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REVIEW ARTICLE

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Predictive value of quantitative fetal fibronectin for spontaneous preterm birth in asymptomatic pregnancies: a systematic literature review and meta-analysis

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ABSTRACT

Objective: Tests capable of accurate prediction of spontaneous preterm birth (sPTB) are crucial to inform clinical decisions to prevent neonatal deaths and reduce the risk of morbidity in surviving infants. A systematic literature review and meta-analysis were performed to assess the utility of the quantitative fetal fibronectin (fFN) test to predict sPTB at different test concentration thresholds.

Methods: Literature searches were conducted in MEDLINE, Embase, and the Cochrane Library in May 2022. Observational studies and clinical trials investigating the clinical utility of the quantitative fFN test in asymptomatic pregnancies prior to 37 weeks of gestation were eligible for inclusion. Meta-analysis quantified the risk of sPTB prior to four gestational age milestones (<28, <30, <34 and <37 weeks) based on quantitative fFN levels. No risk of bias assessment was performed however, clinical and methodological heterogeneity was explored to determine the feasibility of performing analyses.

Results: 11 studies showed a quantitative assessment of fFN can differentiate between very high and very low risks of sPTB in asymptomatic pregnancies with <10% of women with very low fFN (<10 ng/mL) versus 37–67% of women with very high fFN (>200 ng/mL) delivering before 34 weeks. A meta-analysis of two studies showed, albeit with a low number of events, the odds of sPTB prior to 28 weeks was nine times higher in women testing positive at ≥50 ng/mL, whereas the odds of sPTB was 25 times higher in women with fFN concentrations >200 ng/mL (versus <50 ng/mL reference). Similarly, pooling three studies showed the odds of sPTB prior to 37 weeks was four times higher in women who tested positive at ≥50 ng/ml whereas the odds of delivery before 37 weeks was seven times higher for women with fFN concentrations ≥200 ng/ml (versus <50 ng/mL reference).

Conclusion: Quantitative fFN testing demonstrates increased predictive capabilities and utility of fFN testing in clinical practice, potentially preventing unnecessary intervention for women at very low risk and allowing an opportunity to optimize the management of asymptomatic patients at high risk of preterm delivery.

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Introduction

Preterm birth (PTB) is defined as delivery before 37 weeks and 0 days gestation. It is estimated 15 million PTBs occur globally each year [1], accounting for nearly 16% of neonatal deaths globally [2–4]. PTB is associated with substantial morbidity among surviving infants. Children born preterm are prone to a variety of complications such as developmental disorders, respiratory distress syndrome (RDS), hypoglycemia, sepsis, hyperbilirubinemia, and necrotizing enterocolitis, all of which contribute to significant social, psychological, and economic burden [5,6].

Identification of women who are considered to be at risk of spontaneous PTB (sPTB) is crucial in order to find those who may benefit from treatments that delay the onset of preterm labor, such as tocolytics, cervical cerclage, and progesterone therapy, thereby mitigating the threat of neonatal morbidity and mortality [7], as well as maintaining maternal health. Furthermore, identifying women who are at imminent

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risk of preterm delivery is critical for optimizing the administration of antenatal corticosteroids (ACS) to aid fetal lung development and prevent RDS. Therefore, tests capable of accurate prediction of the risk of sPTB are critical to ensuring that intervention is given appropriately, to achieve favorable maternal and neonatal health outcomes.

Fetal fibronectin (fFN) is a glycoprotein that plays an integral role in adhering the fetal membrane to the uterine lining [8]. It has also been suggested that fFN facilitates the separation of the placenta from the uterus after delivery [8]. Typically, fFN is not detected in the cervicovaginal secretions collected from the posterior fornix of the vagina between 16- and 22-weeks of gestational age [8]. However, levels of fFN higher than 50 ng/mL can be observed as early as 22 weeks of gestation in women with risk factors for PTB, and high concentrations of fFN during the third trimester are indicative of an increased risk of sPTB [8].

It is well established that a positive result based on the qualitative fFN test, which uses a 50 ng/mL threshold, is associated with an increased risk of PTB [9]. Furthermore, a meta-analysis of randomized controlled trials found that management with knowledge of the qualitative test result was associated with a lower risk of sPTB before 37 weeks in women with symptoms of threatened preterm labor; however, no benefit was observed regarding PTB before 34 weeks or the risk of maternal hospitalization [10]. It is generally accepted that the clinical utility of the qualitative fFN test is attributed to its high negative predictive value, that is, the ability to identify women at very low risk of imminent delivery, while concerns regarding the rate of false-positive test results may limit the utility of the test to exclusively inform clinician decision-making.

In recent years, a quantitative test has been developed as a diagnostic tool to determine the concentration of fFN in cervicovaginal samples collected from pregnant women. Numerous studies have been conducted to demonstrate the predictive capacity of the quantitative fFN test for assessing risk of sPTB in both symptomatic and asymptomatic women [11–20]. Testing, as well as follow-up after the test, is used among women who exhibit symptoms of being in labor. However, in asymptomatic women, the quantitative fFN test can be critical for identifying patients with elevated fFN levels who require close monitoring. In addition, this information may help reduce unnecessary interventions, hospitalizations, and associated costs by identifying women with negative fFN or low fFN levels who are at lower risk of sPTB.

A systematic literature review (SLR) was conducted to collate all evidence on the rates of sPTB among asymptomatic pregnant women based on quantitative fFN test results. We also performed a meta-analysis to assess the prognostic utility of the test based on the concentration of fFN measured in samples.

Methods

The SLR was conducted in accordance with accepted methodological guidelines [21,22], per a prospectively defined protocol (available upon request) which was not registered. Literature searches, conducted on May 5, 2022, were performed in MEDLINE, Embase, and the Cochrane Library. The database searches had no limits regarding publication type to enable emerging research that may not yet be published in peer-reviewed articles (i.e. conference proceedings) to be captured by the search. In addition, we manually hand searched the proceedings from the Annual Meeting for the Society of Maternal-Fetal Medicine (2020–2022), as these materials are not indexed in Embase (SD).

Observational studies and clinical trials investigating the clinical utility of the quantitative fFN test in asymptomatic pregnant women prior to 37 weeks of gestation were eligible for inclusion in the review. One reviewer screened each record at the title and abstract screening stage (MB and SD). As a quality control measure 10% of studies were validated by a second, independent reviewer (MB and SD). All articles considered eligible for full-text review were reviewed by two independent reviewers (MB and SD), and any discrepancies were resolved through discussion and the involvement of a third reviewer when necessary. Data extraction was performed by a single reviewer (SD) and validated by a second independent reviewer (MB).

Studies were considered for meta-analysis if they reported sPTB rates at comparable gestational ages for comparable fFN thresholds. Other sources of heterogeneity across the literature included differences in the study population and timing of fFN testing. Consequently, data from some studies were deemed unsuitable for inclusion in the meta-analysis.

A meta-analysis was performed (BN) to quantify the risk of sPTB prior to various gestational age milestones ($<$28, $<$30, $<$34, and $<$37 weeks) based on the concentration of fFN measured in cervicovaginal secretions. In the base case, we analyzed high-risk asymptomatic populations. Risk factors included previous PTB, previous cervical surgery, previous miscarriage, uterine anomaly, short cervical length, and

multiple gestations. We also performed a sensitivity analysis that included data on all asymptomatic populations, regardless of risk status. The most frequently reported test thresholds were selected for the analysis. Odds ratios (with 95% confidence interval [CI]) were generated to quantify the risk of sPTB in patients with fFN concentrations measured as ≥50 ng/mL, 50–199 ng/mL and ≥200 ng/mL relative to those with fFN concentrations <50 ng/mL and <200 ng/mL.

Classical (frequentist) inverse-variance weighted meta-analyses were performed in R using the metafor (1.9) package using random-effect models. Cochrane's Q statistic and I^2 test, in addition to estimates of τ^2, were used to determine whether the level of statistical heterogeneity of study-level effects was substantive.

Results

The literature searches retrieved a total of 668 records. After the removal of duplicates, 429 articles were screened at the title/abstract level to determine eligibility for inclusion in the review, and 139 articles were considered eligible for full-text review. Thirty articles, reporting on 11 unique studies, met the criteria for inclusion in the SLR.

Of the included studies, eight observational studies collected data prospectively [11,14,23–27], one was a retrospective case note review [28], and two were based on randomized controlled trials [16,17]. All studies were conducted either in the United Kingdom [12,16,25,28] or the United States [14,17,23,24,26,27]. The eligibility criteria were based on the perceived risk of PTB in several studies: four enrolled high-risk populations [11,14,26,27], and one study each investigated average [14] and low-risk [24] populations. Four of the studies enrolled only women with singleton pregnancies [14,23,24,27], while another enrolled only twin gestation pregnancies [25]. The sample sizes ranged considerably, from only 43 women [28] up to 10,456 women [14].

Table 1.shows the rates of sPTB at different gestational ages (range: <24 weeks up to <37 weeks) for the various fFN test thresholds reported. Across all studies, higher fFN concentrations were associated with an increased risk of preterm delivery, regardless of sPTB risk factors. Figures 1(a,b) present the sPTB rates for selected incremental fFN thresholds to illustrate the trend in sPTB rates at two timepoints frequently reported in the literature (<34 and <37 weeks). Outlier fFN values can distinguish very high and very low risk of sPTB; less than 10% of patients with fFN concentrations measured below 10 ng/mL delivered before 34 weeks of gestation, whereas 37% [11] to 67% [29] of women with concentrations above 200 ng/mL delivered before 34 weeks. Higher fFN concentrations were positively correlated with risk of sPTB at all gestational age thresholds assessed. Quantification of fFN has also been shown to help predict imminent sPTB within two weeks of having taken the fFN test in asymptomatic women [28].

When considering these studies for meta-analysis, heterogeneity regarding the fFN thresholds evaluated and gestational age thresholds for PTB precluded the pooling of most studies in the analysis. Kurtzman 2014 was deemed unsuitable for inclusion as the study investigated only women with twin pregnancies. Three of the remaining studies (EQUIPP, PREMET, and Tran 2019), investigating asymptomatic, high-risk populations, were deemed eligible for inclusion in the meta-analysis to evaluate PTB risk (Table 1). The final study, nuMoM2b, investigated women with unspecified sPTB risk who were assumed to be asymptomatic. Given the ambiguous description of the patient population there was uncertainty as to whether this study was suitable for inclusion in the meta-analysis hence, this study was only included in a sensitivity analysis.

The resulting meta-analyses showed that regardless of gestational age, higher fFN levels were associated with a significantly higher risk of sPTB than lower levels in asymptomatic, high-risk women (Figure 2). The test appeared to have the greatest predictive power to identify sPTB at earlier gestational ages however, due to a low number of events there was greater heterogeneity observed at the earlier timepoints, particularly 28 weeks.

The odds of sPTB by 28 weeks were nine times higher in women who would be considered positive at the qualitative test threshold (≥50 ng/ml) compared to the negative test population at this threshold. In comparison, women with high fFN concentrations (≥200 ng/ml) measured by the quantitative test had 25 times higher odds of delivering <28 weeks compared to the reference population (<50 ng/ml). Similarly, women with the highest measured fFN concentrations (≥200 ng/ml) had 34 times higher odds of delivering prior to 30 weeks compared to those with low fFN concentrations (<50 ng/ml).

The odds of sPTB by 34 weeks were seven times higher in women who would be considered positive at the qualitative test threshold (≥50 ng/ml) compared to the negative test population at this threshold. In comparison, women with high fFN concentrations (≥200 ng/ml) had 13 times higher odds of delivering

Table 1. Summary of included studies and sPTB rates by fFN levels.

Study Name, Country	Study design	Study Population	Gestational age at testing	fFN (ng/ml)	Sample size (*n*)	sPTB by week of gestation and fFN level (%)					
						<28 w	<30 w	<32 w	<34 w	<35 w	<37 w
EQUATE [26] US	Prospective observational study	Asymptomatic high-risk women	Range: 16 weeks and 0 days to 21 weeks and 6 days	<10	921	NR	NR	3.9	NR	10.4	NR
				10-199	532			8.1		16.2	
				200-499	72			15.3		23.6	
				≥500	21			28.6		38.1	
EQUIPP [11] US and UK	Prospective observational study	Asymptomatic high-risk women with singleton pregnancies	Median: 22 weeks 6 days Range: 22 weeks − 27 weeks 6 days	<10	1000	NR	1	NR	2.7	NR	8.1
				10-49	249		3.2		11		20.1
				50-199	121		5		14.9		26.4
				200-499	57		22.8		33.9		45.6
				≥500	21		38.1		47.6		52.4
Goldenberg 2000 [14] US	Prospective observational study	Women with singleton pregnancies[A]	Range: 13 weeks − 22 weeks	0	2253	1.2	NR	2.3	NR	4.1	8.9
				1-24	3341	2.3		3.6		6.3	12.4
				25-49	378	4.8		5.8		7.7	15.9
				≥50	536	7.8		9.1		14.7	22
Jwala 2016 [24] US	Prospective observational study	Asymptomatic low-risk women with singleton pregnancies	Range: 18 weeks − 23 weeks 6 days	<5	288	1.04	NR	1.39	NR	3.13	5.21
				≥5	240	2.5		3.75		7.08	8.75
Kurtzman 2014 [25] UK	Prospective observational study	Asymptomatic patients with twin gestations	Mean: 24 weeks Range: 22 weeks − 27 weeks 6 days	0-9	NR	NR	NR	NR	4.1	NR	NR
				10-49					13.3		
				50-199					33.3		
				≥200					66.7		
Muzaffar 2013 [28] UK	Retrospective study	Women who underwent a fFN test[A]	NR	<50	NR	NR	NR	NR	NR	NR	3[B]
				≥50							64[B]
nuMom2b [23] US	Prospective observational study	Nulliparous women with singleton pregnancies[A]	Median: 28.0 weeks Range: 22–30 weeks 6 days[C]	<10	7727	NR	NR	0.2	NR	NR	3.9
				≥10	749			1.9			11.2
				<50	8187			0.2			4.3
				≥50	289			3.1			10.7
				<200	8369			0.3			4.4
				≥200	107			5.6			14.0
PREMET [16] UK	Post-hoc analysis of randomized prospective multicenter trial	Asymptomatic high-risk women with singleton pregnancies, history of PTB, and no other PTB risk factors	Range: 23 weeks − 24 weeks 6 days	0	497	0.6	0.6	2	5	7.5	18.1
				1-49	41	0	2.5	2.4	12.2	15.1	22
				50-199	17	5.9	11.8	17.7	23.5	29.4	41.2
				≥200	8	25	37.5	37.5	50	50	62.5
Preterm Prediction Study US [14]	Prospective observational study	Asymptomatic women with average risk of sPTB without multiple gestation, cervical cerclage, placenta previa, or major fetal anomaly	24 weeks	0-<20	2596	NR	NR	NR	NR	3	NR
				20-<40	187					6	
				40-<60	40					8	
				60-<90	17					19	
				90-<150	21					19	
				150-<300	31					34	
				≥300	34					34	
	Post-hoc analysis of		Range: 21 weeks − 25 weeks	50-99	NR	NR	NR	NR	NR	NR	12
				100-149							13

(*continued*)

Table 1. Continued.

Study Name, Country	Study design	Study Population	Gestational age at testing	fFN (ng/ml)	Sample size (*n*)	sPTB by week of gestation and fFN level (%)					
						<28 w	<30 w	<32 w	<34 w	<35 w	<37 w
Ramsey 2004 [17] US	prospective randomized trial	Asymptomatic women with fFN ≥50 ng/mL		150-199							27
				≥200							23
Tran 2019 [27] US	Prospective observational study	Asymptomatic high-risk women with singleton pregnancies with prior sPTB	Range: 18 weeks 0 days – 23 weeks 6 days	<10	65	4.6	NR	4.6	NR	6.2	18.5
				≥10	40	10.0		10.0		17.5	17.5
				<50	85	4.7		4.7		5.9	15.3
				≥50	20	15.0		15.0		30.0	30.0
				10-199	32	3.1		3.1		12.5	12.5
				≥200	8	37.5		37.5		37.5	37.5

fFN: fetal fibronectin; NR: not reported; PTB: preterm birth; fFN: fetal fibronectin; sPTB: spontaneous preterm birth; US: United States; w: week.
A. The publication did not report that women were experiencing symptoms of sPTB. Therefore, these populations were assumed to be asymptomatic women.
B. Study simply reported the proportion of patients delivering "preterm" without specifying the gestational age cutoff its assumed that data reported are sPTB rates before 37 weeks completed gestation.
C. Fetal fibronectin testing was performed at three different study visits, and the data reported here are for the final follow-up visit (between 22 weeks, 0 days and 30 weeks, 6 days).
Cells shaded in grey indicate that data were included in the meta-analysis. The nuMom2b study which investigated women with unspecified sPTB risk, who were assumed to be asymptomatic, was included in a sensitivity analyses.

<34 weeks compared to the reference population (<50 ng/ml).

Similarly, the odds of sPTB by 37 weeks were four times higher in women who were positive at the qualitative threshold (≥50 ng/ml) compared to the negative test population. Whereas the odds of delivery before 37 weeks were seven times higher for women with fFN ≥200 ng/ml compared to the reference population (<50 ng/ml). Trends were similar, albeit less pronounced, in the sensitivity analysis, including the nuMoM2b study.

There was considerable heterogeneity observed for the 28- and 30-week analyses although notably heterogeneity was much lower for the 200 ng/ml threshold analyses compared to the analyses of the conventional qualitative test threshold, as illustrated by the I^2 values in Figure 2. No signs of statistical heterogeneity were observed in the 34- and 37-week base case analyses. In the sensitivity analysis (including nuMoM2b), substantial heterogeneity (I^2>75%) was observed for all the comparisons except for 50–199 ng/ml vs. <50 ng/ml, supporting the assumption that this study's population was meaningfully different from the asymptomatic high-risk studies included in the base case. However, despite this heterogeneity, the overall trends and conclusions from this analysis remained the same as those in the base case.

Subgroup analyses were reported only by the EQUIPP [11,19,30–32] and EQUATE [26] studies, which showed that fFN was predictive of sPTB in patients regardless of cervical length, prior cervical surgery, and prior sPTB. fFN was additively predictive in patients with short cervixes or twin pregnancies. Importantly, low fFN levels may be particularly predictive of low sPTB risk in patients with vaginal blood in the samples, as these patients are more likely to experience false-positive results. Subgroup data are presented in the supplementary materials.

Discussion

Existing research has collated evidence on the accuracy of the quantitative fFN test for predicting PTB in asymptomatic high-risk pregnancies, the findings confirmed the quantitative fFN test can predict the risk of sPTB in asymptomatic women [33]. However, to the best of our knowledge, only narrative synthesis of such data has been published to date. Our objective was to establish whether the additional information provided by the quantitative fFN test may increase the utility of fFN testing in clinical practice and, if feasible, to perform a meta-analysis of the published evidence.

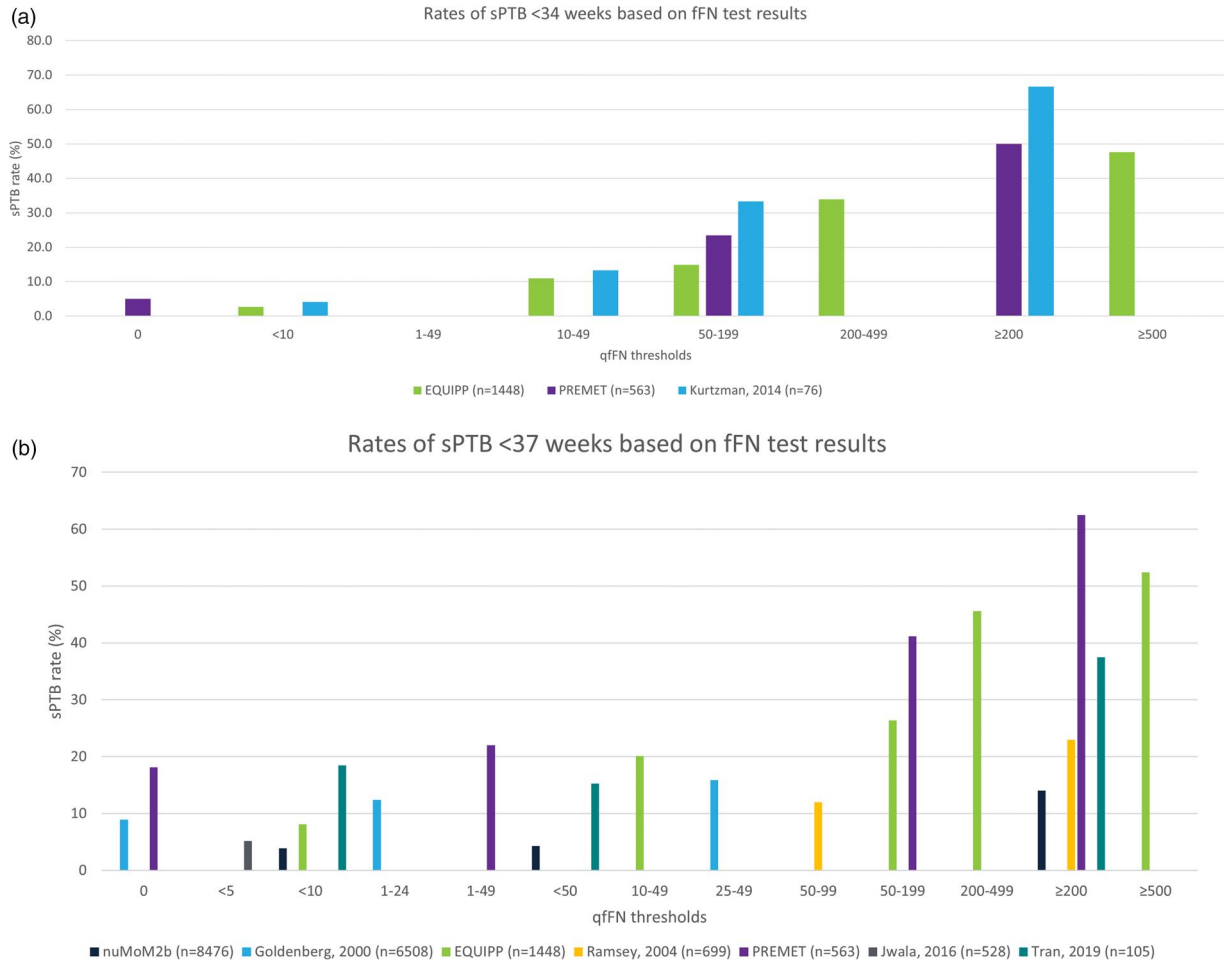

Figure 1. (a) Risk of sPTB before 34 weeks based on fFN concentration. This figure does not present data for all thresholds reported because of the substantial heterogeneity observed. The figure presents thresholds that facilitate an assessment of the trend in sPTB based on the incremental fFN thresholds reported. Outcomes for the other thresholds, not shown here, are reported in Table 1. Data presented here are reported for the overall cohort enrolled in each study; subgroup data are not presented. fFN: fetal fibronectin; sPTB: spontaneous preterm birth. (b). Risk of sPTB before 37 weeks based on fFN concentration. This figure does not present data for all thresholds reported because of the substantial heterogeneity observed. The figure presents thresholds that facilitate an assessment of the trend in sPTB based on the incremental fFN thresholds reported. Outcomes for the other thresholds, not shown here, are reported in Table 1. Data presented here are reported for the overall cohort enrolled in each study; subgroup data are not presented. NuMoM2b collected fFN specimens at three timepoints; data are presented for the final follow-up visit (22–30 weeks). fFN: fetal fibronectin; sPTB: spontaneous preterm birth.

This study demonstrates that the risk of sPTB in asymptomatic women can be meaningfully estimated by measuring exact fFN concentrations.

Specifically, the analysis showed that the odds of sPTB were greater when fFN concentration was higher compared to those with lower concentration. A gradient of odds ratios was observed, at both the study-level and in the meta-analyzed results, when comparing across incremental test thresholds (i.e. 50–199, ≥50, and ≥200 ng/mL vs. the reference of <50 ng/mL). This trend was evident at all gestational periods (<28, <30, <34 and <37 weeks), with the relationship being strongest at the earlier gestational ages. While the results showed greater odds for ≥200 vs <50 ng/mL at 30 weeks than at 28 weeks (OR: 33.72 vs 25.19), we should not infer a higher predictive power at 30 weeks compared to 28 weeks, given the low number of events at the earlier gestational age (resulting in the wide credible intervals observed).

The quantitative test can therefore be an important tool in identifying asymptomatic pregnancies at high risk for sPTB that require additional surveillance to ensure optimal maternal and neonatal outcomes. The utility of very low thresholds provides enhanced clarity regarding which patients are unlikely to experience sPTB. Two studies (EQUIPP and NuMoM2b) reported that at the 10 ng/ml threshold the negative predictive value of the test exceeds 95%, showing that the risk of sPTB is extremely low in patients with very low fFN concentrations [11,23]. However, analyses of the

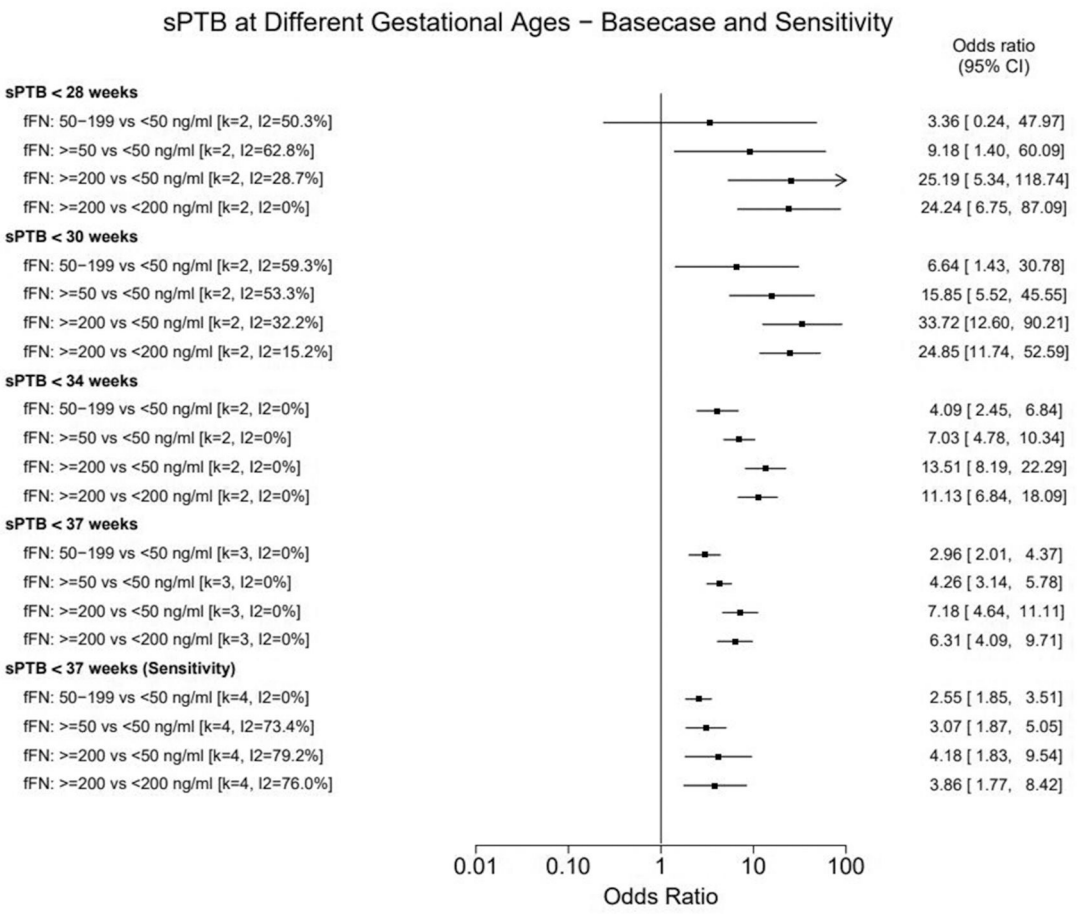

Figure 2. Meta-analysis results: sPTB risk for women with high vs low fFN concentrations. Forest plot showing the results of the random-effects meta-analyses. Results show the likelihood (odds ratio) that patients with higher fFN concentrations will experience sPTB relative to patients with lower fFN concentrations. The higher the odds ratio, the greater risk of sPTB among patients with the higher fFN concentrations relative to the reference group. The 28-week analysis pooled data reported by PREMET and Tran 2019. The 30- and 34-week analysis pooled data reported by EQUIPP and PREMET. The base case 37-week analyses pooled data reported EQUIPP, PREMET and Tran 2019; the sensitivity analysis also adds data from the nuMoM2b study. CI: confidence interval; fFN: fetal fibronectin; sPTB: spontaneous preterm birth

EQUIPP study demonstrated that certain risk factors increase the risk of sPTB so dramatically that high rates of sPTB are observed even in patients with low concentrations of fFN. Therefore, fFN concentrations should be considered in conjunction with the clinical assessment of established risk factors, such as short cervical length, prior cervical surgery, prior sPTB, and twin gestations, to guide patient management. The QUIPP app is a validated tool which combines risk factors and quantitative fFN to predict risk of preterm birth [34]. Other biomarker tests are available for the prediction of sPTB including phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1 or Actim Partus®), or placental alpha macroglobulin-1 (PAMG-1 or Partosure®) [35–38]. Existing research has investigated the utility fFN testing versus other biomarker tests.[39]

We sought to collate all the available literature on the clinical utility of the quantitative fFN test for predicting rates of sPTB in asymptomatic pregnancies. Consequently, the studies included in the review were heterogeneous in terms of study design, patient populations studied, and outcome assessment, which resulted in few studies amenable to pooling in a meta-analysis. Despite these limitations, the results of the meta-analysis showed that statistical significance was observable. Nonetheless, there is insufficient data available to perform a meta-analysis on sPTB risk in particular subgroups of interest, such as twin pregnancies and individuals with shorter cervical length. Furthermore, as with all SLRs there is a possibility that our findings may have been affected by publication bias, to try to mitigate this effect we included evidence from grey literature sources in the review. However, given the small number of studies included in the meta-analyses it was not possible to use statistical methods to assess potential publication biases.

Conclusions

Quantitative estimation of fFN concentrations in the cervicovaginal secretions of pregnant women before 37 weeks' gestation with risk factors for sPTB, but exhibiting no symptoms of labor, may increase the predictive capabilities and utility of fFN testing in clinical practice. Clinicians can implement personalized care for patients who have higher fFN concentrations, as these patients are at greater risk of undergoing preterm delivery compared to those with lower concentrations of fFN measured in the cervicovaginal secretions. For those who are not at imminent risk of sPTB, the quantitative fFN test may offer reassurance to parents and possibly prevent unnecessary medical intervention, thereby reducing healthcare costs. Future research should investigate the utility of quantitative fFN testing in optimizing management decisions and minimizing medical resource use.

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Disclosure statement

Sophie Dodman, Marissa Betts, and Binod Neupane are employed by Evidera, which provides consulting and other research services to pharmaceutical, medical device, and related organizations. In their salaried positions, they work with a variety of companies and organizations and are precluded from receiving payment or honoraria directly from these organizations for services rendered. Evidera received funding from Hologic, Inc. to participate in the study. Michael Ruma is a consultant and member of the Hologic speaker's bureau and received funding from Hologic, Inc. to participate in the study. Hologic, Inc. did not participate in the data collection, analysis, nor interpretation of the research outcomes.

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Data availability statement

Study protocol available upon request. The data used in the analyses are presented in Table 1.

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