Fetal fibronectin testing for prevention of preterm birth in singleton pregnancies with threatened preterm labor: a systematic review and metaanalysis of randomized controlled trials

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OBJECTIVE DATA: Fetal fibronectin is an extracellular matrix glycoprotein that is produced by amniocytes and cytotrophoblasts and has been shown to predict spontaneous preterm birth.

STUDY: The aim of this systematic review and metaanalysis of randomized clinical trials was to evaluate the effect of the use of fetal fibronectin in the prevention of preterm birth in singleton pregnancies with threatened preterm labor.

STUDY APPRAISAL AND SYNTHESIS METHODS: The research was conducted with the use of MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, and Cochrane Library as electronic databases from the inception of each database to February 2016. Selection criteria included randomized clinical trials of singleton gestations with threatened preterm labor that were assigned randomly to management based on fetal fibronectin results (ie, intervention group) or not (ie, comparison group). Types of participants included women with singleton gestations at 23 0/7 to 34 6/7 weeks with threatened preterm labor. Studies that included management that was also based on the use of sonographic cervical length were excluded. The primary outcome was preterm birth at <37 weeks of gestation. The summary measures were reported as relative risk or as mean differences with 95% confidence interval.

RESULTS: Six trials that included 546 singleton gestations with symptoms of preterm labor were included in the metaanalysis. The overall risk of bias of the included trials was low. Women were eligible for the random assignment in case of symptoms that suggested preterm labor at 23–34 weeks of gestation. During admission, before digital examination, a Dacron swab was rotated in the posterior fornix for 10 seconds to absorb cervicovaginal secretions that were then analyzed for the fetal fibronectin qualitative method, with results reported as either positive or negative. Women who were assigned randomly to the fetal fibronectin group had a similar incidence of preterm birth at <37 weeks of gestation (20.7% vs 29.2%; relative risk, 0.72; 95% confidence interval, 0.52–1.01), at <34 weeks of gestation (8.3% vs 7.9%; relative risk, 1.09; 95% confidence interval, 0.54–2.18), at <32 weeks of gestation (3.3% vs 5.6%; relative risk, 0.64; 95% confidence interval, 0.24–1.74), and at <28 weeks of gestation (1.1% vs 1.7%; relative risk, 0.74; 95% confidence interval, 0.15–3.67) compared with the control group. No differences were found in the number of women who delivered within 7 days (12.8% vs 14.5%; relative risk, 0.76; 95% confidence interval, 0.47–1.21), in the mean of gestational age at delivery (mean difference, 0.20 week; 95% confidence interval, −0.26 to 0.67), in the rate of maternal hospitalization (27.4% vs 26.9%; relative risk, 1.07; 95% confidence interval, 0.80–1.44), in the use of tocolysis (25.3% vs 28.2%; relative risk, 0.97; 95% confidence interval, 0.75–1.24), antenatal steroids (29.2% vs 29.2%; relative risk, 1.05; 95% confidence interval, 0.79–1.39), in the mean time in the triage unit (mean difference, 0.60 hour; 95% confidence interval, −0.03 to 1.23) and in neonatal outcomes that included respiratory distress syndrome (1.3% vs 1.5%; relative risk, 0.91; 95% confidence interval, 0.06–14.06), and admission to the neonatal intensive care unit (19.4% vs 8.1%; relative risk, 2.48; 95% confidence interval, 0.96–6.46). Management based on the fetal fibronectin test required higher hospitalization charges (mean difference, $153; 95% confidence interval, 24.01–281.99).

CONCLUSION: Fetal fibronectin testing in singleton gestations with threatened preterm labor is not associated with the prevention of preterm birth or improvement in perinatal outcome but is associated with higher costs.

Key words: cervical length, fetal fibronectin, preterm birth, preterm labor

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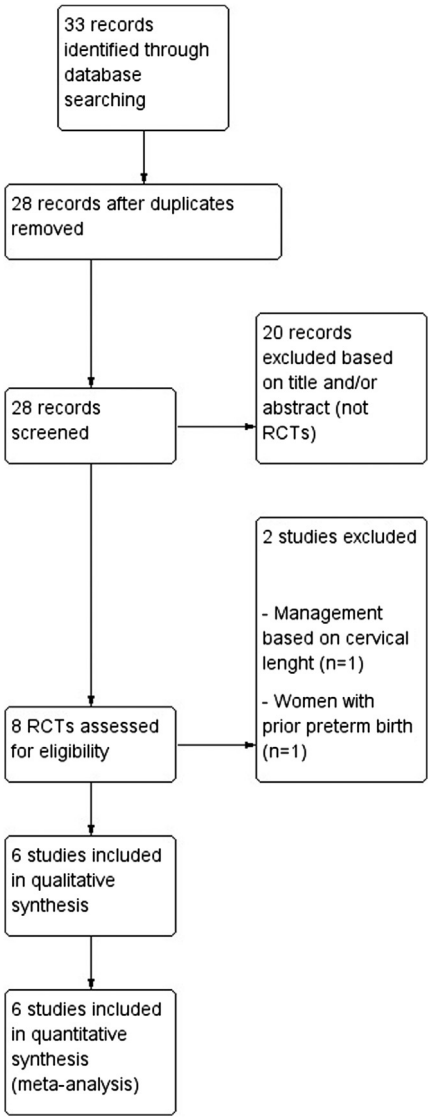
FIGURE 1
Flow diagram of studies identified in the systematic review



Flow diagram using PRISMA template (preferred reporting item for systematic reviews and metaanalyses).

RCTs, randomized controlled trials.

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Spontaneous preterm birth (SPTB) remains the number 1 cause of perinatal morbidity and death in many countries, including the United States.[1] Deaths and morbidities, which include respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis, are associated inversely with gestational age at birth.[1] All members of a family in which an SPTB occurs are affected greatly in several aspects including medical, social, psychological, and financial.[2]

Fetal fibronectin (FFN) is an extracellular matrix glycoprotein that is produced by amniocytes and cytotrophoblasts and is seen throughout gestation in all pregnancies. FFN can be detected in cervical and vaginal secretions at <20 weeks of gestation, and very low levels are found at >22 weeks of gestation (<50 ng/mL). Levels ≥50 ng/mL at >22 weeks of gestation has been associated with an increased risk of SPTB.[3] The efficacy of FFN in the prediction of SPTB has been assessed in several populations that include asymptomatic women and women with preterm labor (PTL).[4]

The aim of this systematic review and metaanalysis of randomized clinical trials (RCTs) was to evaluate the effectiveness of the management of singleton pregnancies with threatened PTL with or without knowledge of FFN testing for the prevention of PTB.

Methods

Search strategy

This metaanalysis was performed according to a protocol recommended for systematic review.[5] The review protocol was designed a priori to define methods for collecting, extracting, and analyzing data. The research was conducted with the use of MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, and Cochrane Library as electronic databases. The trials were identified with the use of a combination of the following text words: "fetal fibronectin," "preterm labor," "threatened," "prediction," "prevention," "birth," "delivery," "prematurity," "neonatal," and "randomized" from the inception of each database to February 2016. Review of articles also included the abstracts of all references that were retrieved from the search.

Study selection

Selection criteria included RCTs of singleton gestations with threatened PTL that were assigned randomly to management based on FFN results (ie, intervention group) or not (ie, comparison group). We included both studies in which FFN was collected on all women and studies in which FFN screening was done only on women who were assigned randomly to the FFN group. In the studies in which FFN was collected on all women, women were assigned randomly so that, in 50% of them, the result was available to them and the managing obstetrician, and, in 50% of them, the FFN was blinded to them and the managing obstetricians. Types of participants included women with singleton gestations at 23 0/7 to 34 6/7 weeks of gestation with threatened PTL.

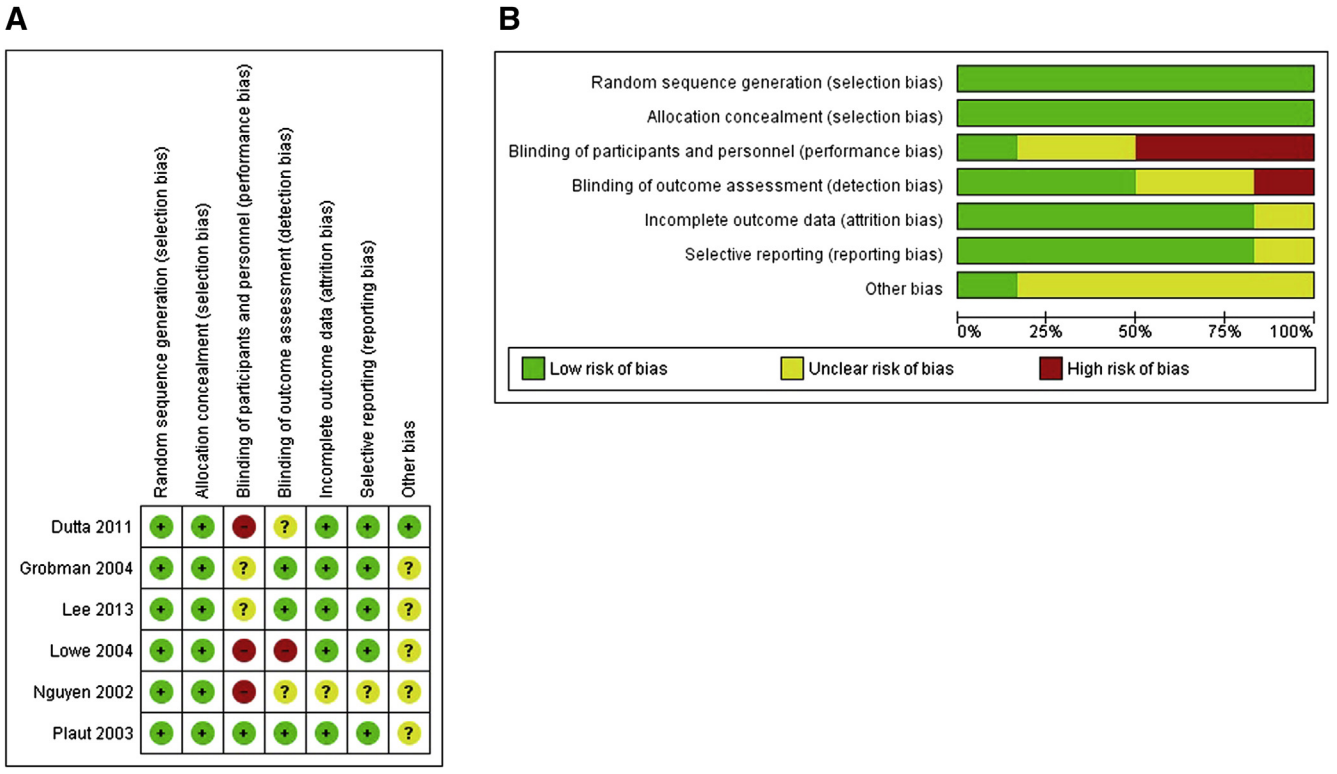
Studies that included management that was based also on the use of sonographic cervical length were excluded. Quasirandomized trials (ie, trials in which allocation was done on the basis of a pseudo-random sequence [eg, odd/even hospital number or date of birth] alternation) and studies on multiple pregnancies were also excluded.

Data extraction and risk of bias assessment

The risk of bias in each included study was assessed by the use of the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[5] Seven domains that are related to risk of bias were assessed in each included trial because there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.[5]

All analyses were done with an intention-to-treat approach; conditions were evaluated according to the treatment group to which they were allocated randomly in the original trials. The primary outcome was the incidence of PTB <37weeks. Secondary maternal outcomes were PTB at <34, <32, and <28 weeks of gestation, delivery within 7 days, mean gestational age at delivery (in weeks), maternal hospitalization, tocolysis, use of

FIGURE 2
Assessment of risk of bias



A, Summary of risk of bias for each trial. A plus sign indicates a low risk of bias; a minus sign indicates a high risk of bias; a question mark indicates an unclear risk of bias. **B,** Risk of bias graph about each risk of bias item presented as percentages across all included studies.

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antenatal steroids, mean time to evaluate (in hours), neonatal outcomes (ie, incidence of respiratory distress syndrome and of admission to neonatal intensive care unit) and hospitalization charges. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Data not present in the original publications were requested from all the principal investigators.

Data analysis

The data analysis was completed independently by the authors who used Review Manager (version 5.3; The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark).[5] The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Between-study heterogeneity was explored with the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values of $\geq$50% indicate a substantial level of heterogeneity. A fixed effects model was used if substantial statistical heterogeneity was not present. On the contrary, if there was evidence of significant heterogeneity between the studies that were included, a random effect model was used.[5]

Potential publication biases were assessed statistically with Begg's and Egger's tests.[5] A probability value of $<.05$ was considered statistically significant. Tests for funnel plot asymmetry were carried out with only an exploratory aim when the total number of publications that were included for each outcome was <10. In this case, the power of the tests was too low to distinguish chance from real asymmetry.

The summary measures were reported as relative risk (RR) or as mean difference (MD) with 95% confidence interval (CI).

All review stages were conducted independently by the authors who independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction, and data analysis. Disagreements were resolved by discussion.

The metaanalysis was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[6] Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No.: CRD42016035939).

Results

Study selection and study characteristics

Figure 1 shows the flow diagram (PRISMA template) of information derived from the review of potentially

TABLE 1
Characteristics of the included trials

	Nguyen et al, 2002[7]	Plaut et al, 2003[8]	Grobman et al, 2004[9]	Lowe et al, 2004[10]	Dutta and Norman, 2011[11]	Lee et al, 2013[12]
Study location	**United States**	**United States and Canada**	**United States**	**United States**	**United Kingdom**	**United States**
Sample size[a]	77 (42 vs 35)	108 (51 vs 57)	100 (50 vs 50)	97 (46 vs 51)	88 (44 vs 44)	76 (44 vs 32)
Inclusion criteria	Singleton gestations with symptoms of preterm labor	Singleton gestations with symptoms of preterm labor	Singleton gestations with symptoms of preterm labor	Singleton gestations with symptoms of preterm labor	Singleton gestations with symptoms of preterm labor	Singleton gestations with symptoms of preterm labor
Definition of preterm labor	Uterine contractions, low back pain, or bloody show[b]	Not reported	>6 Contractions per hour by external tocodynometry	Not reported	Uterine contractions, low back pain, pelvic pressure, or low abdominal pressure	>3 Contractions per 30 minutes by external tocodynometry, abdominal pressure or cramping, low back pain
Gestational age at randomization (range in weeks)	24^0—34^6	24^0—34^6	24^0—34^6	24^0—34^6	24^0—34^6	24^0—33^6
Exclusion criteria	Cervical manipulation or sexual intercourse within the previous 24 hours, ruptured membranes, gross bleeding, cervical dilation ≥3 cm, cerclage in situ, multiple pregnancies	Cervical manipulation or sexual intercourse within the previous 24 hours, ruptured membranes, gross bleeding, cervical dilation ≥3 cm, cerclage in situ, multiple pregnancies	Cervical manipulation or sexual intercourse within the previous 24 hours, ruptured membranes, gross bleeding, cervical dilation ≥3 cm, cerclage in situ, multiple pregnancies	Cervical manipulation or sexual intercourse within the previous 24 hours, ruptured membranes, gross bleeding, cervical dilation ≥3 cm, cerclage in situ, multiple pregnancies	Cervical manipulation or sexual intercourse within the previous 24 hours, ruptured membranes, gross bleeding, cervical dilation ≥3 cm, cerclage in situ, multiple pregnancies	Cervical manipulation or sexual intercourse within the previous 24 hours, ruptured membranes, gross bleeding, cervical dilation ≥3 cm, cerclage in situ, multiple pregnancies
Fetal fibronectin immunoassay test	Adeza Biomedical	Adeza Biomedical	Adeza Biomedical	Adeza Biomedical	Not reported	Adeza Biomedical
Fetal fibronectin cut-off	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL	50 ng/mL
Control group	Fetal fibronectin not done	Fetal fibronectin blinded	Fetal fibronectin blinded	Fetal fibronectin blinded	Fetal fibronectin blinded	Fetal fibronectin blinded
Previous spontaneous preterm birth[a]	11/42 (26.2%) vs 8/35 (22.9%)[b]	17/51 (33.3%) vs 25/57 (43.9)	4/50 (8.0%) vs 8/50 (16.0%)	12/46 (26.1%) vs 14/51 (27.5%)	Not reported	12/44 (27.3%) vs 9/32 (28.1%)
Primary outcome	Cost-effectiveness	Transport to tertiary care centers	Health care costs	Length of stay	Inpatient hospital admission	Triage evaluation time

[a] Data are presented as number in the intervention group (ie, fetal fibronectin group) vs number in the control group; [b] Additional data provided by the authors of the original trial.

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TABLE 2
Treatment of women according to fetal fibronectin results

Variable	Nguyen et al, 2002[7]	Plaut et al, 2003[8]	Grobman et al, 2004[9]	Lowe et al, 2004[10]	Dutta and Norman, 2011[11]	Lee et al, 2013[12]
Fetal fibronectin positive	Further observation	Physician's discretion[a]	Physician's discretion[a]	Physician's discretion[a]	Admit for preterm labor, administration of tocolytics and steroids	Admit for preterm labor[b] or discharge
Fetal fibronectin negative	Discharged home	Physician's discretion[a]	Physician's discretion[a]	Physician's discretion[a]	Discharged home	Discharged home
Fetal fibronectin blinded or not done	Physician's discretion	Physician's discretion	Physician's discretion	Physician's discretion	Physician's discretion	Physician's discretion

[a] Decision made by attending physician who was aware of the test results and test characteristics (sensitivity, specificity, and positive and negative predictive value) of the fetal fibronectin assay; [b] If cervical change in serial cervical examinations or if persistent contractions.

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relevant articles. Eight studies were assessed for eligibility.[7-14] Two studies were excluded[13,14]: one study was excluded because it assessed the efficacy of FFN in women with previous SPTB[13]; Ness et al[14] was excluded because the management was based also on the use of ultrasound cervical length. Six trials therefore were included in the meta-analysis.[7-12] Tests for funnel plot asymmetry were carried out only with an exploratory aim because the total number of publications that were included for each outcome was <10. Despite this, the overall risk of bias of the included trials was low (Figure 2). All studies had a low risk of bias in "random sequence generation," "incomplete outcome data," and "selective reporting." Adequate methods for allocation of women were used. All randomly assigned women were included in an intention-to-treat analysis. In 3 studies, laboratory personnel who performed the FFN test were blinded to women's characteristics and outcomes (ie, blinding of outcome assessment).[8,9,12] Physicians were not blinded to the FFN assay result. Publication bias, which was assessed with the use of Begg's and Egger's tests, was not significant ($P = .84$ and .91, respectively). Authors of 4 trials were able to provide us additional unpublished data from their studies.[7,9,10,12]

Table 1 shows the characteristics of the included trials. Women were eligible for the randomization in case of symptoms that suggested PTL between 23 and 34 weeks of gestation. During admission, before digital examination, a Dacron swab was rotated in the posterior fornix for 10 seconds to absorb cervicovaginal secretions that were then analyzed for the FFN qualitative method, with results reported as either positive or negative. Women with cervical manipulation or sexual intercourse within the previous 24 hours, ruptured membranes, gross bleeding, cervical dilation ≥3 cm, cerclage in situ, and multiple pregnancies were excluded in all the trials. The treatment of the women was mostly at the physician's discretion (Table 2).

Synthesis of results

Table 3 shows the pooled results for the primary and secondary outcomes. Of the 546 singleton gestations with symptoms of PTL that were included in the meta-analysis, 277 gestations (50.7%) were assigned randomly to the FFN group, and 269 gestations (49.3%) were assigned to the comparison group. Statistical heterogeneity was low with no inconsistency ($I^2 = 0$) in the primary outcome. Compared with control group, women who were assigned randomly to FFN group had a similar incidence of PTB at <37 weeks of gestation (20.7% vs 29.2%; RR, 0.72; 95% CI, 0.52−1.01; Figure 3), <34 weeks of gestation (8.3% vs 7.9%; RR, 1.09; 95% CI, 0.54−2.18), <32 weeks of gestation (3.3% vs 5.6%; RR, 0.64; 95% CI, 0.24−1.74), and <28 weeks of gestation (1.1% vs 1.7%; RR, 0.74; 95% CI, 0.15−3.67). No differences were found in the number of women who delivered within 7 days (12.8% vs 14.5%; RR, 0.76; 95% CI, 0.47−1.21), in the mean of gestational age at delivery (MD 0.20 week; 95% CI, −0.26−0.67; Figure 4), in the rate of maternal hospitalization (27.4% vs 26.9%; RR, 1.07; 95% CI, 0.80−1.44), in use of tocolysis (25.3% vs 28.2%; RR, 0.97; 95% CI, 0.75−1.24; Figure 5), antenatal steroids (29.2% vs 29.2%; RR, 1.05; 95% CI, 0.79−1.39), in the mean time in the triage unit (MD, 0.60 hour; 95% CI, −0.03−1.23), and in neonatal outcomes that included respiratory distress syndrome (1.3% vs 1.5%; RR, 0.91; 95% CI, 0.06−14.06) and admission to neonatal intensive care unit (19.4% vs 8.1%; RR, 2.48; 95% CI, 0.96−6.46). Management based on FFN testing required higher hospitalization charges (MD, $153; 95% CI, 24.01−281.99).

Comment

Main findings

This metaanalysis from 6 low risk of bias RCTs that included 546 women shows that FFN testing in singleton gestations with symptoms of PTL does not reduce the PTB rate or improve perinatal outcome, but is associated with higher cost of approximately $150. Our metaanalysis represents level-1 data and includes well-designed RCTs. The test of heterogeneity and pooled data all point to the non-efficacy of FFN testing as studied so far.

Comparison with existing literature

Our data support earlier findings of a Cochrane review of 5 trials that included

TABLE 3
Primary and secondary outcomes

Variable	Nguyen et al, 2002[7]	Plaut et al, 2003[8]	Grobman et al, 2004[9]	Lowe et al, 2004[10]	Dutta and Norman, 2011[11]	Lee et al, 2013[12]	Total	Relative risk (95% confidence interval)
Sample size[a]	77 (42 vs 35)	108 (51 vs 57)	100 (50 vs 50)	97 (46 vs 51)	88 (44 vs 44)	76 (44 vs 32)	546 (277 vs 269)	—
Preterm birth[a]								
At <37 weeks of gestation	11/42 (26.2%) vs 9/35 (25.7%)[b]	5/43 (11.6%) vs 12/47 (25.5%)	10/50 (20.0%) vs 13/50 (26.0%)	13/46 (28.3%) vs 24/51 (47.1%) [b]	Not reported	7/41 (17.1%) vs 4/29 (13.8%)	46/222 (20.7%) vs 62/212 (29.2%)	0.72 (0.52–1.01)
At <34 weeks of gestation	Not reported	2/43 (4.7%) vs 2/47 (4.3%)	5/50 (10.0%) vs 3/50 (6.0%)	5/46 (10.9%) vs 9/51 (17.7%) [b]	Not reported	3/41 (7.3%) vs 0/29	15/180 (8.3%) vs 14/177 (7.9%)	1.09 (0.54–2.18)
At <32 weeks of gestation	Not reported	2/43 (4.7%) vs 1/47 (2.1%)	3/50 (6.0%) vs 2/50 (4.0%)	1/46 (2.1%) vs 7/51 (13.7%)[b]	Not reported	0/41 vs 0/29[b]	6/180 (3.3%) vs 10/177 (5.6%)	0.64 (0.24–1.74)
At <28 weeks of gestation	Not reported	0/43 vs 0/47	2/50 (4.0%) vs 2/50 (4.0%)	0/46 vs 1/51 (1.9%)[b]	Not reported	0/41 vs 0/29[b]	2/180 (1.1%) vs 3/177 (1.7%)	0.74 (0.15–3.67)
Delivery within 7 days[a]	1/42 (2.4%) vs 2/35 (5.7%)[b]	Not reported	2/50 (4.0%) vs 3/50 (6.0%)[b]	3/46 (6.5%) vs 4/51 (7.8%)[b]	Not reported	17/41 (41.5%) vs 15/29 (51.7%)[b]	23/179 (12.8%) vs 24/165 (14.5%)	0.76 (0.47–1.21)
Gestational age at delivery, wk[c]	34.2±2.9 vs 33.7±2.7[b]	29.9±3.2 vs 30.4±2.7	38±3 vs 38±3	38.3±2.8 vs 37.4±3.4	38.1±3.25 vs 38.1±2.33	38.6±2.1 vs 38.3±1.7[b]	—	0.20 week (−0.26–0.67)
Maternal hospitalization[a]	9/42 (21.4%) vs 7/35 (20.0%)[b]	Not reported	13/50 (26.0%) vs 14/50 (28.0%)	16/46 (34.8%) vs 12/51 (23.5%)	21/44 (47.7%) vs 22/44 (50.0%)	3/44 (6.8%) vs 2/32 (6.3%)	62/226 (27.4%) vs 57/212 (26.9%)	1.07 (0.80–1.44)
Tocolysis[a]	7/42 (16.7%) vs 7/35 (20.0%)[b]	25/43 (58.1%) vs 28/47 (59.6%)	8/50 (16.0%) vs 9/50 (18.0%)	22/46 (47.8%) vs 23/51 (45.1%)	3/44 (6.8%) vs 4/44 (9.1%)	3/44 (6.8%) vs 2/32 (6.3%)[b]	68/269 (25.3%) vs 73/259 (28.2%)	0.97 (0.75–1.24)
Steroids[a]	9/42 (21.4%) vs 7/35 (20.0%)[b]	Not reported	8/50 (16.0%) vs 10/50 (20.0%)	23/46 (50.0%) vs 22/51 (43.1%)	17/44 (38.6%) vs 21/44 (47.7%)	9/44 (20.5%) vs 2/32 (6.3%)[b]	66/226 (29.2%) vs 62/212 (29.2%)	1.05 (0.79–1.39)
Time in the triage unit, hr[c,d]	3.3±1.7 vs 2.7±1.7	6.3±8 vs 10±28.1	4.12±3.59 vs 4.49±3.90[b]	16±7.4 vs 12±4.9	16.8±25.3 vs 17.7±25.5	3±1.8 vs 2.8±1.6	—	0.60 hour (−0.03–1.23)
Respiratory distress syndrome[a]	Not reported	Not reported	Not reported	Not reported	1/44 (2.3%) vs 1/40 (2.5%)	0/37 vs 0/27[b]	1/81 (1.3%) vs 1/67 (1.5%)	0.91 (0.06–14.06)
Admission to neonatal intensive care unit[a]	Not reported	Not reported	Not reported	Not reported	10/30 (33.3%) vs 3/30 (10.0%)	3/37 (8.1%) vs 2/32 (6.3%)	13/67 (19.4%) vs 5/62 (8.1%)[b]	2.48 (0.96–6.46)
Hospitalization charges, $[c]	452±381 vs 299±175	Not reported	Not reported	Not reported	Not reported	Not reported	—	$153 (24.01–281.99)[e]

[a] Data are presented as the number of participants in the fetal fibronectin group vs the number of participants in the control group with percentage; [b] Additional data obtained from the authors of the original trial; [c] Data are given as mean ± standard deviation; [d] Time to evaluate; [e] Statistically significant.

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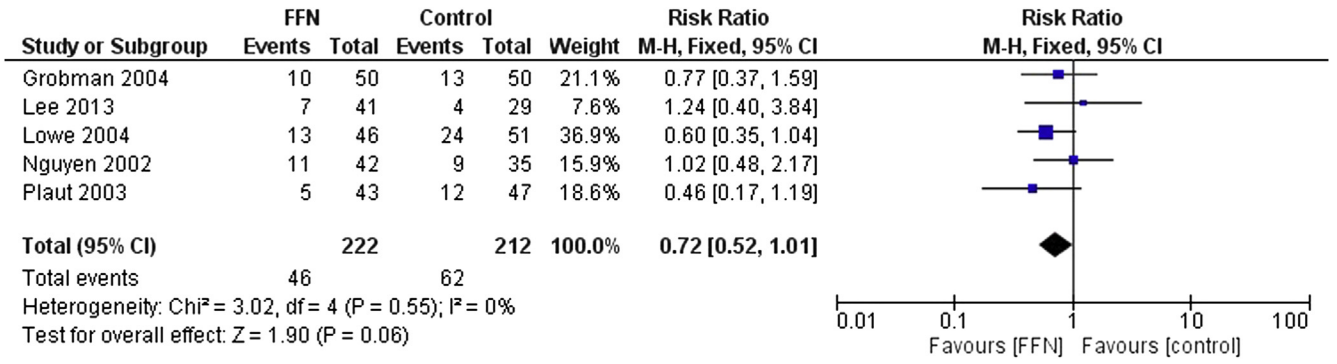
FIGURE 3
Forest plot for the risk of the primary outcome, PTB <37 weeks



Incidence of preterm birth at <37 weeks of gestation. The *rectangles* represent the point estimates for each study, the size of the rectangle represents the weight allocated to each study, and the *horizontal lines* represent the 95% confidence intervals. The *diamond* represents the summary estimate and the size of the diamond represents the 95% confidence intervals.

CI, confidence interval; *df*, degrees of freedom; *FFN*, fetal fibronectin; *M-H*, Mantel-Haenszel.

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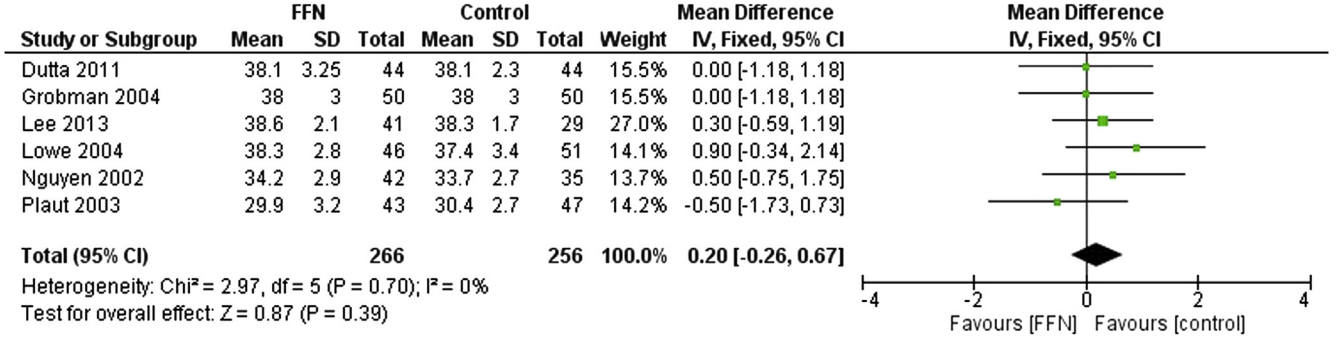
747 women and concluded that, although FFN is used commonly in labor and delivery units to help in the treatment of women with PTL, currently there is not sufficient evidence to recommend its use. That Cochrane reviews also includes asymptomatic women; our study focused only on women with threatened PTL.[15]

Strengths and limitations

Our study has several strengths. This metaanalysis includes all studies of high quality and with a low risk of bias according to the Cochrane risk of bias tools that have been published so far on the topic. To our knowledge, no previous metaanalysis on this issue is as large, up-to-date, or comprehensive. We obtained additional unpublished data for several outcomes. The protocol of this review was a priori registered on PROSPERO. Statistical tests showed no significant potential publication biases. Intent-to-treat analysis was used, and both random and mixed effects models were used when appropriate. The statistical heterogeneity within the studies was very low. We obtained unpublished data from 4[7,9,10,12] of the 6 included randomized studies. These are key elements that are needed to evaluate the reliability of a metaanalysis.[5]

Limitations of our study are inherent to the limitations of the included RCTs. Only 6 trials were included in the metaanalysis. The small number of studies did not permit meaningful stratified metaanalyses to explore the test performance in subgroups of patient

FIGURE 4
Forest plot for mean of gestational age at delivery



The *rectangles* represent the point estimates for each study, the size of the rectangle represents the weight allocated to each study, and the *horizontal lines* represent the 95% confidence intervals. The *diamond* represents the summary estimate and the size of the diamond represents the 95% confidence intervals.

CI, confidence interval; *df*, degrees of freedom; *FFN*, fetal fibronectin; *IV*, independent variable.

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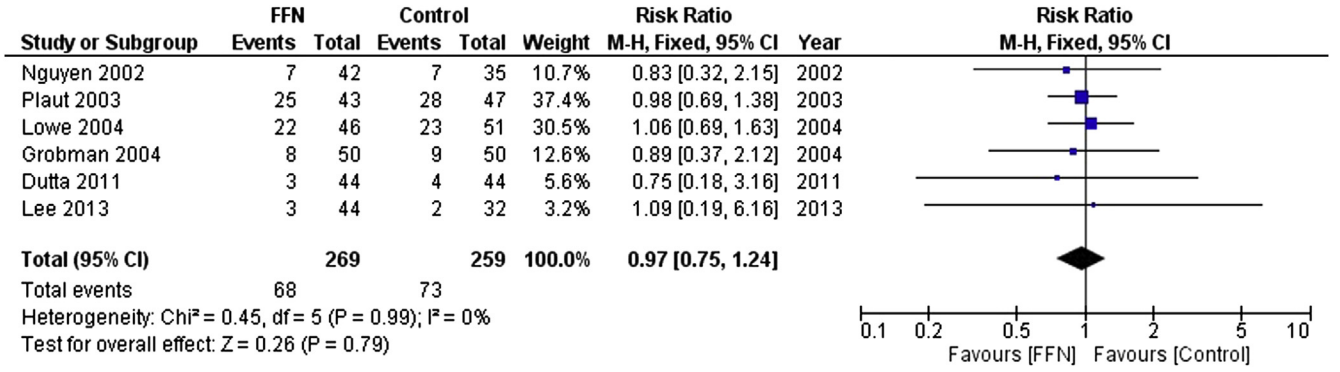
FIGURE 5
Forest plot for the risk of tocolysis



The *rectangles* represent the point estimates for each study, the size of the rectangle represents the weight allocated to each study, and the *horizontal lines* represent the 95% confidence intervals. The *diamond* represents the summary estimate and the size of the diamond represents the 95% confidence intervals.

CI, confidence interval; *df*, degrees of freedom; *FFN*, fetal fibronectin; *M-H*, Mantel-Haenszel.

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that may be less or more susceptible to bias. The small number of included trials, different primary outcome of the original trials, and different definition of PTL represent the major limitations of this systematic review.

Conclusion and implications

In summary, based on these level-1 data, there seems (at least as used so far in these trials) to be no reason to justify the routine use of FFN in women with threatened PTL. Given that we found a nonsignificant reduction by 28% in the primary outcome, further study must be undertaken to better understand whether and under what circumstances the predictive characteristics of the FFN test can be translated into better clinical management. Currently, the only treatment protocol for screening of women with threatened PTL that has been shown by randomized trial data to decrease PTB has been based mainly on transvaginal ultrasound cervical length, with FFN only in women with transvaginal ultrasound cervical length if 20–29 mm.[14]

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