge, Outcome 11 Time to evaluate (hours), Outcome 1 Outcome 11 Time to evaluate.

Review: Fetal fibronectin testing for reducing the risk of preterm birth

Comparison: 11 Comparison 01 FFN knowledge versus no knowledge, Outcome 11 Time to evaluate (hours)

Outcome: 1 Outcome 11 Time to evaluate

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Ness 2007	32	2.23 (1.09)	35	2.44 (1.09)		67.9 %	-0.21 [-0.73, 0.31]
Nguyen 2002	42	3.3 (1.7)	35	2.7 (1.7)		31.9 %	0.60 [-0.16, 1.36]
Plaut 2003	43	6.3 (8)	47	10 (28.1)		0.3 %	-3.70 [-12.08, 4.68]
Total (95% CI)	**117**		**117**			**100.0 %**	**0.04 [-0.39, 0.47]**

Heterogeneity: Chi² = 3.72, df = 2 (P = 0.16); I² =46%

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable

-0.5 -0.25 0 0.25 0.5

Favours treatment   Favours control

APPENDICES

Appendix 1. Other searches

#1 exp Obstetric labor, premature/
#2 Fibronectins/
#3 #1 and #2
#4 fetal adj3 fibronectin
#5 #3 or #4

WHAT'S NEW

Date	Event	Description
16 December 2007	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Jason K. Baxter, Edward Hayes, and John Visintine:

1. helped with the initial idea of a fetal fibronectin review;

2. met several times with the main author (Vincenzo Berghella (VB)) regarding all aspects of the development of the protocol and review;

3. contributed to the writing and the editing of the protocol and the review;

4. helped to revise and respond to the feedback received on the first draft of the protocol and the review.

VB prepared the first draft and finalised the revised draft of the protocol and the review in response to feedback. VB is the guarantor of the review.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS
Medical Subject Headings (MeSH)

Biomarkers [analysis]; Fetus; Fibronectins [*analysis]; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy